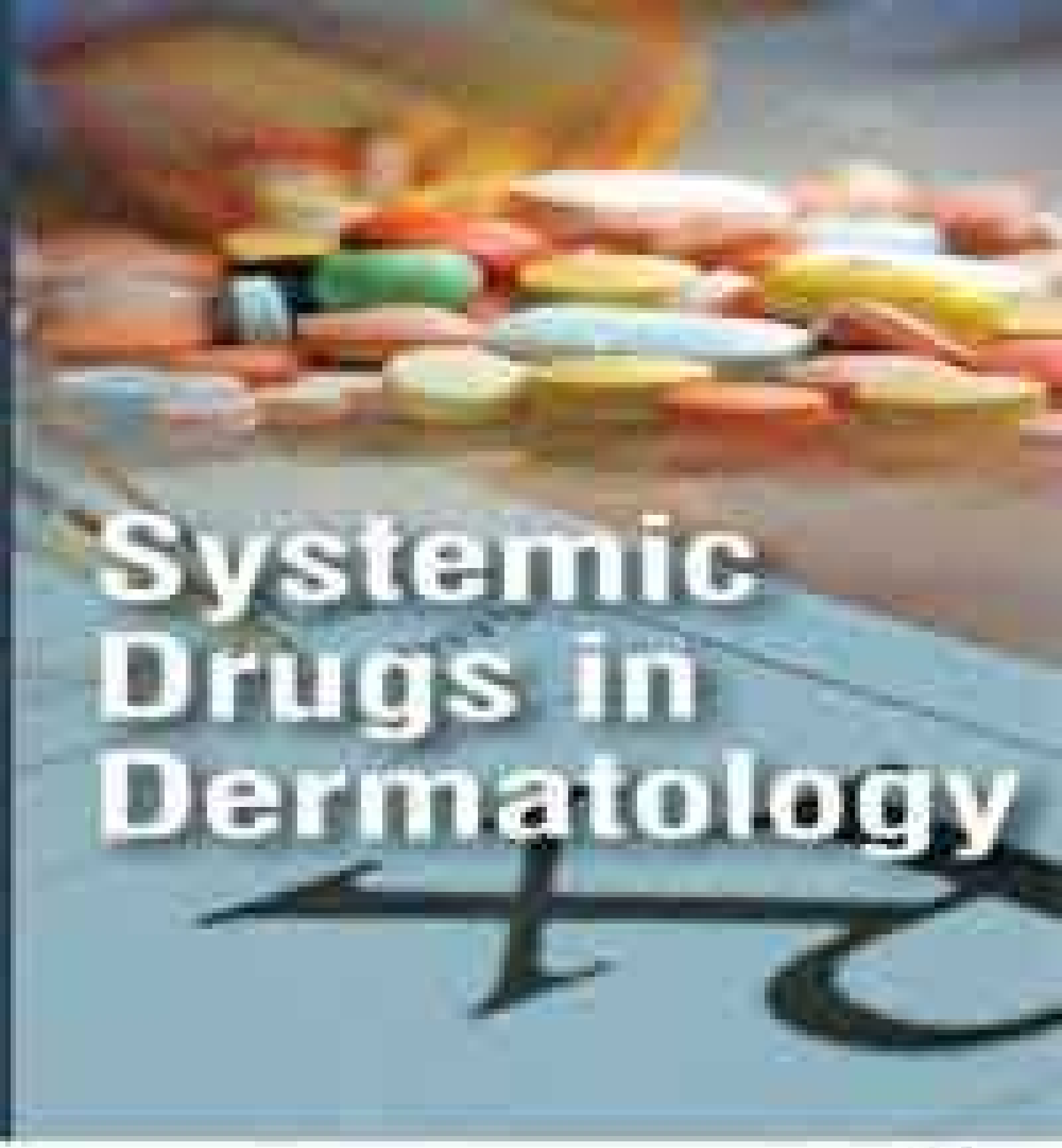


Kabir Sardana

Systemic Drugs in Dermatology

Systemic Drugs in Dermatology

Kabir Sardana
MD DNB MNAMS
Professor
Department of Dermatology and STD
Dr Ram Manohar Lohia Hospital
and
Post Graduate Institute of Medical Education & Research
New Delhi, India

JAYPEE *The Health Sciences Publisher*
New Delhi | London | Philadelphia | Panama

Jaypee Brothers Medical Publishers (P) Ltd

Headquarters
Jaypee Brothers Medical Publishers (P) Ltd
4838/24, Ansari Road, Daryaganj
New Delhi 110 002, India
Phone: +91-11-43574357
Fax: +91-11-43574314
Email: jaypee@jaypeebrothers.com

Overseas Offices

J.P. Medical Ltd
83 Victoria Street, London
SW1H 0HW (UK)
Phone: +44 20 3170 8910
Fax: +44 (0)20 3008 6180
Email: info@jpmedpub.com

Jaypee-Highlights Medical Publishers Inc
City of Knowledge, Bld. 235, 2nd Floor, Clayton
Panama City, Panama
Phone: +1 507-301-0496
Fax: +1 507-301-0499
Email: cservice@jphmedical.com

Jaypee Medical Inc
325, Chestnut Street
Suite 412, Philadelphia, PA 19106, USA
Phone: +1 267-519-9789
Email: support@jpmedus.com

Jaypee Brothers Medical Publishers (P) Ltd
17/1-B Babar Road, Block-B, Shaymali
Mohammadpur, Dhaka-1207
Bangladesh
Mobile: +08801912003485
Email: jaypeedhaka@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd
Bhotahity, Kathmandu, Nepal
Phone: +977-9741283608
Email: kathmandu@jaypeebrothers.com

Website: www.jaypeebrothers.com
Website: www.jaypeedigital.com

© Digital Version 2017, Jaypee Brothers Medical Publishers

The views and opinions expressed in this book are solely those of the original contributor(s)/author(s) and do not necessarily represent those of editor(s) of the book.

All rights reserved. No part of this publication may be reproduced, stored or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission in writing of the publishers.

All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book.

Medical knowledge and practice change constantly. This book is designed to provide accurate, authoritative information about the subject matter in question. However, readers are advised to check the most current information available on procedures included and check information from the manufacturer of each product to be administered, to verify the recommended dose, formula, method and duration of administration, adverse effects and contraindications. It is the responsibility of the practitioner to take all appropriate safety precautions. Neither the publisher nor the author(s)/editor(s) assume any liability for any injury and/or damage to persons or property arising from or related to use of material in this book.

This book is sold on the understanding that the publisher is not engaged in providing professional medical services. If such advice or services are required, the services of a competent medical professional should be sought. Every effort has been made where necessary to contact holders of copyright to obtain permission to reproduce copyright material. If any have been inadvertently overlooked, the publisher will be pleased to make the necessary arrangements at the first opportunity.

Inquiries for bulk sales may be solicited at: jaypee@jaypeebrothers.com

Systemic Drugs in Dermatology

First Edition: **Digital Version 2017**

ISBN 978-93-85891-24-3

Dedicated to

the divine grace of

Sri Ramana Maharishi

Who said that
All actions performed with unselfish devotion
With the aid of the three purified instruments
(body, speech and mind)
In the capacity of the servant of the Lord, became the Lord's action
Thus one should stand free from the sense of "I" and "mine"

Contributors

Aayushi Mehta
Resident
Dr DY Patil Hospital
Mumbai, Maharashtra, India

Chanchal Singh
MD (Obs & Gyn) MRCOG
Clinical Fellow
Maternal Fetal Medicine
Singapore
Consultant
Department of Fetal Medicine
Indraprastha Apollo Hospitals
New Delhi, India

Deepika Pandhi MD
Associate Professor
Department of Dermatology and STD
University College of Medical Sciences and GTB Hospital
New Delhi, India

Isha Narang
MBBS
Postgraduate Student
Maulana Azad Medical College and Lok Nayak Hospital
New Delhi, India

Kabir Sardana
MD DNB MNAMS
Professor
Department of Dermatology and STD
Dr RML Hospital and PGIMER
New Delhi, India

Kiran Godse
MD FRCP
Dr DY Patil Hospital
Mumbai, Maharashtra, India

Pooja Arora
MD DNB MNAMS
Assistant Professor
Department of Dermatology
PGIMER and Dr RML Hospital
New Delhi, India

Rahul Arora MD
Senior Resident
Department of Dermatology and STD
University College of Medical Sciences and GTB Hospital
New Delhi, India

Rajiv Sekhri MD (Derma)
Dermatologist
Fortis Hospital
Noida, Uttar Pradesh, India

Roshni Menon MD DVD
Professor
Department of Dermatology and Venereology
Sri Venketeshwaraa Medical College and Research Centre
Ariyur, Puducherry, India

Shankila Mittal
Postgraduate Student
Maulana Azad Medical College and Lok Nayak Hospital
New Delhi, India

Shivani Bansal MD DNB
Consultant
Max Multi-Speciality Centre
Panchseel Park, New Delhi
Consultant
Kaya Skin Clinic
Preet Vihar, New Delhi, India

Sujay Khandpur
MD DNB MNAMS
Additional Professor
Department of Dermatology and Venereology
All India Institute of Medical Sciences
New Delhi, India

Surabhi Sinha
MD DNB MNAMS
Specialist
Department of Dermatology and Venereology
Dr RML Hospital
New Delhi, India

Trilok Raj Tejasvi MD
Clinical Lecturer
Department of Dermatology
University of Michigan, USA

Usha Ranganathan MD
Dermatologist
New Jersey, USA

Vikrant Choubey
Postgraduate Student
Maulana Azad Medical College
and Lok Nayak Hospital
New Delhi, India

Vinoo Sekhri MD (Path)
Fellowship Dermatopathology
Boston University School of
Medicine
Consultant Pathologist
Fortis Hospital
Noida, Uttar Pradesh, India

V Ramesh MD FRCP
Professor
Vardhman Mahavir Medical
College and
Safdarjang Hospital
New Delhi, India

Preface

There are a few dermatological drug books available in India, for the simple reason that there are so many drugs to be covered, unlike the West where getting regulatory clearance is difficult! My aim was to make drug reading enjoyable and quick. That is why, this book includes images of the mode of action of drugs, tabular listing of mode of action, indications, doses that are interspersed with a brief overview of guidelines. Wherever needed, brand names are mentioned, but I have no affiliation to any of the companies mentioned, they are just commonly used brands!

In India, unlike the West, almost all varieties of drugs are available, and this book discusses them in a prescribed format, which the reader can refer to depending on his/her needs (*See* How to Use the Book).

As no one can be an expert in all drugs, I have tried to involve experts in their fields. Some chapters are totally contributed by my brilliant contributors like the one on biological drugs. The chapters range in size depending on the controversies and importance attached to them. Thus, the chapter on immunosuppressants and steroids are long as they are probably the most commonly prescribed agents by dermatologists. The same is true of the chapter on antibiotics. The chapter on nutrition and skin is long only because there is so much data on it. Though I daresay not all of the drugs deliver results consistently, but as so many health supplements are consumed by the patient, a knowledge of these is important. A few chapters like the one on psychotropic drugs might seem an overkill, but a lot of our patients can be handled better, if we know how to use these drugs correctly. The miscellaneous drugs is probably wrongly titled but has many commonly used drugs.

A book of this nature was not easy to write and has been in progress for three years now! It went through a lot of hitches and I thank the publisher for tolerating them. I thank Shri Jitendar P Vij (Group Chairman), Mr Ankit Vij (Group President), Mr Tarun Duneja (Director–Publishing), Mr PN Venkatraman (Director, International Marketing) and the entire production team of M/s Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, for their constant support and guidance in bringing out this book.

Though I have tried to make the book comprehensive and easy to refer and read, there may be drug or topics that I may have missed out. The reader can jot them down and maybe mail them to me for their incorporation in the next edition. We do plan to take out a handy drug book with the bare essentials and the readers suggestions are pertinent in this respect.

Kabir Sardana

Acknowledgments

There is a saying that when the chips are down, of the three, colleagues, friends and family, the first to disappear are the first on the list! And sometimes or some say invariably, they are the reason for the problems!

Thats, when family and God , or the mystical force steps in. I could and would pen down my first hand experience in this regard, but for now I am fortunate to have seen the invisible hand of God, doing miracles, through the innumerable friends, that he sent along to help me along the way. This book is dedicated to them, some of whom may never read this book.

To my source of strength, my life partner and fellow dermatologist, Dr Supriya Mahajan who is always there for me even though I may not be able to reciprocate suitably.

My daughter Zoya

My Parents, Amba Sardana and Maj. Gen. KN Sardana in Dehradun

All my Teachers, Students

and Dermatologists, specially Dr RP Gupta and Dr HK Kar.

How to Use the Book

The book can be referenced by the different readers in different ways depending on their needs.

1. *For the busy practitioner:* Tabular list of uses, doses and drug monitoring.
   As most busy practitioners have little time to run through the book, an **alphabetic listing** of the drugs is given immediately after the Contents of the book.
2. *For the student,* most chapters have a **graphical depiction** of the mode of action of drugs, with a table listing the same. Also an **introductory section** is given with graphics which serve as an overview of the chapter. This helps to give an understanding of the drug's action and its clinical implications.
3. For the reader who wants to read **disease specific therapy,** a good starting point, would be the *Therapeutic Vignette* where a listing of the various disorders being covered in this book are given. Also, in the index, common disorders are marked in *bold.*
4. For the reader who is desirous of crosschecking the facts in the chapter, this book has done away with verbose referencing, though within the text under the section of uses, salient studies are mentioned with the lead author names. I feel this method of referencing gives credence to the authors work than just a numerical insert.
   A list of references is also given at the end of each drug, within which are the books that have been referenced. A mix of core pharmacology, rheumatology books and dermatological therapeutic books are listed in most chapters.

Contents

Chapter 1:	**Antibiotics** *Kabir Sardana*	**1**
Chapter 2:	**Antifungal Medications** *Surabhi Sinha, Kabir Sardana*	**82**
Chapter 3:	**Antihistaminics** *Kabir Sardana, Usha Ranganathan*	**121**
Chapter 4:	**Antiandrogens** *Kabir Sardana, Chanchal Singh*	**175**
Chapter 5:	**Antiparasitic/Antiprotozoal Agents** *V Ramesh, Kabir Sardana*	**224**
Chapter 6:	**Antiviral Agents** *Pooja Arora, Kabir Sardana*	**250**
Chapter 7:	**Biologicals** *Kabir Sardana, Trilok Raj Tejasvi, Deepika Pandhi, Rahul Arora, Roshni Menon, Sujay Khandpur, Kiran Godse, Aayushi Mehta*	**266**
Chapter 8:	**Immunosuppressive Drugs** *Rajiv Sekhri, Vinoo Sekhri, Kabir Sardana*	**304**
Chapter 9:	**Corticosteroids** *Kabir Sardana*	**387**
Chapter 10:	**Nonsteroidal Anti-inflammatory Drugs** *Kabir Sardana*	**437**
Chapter 11:	**Psoralens (UVA)** *Shivani Bansal, Kabir Sardana*	**446**
Chapter 12:	**Retinoids** *Kabir Sardana, Usha Ranganathan*	**481**
Chapter 13:	**Vasoactive Drugs** *Kabir Sardana*	**517**
Chapter 14:	**Psychotropic Agents** *Kabir Sardana*	**535**
Chapter 15:	**Nutritional Supplements** *Kabir Sardana*	**571**

Chapter 16: Analgesics **663**
Kabir Sardana

Chapter 17: Miscellaneous Agents **681**
Vikrant Choubey, Isha Narang, Shankila Mittal, Kabir Sardana

Index *771*

List of Drugs

β-lactam antibiotics 14
Acitretin 506
Acyclovir 254
Adalimumab 288
Albendazole 247
Alitretinoin 516
Alopecia 178
Alpha lipoic acid 641
Alprazolam 567
Amitriptyline 559
Amlodipine 519
Amphotericin B 85, 238
Anidulafungin 117
Antioxidant 578
Apremilast 277
Aripiprazole 543
Aspirin 437, 441
Azathioprine 349
Azithromycin 37, 38
Aztreonam 31
Betamethasone 389
Bexarotene 514
Bilastine 160
Biotin 623
Bosentan 531
Brodalumab 273
Buspirone 568
Carbapenems 30
Carotene 610
Caspofungin 117, 118
Cephalosporins 9, 21
Certolizumab pegol 275
Cethromycin 37
Cetirizine 145
Chloroquine 688
Chlorpheniramine maleate 162
Chlroquine 691
Ciprofloxacin 74
Clarithromycin 37
Clindamycin 40
Clofazimine 688
Codeine 672
Coenzyme Q10 (Ubiquinone) 637
Colchicine 681
Colistin 80
Corticosteroids 387
Cortisone 389
Curcumin 638
Cyclophosphamide 373
Cyclosporine 360
Cyproterone acetate 192
Dalbavancin 32
Danazol 202
Dapsone 706
Daptomycin 80
Deflazacort 389
Desloratadine 155
Dexamethasone 389
Diazepam 567
Diltiazem 517
Diltiazem 518
Doripenem 30
Doxepin 165, 558
Doxycycline 44, 47, 48
Drospirenone 190, 218
Duloxetine 666
Dutasteride 200
Erythromycin 37
Escitalopram 561
Essential fatty acids 574, 588
Etanercept 281
Ethinyl estradiol 218
Famciclovir 264
Faropenem 30
Fexofenadine 152
Finasteride 193
Fluconazole 105
Fluoroquinolones 4
Fluoxetine 561
Gabapentin 667
Gabapentin 668
Gatifloxacin 74
Glutathione 639
Green tea 640
Griseofulvin 92
Guselkumab 274
Hydrocortisone 389
Hydroxychloroquine 691
Hydroxyzine hydrochloride 163
Idebenone 638
Imipenem 30
Infliximab 286
Inocoterone 179
Iron 572
Isotretinoin 484
Isotretinoin micronized 503
Isotretinoin-lidose 503
Itolizumab 289
Itraconazole 97
Ivermectin 243

Ixekizumab 273
Ketoconazole 110
Ketotifen 169
Leflunomide 717
Lenalidomide 763
Leucovorin 722
Levocetirizine 147
Levofloxacin 74
Liarozole 516
Linezolid 59
Loratidine 153
Lycopene 638
Lymecycline 48
Mebendazole 247
Meropenem 30
Mesalamine 754
Metformin 723
Methotrexate 326
Methoxsalen 446
Methylprednisolone 389
Micafungin 117
Miltefosine 231
Minocycline 44, 46, 48
Mirtazapine 564
Mizolastine 158
Moxifloxacin 75
Mycophenolate mofetil 319
Naltrexone 673
Naltrexone 673
Nifedipine 517
Nonsteroidal anti-inflammatory drugs 437
Norfloxacin 74
Nortriptyline 559
Ofatumumab 279
Ofloxacin 74
Olanzapine 543
Omalizumab 299
Oral contraceptives 209
Oritravancin 32
Oxybutynin hydrochloride 727
Paroxetine 561
Penicillamine 732
Penicillins 4
Pentoxifylline 735
Pimozide 543
Polymyxins 80
Pomalidomide 763
Posaconazole 117
Potassium iodide 742
Prednisolone 389
Pregabalin 670
Promethazine 167
Propranolol 520
Psoralen 446
Quetiapine 542
Quinupristin-dalfopristin 69
Retinoic acid metabolism blocking agents 516
Rifabutin 63
Rifamycins 62
Rifaximin 63
Risperidone 542
Rituximab 294
Saw palmetto 206
Secukinumab 272
Serenoa repens 206
Sertraline 561
Sildenafil 526
Sodium stibogluconate 227
Sparfloxacin 74
Spironolactone 184
Sulfasalazine 746
Talarozole 516
Tapentadol 673
Telavancin 32
Telithromycin 37
Terbinafine 111
Thalidomide 757
Tigecycline 44, 58
Tildrakizumab 274
Tofacitinib 312
Tramadol 672
Tranexamic acid 755
Triamcinolone 389
Trimethoprim-sulfamethoxazole 70
Valacyclovir 262
Vancomycin 33
Venlafaxine 565
Verapamil 519
Vitamin A 588
Vitamin B2 (Riboflavin) 619
Vitamin B3 (Niacin)
Vitamin B6 618
Vitamin C 627
Vitamin D 579
Vitamin E 637
Vitamin K 618
Voclosporin 272
Voriconazole 114
Zinc salts 763

Therapeutic Vignettes

Page numbers followed by f and t refer to figure and table, respectively

Acne, antiandrogens 178
Acne, diet in 588
Alopecia, antiandrogens 178
Alopecia, nutritional agents 571
Antidepressant, how to choose 553
Antifungal drugs, salient features 82
Antifungal drug*s* 82
Antihistamine use in clinical practice 135
Antiprotozoal drugs in dermatology 225*t*
Anxiety and panic disorders 566
Atopic dermatitis, antihistamines 143
Atopic dermatitis, nut*r*itional agents 579
Bullous disorders, diet 586
Chronic neuropathic pain, management 675
Hemangioma, propon*a*lol 522*t*
Herpes genitalis 250
Hirsutism, antiandrogens 180
Hirsutism, drugs therapy 182*t*
Hormonal acne 186
HSV infections, anti*v*iral agents 252
Hyperandrogenic s*t*ates, OCP 214
Immunopharmacological drugs, mode of action 313
Isotretinoin, dose regimens 487*t*
Isotretinoin use for acne 493*t*
Male pattern alopecia, finasteride 195*t*
MRSA infections and treatment 10
NIH protocol of administering cyclophosphamide and steroids in lupus nephritis 377
Panic disorders 566
Pruritus, antihistamines 142
Psoriasis, biologicals 266
Psoriasis, nutritional agents 577
Psychiatric afflictions, treatment 536
Psychotic/Delusional, treatment 539
Steroid dosimetry and tapering schedule 414*f*
Urticaria, antihis*t*amines 136
Urticaria, diet 582
Vitiligo, treatment, PUVA 457
Vitiligo, treatment 471

1
CHAPTER

Antibiotics

Kabir Sardana

INTRODUCTION

We will give a brief overview of how antibiotics work and summarize the various agents used in dermatology. As an applied aspect we will briefly cover important conditions seen clinically and discuss the options of treatment in MRSA infections.

The action of antibacterial drugs have to be understood in the context of the bacterial structure as the classification of drugs is largely based on the site of action (Fig. 1.1).

Typical Structure of a Bacterial Cell (From Inside to Outside) (Fig. 1.1)

1. DNA Bacterial Genetic Material
   This has the ribosomes (protein-making factories), energy-generating systems, digestive system, and everything else are located in the cytoplasm.
2. Cytoplasmic Membrane or Inner Membrane
   It consists of phospholipids and other membrane proteins. It is semipermeable and regulates pH, osmotic pressure and availability of essential nutrients.
3. Bacterial Cell Wall or Peptidoglycan
   Cross-linked mesh that gives a cell its shape, strength and osmotic stability, a protective suit of armor and is porous up to 100,000 Da.
4. The outer layer of lipopolysaccharide (LPS) and phospholipid material help protect bacteria from bacteriophages, pH, enzymes and phagocytosis.
   To multiply, the bacteria must be able to synthesize peptidoglycan, proteins and DNA.

The *cell wall, the ribosomes and DNA* are all potential antibiotic targets as depicted in Figure 1.1.

Gram-positive Bacteria

The gram-positive cell wall is thick and consists of 90% peptidoglycan (Fig. 1.2). The teichoic acids links various layers of peptidoglycan together. It also regulates

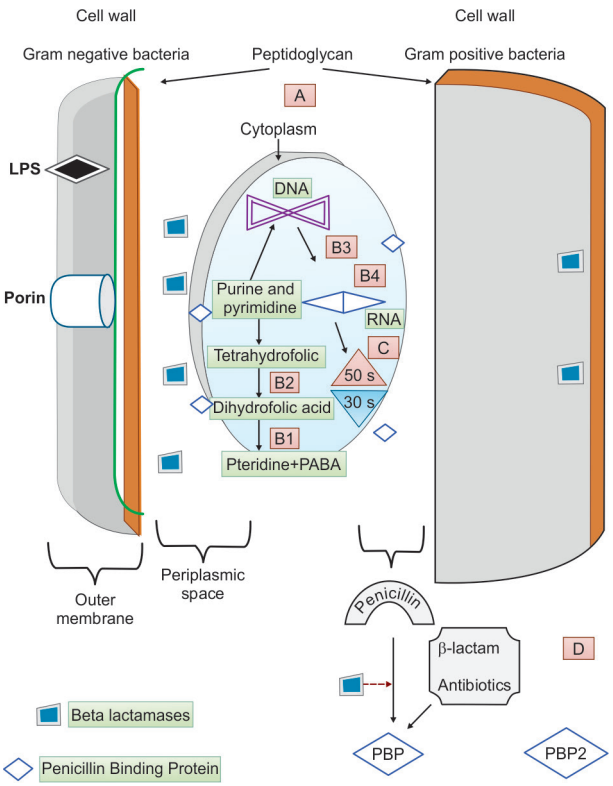


Fig. 1.1: Depiction of bacterial cell wall—site of action of major classes of antibiotic; **A:** Penicillins, cephalosporins, vancomycin, bacitracin, polymixin, colistin, teicoplanin; **B1:** Sulfonamides, trimethoprim (works by inhibiting dihydropteroate synthetase); **B2:** Trimethoprim (works by inhibiting dihydrofolate reductase); **B3:** Quinolones (inhibit DNA gyrase), silver sulfadiazine; **B4:** rifampicin (inihibits RNA polymerase). Mupirocin (reversible inhibition of tRNA synthase; **C:** Protein synthesis; *30s inhibitors:* Tetracycline, streptomycin; *50S inhibitors:* erythromycin, chloramphenicol, lincomycin, quinupristin and dalfopristin, linezolid, retapamulin. Penicillin works via PBP (penicillin-binding protein)

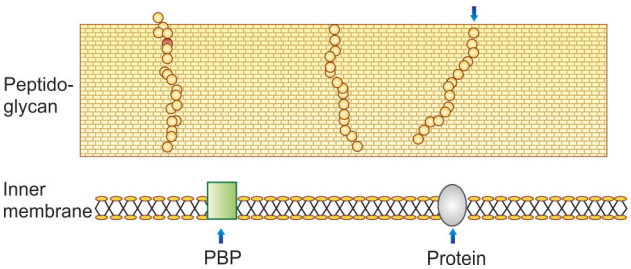


Fig. 1.2: Structure of a gram-positive organism

the autolysin activity in this complex equilibrium. The cytoplasmic membrane (which defines the intracellular space) consist of, a lipid bilayer and intrinsic proteins, which are hydrophobic and extrinsic proteins, which are hydrophilic. They also contain penicillin-binding proteins (PBPs) which are periplasmic space proteins involved in

peptidoglycan synthesis (glycosyltransferase, transpeptidase and carboxypeptidase activities) (Fig. 1.2).

Gram-negative Cell Structure

The outer membrane is made up of **phospholipids, endotoxin** or lipopolysaccharide (LPS) which plays an important role in the antibiotic entry into the cell, **porins** (complexes of three proteins) form aqueous channels that provide a route across the outer membrane for all the water-soluble compounds needed by the bacterium (Fig. 1.3).

The periplasmic space contains, peptidoglycan—5–20% of cell wall and, various enzymes (in particular, ß-lactamases). The cytoplasmic membrane (which defines the intracellular space) consists of, a lipid bilayer and intrinsic proteins which are hydrophobic (mostly enzymes involved in respiration and transmembrane transport). It also contains extrinsic proteins which are hydrophilic and penicillin-binding proteins (PBPs) (Fig. 1.3).

A summary of the common agents used for treating infections is given in Table 1.1.

Classification Based on Mechanism of Action

Antimicrobial agents are classified based on proposed mechanism of action as in Table 1.2.

1. Agents that inhibit synthesis of bacterial **cell walls**, including the beta-lactam class and other agents such as vancomycin.
2. Agents that act directly on the **cell membrane** to increase permeability and cause leakage of intracellular compounds.
3. Agents that disrupt function of ribosomal subunits to reversibly inhibit **protein** synthesis (e.g. chloramphenicol, the tetracyclines, erythromycin, and clindamycin).
4. Agents that bind to the 30S ribosomal subunit and alter **protein** synthesis (e.g., the aminoglycosides).

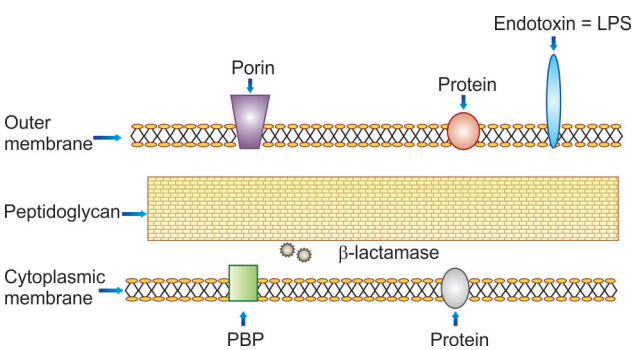


Fig. 1.3: Structure of a gram-negative organism

Table 1.1: Overview of antibiotics and their action on bacteria

Gram-positive	*Gram-positive and negative*
Penicillins (Disruption of peptidoglycans)	**Tetracyclines** (Broad spectrum and atypical mycobacteria)
Macrolide Azithromycin, clarithromycin, erythromycin (inhibit protein synthesis of 50S)	**Cephalosporins** 1st Gen: Gram (+) 2nd Gen: Gram (–) > Gram (+) 3rd Gen: Gram (–) >> Gram (+), 4th Gen: Pseudomonas 5th Gen: MRSA
Lincosoamines **Clindamycin** (Inhibit protein synthesis of 50S)	**Fluoroquinolones** (Inhibits DNA gyrase) Ciprofoloxacin (Gram negative) Levofloxacin, moxifloxacin (Gram positive)
Quinupristin and dalfopristin **Linezolid** (penicillin-resistant strains of S. pneumoniae; methicillin-resistant, vancomycin-intermediate and vancomycin-resistant strains of staphylococci; and vancomycin-resistant strains of enterococci)	**Sulfonamides** **Carbapenams** Meropenem/Imipenem (binds to PBPs, disrupts bacterial cell wall synthesis, and causes death of susceptible microorganisms) **Mupirocin**

5. Agents that affect bacterial **nucleic acid** metabolism by inhibiting RNA polymerase (e.g., rifampin) or topoisomerase (e.g., the quinolones).
6. The antimetabolites, including trimethoprim and the sulfonamides, which block essential enzymes of folate metabolism.

Though a detailed discussion follows, an overview of two common classes of drugs is given below.

PENICILLINS

One of the most classes of drug are the penicillins and a brief overview will be given in Table 1.3.

1. Penicillin G and its close congener penicillin V are highly active against sensitive strains of gram-positive cocci but are readily hydrolyzed by penicillinase and therefore ineffective against most strains of *S. aureus*. They are also effective against some anaerobes and spirochates.
2. The **penicillinase-resistant penicillins** (oxacillin, cloxacillin, and dicloxacillin) have less potent antimicrobial activity against microorganisms that are sensitive to penicillin G but are the agents of first choice for treatment of penicillinase-producing *S. aureus* and *S. epidermidis* that are not methicillin-resistant.

Table 1.2: Classification of antibacterial agents

Protein Synthesis Inhibitors			
30S	Aminoglycosides		• Streptomycin, Neomycin, • Framycetin, Amikacin • Gentamicin, Netilimicin
	Tetracycline antibiotics	Tetracycline Glycylcycline	Doxycycline, Minocycline Tigecycline
50S	Oxazolidinone		Linezolid/Tedizolid*
	Peptidyl transferase	Pleuromutilin	Retapamulin
	MLS Group	Macrolides Lincosamides Streptogramins	Azithromycin Clindamycin Quinupristin/Dalfopristin
EF-G (elongation factor)	Steroid antibacterials		Fucidin
Cell Envelope Antibiotics			
Glycopeptide			Vancomycin Dalbavancin Oritavancin Telavancin Teicoplanin
Lipoglycopeptides			

Beta Lactams	Penicillin	• Aminopenicillins • Extended spectrum • Extended-spectrum penicillins/ B-lactamase inhibitors	Ampicillin, Amoxycillin • Carboxypenicilins: Carbenicillin (IV) • Ureidopenicilin: Piperacillin (IV) Piperacillin-tazobactam, Ticarcillin-clavulanate (IV)
		• B-lactamases sensitive • B-lactamases resistant (isoxazolyl penicillins) • Aminopenicillins /Beta-lactamase inhibitors	• Penicillin G, Benzathine penicillin(IV) • Cloxacillin, Dicloxacillin • Ampicillin-sulbactam, Amoxicillin-clavulanate
		• Beta lactamases inhibitors	• Sulbactam, Tazobactam, Clauvalanic acid
	Carbapenems		• Imipenem/cilastatin, Meropenem, Ertapenem, Doripenem
	Cephalosporins	• Ist generation • 2nd generation • 3rd generation	• Cefadroxil, Cephalexin • Cefprozil, Cefuroxime axetil, Cefaclor, Cefoxitin (IV), Loracarbef • Cefotaxime (IV), Ceftazidime (IV), Ceftriaxone (IV), Cefoperazone (IV), Cefdinir, Cefpodoxime, Cefixime,

		• 4th generation • 5th generation	• Cefepime (IV) • Ceftaroline, Ceftaroline fosamil (IV)
	• Monobactam		Aztreonam
Others	• Polymyxins/detergent • Depolarizing agents cyclic lipopeptide		• Colistin Polymyxin B • Daptomycin
Nucelic Acid Inhibition			
	Antifolate inhibitors	• DHFR Inhibitor • Sulfonamides	• Trimethoprim
	Topoisomerase inhibitors	• Quinolones	Group I: Norfloxacin Group II: Enoxacin, Ofloxacin, Ciprofloxacin Group III: Levofloxacin Group IV: Moxifloxacin*
	Anaerobic DNA inhibitors		Metronidazole
	RNA synthesis	• Rifamycins	Rifampin, Rifabutin, Rifapentine, and Rifaximin

Moxifloxacin is therapeutically equivalent to cefuroxime axetil and trovafloxacin for acute bacterial sinusitis, to clarithromycin and azithromycin for acute bacterial exacerbations of chronic bronchitis, and to amoxicillin and clarithromycin for community-acquired pneumonia. Moxifloxacin would be as effective as levofloxacin, sparfloxacin, trovafloxacin, and gatifloxacin. Moxifloxacin's antistaphylococcal and antistreptococcal activity suggests that moxifloxacin may be useful in the treatment of uncomplicated skin and soft-tissue infections, although it currently does not have this indication

Table 1.3: Classification of the penicillins and summary of the drugs in each class

Penicillinase-stable penicillins Antistaphylococcal penicillins	Oxacillin Methicillin
Aminopenicillins	Ampicillin Amoxicillin
Carboxypenicillins	Ticarcillin
Ureidopenicillins	Piperacillin
β-lactam/β-lactamase inhibitor combinations	Amoxicillin + clavulanic acid Ampicillin + sulbactam Ticarcillin + clavulanic acid Piperacillin + tazobactam
Amidinopenicillin	Mecillinam

3. Ampicillin, amoxicillin, and others comprise a group of penicillins whose antimicrobial activity is extended to include such gram-negative microorganisms as *Haemophilus influenzae*, *Escherichia coli*, and *Proteus mirabilis*. Frequently these drugs are administered with a b-lactamase inhibitor to prevent hydrolysis by broad-spectrum b-lactamases that are found with increasing frequency in clinical isolates of these gram-negative bacteria.
4. The antimicrobial activity of carbenicillin, its indanyl ester (carbenicillin indanyl), and ticarcillin includes *Pseudomonas*, *Enterobacter*, and *Proteus* spp. These agents are inferior to ampicillin against gram-positive cocci and *Listeria monocytogenes* and are less active than piperacillin against *Pseudomonas*.
5. Mezlocillin, azlocillin (both discontinued in the U.S.), and piperacillin have excellent antimicrobial activity against *Pseudomonas*, *Klebsiella*, and certain other gram-negative microorganisms. Piperacillin retains the activity of ampicillin against gram-positive cocci and *L. monocytogenes*.

β-Lactamase Inhibitors

Certain molecules can inactivate β-lactamases, thereby protecting β-lactam antibiotics that are their substrates. These β-lactamase inhibitors are most active against plasmid-encoded β-lactamases (including those that hydrolyze ceftazidime and cefotaxime) but are inactive against the chromosomal β-lactamases induced in gram-negative bacilli (such as *Enterobacter*, *Acinetobacter*, and *Citrobacter*) by treatment with second- and third-generation cephalosporins.

Clavulanic acid is a "suicide" inhibitor that irreversibly binds β-lactamases from a wide range of gram positive and gram-negative microorganisms. It is combined with amoxicillin for oral administration (Augmentin) and with ticarcillin for

parenteral administration. Amoxicillin plus clavulanate is effective for β-lactamase-producing strains of staphylococci, *H. influenzae*, *Gonococci*, and *E. coli*. It also is effective in the treatment of acute otitis media in children, sinusitis, animal or human bite ounds, cellulitis, and diabetic foot infections. The addition of clavulanate to ticarcillin extends its spectrum to include aerobic gram-negative bacilli, *S. aureus*, and *Bacteroides* spp. There is no increased activity against *Pseudomonas* spp. The combination is especially useful for mixed nosocomial infections and often is used with an aminoglycoside. The dosage should be adjusted in patients with renal insufficiency.

Sulbactam is combined with ampicillin for intravenous or intramuscular use. The combination has good activity against gram-positive cocci, including β-lactamase-producing strains of *S. aureus*, gram-negative aerobes (but not Pseudomonas), and anaerobes; it has been used for the treatment of mixed intra-abdominal and pelvic infections. Dosage must be adjusted in patients with impaired renal function.

Tazobactam is a penicillanic acid sulfone β-lactamase inhibitor that has good activity against many of the plasmid β-lactamases, including some of the extended-spectrum class. It has been combined with piperacillin as a parenteral preparation.

CEPHALOSPORINS

The *first-generation* cephalosporins (e.g. cephalothin and cefazolin) have good activity against **gram-positive bacteria** and relatively modest activity against gram-negative microorganisms. Most gram-positive cocci (with the exception of enterococci, methicillin-resistant *S. aureus*, and *S. epidermidis*) are susceptible. Most mouth anaerobes are sensitive, but the *B. fragilis* group is resistant.

Second-generation cephalosporins have somewhat increased activity against gram-negative microorganisms but are much less active than the third-generation agents. A subset of second-generation drugs (e.g., cefoxitin, cefotetan, and cefmetazole) also is active against *B. fragilis.*

Third-generation cephalosporins generally are less active than first-generation agents against gram-positive cocci but are much more active against the **Enterobacteriaceae,** including β-lactamase-producing strains. A subset of third generation agents (e.g., ceftazidime and cefoperazone) are also active against ***P. aeruginosa*** but less active than other third-generation agents against gram-positive cocci.

Fourth-generation cephalosporins, such as cefepime, have an extended activity spectrum compared with the third generation and resist hydrolysis by β-lactamases. Fourth-generation drugs are particularly useful for the empirical treatment of serious infections in hospitalized patients when

gram-positive microorganisms, Enterobacteriaceae, and *Pseudomonas* all are potential etiologies.

MRSA INFECTIONS AND TREATMENT

Methicillin resistant *S. aureus* (MRSA) is a growing problem and we will cover it here as it is probably the most important bacterial skin problem. To circumvent the issue of beta lacamases, antistaphylococcal penicillins, which are modified to resist cleavage by staphylococcal β-lactamases, are used. This group of agents includes nafcillin, oxacillin, and methicillin. In addition, cephalosporins resistant to cleavage by the staphylococcal β-lactamases were also developed.

First-generation cephalosporins (cefazolin) and some second-generation cephalosporins (cefuroxime) are quite potent in this regard, while third-generation cephalosporins (ceftriaxone, cefotaxime) are less potent. The advent of β-lactamase inhibitors clavulanate, sulbactam, and tazobactam, which inactivate the staphylococcal β-lactamases, were developed. This lead to combinations like ampicillin-sulbactam, piperacillin-tazobactam, and ticarcillin-clavulanate, and carbapenems (imipenem, meropenem, doripenem) for treating these infections.

The production of **PBP2a** lead to the emergence of methicillin-resistant *S. aureus* (MRSA) (Fig. 1.4) which are resistant to all penicillins (including all antistaphylococcal penicillins), cephalosporins, and carbapenems. Though vancomycin is the drug of choice, vancomycin-resistant *S. aureus* (VRSA) strains have already been reported. PBP2a is the protein product of the *mecA* gene, which is located within a specific mobile genetic element called the staphylococcal cassette chromosome *mec* (SCC*mec*). Acquisition of different SCC*mec* elements by *S. aureus* led to the emergence of **HA-MRSA** (usually SCC*mec* types I–III) and **CA-MRSA** (usually SCC*mec* types IV and V) strains. Many CA-MRSA strains also encode virulence factors, such as Panton-Valentine leukocidin (PVL), a pore-forming cytotoxin that can cause destruction of leukocytes and tissue necrosis.

VMRSA: One of the most important clinical applications of vancomycin is in the treatment of staphylococcal infections that are resistant to several more conventional antibiotics, such as those caused by MRSA and methicillin resistant coagulase-negative staphylococci.

Resistance to vancomycin is reportedly mediated by a plasmid that reduces the permeability of the drug, and reduces binding of vancomycin to receptor molecules in the bacterial cell wall. Due to VMRSA increasing numbers of therapeutic failures have been observed with vancomycin for MRSA infections, due in large part to increases in minimum inhibitory concentrations (MIC) of vancomycin for many

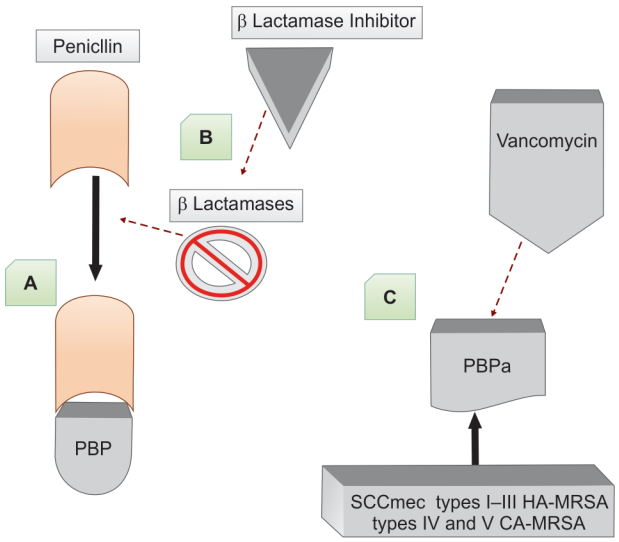


Fig. 1.4: **(A)** Initially penicillin was effective by binding with PBP of *Staph. aureus* but most strains now produce β-lactamases that cleave penicillin. **(B)** For this reason, antistaphylococcal penicillins that are resistant to cleavage by staphylococcal β-lactamases were developed. **(C)** Methicillin-resistant *S. aureus* (MRSA) strains, however, produce an altered penicillin-binding protein (PBPa) that is not recognized by these compounds or other β-lactam agents. Now drugs like vancomycin, a glycopeptide, are used, for MRSA infections

Gram-positive pathogens, including MRSA. Other organisms showing increasing resistance to vancomycin, predominantly in the hospital setting, include vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRS), and vancomycin-resistant enterococci (VRE).

Management

In general, CA-MRSA derives its resistance pattern via staphylococcal cassette type IV chromosome *mec* element (SCC-MEC IV). Most CA-MRSA infections seen in dermatologic practice cause USSTI that are susceptible to incision and drainage (when presenting as abscesses) and oral therapy with minocycline, doxycycline, clindamycin, or TMP-SMX; however, exceptions exist and the patterns of resistance to vancomycin, such as strains of *S. aureus*, are among the most common infections treated in hospitals today, often presenting as CSSTI (Table 1.4). The increasing prevalence of this resistance to major pathogens, such as *S. aureus* and VRE, has prompted the development of multiple new antibiotic classes that are currently under investigation. Some of these lipoglycopeptides, fluoroquinolones, oxazolidinones, and dihydrofolate inhibitors which are discussed later in this chapter.

While CA-MRSA is typically susceptible to multiple non-β-lactam antibiotics, **HA-MRSA** is usually resistant to several antimicrobial classes, including aminoglycosides, macrolides

Table 1.4: Empiric therapy for skin infections suspected to be caused by community-associated methicillin-resistant *Staphylococcus aureus*

Minor infections		*Severe infections*		
First-line	*Second-line*	*First-line*	*Second-line*	*Third-line*
Trimethoprim–sulfamethoxazole Minocycline Doxycycline Clindamycin	Linezolid	Vancomycin	Linezolid Daptomycin Telavancin ceftaroline	Quinupristin-dalfopristin Tigecycline

and clindamycin. Only a few relatively new antibiotics, such as *linezolid, tigecycline, quinupristin-dalfopristin, daptomycin, and ceftaroline,* are reliably active against these staphylococci.

Most cases of **CA-MRSA** seen by dermatologists though are responsive to clindamycin, the quinolones (ciprofloxacin, levofloxacin, moxifloxacin), trimethoprim-sulfamethoxazole and some tetracyclines (minocycline, doxycycline).

DRUGS INHIBITING CELL ENVELOPE

The drugs in this category are divided into three basic classes of which the most important are the beta lactamases:

1. **Beta-lactams**
   - Penicillins
   - Cephalosporins
   - Monobactams
   - Carbapenems
2. **Glycopeptides**
3. **Lipoglycopeptides (Dalbavancin,Oritavancin)**
4. **Fosfomycins**

Mechanism of Action of the Penicillins and Cephalosporins

Peptidoglycan is a heteropolymer that provides rigid mechanical stability to the bacterial cell wall by virtue of its highly cross-linked structure. In gram-positive bacteria, the cell wall is thicker than gram-negative bacteria. The peptidoglycan is composed of glycan chains, which are linear strands of two alternating amino sugars (N-acetylglucosamine and N-acetylmuramic acid) cross-linked by peptide chains. Peptidoglycan precursor formation takes place in the cytoplasm. The cross-link is completed by a transpeptidation reaction that occurs outside the cell membrane. The beta -lactam antibiotics inhibit this last step in peptidoglycan synthesis. The target of the β-lactam antibiotics for all bacteria is the PBP (penicillin binding protein) in the cytoplasmic membrane (Fig. 1.5).

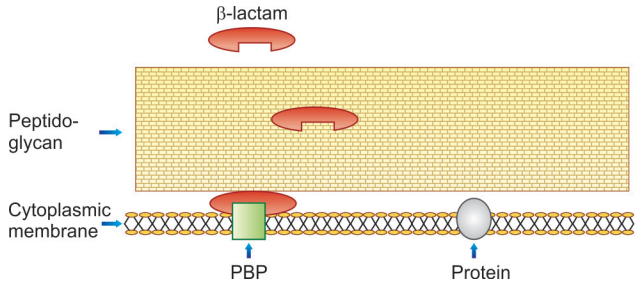


Fig. 1.5: A depiction of the entry of β-lactams in gram-positive bacteria

Mechanisms of Bacterial Resistance to Penicillins and Cephalosporins

A sensitive strain may acquire resistance by mutations that decrease the affinity of PBPs for the antibiotic. Because beta-lactam antibiotics inhibit many different PBPs, their affinity for several PBPs must decrease to confer resistance. *Methicillin-resistant S. aureus* are resistant via acquisition of an additional high-molecular-weight PBP (via a transposon) with a very low affinity for all β-lactam antibiotics; this mechanism is responsible for methicillin resistance in the coagulase-negative staphylococci.

Bacterial resistance to beta-lactam antibiotics also results from the inability of the drug to *penetrate* to its site of action. In gram-positive bacteria, the peptidoglycan polymer is very near the cell surface and antibiotic penetration is not a problem. In gram-negative bacteria (Fig. 1.6), the inner membrane is covered by the outer membrane, lipopolysaccharide, and capsule, which block access of some antibiotics. Some small hydrophilic antibiotics, including β-lactam antibiotics, diffuse through aqueous channels in the outer membrane formed by proteins called *porins*. These porins vary among different gram-negative bacteria, thereby providing greater or lesser antibiotics access to site of action.

Active *efflux* pumps also can remove the antibiotic before it can act. Bacteria also can destroy β-lactam antibiotics enzymatically via the actions of β-lactamases, such enzymes are sometimes referred to as penicillinases or cephalosporinases.

In general, gram-positive bacteria produce and secrete large amounts of β-lactamase. Most of these enzymes are penicillinases. The staphylococcal penicillinase is encoded in a plasmid that may be transferred to other bacteria and is inducible by substrate. In gram-negative bacteria, β-lactamases are strategically located in the periplasmic space between the inner and outer cell membranes for maximal protection of the microbe (Fig. 1.6).

β-LACTAM ANTIBIOTICS

In 1928, Alexander Fleming noticed that a mold contaminating one of his cultures prevented the growth of bacteria. The mold was of the genus *Penicillium,* Fleming named the antibacterial substance "penicillin,". The essential core of penicillin is a four-member ring called a beta-lactam ring.

Modifications of this basic structure have led to the development of several useful antibacterial compounds, each with its own characteristic spectrum of activity and pharmacokinetic properties. These include the *penicillins, cephalosporins, carbapenems, and monobactams.*

Mechanism of Action

Beta-lactam antibiotics can be viewed as inhibitors of penicillin-binding proteins (PBPs) that normally assemble the peptidoglycan layer surrounding most bacteria. It has been hypothesized that the beta-lactam ring mimics the d-alanyl–d-alanine portion of the peptide side chain that is normally bound by PBPs. PBPs thus interact with the beta-lactam ring and are not available for synthesis of new eptidoglycan. The disruption of the peptidoglycan layer leads to lysis of the bacterium.

The origin of beta lactamases have complicated the action of these drugs. These are produced by the organism and can lead to disruption of the action of beta lactams. The beta-lactamase of *staphylococcus aureus* is relatively specific for some of the penicillins, whereas the extended-spectrum Beta-lactamases made by some strains of *Escherichia coli* and *Klebsiella* spp. (abbreviation for the plural of species) degrade nearly all penicillins, cephalosporins, and monobactams (Figs 1.5 and 1.6).

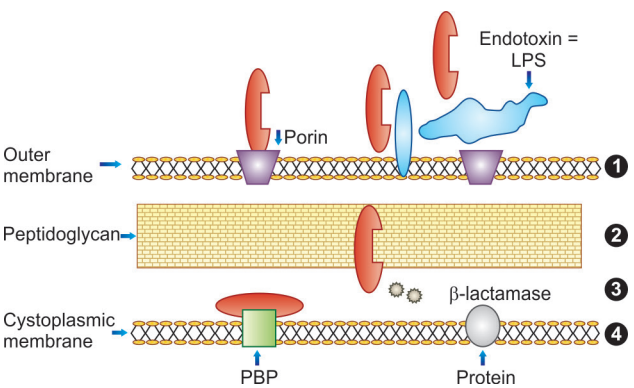


Fig. 1.6: Entry of β-lactams in gram-negative bacteria

Table 1.5: Clasification of penicillins

Natural penicillins		Penicillin G Penicillin V
Semisynthetic 1st Generation	Penicillinase-stable penicillins/ Penicillinase-resistant penicillins (isoxazolyl penicillins) Antistaphylococcal penicillins	Dicloxacillin Methicillin
2nd Generation	Aminopenicillins	Ampicillin Amoxicillin
3rd Generation	Carboxypenicillins	Ticarcillin
	Ureidopenicillins	Piperacillin
β-lactam/ β-lactamase inhibitor combinations		Amoxicillin + clavulanic acid Ampicillin + sulbactam Ticarcillin + clavulanic acid Piperacillin + tazobactam
Amidinopenicillin		Mecillinam

Classification

The penicillins each consist of a thiazolidine ring attached to a beta-lactam ring that is itself modified by a variable side chain ("R"). Whereas the thiazolidine-beta-lactam ring is required for antibacterial activity, the side chain has been manipulated to yield many penicillin derivatives that have altered pharmacologic properties and antibacterial spectra of activity.

As a result of modifications to the R side chain, penicillins come in several classes: the natural penicillins, the antistaphylococcal penicillins, the aminopenicillins, and the extended-spectrum penicillins (Table 1.5). In addition, some of the penicillins have been combined with beta-lactamase inhibitors, which markedly expand the number of bacterial species that are susceptible to these compounds.

Spectrum

1. **Natural Penicillins:** Natural penicillins are still used to treat infections caused by some gram-positive bacteria, especially the streptococci, some anaerobic bacteria, and some spirochetes (Table 1.6). Even a few gram-negative bacteria, such as *Neisseria meningitidis* and some strains of *Haemophilus influenzae* that do not make beta-lactamases, remain susceptible to penicillin.But for most other infections they have been replaced by other classes, with the notable exception of syphilis where it still remains

Table 1.6: Antimicrobial activity of natural penicillins

Gram-positive bacteria	*Streptococcus pyogenes* Viridans group Streptococci Some *Streptococcus pneumoniae* Some enterococci *Listeria monocytogenes*
Gram-negative bacteria	*Neisseria meningitidis* Some *Haemophilus influenzae*
Anaerobic bacteria	*Clostridia* spp. (except *C. difficile*) *Actinomyces israelii*
Spirochetes	*Treponema pallidum* *Leptospira* spp.
Antistaphylococcal Penicillins	
Gram-positive bacteria	Some *Staphylococcus aureus* Some *Staphylococcus epidermidis*
Aminopenicillins	
Gram-positive bacteria	Streptococcus pyogenes Viridans streptococci Some *Streptococcus pneumoniae* Some enterococci *Listeria monocytogenes*
Gram-negative bacteria	*Neisseria meningitidis* Some *Haemophilus influenzae* Some *Enterobacteriaceae*
Anaerobic bacteria	Clostridia spp. (except *C. difficile*) *Actinomyces israelii*
Spirochetes	Borrelia burgdorferi
Extended Spectrum	
Gram-positive bacteria	*Streptococcus pyogenes* *Viridans streptococci* Some *Streptococcus pneumoniae* Some enterococci
Gram-negative bacteria	*Neisseria meningitidis* Some *Haemophilus influenzae* Some *Enterobacteriaceae* *Pseudomonas aeruginosa*
Anaerobic bacteria	*Clostridia* spp. (except *C. difficile*) Some *Bacteroides* spp.

the drug of choice. Importantly, methicillin-sensitive *S. aureus* (MSSA) and MRSA are almost uniformly resistant to penicillin G and penicillin V.

2. **Antistaphylococcal penicillins:** They are also called the "penicillinase-resistant penicillins" and have bulky residues on their R side chains that prevent binding by the staphylococcal beta-lactamases. While they are useful in treating infections caused by *S. aureus* and *Staphylococcus epidermidis,* they are unable to bind the PBPs of two special groups of staphylococci called methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE).
3. **Aminopenicillins:** An additional amino group in their side chain increases their hydrophilicity and allows them

to pass through the porins (Fig. 1.6) in the outer membranes of some enteric gram-negative rods, such *E. coli*, *P. mirabilis*, *S. enterica*, and *Shigella* spp. But they are vulnerable to beta-lactamases.

4. **Extended-spectrum penicillins:** The side chains of these agents allow for even greater penetration into *gram-negative bacteria* than is seen with the aminopenicillins. Though they are more resistant to cleavage by gram-negative beta-lactamases they remain susceptible to some of these enzymes.

   Carboxypenicillins: More stable than aminopenicillins to hydrolysis by the β-lactamases of most *Enterobacteriaceae* and *Pseudomonasaeruginosa*

   Ureidopenicillins: Greater activity than carboxypenicillins against Gram-positives, enterics and *P. aeruginosa*

5. **Beta-lactamase inhibitor combinations:** β-lactamase inhibitors alone do not possess relevant antibacterial activity, but when they are combined with a β-lactam antibiotic, they act by inhibiting plasmid-mediated β-lactamase, thereby restoring the spectrum of activity of the β-lactams. They have a very high affinity for β-lactamases and act like a trap, and are hydrolyzed in preference to the β-lactam drug.

Significant activity against β-lactamase produced by MSSA, *Haemophilus* spp, *Klebsiella* spp, *E coli*, *Proteus* spp, and *B. fragilis* has been noted. However, the β-lactamase inhibitors have not been found to provide effective inhibition of β-lactamases produced by *Pseudomonas aeruginosa*, *Enterobacter* and *Citrobacter* spp.

Similarly, a combination with extended spectrum penicillins exist piperacillin-tazobactam and ticarcillin-clavulanate. Thus, piperacillin-tazobactam and ticarcillin-clavulanate have the activity against most aerobic gram-positive bacteria, including many β-lactamase–producing staphylococci, most aerobic gram-negative bacteria, and nearly all anaerobic bacteria except *Clostridium difficile*. Piperacillin-tazobactam has a broader spectrum than ticarcillin-clavulanate.

Pharmacology

Absorption and Distribution

As most dermatological indications entail an oral use of antibiotics we will largely focus on these drugs. Dicloxacillin exhibits very favorable pharmacologic and pharmacokinetic (PK) properties and should be given one hour before or after a meal. Amoxicillin is superior to ampicillin, exhibiting greater GI absorption, a lower incidence of diarrhea, and comparable efficacy.

All β-lactams are excreted *renally* with the exception of nafcillin, oxacillin, and piperacillin, which are eliminated predominantly through the biliary system.

Ampicillin–sulbactam (Amp/Sulb), ticarcillin–clavulanate (Ticar/Clav) and piperacillin–tazobactam (Pip/Tazo) are administered intravenously. Amp/Sulb can also be administered intramuscularly. In patients with renal impairment, it has been found that the half-life of the β-lactam/β-lactamase combination of drugs is prolonged and blood levels are elevated, thus warranting dosage adjustment in some cases.

Clinical Use in Dermatology

They are largely used for pyodermas, where MRSA population is in a minority. Dicloxacillin is the preferred drug for most USSTI. As beta lactamases are common, combinations (Amoxicillin-clavulanate) have a major role now in most dermatological prescriptions. The 875 mg formulation twice daily is increasingly used.

Dose

Dicloxacillin	:	125–500 mg PO q6h
Amoxicillin	:	250–500 mg PO q8h or 500–875 mg PO q12h
Amoxicillin-clavulanate	:	250 mg amoxicillin/125 mg clavulanate, 1 tab PO q8h 500 mg amoxicillin/125 mg clavulanate, 1 tab PO q8–12h or 875 mg amoxicillin/125 mg clavulanate, 1 tab PO q12h
Ampicillin-sulbactam	:	1.5–3 g IV/IM q6h (maximum: 12 g/day)
Piperacillin	:	3–4 g IV/IM q4–6h (maximum: 24 g/day)
Piperacillin-tazobactam	:	3.375 g q6h or 4.5 g IV q8h (4.5 g IV q6h for *Pseudomonas aeruginosa*)
Ticarcillin-clavulanate	:	3.1 g IV q4–6h

Usage Guidelines

1. **Pyodermas:** The antistaphylococcal penicillins show good coverage for *Streptococcus pyogenes* and MSSA, and is the preferred drug for uncomplicated skin infections USSTI (erysipelas, cellulitis, impetigo, folliculitis, furunculosis, bacterial paronychia, and ecthyma). Some prefer the intramuscular (IM) penicillin administered weekly to prophylactically inhibit recurrent erysipelas.

   The broad-spectrum antimicrobial coverage provided by Amox/Clav, Amp/Sulb, Ticar/Clav, and Pip/Tazo makes

these agents useful for the treatment of polymicrobial infections. The recommended oral agent for treatment of **animal or human bites** infected by combined aerobic and anaerobic pathogens is **Amox/Clav**.

Ticar/Clav and Pip/Tazo exhibit an even broader antibacterial spectrum, and are effective in treating CSSTI such as diabetic foot ulcers, infected decubiti, and burn wounds.

2. **Other infections:** Penicillins have also been used for the treatment of erysipeloid, scarlatina, cutaneous anthrax, lyme disease, actinomycosis, listeriosis, gas gangrene, gingivostomatosis, and leptospirosis (Weil's disease).
3. **Syphilis:** Benzathine penicllin G 2.4 MU –Single dose for early syphilis, 3 doses for late syphilis and those with unknown duration.
4. **Morphea:** Penicillin G has been used with some success to treat dermal fibrosis in patients with circumscribed and systemic sclerosis, hypothesizing the role of *Borrelia burgdorfer*i in the development of scleroderma.
5. **Erythema nodosum:** The addition of benzanthine penicillin therapy (IM) once every 3 weeks reduced the frequency of oral and genital aphthae and benefited erythema nodosum-like lesions in patients with Behçet's disease. A similar dose has been used in Erythema nodosum.

Special Considerations

Penicillin Allergy Testing

If the full battery of skin-test reagents is available, including both major and minor determinants, patients who report a history of penicillin reaction and who are skin-test negative can receive conventional penicillin therapy. Skin-test–positive patients should be desensitized before initiating treatment.

If the full battery of skin-test reagents, including the minor determinants, is not available, the patient should be skin tested using benzylpenicilloyl poly-L-lysine (i.e., the major determinant) and penicillin G. Patients who have positive test results should be desensitized. If the major determinant (Pre-Pen) is not available for skin testing, all patients with a history suggesting IgE-mediated reactions to penicillin (e.g., anaphylaxis, angioedema, bronchospasm, or urticaria) should be desensitized in a hospital setting. Patients at high risk for anaphylaxis, including those who 1) have a history of penicillin-related anaphylaxis, asthma, or other diseases that would make anaphylaxis more dangerous or 2) are being treated with beta-adrenergic blocking agents, should be tested

with 100-fold dilutions of the full-strength skin-test reagents before being tested with full-strength reagents. In these situations, patients should be tested in a monitored setting in which treatment for an anaphylactic reaction is available. If possible, the patient should *not* have taken antihistamines recently (e.g., chlorpheniramine maleate or fexafenadine during the preceding 24 hours, diphenhydramine HCl during the preceding 4 days, or hydroxyzine or phenathiazines during the preceding 3 weeks).

Procedures

Dilute the antigens either 100-fold for preliminary testing (if the patient has had a life-threatening reaction to penicillin) or 10-fold (if the patient has had another type of immediate, generalized reaction to penicillin within the preceding year).

Epicutaneous (Prick) Tests

Duplicate drops of skin-test reagent are placed on the volar surface of the forearm. The underlying epidermis is pierced with a 26-gauge needle without drawing blood. An epicutaneous test is positive if the average wheal diameter **after 15 minutes is ≥4 mm larger** than that of negative controls; otherwise, the test is negative. The histamine controls should be positive to ensure that results are not falsely negative because of the effect of antihistaminic drugs.

Intradermal Test

If epicutaneous tests are negative, duplicate 0.02-mL intradermal injections of negative control and antigen solutions are made into the volar surface of the forearm by using a 26- or 27-gauge needle on a syringe. The margins of the wheals induced by the injections should be marked with a ball point pen. An intradermal test is positive if the average wheal diameter **15 minutes after injection is >2 mm larger** than the initial wheal size and also is >2 mm larger than the negative controls. Otherwise, the tests are negative.

Major Determinant
- Benzylpenicilloyl poly-L-lysine (PrePen)

Minor Determinant Precursors
- Benzylpenicillin G (10-2M, 3.3 mg/mL, 10,000 units/mL): Penicllin G can be used
- Benzylpenicilloate (10-2M, 3.3 mg/mL)
- Benzylpenicilloate (or penicilloyl propylamine) (10-2M, 3.3 mg/mL)

Positive Control
- Commercial histamine for intradermal skin testing (1.0 mg/mL)

Negative Control
- Diluent (usually saline) or allergen iluents

Drug Interactions

Few clinically significant drug interactions are noted with the penicillins. Probenecid prolongs the renal excretion of penicillins. Oral antibiotics, including β-lactams, may potentially alter the anticoagulant effects of warfarin, warranting closer monitoring of international normalized ratio (INR) values.

Adverse Effects

1. Hypersensitivity reactions: The two commonly implicated drugs include benzylpenicillin and amoxicillin. The common manifestations include morbilliform eruptions, urticarial fatal anaphylaxis.

In patients with infectious mononucleosis or lymphocytic leukemia, a reaction can be seen with amoxicillin and is characterized by a generalized, maculopapular, and pruritic on which typically manifests within 7–10 days after the initiation of the antibiotic, with usual persistence for up to 1 week after ampicillin is discontinued. This is not believed to be a contraindication to treatment with other penicillins at a later date.

For practical purposes it should be assumed that all of the penicillins cross-react, and that if a patient has a true allergic reaction to one form of penicillin they may react to all penicillins, and possibly to cephalosporins as well. This will be discussed in detail in a later section.

2. GIT: GI disturbances, including nausea and antibiotic-associated diarrhea are not uncommon. Concomitant use of lactobacilli may help in avoiding these issues.

3. Rare side effects: Hemolytic anemia, neutropenia, platelet dysfunction, seizures, and electrolyte disturbances, when seen, are associated with very large doses given via parenteral formulations.

Nail: Onychomadesis and photo-onycholysis have been noted following cloxacillin use.

Blood: Ticarcillin and piperacillin can prolong bleeding times and cause platelet aggregation dysfunction. Hypernatremia has been reported with both ticarcillin and piperacillin administration.

Liver: Cholestatic injury has been reported in up to 1 in 100,000 prescriptions of Amox/Clav.

Special Groups

Pregnancy B
Lactation B.

CEPHALOSPORINS

The cephalosporins received their name from the fungus *Cephalosporium acremonium,* which was the source of

the first members of this class. Each cephalosporin is composed of a nucleus with two-side chains. The nucleus is 7-aminocephalosporanic acid, which is similar to the nucleus of penicillin except that the beta-lactam ring is fused to a six-member dihydrothiazine ring instead of a five-member thiazolidine ring. The cephalosporin core has ***two*** major advantages over the penicillin core: (1) It is more resistant to cleavage by beta-lactamases and (2) it has two sites, R1 and R2, at which it can be modified. This in part explains the large number of cephalosporins commercially available today.

But as the mode of action is similar to that of penicillin's they do *not* work against MRSA except the fifth generation agents.

A classification of the different drugs in this class is given in Table 1.7.

Spectrum

Several generalizations about the spectra of activity of cephalosporins can be made (Table 1.8). First, with the exception of the new fifth-generation agents, each successive generation of agents has broader activity against aerobic gram-negative bacteria. Second, with few exceptions (Cefoxitin and cefotetan/5th generation cephalosporins), they have limited activity against anaerobes. Third, the activities of these agents against aerobic gram-positive bacteria are variable, with the fifth-generation agent ceftaroline having the strongest activity against these bacteria.

First Generation

The strength of the first-generation cephalosporins is their activity against aerobic gram-positive cocci, such as staphylococci and streptococci. The R1 side chains of these agents protect their beta-lactam rings from cleavage by the staphylococcal beta-lactamase. But they cannot bind the PBPs of MRSA and MRSE or many highly penicillin-resistant *Streptococcus pneumoniae*; these agents are ineffective against these bacteria. They are active against many of the oral anaerobes, except the *Bacteroides fragilis* group.

It is important to understand that this class is *not* effective against MRSA, penicillin-resistant *Streptococcus pneumonia*, and Gram-negative organisms including *H. influenzae* and enterococci. They are not useful when *Pseudomonas* spp, *Haemophilus influenzae,* and nosocomial Gram-negative infections]

They primarily used in pyodermas (USSTI) and as an extension in combination with beta lactamases (Droxyclav) to treat USSTI.

Table 1.7: Classification of cephalosporins with a mention of the common Brands in India

	Oral	*IV*
1st generation	**Cefadroxil** **Cephalexin** **Combinations** (*Droxyclav*: Cefadroxil 500 mg, Clavulanic acid 125 mg)	**Cefazolin**
2nd generation	**Cefprozil** (*Rafzilo*), **Cefuroxime axetil** (*Bigcef/CV, Cefakind/CV*) **Cefaclor** (*Distaclor*) **Loracarbef** **Combinations** (*Bigcef CV:* Clavulanic Acid 125 mg, Cefuroxime axetil 250/500 mg)	**Cephamycin:** Cefotetan, Cefoxitin
3rd generation	**Cefdinir** **Cefpodoxime** *(Monocef O, Gudcef)* **Cefixime** *(Zifi, Mahacef, Taxim O)* Ceftibutan *(Ceftorin)* **Combinations** *1. ZIFI-LBX* + dispertab: Cefixime IR 200 mg, Dicloxacillin (MR) 500 mg, lactobacillus 2.5 billion cells. *2. Mahacef XL* Cefixime 200 mg, Cloxacillin (ER) 500 mg) *3. TAXIM-O CV* Cefixime 200Mg + Clavulanic acid 125Mg) *4. Monocef-O- CV* Cefpodoxime 200 mg+Clauvalinic acid 125 mg. *5. GUDCEF-XL tab* Cefpodoxime proxetil 200 mg, Cloxacillin (ER) 500 mg, Lactobacillus sporogenes 90 million cells) *6. GUDCEF-CV film-coated tab* (Cefpodoxime proxetil 200 mg, Clavulanic acid 125 mg)	Cefotaxime *(TAXIM),* Ceftazidime *(Fortum),* Ceftriaxone *(Monocef),* Cefoperazone **Combinations** *Monocef SB:* Ceftriaxone+ Sulbactam: *Montaz* Ceftriaxone+ Tazobactum *Magtam* cefoperazone+ Sulbactam *Hospitaz* (cefoperazone+ Tazobactum)
4th generation		Cefepime (IV) Combinations (Cefepime +Sulbactam)
5th Generation	Ceftaroline Ceftobiprole	Ceftaroline fosamil (IV)

Second Generation

Individual second-generation cephalosporins differ in their activity against aerobic gram-positive bacteria. The true cephalosporins are in general as active against aerobic gram-

Table 1.8: Spectrum of activity of cephalosporins

Ist generation	Gram-positive bacteria	*Streptococcus pyogenes* Some *Viridans streptococci* Some *Staphylococcus aureus* Some *Streptococcus pneumoniae*
	Gram-negative bacteria	Some *Escherichia coli* Some *Klebsiella pneumoniae* Some *Proteus mirabilis*
	Anaerobe	*Bacteroides fragilis*
2nd generation	Gram-positive bacteria	Same as Ist Generation
	Gram-negative bacteria	*Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis* *Haemophilus influenzae* *Neisseria* spp.
	Anaerobic bacteria	Cefoxitin and cefotetan
3rd Generation	Gram-positive bacteria	*Streptococcus pyogenes* *Viridans streptococci* Many *Streptococcus pneumoniae* Modest activity against *Staphylococcus aureus*
	Gram-negative bacteria	*Escherichia coli* *Klebsiella pneumoniae* *Proteus* spp. *Haemophilus influenzae* *Neisseria* spp. Some *Enterobacteriaceae*
	Spirochetes	*Borrelia burgdorferi*
4th Generation	Gram-positive bacteria	*Streptococcus pyogenes* *Viridans streptococci* Many *Streptococcus pneumoniae* Modest activity against *Staphylococcus aureus*
	Gram-negative bacteria	*Escherichia coli* *Klebsiella pneumoniae* *Proteus* spp. *Haemophilus influenzae* *Neisseria* spp. Many other *Enterobacteriaceae* *Pseudomonas aeruginosa*
5th generation	Gram-positive bacteria	*Streptococcus pyogenes* *Viridans streptococci* *Streptococcus pneumoniae* *Staphylococci*
	Gram-negative bacteria	*Escherichia coli* *Klebsiella pneumonia* *Proteus* spp.
	Anaerobic bacteria	Some *Clostridium* spp.

positive cocci as the first-generation agents. The cephamycins (cefotetan and cefoxitin) have relatively limited activity against this group of bacteria.

The strength of the second-generation agents is their increased activity against aerobic and facultative gram-negative bacteria. Second-generation agents are more potent against *E. coli*, *K. pneumoniae*, and *P. mirabilis* than first-generation agents and are also active against *Neisseria* spp. and, in the case of the true cephalosporins, *H. influenzae* (including beta-lactamase-producing strains). Cephamycins have an anerobic spectrum also.

Third Generation

This class have moderate activity against aerobic gram-positive bacteria and inhibit most strains of penicillin-susceptible *S. pneumoniae*. Third-generation cephalosporins are also active against the spirochete *Borrelia burgdorferi* but have little activity against anaerobic bacteria.

A modification that is common in many third-generation cephalosporins is the use of an aminothiazolyl group at R1. This helps in increased *penetration* of these agents through the bacterial outer membrane, increased affinity for *PBPs*, and increased *stability* in the presence of some of the plasmid-encoded beta-lactamases of aerobic and facultative gram-negative bacteria. The enhanced coverage inlcudes *E. coli*, *Klebsiella* spp., *Proteus* spp., *Neisseria* spp., and *H. influenzae* relative to the second-generation cephalosporins.

As some of these organisms harbor chromosomally encoded inducible AmpC Beta-lactamases that may allow the emergence of resistance during treatment, it is advised that another active agent must be used even if they appear to be susceptible by in vitro testing. Agents such as ceftazidime, cefepime, and cefoperazone have antipseudomonal coverage. Cefdinir has good coverage against both *S. aureus* and *S. pyogenes*, making this antibiotic effective for USSTI.

Combinations: In India two types of combinations are marketed (Table 1.7), one is the combination with beta lactamases, which is to increase the spectrum though this class has an intrinsic activity against beta lactamases and the combination does not seem to be justified.

The second combination is with cloxacillin which helps to cover gram positive skin infections, though here it does not cover MRSA.

Fourth-Generation Cephalosporins

The side chains of Cefepime allow more rapid penetration through the outer membrane of many gram-negative bacteria,

including *P. aeruginosa*. It also binds at a high affinity to many of the PBPs of these bacteria but is relatively resistant to hydrolysis by gram-negative beta-lactamases.

This antibiotic has the best features of the various third-generation cephalosporins (antipseudomonal activity without loss of antistaphylococcal activity) and may also have enhanced activity against many of the Enterobacteriaceae.

Fifth-Generation Cephalosporins

Ceftaroline is a new cephalosporin that has expanded activity against aerobic gram-positive cocci. This is because of the addition of a1,3-thiazole ring to the R2 side chain of this cephalosporin, which confers upon it the ability to bind to the PBP of methicillin-resistant staphylococci. This drug has excellent activity against multidrug-resistant *S. aureus*, including MRSA, vancomycin-intermediate *S. aureus* (VISA), heteroresistant vancomycin-intermediate *S. aureus* (hVISA), and vancomycin-resistant *S. aureus* (VRSA), in addition to MSSA and coagulase-negative staphylococci.

Ceftaroline has shown weak coverage against *Pseudomonas* spp. and is indicated for acute skin infections caused by *S. aureus* (including MRSA), *S. pyogenes, S. agalactiae, E. coli* and *Klebsiella*. Its activities against aerobic gram-negative bacteria are similar to that of cefotaxime and ceftriaxone and it lacks antipseudomonal activity. Ceftaroline also has activity against anaerobic gram-positive bacteria but not against anaerobic gram-negative bacteria.

Pharmacology

The half-life of most parenterally administered agents is between 0.5 and 2 hours, although the longer half-life of ceftriaxone permits once-daily dosing.

Cefaclor, cefadroxil, cephalexin, and cephradine are best absorbed from an empty stomach.

Cefuroxime axetil absorption is ***increased*** when taken with food.

Excretion

- First- and sbecond-generation agents are excreted primarily by the kidneys.
- Cefoperazone and ceftriaxone undergo predominantly hepatic metabolism and excretion.

Dosages

As most dermatological indications require oral dosages we will largely restrict to such molecules.

First-generation Cephalosporins

- Cefadroxil 1–2 g PO in divided doses q12–24h
- Cephalexin 0.25–1 g PO q6h (maximum: 4 g/day).

Second-generation Cephalosporins

- Cefuroxime axetil 250–500 mg PO q12h
- Cefprozil 250 mg PO q12h or 500 mg PO q12–24h
- Cefaclor 250–500 mg PO q8h
- Loracarbef 200–400 mg PO q12h
- Cefotetan 1–3 g IV/IM q12h (maximum: 6 g/day)
- Cefoxitin 1–2 g IV/IM q4–8h or 1–2 g IV q4h (maximum: 12 g/day)
- Cefuroxime 0.75–1.5 g IV/IM q8h Meningitis: 3 g IV q8h.

Third-generation Cephalosporins

- Cefdinir 300 mg PO q12h or 600 mg PO q24h
- Cefpodoxime 100–400 mg PO q12h
- Ceftibuten 400 mg PO q24h
- Cefixime 400 mg/day PO in divided doses q12–24h
- Cefotaxime 1 g IV q8–12h to 2 g IV q4h
- Ceftazidime 1–2 g IV q8–12h
- Ceftriaxone 1–2 g IV q12–24h.

Fourth-generation Cephalosporin

Cefepime 1–2 g IV q8–12h.

Fifth-generation Cephalosporin

Ceftaroline 600 mg IV q12h.

Indications

In dermatology, they are primarily used in pyodermas, though except for the first generation agents, the use of the rest cannot be justified in dermatology. Also, they do not work on MRSA, except for the fifth generation agents.

First Generation

They are primarily used for uncomplicated skin and soft tissue infection (USSTI) caused by MSSA and *S. pyogenes*. Both cephalexin and cefadroxil can be used. The latter has a twice daily dosage and has a better compliance.

A FDC with clauvalinic acid is available which helps to enhance the spectrum against Gram-positive organisms as it covers beta lactamases.

Second Generation

As the spectrum against gram-positive organism is similar to that of the first generation they can be used in pyodermas, but are especially indicated if a gram-negative bacteria co-infection is suspected. Both cefprozil and cefaclor are available in oral formulations.

Second-generation agents have been efficacious in treating Gram-negative cellulitis caused by *H. influenzae* or Enterobacteriaceae. *Cefuroxime axetil* can be used to treat cases of Lyme borreliosis and gonorrhea.

Third Generation

They have a largely gram negative cover and are used in the treatment of soft tissue abscesses and diabetic foot ulcers. A combination of cefixime and cloxacillin can broaden the spectrum to cover gram positive infections. A single intramuscular injection of ceftriaxone is an effective treatment for uncomplicated gonorrhea, as are single oral doses of cefpodoxime and cefixime.

Ceftazidime is used for the treatment of *P. aeruginosa* infections, like ecthyma gangrenosum, diabetic foot ulcers, and infections in burn patients.

Fifth Generation

Most recently, ceftaroline, a fifth-generation agent, has been approved for the treatment of acute bacterial skin and skin structure infections, including those caused by MRSA. Additionally, ceftobiprole, another fifth-generation cephalosporin, has also shown promise for the treatment of skin and soft tissue infections.

Interactions

Increase the effect of cephalopsorins: Probenecid.

Decrease the effect of cephalosprins: H_2 antihistamine, oral antacids and possibly proton-pump inhibitors.

Increase the effect of other drugs: Cefotetan which contain an NMTT ring have been reported to induce disulfiram-like reactions with alcohol ingestion.

Increased risk of nephrotoxicity when co-administered with aminoglycosides.

Adverse Effects

GIT

They are frequent with symptoms of nausea, vomiting, or diarrhea. Mild elevation of liver transaminaes may occur

and Ceftriaxone has been associated with biliary sludge formation, which can be a issue in children receiving high doses of prolonged therapy.

Hypersensitivity Reactions and Cross-reaction Potential

1. Hypersensitivity reactions, reported in 1–3% of treated individuals, include cutaneous findings such as urticaria, maculopapular eruptions, and pruritus. The degree of this cross-reactivity likely depends on the generation of cephalosporin, and very likely is due to structural differences in side chains among individual cephalosporins.

   The cross reactivity with penicillin (5–10%) is much less than believed specially with the newer cephalosporins. Mitropoulos IF stated that the risk of a reaction to a cephalosporin in a pencillin-allergic, patient is no greater than the risk of developing a reaction to the drug by itself. Apter concluded that in patients with penicillin allergy the risk of serious adverse events, and specifically anaphylaxis, was 0.001%. Inspite of this it is generally advised that in patients with a history of an immediate or accelerated reaction to penicillin (IgE-mediated or severe type IV delayed hypersensitivity reactions) cephalosporins must be avoided.
2. **Serum sickness-like reaction:** Cefaclor and rarely with cefprozil.
3. **Jarisch–Herxheimer reaction:** Cefuroxime axetil (12%–29%).
4. **Nail changes:** Cephalexin (acute paronychia).

Hematologic Effects

- Drug-induced immune hemolytic anemia: cefotetan and ceftriaxone
- Hypoprothrombinemia: cefotetan and cefoperazone.

Miscellaneous Side Effects

1. Vaginal infections from overgrowth of *Candida* spp.
2. Cefaclor-induced serum sickness-like reaction
3. Jarisch–Herxheimer reaction: Cefuroxime axetil
4. Nail changes: Cephalexin (acute paronychia).

Special Populations

Most cephalosporins are considered safe in children. They are generally pregnancy **category B**, with a low likelihood of congenital malformations when used during the second and third trimesters. Caution is suggested in women who are

breastfeeding, as the small quantities in breast milk have been associated with reports of diarrhea, candidal infections, and skin eruptions in the nursing infants.

- Pregnancy: B
- Children safe
- Lactation safe.

CARBAPENEMS

Beta-lactams: Penems

Slightly different structure than the other ß-lactams, make the Penems much more resistant to beta-lactamase hydrolysis.

These antibiotics are among the most broadly active antibiotics in use today. As such, they are often the last line of defense against many organisms that are resistant to other antimicrobial agents. Four members of this class are, imipenem, meropenem, doripenem, and ertapenem.

Spectrum of Action

Carbapenems: β-lactams with a broad spectrum of action. Gram-positives, except MRSA. Gram-negatives, *P. aeruginosa* (except Ertapenem) and anaerobes. Very efficient against high level cephalosporinase and ESBL.

Doripenem (new): Broad spectrum. Particularly good for Pseudomonas and other non-fermenters.

Penem (Faropenem): Oral. Primarily for respiratory tract infections. Poor activity with *Serratia, Pseudomonas, Stenotrophomonas.*

This class of drugs have some unique properties: First, these molecules are quite small and have charge characteristics that allow them to utilize special porins in the outer membrane of gram-negative bacteria to gain access to the PBPs. Second, the structures of the carbapenems make them resistant to cleavage by most beta-lactamases. Third, the carbapenems have an affinity for a broad range of PBPs from many different kinds of bacteria. As a result of these three properties, the carbapenems are adept at gaining access to the periplasm, resisting destruction by beta-lactamases that reside there, and binding to PBPs to cause bacterial cell death. *Enterococcus faecium* and methicillin-resistant staphylococci are resistant because they produce altered PBPs that do not bind these carbapenems.

Carbapenems have excellent activity against a broad spectrum of bacteria, including many aerobic gram-positive bacteria, most aerobic gram-negative bacteria, and most anaerobes. As a result, these compounds are among the most

powerful antibacterial agents in use today. They are rarely used in dermatological practice.

MONOBACTAMS

Aztreonam, the only commercially available monobactam, and it is a potent drug for aerobic gram-negative bacteria. It is available for parenteral use only. As a result of its designer structural properties, aztreonam gains access to and binds quite well to the PBPs of aerobic gram-negative bacteria and is stable against many of the beta-lactamases produced by these organisms.

It has excellent activity against *Neisseria* and *Haemophilus* spp. and intermediate activity against *P. aeruginosa*. Unfortunately, it does not bind the PBPs of gram-positive or anaerobic bacteria and therefore is not useful for infections caused by these organisms.

The drug has been employed as a sole agent in treating Gram-negative cutaneous infections, including postoperative wounds, ulcers, burns, and ecthyma gangrenosum, and in conjunction with other drugs that inhibit Gram-positive or anaerobic flora.

GLYCOPEPEPTIDE

Glycopeptide antibiotics are peptides with sugar moieties attached to them. The molecules under this category include *Vancomycin, Telavancin, Dalbavancin and Oritavancin.*

Mode of Action

Glycopeptides kill bacteria by preventing synthesis of the cell wall. They bind to the d-alanyl–d-alanine portion of the peptide side chain of precursor peptidoglycan subunits. Because of the bulk of the large glycopeptide molecule, this binding prevents these subunits from being accessed by the PBPs that would normally incorporate them into the growing peptidoglycan polymer (Figs 1.7 and 1.8).

Spectrum

As they are extremely large molecules they are unable to pass through the porins in the outer membranes of gram-negative bacteria thus, their activity is restricted to gram-positive organisms. Vancomycin and telavancin are active against nearly all staphylococci and streptococci, including methicillin-resistant staphylococci and strains of penicillin-resistant *S. pneumoniae*. Glycopeptides also have good activity against anaerobic gram-positive bacteria, including *C. difficile*.

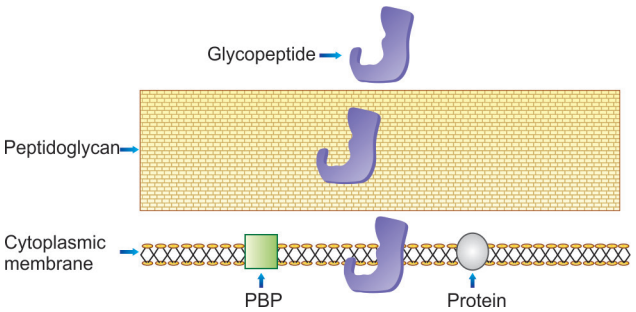


Fig. 1.7: Entry of glycopeptides in Gram-positive bacteria: In gram-positives the drugs enter without any problem because peptidoglycan does not act as a barrier for the diffusion of these molecules

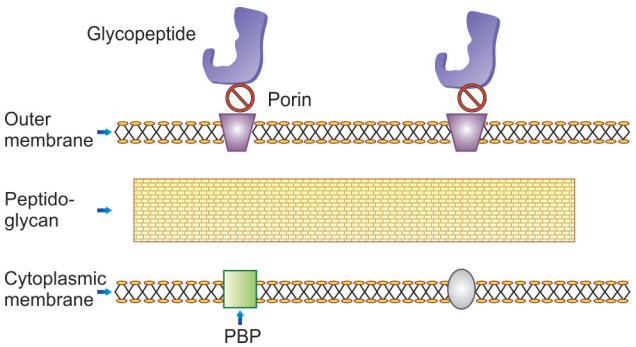


Fig. 1.8: Entry of glycopeptides in gram-negative bacteria: Glycopeptides are of high molecular weight (1500-2000 daltons), thus they do not pass through the porins of gram-negative bacteria (thus glycopeptides have no activity against gram-negative bacteria)

Spectrum of Activity of Glycopeptides

Gram-positive bacteria	*Staphylococcus aureus* MRSA (*Methicillin-resistant Staph. aureus*) *Staphylococcus epidermidis* *Streptococcus pyogenes* Viridans group streptococci *Streptococcus pneumoniae* Some enterococci
Anaerobic bacteria	*Clostridium* spp. Other gram-positive anaerobes
Lipoglycopeptide	
Telavancin	More potent than vancomycin Approved for SSTI Once daily administration Bactericidal for all Gram-positive organisms
Dalbavancin	2nd generation lipoglycopeptide Bactericidal for MRSA and MRSE 1/week IV dosing—long acting
Oritravancin	2nd generation glycopeptide IV – once per day dosing Activity similar to Vancomycin—better for Staphyloccus and Enterococcus Bactericidal

Pharmacology

Intact glycopeptides are poorly absorbed in the gastrointestinal tract, so these agents must be given intravenously to treat systemic infections. Most of it is excreted by the kidney. The serum half-life is 4–8 hours.

Dosages

Vancomycin: 15 mg/kg 12 hourly.

Indications

It is primarily used for the treatment of staphylococcal infections that are resistant to several more conventional antibiotics, such as those caused by **MRSA and methicillin-resistant coagulase-negative staphylococci.** Though still effective rising resistance has been reported against MRSA infections, vancomycin intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRS), and vancomycin resistant enterococci (VRE).

Clinical Use

Dermatologic indications

1. SSTI caused by MRSA and methicillin-resistant coagulase-negative staphylococc is one of the listed uses but now it is largely reserved for treatment of hospital-acquired MRSA (HA-MRSA).
2. Most cases of CA- MRSA respond to oral- non β-lactam antibiotics. In recalcitrant cases vancomycin may be used.

Drug Interactions

1. Concurrent administration with aminoglycosides increases the risk of nephrotoxicity.
2. It may enhance the activity of non-deporlarizing muscle relaxants.

Adverse Effects

Dermatological Side Effects

1. Red man syndrome and shock secondary to histamine release can be caused by rapid transfusion
2. Toxic epidermal necrolysis (TEN).
3. Linear IgA bullous dermatosis (LABD). They may mimick TEN. The target antigens in idiopathic LABD are believed to be heterogeneous, IgA antibodies to LAD285 with reports of antibody formation (IgA and IgG) to BP180.

Systemic Side Effects

1 Dose-related hearing.
2 Fever, neutropenia, thrombocytopenia, and phlebitis at the infusion site.

Special Population

- Children Safe
- Pregnancy C
- Lactation safe.

Renal: Modification is needed.

INHIBITORS OF PROTEIN SYNTHESIS

Aminoglycosides	Gentamicin Tobramycin Amikacin
MLSK	Macrolides: Erythromycin Lincosamides: Clindamycin Streptogramins: Quinupristin-Dalfopristin Azalides: Clarithromycin, Azithromycin Ketolides: Telithromycin
Tetracyclines **Glycylcyclines**	Tetracycline Doxycycline (IR,MR, 20 mg) Minocycline (IR/ER) Tigecycline
Phenocols	Chloramphenicol
Oxazolidinones	Linezolid, Tedizolid
Ansamycins	Rifampin

Of the list of drugs one of the most important drug classes that is used widely by dermatologist is the MLSK class of drugs and tetracylines. The class of drugs under Oxazolidinones has use in pyodermas while rifampicin is primarily used in TB.

Drugs of the MLSK and tetracycline group have action against anerobes which is the reason why they are used in acne.

Mode of Action

The code for the 20 essential amino acids consists of at least a 3-base set (triplet) of the 4 bases. If one considers the possibilities of arranging four things 3 at a time (4×4×4), we get 64 possible code words, or codons (a 3-base sequence on the mRNA that codes for either a specific amino acid or a control sequence).

Proteins are manufactured in the cell using a code in the DNA. DNA is transcribed into RNA by an enzyme called RNA polymerase (Fig. 1.9). The RNA strand is translated into proteins by the ribosomes. Each ribosome consists of one small sub-unit (30S) and a larger one (50S). The ribosome crawls along the messenger-RNA molecule translating

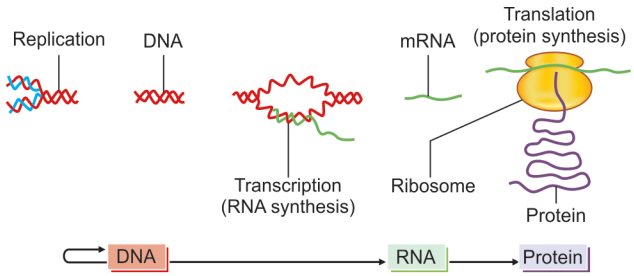


Fig. 1.9: Protein synthesis pathway

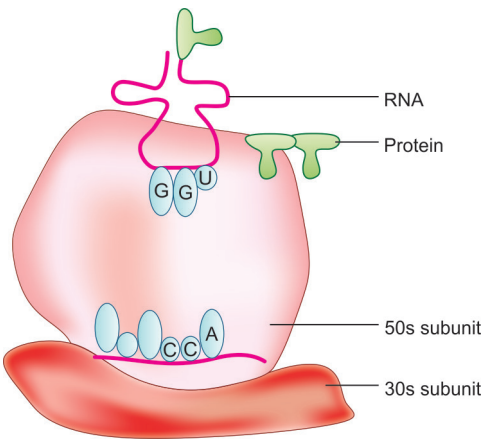


Fig. 1.10: Protein synthesis: Each ribosome consists of one small sub-unit (30S) and a larger one (50S). The ribosome crawls along the messenger-RNA molecule translating the code and assembling the amino acids in the correct order before chemically joining them to create the protein

the code and assembling the amino acids in the correct order before chemically joining them to create the protein (Fig. 1.10).

Macrolides work by inhibiting the 50S subunit while tetracyclines work by inhibiting the 30S subunit.

MLSK (MACROLIDES, LINCOSAMIDES, STREPTOGRAMINS, KETOLIDES)

Their spectrum of activity is limited to gram-positive cocci such as Streptococci and Staphylococci. These antibiotics are also active against anaerobes.

Classification

Macrolides	Erythromycin
Lincosamides	Lincomycin Clindamycin
Streptogramins	Quinupristin/Dalfopristin Pristinamycin
Ketolides	Telithromycin, Cethromycin, CEM-101

Spectrum of Action

Macrolides: Respiratory infections due to *S. pneumoniae* and *S. pyogenes*, *Mycoplasma*, *Legionella*, less serious Staphylococcal infections.

Lincosamides: Gram-positive skin infections and anaerobe infections. Oral administration appropriate for out-patient settings.

Streptogramins: Quinupristin/Dalfopristin: consists of an A and B component.
A—prevents peptide bond formation and changes the ribosome to attract the B component.
Causes early release of incomplete peptide chains.
Used for *E. faecalis* (VRE) and MRSA.

Ketolides: Ketolides are semi-synthetic derivatives of erythromycin.

FDA approved for bronchitis, sinusitis, community acquired pneumonia due to *S.pneumoniae* (including Macrolide Resistant strains), *H. influenza*, *M. catarrhalis*, *S. aureus* (sinusitis), *M. pneumoniae*, and *C. pneumoniae*.

Telithromycin: Represents a novel class that has received much attention recently due to their excellent activity against resistant organisms.

Mode of Action

These drugs enter a Gram-positive cell without any problem because peptidoglycan does not act as a barrier for the diffusion of these molecules nor does the cytoplasmic membrane (Fig. 1.11). In Gram-negative bacteria there is no entry because MLSK are lipophilic molecules. They cannot cross the outer membrane which is hydrophilic. As they are large molecules they cannot pass through the porins (which are also aqueous channels). Thus most Gram-negatives are naturally resistant to MLSK (Fig. 1.12). Antibiotics in the MLSK group are structurally distinct but have a similar mode of action by binding the 50S ribosomal subunit. During translation, it blocks the initiation step, elongation step or peptide release step of protein synthesis.

Macrolides

Macrolide antibiotics as a class follow the old adage "jack of all trades, master of none." These agents are active against some gram-positive bacteria, some gram-negative bacteria, some atypical bacteria, some mycobacteria, and even some spirochetes. But they are *not* reliably effective against most bacteria in any one group.

They remain very useful agents for respiratory infections, and for treatment directed toward specific organisms.

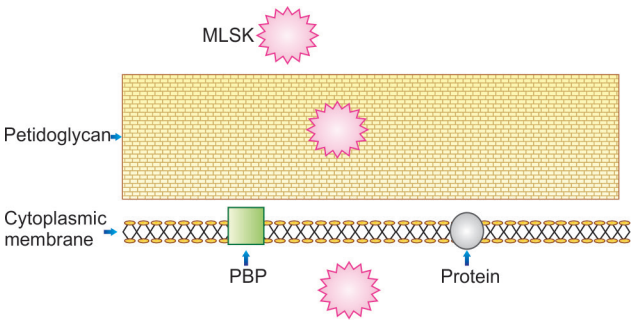


Fig. 1.11: Entry of MLSK antibiotic in gram-positive bacteria: The drugs enter a gram-positive cell without any problem because peptidoglycan does not act as a barrier for the diffusion of these molecules nor does the cytoplasmic membrane

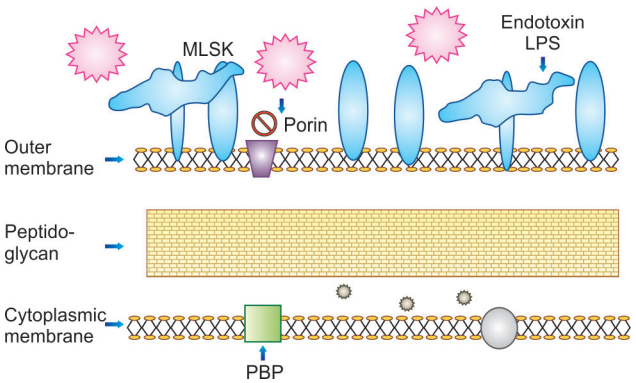


Fig. 1.12: Entry of MLSK in gram-negative bacteria: In gram-negative bacteria there is no entry because MLSK are lipophilic molecules. They cannot cross the outer membrane which is hydrophilic. MLSK are also large molecules that cannot pass through the porins (which are also aqueous channels)

The macrolide group of antibiotics consists of erythromycin, azalides consist of clarithromycin, and azithromycin while ketolides has one drug Telithromycin. Cethromycin is a newer ketolide submitted for FDA approval in 2008 for treatment of mild to moderate community-acquired pneumonia (CAP) that exhibits inhibition of both gram-positive and gram-negative respiratory organisms. CEM-101 is the newest ketolide for which the structure of telithromycin has been modified somewhat, with enhanced activity against telithromycin-resistant organisms.

Macrolides have also been reported to demonstrate specific anti-inflammatory properties, unrelated to their antibiotic activities, which may potentially contribute to their therapeutic benefit in inflammatory facial dermatoses such as acne and rosacea. Traditional macrolides are not used commonly as they have drug interactions and in acne resistance has developed against this class. Thus, we will largely focus on azithromycin.

Mechanism of Action

- Bacteriostatic antibiotics
- Binds reversibly to the large (50S) subunit of the bacterial ribosome, inhibiting RNA-dependent protein synthesis.
- Also has anti-inflammatory properties.

Pharmacology

It is active against Gram-positive organisms, with the notable exceptions of MRSA and enterococcus. Although, the in vitro activity of azithromycin against Gram-positive organisms is 2–4 times less than that of erythromycin, its efficacy is enhanced by its ability to achieve high levels in several tissues. Unlike erythromycin, clarithromycin and azithromycin possess increased activity against several Gram-negative pathogens, including *H. influenzae*.

Absorption and Distribution

Azithromycin absorption is decreased with food (best taken 1–2 hours *before* a meal).

It is primarily metabolized by the liver, no adjustments are required in renal disease. T1/2: initial 11–14 hours; prolonged half-life of 68 hours.

One of its main advantages is that it is taken up in high amounts by tissues and then slowly released over subsequent days. Thus, a 5-day course of oral therapy results in therapeutic drug levels in the blood for 10 days.

Clinical Use in Dermatology

1. Acne

The long elimination half-life and persistent tissue levels with azithromycin, makes a intermittent dosing regimens useful (250 mg three times weekly, after an initial 'tissue load,' with daily dosing for 5 days). It is useful for cases *intolerant* to tetracycline though the efficacy is *similar* to tetracycline.

Recent studies have noted a rising trend of resistance in acne patients and thus it should be used only in acne in *children* or *pregnant* females where tetracyclines cannot be given. It is possible that the antinflammatory action works in acne, which can be easily replaced by doxycyline or minocycline, as the latter have little resistance potential.

Though various regimens have been used, it is to be pointed out that as this drug is used for various medically important indications it should *not* be used as a primary therapy in acne, in view of the rising trends of resistance the prolonged therapy required in acne.

Dose Regimen

1. 500 mg daily, 4 consecutive days per month for 3 consecutive months or total dose 6.0 g in 10 weeks (Basta-Juzbasić A).
2. Dose: 500 mg 3 consecutive days a week for 1 month and then 250 mg every other day for the following 2 months (Rafiei R).
3. 250 mg 3 times a week.

An interesting study examine the efficacy of Azithromycin with doxycycline and found that it is at least *as effective* as doxycycline in the treatment of moderate acne vulgaris; however, in patients older than 18 years *doxycycline* is *better*. (Babaeinejad S). Thus in cases where antibiotics are to be given in acne doxycycline is probably a better antibiotic.

The safety of chronic use in pregnancy for acne vulgaris, rosacea, or perioral dermatitis has not been adequately addressed.

2. Cheilitis Granulomatosa

A recent report has found the drug to be of use in this condition, probably on account of its anti-inflammtory action.

3. STD

It has been primarily been used in Urethritis (*N. gonorrhoea* and *C. trachomatis*) and controversially in syphilis. Though a dose of 2 g of orally was equivalent to that of benzathine penicillin G this is restricted to early syphilis (Hook EW 3rd). The rising trends of resistance are a cause of worry and it has a restricted use in syphilis (Chen CY, A2058G Prevalence Workgroup.)

4. Other uses

Cat-scratch disease, toxoplasmosis, and human and animal bites.

5. Pyoderma

MRSA is not responsive to treatment with macrolide or azalide antibiotics. Thus most clinicians do not use the drug-though it is effective in uncomplicated pyoderma.

6. Pityriasis Rosea

Though, this is widely used for this indication, a recent study (Pandhi D) has found it to be no better than a placebo.

Usage Guidelines

Dose: 500 mg given as a single dose (Ist day) followed by 250 mg once daily for 4 days.

Special Considerations

- Often used as outpatient medication and inpatient for community-acquired pneumonia.
- It may be combined with ceftriaxone or cefuroxime for community-acquired pneumonia.
- Increasing resistance in *Streptococcus pneumoniae* is a problem.
- It is also useful for otitis media, sinusitis, and as a single 1-g dose for nongonoccocal urethritis.

Drug Interactions

Azithromycin does not significantly affect CYP isoenzymes, and so may be safely co-administered with other drugs.

Uncommonly there is toxicity related to co-administration of azithromycin and lovastatin, warfarin, cyclosporine, disopyramide, and theophylline.

Adverse Effects

Irreversible deafness, angioedema, photosensitivity, hypersensitivity syndrome, and contact dermatitis.

Rare: Pseudomembranous colitis, ventricular arrhythmias, nephritis, cholestatic jaundice, angioedema. Irreversible deafness, angioedema, photosensitivity, hypersensitivity syndrome, and contact dermatitis.

Special Groups

- Pregnancy B
- Lactation B
- Kidney disease: None.
- Liver disease: None.
- Elderly: None.

Pediatric: Safety and efficacy have not been established for children <6 months for treatment of acute otitis media and <2 years for treatment of pharyngitis/tonsillitis.

Clindamycin

Clindamycin, is a synthetic derivative of the antibiotic lincomycin. The interest in clindamycin is because of its activity against many strains of community-acquired methicillin-resistant *S. aureus* and because of its potential

efficacy in the treatment of toxin-mediated diseases caused by staphylococci and streptococci.

Mode of Action

The lincosamide antibiotics bind to the 50S subunit of the bacterial ribosome and inhibit protein synthesis. Clindamycin's mechanism of action is very similar to that of the macrolides which is primarily as their binding sites overlap. Thus, some strains of bacteria that are resistant to erythromycin because of ribosomal modification are also resistant to clindamycin. Notably, this includes *P. acnes* thus there is no logic in prescribing this antibiotic orally for acne. Most gram-negative bacteria are intrinsically resistant to clindamycin because their outer membranes resist penetration by this drug.

Spectrum

Clindamycin's is active against two groups of bacteria: aerobic gram-positive bacteria and anaerobic bacteria. It is active against many staphylococci and streptococci, including some strains of community-acquired methicillin-resistant *S. aureus*. Likewise, it has relatively broad activity against anaerobic bacteria, although some *B. fragilis* and clostridial strains are resistant.

Though some strains of CA-MRSA are sensitive to clindamycin however, inducible lincosamide resistance has led to reduced clindamycin activity against many CA-MRSA strains even when there is a laboratory report of erythromycin-resistant and clindamycin-sensitive, strains. Cross resistance to macrolides can be seen if the *erm*-encoded enzymes are affected.

Pharmacology

Absorption: The drug is well absorbed orally, independent of food, with wide tissue distribution.

Metabolism/excretion: Clindamycin is metabolized predominantly in the liver, with a plasma half-life of 2.4–3.0 hours in adults and 2.5–3.4 hours in infants and children. The drug is highly protein-bound (92–94%), with over 85% excreted in urine as inactive metabolites, the remainder in urine (10%) or feces (3.6%) as clindamycin.

Dosage

Dosages: 150-450 (6-8 hrly :max 1.8g/d); IV 0.6-2.7g IV/IM 6-12 hrly.

Dermatological Indications: 150–300 mg twice daily. Conditions such as severe hidradenitis suppurativa may

rarely require 300 mg three times daily. In children weighing ≤10 kg the minimum recommended dose is 37.5 mg every 8 hours.

Uses

1. Pyoderma

It is used to treat USSTI, primarily those caused by staphylococci, including susceptible strains of CA-MRSA. Thus, it is useful for cellulitis, folliculitis, furunculosis, carbuncles, impetigo, ecthyma, and hidradenitis suppurativa.

2. CSSTI

Deep soft tissue infections, including streptococcal myositis, necrotizing fasciitis, and *C. perfringens* infection, may also be treated with this agent. Clindamycin is also used as part of a combination regimen to treat infected diabetic foot ulcers.

Drug Interactions

Clindamycin has been shown to have neuromuscular blocking properties that may enhance other neuromuscular agents, such as tubocurare and pancuronium.

Adverse Effects

GI Effects

Antibiotic-associated colitis (originally named 'pseudomembraneous enterocolitis'), caused by toxins produced by *C. difficile*, has been reported in 0.1–10% of clindamycin-treated patients. Clindamycin should be discontinued within 24 hours of diarrhea onset.

Management: Management of fluid/electrolyte balance, protein replacement, antibiotic therapy (i.e., metronidazole, oral vancomycin), and cholestryamine resin. Other GI adverse effects associated with clindamycin include nausea, vomiting, and elevated transaminases.

Rare Effects

Bone marrow suppression and renal impairment are rare.

Cutaneous

Maculopapular or urticarial eruptions. Rarely anaphylaxis, erythema multiforme, and an SJS-type reaction have been reported.

Special Populations

Dosage adjustment of clindamycin is necessary for patients with liver failure; no dosage adjustment is needed in renal failure patients.

Pregnancy: B

BIBLIOGRAPHY

1. A2058G Prevalence Workgroup. Prevalence of the 23S rRNA A2058G point mutation and molecular subtypes in Treponema pallidum in the United States, 2007 to 2009. Sex Transm Dis. 2012;39(10):794-8.
2. Antonio JR, Pegas JR, Cestari TF, Do Nascimento LV. Azithromycin pulses in the treatment of inflammatory and pustular acne: efficacy, tolerability and safety. J Dermatolog Treat. 2008;19(4):210-5.
3. Babaeinejad S, Khodaeiani E, Fouladi RF. Comparison of therapeutic effects of oral doxycycline and azithromycin in patients with moderate acne vulgaris: What is the role of age? J Dermatolog Treat. 2011;22(4):206-10.
4. Basta-Juzbasić A, Lipozencić J, Oremović L, Kotrulja L, Gruber F, Brajac I, et al. A dose-finding study of azithromycin in the treatment of acne vulgaris. Acta Dermatovenerol Croat. 2007; 15(3):141-7.
5. Chen CY, Chi KH, Pillay A, Nachamkin E, Su JR, Ballard RC. Detection of the A2058G and A2059G 23S rRNA gene point mutations associated with azithromycin resistance in Treponema pallidum by use of a TaqMan real-time multiplex PCR assay. J Clin Microbiol. 2013;51(3):908-13.
6. Hook EW 3rd, Behets F, Van Damme K, Ravelomanana N, Leone P, Sena AC, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. J Infect Dis. 2010;201(11):1729-35.
7. Nikolaou V, Strimpakos AS, Stratigos A, Katsambas A, Antoniou C, Syrigos KN. Azithromycin pulses for the treatment *of epidermal gro*wth factor receptor inhibitor-related papulopustular eruption: an effective and convenient alternative to tetracyclines. Dermatology. 2012;224(4):315-9.
8. Pandhi D, Singal A, Verma P, Sharma R. The efficacy of azithromycin in pityriasis rosea: a randomized, double-blind, placebo-controlled trial. Indian J Dermatol Venereol Leprol. 2014;80(1):36-40.
9. Rafiei R, Yaghoobi R. Azithromycin versus tetracycline in the treatment of acne vulgaris. J Dermatolog Treat. 2006;17(4):217-21.
10. Rafiei R, Yaghoobi R. Azithromycin ver*sus tetracycline in* the treatment of acne vulgaris. J Dermatolog Treat. 2006;17(4):217-21.

TETRACYCLINES (TCN)

They are a commonly used broad spectrum antibiotic, but resistance can develop which limits their use. They are used primarily for treatment of genital infections (*chlamydiae*) and atypical infection (*Rickettsiae, Mycoplasma*).

Its primarily used in acne, though modified dose regimens have been proposed to circumvent the issue of resistance. It is important to note that the *modified* and extended *release* preparation with a U.S. FDA licensing, MR and ER are **not** same as the generics in India some of which like CNN-MR or even Minoz-OD "claim" to have this action.

As a thumb rule, if an organism is tetracycline sensitive, then minocycline and doxycycline are also sensitive, but if tetracyline is resistant, it is advisable to test for minocyline and doxycycline as the latter may still be sensitive.

Three members of this group are commonly used: tetracycline, doxycycline,and minocycline. Tigecycline, a member of a related class of antibiotics called the glycylcyclines, has recently been approved for use. Alterations of the TCN structure may alter its phototoxic potential, which is a dose-related phenomenon more commonly associated with doxycycline >TCN, and minimally from minocycline.

The drug interact with the 30S subunit of the bacterial ribosome and prevent binding by tRNA molecules loaded with amino acids. Thus, it works by blocking protein synthesis.

Mechanism of Action

They have both antibacterial and anti-inflammatory action (Table 1.9). The latter has a role disorders such as acne vulgaris, rosacea, immunobullous diseases, and sarcoidosis.

Spectrum

Tetracyclines are active against some aerobic gram-positive bacteria and aerobic gram-negative bacteria, some anaerobes including *P. acnes* (Table 1.10). Doxycycline and minocycline are used for CA-MRSA. Its major activity though is against atypical bacteria, including *Rickettsiae*, *Chlamydiae*, and *Mycoplasmas*.

P. acnes Resistance

Antibiotic resistance is a global concern and though some experts believe that it may not have an in vivo significance. Studies throughout the world have confirmed that a reduction in community antibiotic exposure over time correlates with a reduction in the antibiotic resistance patterns with specific antibiotics (Sardana K et al.).

There are two mechanisms for resistance. One is by acquisition of exogenous genes are acquired that encode for efflux pumps, which prevent intracellular accumulation of these drugs. Secondly genes may be acquired that encode ribosomal protection proteins. In *P. acnes*, the TCN resistance is mediated exclusively through point mutation in

Table 1.9: Mechanism of action

Antibacterial	Inhibits protein synthesis
Neutrophil	Inhibition of the production of neutrophil chemoattractants by *P. acnes* (i.e., peptide chemotactic factor, lipase) Inhibition of neutrophil migration in vitro and in skin window studies in vivo
Immunological	Inhibitory activity against granuloma formation in vitro, likely due to protein kinase C inhibition
Cytokine	Down regulation of cytokines involved in the innate immune response
Others	Inhibition of multiple matrix metalloproteinases (MMP), which are involved in dermal matrix degradation of both collagen and elastic tissue Scavenger effect against reactive oxygen species (ROS)

Table 1.10: Spectrum

Gram-positive bacteria	Streptococcus pneumonia *Staph. aureus* (doxycycline/ minocycline)
Gram-negative bacteria	*Haemophilus influenzae* *Neisseria meningitidis*
Anaerobic bacteria	Some *Clostridia* spp, *P. acnes*
Spirochetes	*Borrelia burgdorferi* *Treponema pallidum*
Atypical bacteria	*Rickettsia* spp. *Chlamydia* spp. *Mycoplasma* spp.

genes encoding the 16S ribosomal RNA. *P. acnes* antibiotic resistance patterns correlate with the extent of oral antibiotic use in various countries. The greatest prevalence of *P. acnes* resistance is with TCN, reported in 20–26.4% of patients.

Pharmacology

The TCN are divided into the short acting (T1/2 6-12 hrs); intermediate acting (T1/2 16 hrs) and the long acting (T1/2 18-22 hrs) variant.

The long-acting variant can have various preparations of doxycycline and minocycline including the, IR (immediate release), MR (modified release) and ER (extended release). Multiple in vitro, in vivo microbiologic and PK studies, have shown a *dissociation* between the antibiotic and biologic/ anti-inflammatory properties of doxycycline based on dose. Thus, subantimicrobial dosing of doxycycline *may* not induce antibiotic-resistant bacterial strains.

Minocycline *(Extended Release versus Immediate Release) (Del Rosso J)*

Clinical and pharmacokinetic data with multiple formulations of minocycline IR indicate that the occurrence of vestibular AEs correlates with the dissolution rate and C_{max} of minocycline (Fig. 1.13). Also vestibular AEs are more frequent in patients with *lower* body weight unless the dose is adjusted to body weight. This is due to a rapid influx of minocycline into the blood, which produces high spikes in serum concentrations following administration of minocycline IR.

The extended-release (ER) minocycline hydrochloride tablet formulation developed has a delayed time of maximum concentration [T_{max}, 3 (1/2)–4 hours] compared with a nonmodified-release minocycline [T_{max}, 2 (1/4) – 3 hours], and a lower maximum concentration of drug (C_{max}) in the blood (90%) compared with nonmodified-release formulations. At steady state (day 6), the ER-minocycline formulation had a 0- to 24-hour area under the curve [AUC (0-24)] and C_{max} of 33.32 μg × h/mL and 2.63 μg/mL, respectively, compared with 46.35 μg h/mL and 2.92 μg/mL, respectively, for the nonmodified-release minocycline. These studies demonstrated that the new ER-minocycline hydrochloride formulation is **not** bioequivalent to the immediate-release (IR) minocycline hydrochloride formulation currently on the market. The favorable pharmacokinetic profile of ER minocycline also was not affected by concomitantly ingested food, including dairy products.

The use of extended-release (ER) minocycline, administered at 1 mg/kg/day, produces subantimicrobial

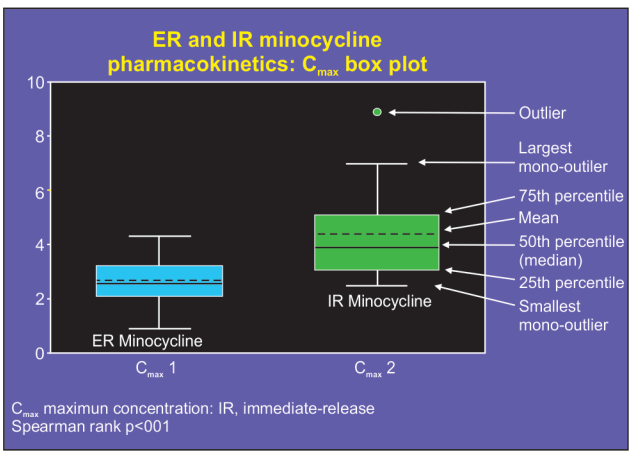


Fig. 1.13: Comparison of pharmacology of ER and IR minocycline
Source: Del Rosso JQ et al. American Academy of Dermatology. Dermatology conference. October 19-20, 2008. Las Vegas. NY

drug levels and so is indicated only for inflammatory lesions of moderate to severe acne vulgaris. The ER formulation of minocycline slows the rate of drug release and thus systemic minocycline ER would be less likely to have extreme elevations in C_{max} and AUC and therefore be more likely to better tolerate therapy. Studies with this new ER preparation (Fleischer et al, Stewart et al) confirm its efficacy in acne. But these preparations do *not* prevent resistance.

Doxycline (MR/Low Dose)

Doxycycline-MR is formulated as a bead-containing capsule with immediate release of 30 mg of the drug and delayed release of 10 mg. Subantimicrobial dosages are useful as a separation of the antibiotic and anti-inflammatory effect has been shown. This is important as subantimicrobial doses do not induce antibiotic-resistant bacterial strains. There are *two dosages* regimens using this principle, the MR dose and 20 mg dose.

Studies by Skidmore et al and Toossi P on this low dose therapy have shown that it is effective in **acne**. A recent study by Moore et al have again shown that MR-doxycycline 40 mg demonstrated comparable efficacy and superior safety to DC 100 mg in the treatment of moderate to severe inflammatory acne.

Please note that the brand in India (CNN-MR) is *not* the same as the patented MR preparation of doxycycline. Also doses of doxycycline ≥50 mg daily achieve serum levels that exceed the MIC of some bacteria and thus are **no** longer subantimicrobial (Del Rosso JQ).

Absorption and Distribution

The order of lipophilicity among TCNs is minocycline > doxycycline > tetracycline. Tissue concentrations of doxycycline IR are approximately 5-fold greater in soft tissues than in serum with minocycline IR achieving 47% higher concentrations in skin than in serum.

GI absorption of doxycycline (IR and MR) is *reduced* when taken *with* food by approximately 20% and of minocycline IR by 12%. With regard to minocycline, co-administration of iron (ferrous sulfate) with minocycline IR reduced minocycline absorption by 77%. Enteric coating of doxycycline, which delays release of doxycycline beyond the stomach and into the small intestine, has been shown to reduce GI adverse effects compared to IR formulations of doxycycline.

A comparison of the two agents, is given in Table 1.11, and the basic advantage of minocycline is that it can be taken with food.

Table 1.11: Comparison of doxycyline and minocycline

	Doxycycline	*Minocycline*
Absorption	73–95%	95–100%
Solubility	High	High
Permeability	High	High
Volume of distribution	50–80L	80–115L
Protein binding	82–93%	76%
Lipophilicity	Intermediate	High
Dietary factors affecting absorption	Food (less affected than tetracycline), iron, calcium, magnesium, aluminum	Food (less affected than tetracycline or doxycycline), iron, calcium, magnesium
Formulations	MR/IR	IR/ER

Usage Guidelines

A summary of the uses of this class of drugs is given below with the type of preparation approved.

1. **Tetracyline:** 250-500 mg (OD/BD)
2. **Doxycyline:**
   - 50 mg, 100 mg (OD/BD) (Enteric-coated preparations are not same as ER)
   - 20 mg: Subantimicrobial doses of doxycycline without loss of anti-inflammatory activity is achieved if doxycycline 20 mg twice daily is given (Approved in periodontal disease).

   Doxycyline MR: Doxycycline modified-release (MR) 40 mg once daily. Doxycycline-MR is formulated as a bead-containing capsule with immediate release of 30 mg of the drug and delayed release of 10 mg (antinflammatory effect). Approved for rosacea.

   (Please note that the minocycline MR in India is **not** the same as the doxycycline MR the latter has a patented delivery dynamics).
3. **Minocycline:** 50–100 mg OD

   Minocyline IR : 50,75,100 (OD/BD)

   Minocyline ER: Extended release (1 mg/kg/day) ; various strengths in mg (45, 55, 65, 80, 90, 105, 115, 125), which depends on the weight of the person.
4. **Lymecycline (300 mg; 408 mg)**

   The usual dosage for the chronic treatment of acne is 1 capsule daily: treatment should be continued for at least 8 weeks. For other infections, the usual dosage is 1 capsule BD. If higher doses are required, 3-4 capsules may be given over 24 hours. Lower doses may be given for prophylaxis.

A study has shown that there was no differences (Ocampo-Candiani J) between the groups with non-inflammatory and inflammatory lesion counts, and in the safety profile between lymecycline and minocyline. But it must be pointed the molecule is prone to resistance and thus apart from the cost difference there is no superiority over other TCN.

Clinical Use

A few general principle guide the use of tetracylines in dermatology. Firstly, the IR preparations which are most commonly used should be used ideally in cases where the *antimicrobial* effect is required. Conversely, the MR preparation is *sub-antimicrobial* and should not be used in infections. As the latter has a lower dose they have less side effects including vaginitis in females. Thus, the anti-inflammatory dose doxycline (30 mg IR + 10 mg MR capsule once daily) produces anti-inflammatory effects without antibiotic effect and is FDA-approved for treatment of inflammatory lesions of rosacea. The minocycline ER is the ***only*** tetracycline approved for Acne.

1. Acne

This is by far the most common dermatological indication and recently the novel ER preparation has been launched in India.

The conventional doxycycline and minocycline IR formulations achieved a reduction of inflammatory lesions is >50% at 12 weeks, with improvement observed in 70% of 90% of patients treated. But they have *not* been FDA approved for acne vulgaris. The initial results are seen in 3 weeks and maximum benefit are achieved between 3 and 6 months (with notable exceptions to these ranges). About 50% of patients relapse within 8 weeks of oral antibiotic cessation.

Combined use of an oral TCN with topical therapy, especially a benzoyl peroxide-containing regimen, is used to achieve the dual goal reducing antibiotic-resistant *P. acnes* strains, and augmenting efficacy. It must be remembered though that all TCN have equal efficacy and no clear relationship between dose and efficacy was found in a systematic review of clinical trials from 1962 to 1996 (Simonart T et al). Doxycycline and minocycline IR are better than conventional TCN as, they have less frequent dosing, and a lower prevalence of resistant *P. acnes* strains.

Minocyline ER tablets has been found to be equivalent in efficacy (Stewart DM) in a wide range of doses (1, 2, 3 mg/kg) and minocycline ER (1 mg/kg/day) has also been shown to be superior to placebo in reducing inflammatory acne lesions and is FDA approved for acne (Fleischer Jr AB). In fact Stewart et al suggested that even at low doses of 1mg/kg/d the lipophilicity

of minocycline ensured that the plasma levels did not need to be high and thus theoretically you could 'get away" with a lower dose because of the theorized concentration of the drug in the follicles.

Recently, Moore et al found that doxycyline MR 40 mg was found to be as effective as doxycycline 100 mg IR in acne. Similarly, subantimicrobial dose of doxycycline IR, 20 mg twice daily, has been found to be superior to placebo in reducing acne lesions (Skidmore R), but neither of these two doxycycline molecules has received FDA approval for Acne. The other low dosage regimens like 50 mg minocycline IR or lymecycline 150 mg are ***not*** subantimicrobial and should *ideally* not be administered in acne, as they predispose to resistance.

Thus, it is a good practice to use the MR and ER preparations as a **"step-down therapy"** from full-dose antibiotics (IR), which can be used for the acute and more significant acne, and as they get better, perhaps changing over to the lower, anti-inflammatory doses of doxycycline. In India, the IR preparation of minocycline has been doing pretty well commercially, with no marked side effects and the ER preparation launched recently may be safer but is markedly expensive which probably negate its other advantages.

2. Rosacea

The only FDA-approved oral agent for papulopustular rosacea is doxycycline MR 40 mg once daily, which produces a anti-inflammatory activity, yet being a subantimicrobial dose is devoid of any antibiotic effects. The subantimicrobial dose doxycycline IR 20 mg twice daily has also been found to be useful in acne rosacea.

Though conventionally, most clinicians use minocycline IR and doxycycline IR, there is little data to support their use in rosacea. But doxycycline 100 mg daily for 12 weeks is used which markedly improves ocular symptoms of dryness, pruritus, blurred vision, and photosensitivity in patients with cutaneous rosacea and signs and symptoms of ocular rosacea. Ocular findings of rosacea, including scales, erythema, telangiectasia, ciliary base injection, bulbar injection, papillary hypertrophy, and punctate epithelial erosions, also improve.

In Morbihans Disease a dose of minocycline at 50 mg/day gradually increased to 100 mg/day, after 4 weeks and maintained for 4 months has been found to be effective (Noriki Fujimoto).

3. Perioral Dermatitis

The duration of therapy of the TCNs agent is generally over a range of 1–3 months. A 4–8 week course of doxycycline MR 40 mg once daily is efficacious for perioral dermatitis, both

as monotherapy and in combination with topical agents. In the absence of the MR and ER preparations conventional preparations can be used but may require 1-3 months for a response

4. Granulomatous Dermatoses

The mechanism of action is probably a inhibition of T-cell proliferation and granuloma formation is the primary mode of the efficacy in sarcoidosis. A higher dose is required, thus doxycycline 200 mg/day or minocycline IR 200 mg daily for 12 months is administered.

They have also been used in silicone granuloma (minocycline IR) and Melkersson–Rosenthal syndrome (prednisone + minocycline IR).

5. Immunobullous Dermatoses

TCNs have been used, most often in combination with nicotinamide, for the treatment of immunobullous diseases such as bullous pemphigoid, linear IgA bullous dermatosis, pemphigus vulgaris, pemphigus foliaceus, benign familial pemphigus (Hailey–Hailey disease), and cicatricial pemphigoid.

6. CA-MRSA Infections

Here only the conventional doxycline/minocycline IR should be administered. Duration of therapy may range from 2 to 4 weeks, depending on clinical response and extent of infection. A review of studies (Elston D) suggests that the IR formulations of doxycycline and minocycline should be used as a 'first-line' agents for USSTI caused by CA-MRSA, including abscesses and furuncles (combined with incision and drainage).

7. Rickettsial Diseases

Doxycycline IR 100 mg twice daily is recommended until patients are afebrile for at least 2 days, with a total duration of no less than 7 days.

8. Syphilis

Doxycycline 100 mg twice daily for 14 days or TCN 500 mg 4 times daily for 14 days can be used for the treatment of primary, secondary, or early latent syphilis. The same daily dosage for either agent is recommended for uncomplicated late latent syphilis or syphilis of unknown duration in immunocompetent patients, with extension of the treatment course to 28 days.

9. Lymphogranuloma Venereum (LGV)

Doxycycline IR 100 mg twice daily for 21 days is the preferred approach for treatment of lymphogranuloma venereum

(LGV), which is caused by *C. trachomatis* serovars L1, L2, and L3.

10. Atypical Mycobacterial Infections

Treatment of atypical mycobacterial infections of the skin is dependent on various factors and rarely does monotherapy suffice. As cutaneous infections are caused by many atypical mycobacterial organisms, no specific treatment guidelines are available, so clinical experience, available literature, and susceptibility testing guide the regimens (Bhambri S, Majmudar V).

Monotherapy

M. marinum: Minocycline IR 100–200 mg (12 weeks)/ doxycycline (IR formulation) 100 mg twice daily for 12–16 weeks.

M. kansasii: Minocycline IR 100–200 mg daily for 16 weeks.

Combination Therapy

M. scrofulaceum and *M. szulgai*

M. fortuitum complex therapy

M. ulcerans (Buruli ulcer), *M. simiae* complex and *M. haemophilum*.

11. Vitiligo

The role of minocyline is based on the concept that high H_2O_2 level can cause destruction of melanocytes in vitiligo while minocycline, which possesses antioxidant activity, is capable of attenuating oxidative stress-induced neurotoxicity.

Two studies have been published with opposite results using minocycline. One study examined minocycline 100 mg and NBUVB in terms of stability of the disease (Siadat AH) and found that the effect of oral minocycline was attributable to the sunscreen effect and not quantitatively significant. This is in contrast with other studies where minocyline 100 mg has been found to be better than oral minipulse (Singh A).

Monitoring

On long-term therapy, periodic laboratory evaluations of organ systems, including hematopoietic, renal, and hepatic studies should be performed. There is no explicit recommendation for baseline testing.

Special Considerations

1. Metallic ions, contained in high quantities in dairy products (i.e. milk, yogurt), vitamin/mineral supplements, antacids, and anti-diarrheal products, can markedly reduce the GI absorption of TCNs through chelation of TCNs in the stomach.

2. Other substances that can reduce TCN absorption include calcium, aluminum, magnesium, iron, zinc, and bismuth.
3. A higher gastric pH may reduce GI absorption of TCN.
4. Bismuth subsalicylate and kaolin–pectin, found in anti-diarrheal agents, have been shown independently to reduce GI absorption of TCN by approximately 50%. Thus, it is important to question patients about OTC products for indigestion, diarrhea or stomach upset which may reduce serum levels of various TCNs.
5. With minocycline, co-administration of iron (ferrous sulfate) with minocycline IR reduced minocycline absorption by 77%.
6. Enteric coating of doxycycline, which delays release of doxycycline beyond the stomach and into the small intestine, has been shown to reduce GI adverse effects compared to IR formulations of doxycycline.
7. Minocycline ER, designed for subantimicrobial doses, reduces vestibular adverse effects.

Drug Interactions

Tetracyclines and other oral antibiotics have been reported to reduce the effectiveness of oral contraceptives (OC), although the scientific basis of this alleged interaction is controversial (except for rifamycins such as rifampin), and has *not* been definitively supported by several reviews (Archer, Dickinson, Miller).

The other interactions are listed below:

Decreased efficacy of tetracyclines (reduced absorption)	ACE inhibitors, Antacids, Cholestyramine, Colestipol, Bismuth salts, Iron, Zinc
Decreased efficacy of Tetracyclines (CYP3A4 induction)	Rifampcin, anticonvulasnts
Increase level of other drugs	Warfarin, Theophylline, Digoxin, Lithium
Photosensitivity	Psoralens, Retinoids
Others	Tetracyclines may ↓ insulin requirements Retinoids: Pseudotumor cerebri

Adverse Effects

Common

1. **GIT:** Nausea, vomiting, and abdominal discomfort is most commonly with doxycycline IR. Again pill esophagitis' is much more common with doxycycline than with other TCNs. Symptoms develop typically in the first few days, presenting most often as odynophagia, dysphagia, and

retrosternal pain, and are usually avoidable with proper patient education to ingest with a large volume of water and not to take before reclining.

2. **Photosensitivity:** Doxycycline exhibits the highest potential for photoxicity at doses of at least 100 mg/day and this rare with doxycycline MR 40 mg once daily. Minocycline on the contrary has been shown to exhibit negligible or absent phototoxicity potential.
3. **Dyspigmentation:** This is largely seen with minocycline IR preparations and occurs after a cumulative dose of >70 g. Hyperpigmentation, may vary from blue to gray to brown and can be focal or a diffuse distribution, with some patients exhibiting more than one pigmentation pattern over time. The various subtypes of cutaneous hyperpigmentation observed include.
   a. Type I describes blue-black/gray pigmentation confined to *facial* sites of scarring or inflammation associated with acne (typically resolves slowly) that stains for iron and melanin.
   b. Type II describes blue-gray pigmentation of normal skin on the *lower legs* (especially anterior) and forearms (typically resolves slowly) that stains for iron and melanin.
   c. Type III describes diffuse, muddy brown pigmentation of normal skin, predominantly in *sun-exposed skin* (tends to persist); stains for melanin only.
   d. Type IV, a rarely reported type, describes circumscribed blue-gray pigmentation in acne scars on the back (long-term course unknown) with calcium-containing melanin-like substance without iron.

   It is not known at present if minocycline ER will be associated with dyspigmentation. Doxycyline has been associated with nail discoloration in pediatric age group. Minocycline can cause pigmentation in Indian skin is a reason why most clinicians do not use this drug in acne.
4. **Secondary infections:** Antimicrobial selection pressure with alteration of normal flora associated with use of TCN can precipitate vaginal candidiasis (Blankenship ML). gram-negative folliculitis, which may be the result of long-term antibacterial treatment in acne patients, is caused by bacterial interference and replacement of the gram-positive flora of the facial skin and the mucous membranes of the nose and infestation with gram-negative bacteria. These gram-negative bacteria include *Escherischia coli, Pseudomonas aeruginosa, Serratia marescens, Klebsiella* and *Proteus mirabilis*. The occurrence of gram-negative folliculitis should be considered in acne patients in whom

oral treatment with tetracyclines has not resulted in a significant improvement of acne lesions after 3–6 months' treatment.

The occurrence of gram-negative folliculitis in acne patients is believed to be generally underestimated, since correct sampling and bacteriology is rarely performed by clinicians. Gram-negative folliculitis in acne and rosacea patients is best treated with isotretinoin (0.5–1 mg/kg daily for 4–5 months).

Vaginal candidiasis has been estimated to occur in 3.7% of women treated with TCNs using doses known to have antibiotic activity, with a negligible or absent risk in patients treated with subantimicrobial doses of doxycycline.

Rare Side Effects

1. CNS

Acute Vestibular Toxicity: This is commonly seen with IR preparations. If AVSE vestibular adverse effects do not occur in the first few weeks of treatment they are not likely to occur later. There is a wide variation between various minocycline IR generic and trade name formulations. There are also fast and slow metabolizers which may make these side effects variable. The minocycline ER, at 1 mg/kg once daily, has a less chance of causing this side effect.

Benign intracranial hypertension: This is also known as pseudotumor cerebri and is an uncommon idiopathic reaction to the TCNs. A high index of suspicion is needed with symptom of headache and visual disturbances, when accompanied by nausea and/or vomiting, to allow early detection of BIH, as persistence of this disorder can lead to severe loss of vision which may be permanent

The augmented risk of BIH caused by concurrent use of TCNs and oral retinoids (i.e., isotretinoin, acitretin) is ***controversial***, and is based on the product monograph from the original manufacturer of the brand oral isotretinoin (Tataro DS). As TCNs and oral retinoids have both been independently associated with BIH, concern regarding an additive or synergistic effect has been noted, although not scientifically evaluated. Published clinical data are needed to more definitively assess the true risk of this interaction.

2. Cutaneous Side Effects

Urticaria, fixed drug eruption, and drug-induced Sweet's syndrome.

3. Hypersensitivity Reactions

1. **Serum sickness-like reactions (SSLR):** Minocycline IR followed by doxycycline IR. It occurs in the the first

1–2 months of therapy. Risk factors include HIV infection and black African ethnicity.

2. Stevens–Johnson syndrome : doxycycline or minocycline (rare).
3. Autoimmune adverse reactions (autoimmune hepatitis, systemic lupus-like reactions, and ANCA vasculitis): Minocycline IR. This is a delayed reaction and may take months to years to develop.
4. **Drug hypersensitivity syndrome (Minocyline):** This is largely restricted to minocycline and can present with single-organ dysfunction or involve multiple organ systems, with hepatitis being the most common component of multisystem involvement. It is also known as drug hypersensitivity syndrome (DHS) or drug reaction with eosinophilia and systemic symptoms (DRESS).
   CF: High fever, morbilliform rash, facial edema, malaise, hepatosplenomegaly, elevated transaminases and atypical lymphocytosis (along with eosinophilia), simulating a viral syndrome, such as Epstein–Barr virus (EBV) infection. Other organ systems can be involved, including pneumonitis, nephritis, myocarditis, cerebritis, and/or thyroiditis.
   Sequelae: Resolution of DHS can be followed by hypothyroidism, autoimmune hyperthyroidism, autoimmune type 1 diabetes, and myocarditis after 2 months.
5. **Lupus-like syndrome:** This is unique to minocycline, with multiple case reports, case series and reviews published in association with minocycline IR. Minocycline was associated with an 8.5-fold higher risk of developing LLS than in non-users and past users of TCN combined (Sturkenboom MC). A retrospective cohort study showed that of the patients of acne, 24.8% were exposed to minocycline IR, 49% to doxycycline, 42.3% to TCN, and 17% not exposed to any TCN. A hazard ratio of 3.11 for minocycline and lupus erythematosus (LE) was noted. (Margolis DJ).

   Patients who develop lupus, can also have positive ANA, dsDNA and ANCA, though they do not satisfy the ARA criterion of SLE. As with drug-induced DHS and SSLR, discontinuation of the causative agent as soon as possible is vital, although the resolution for minocycline-LLS upon dechallenge varies greatly.

4. Vasculitis

Minocycline-induced cutaneous polyarteritis nodosa (PAN) and vasculitis, presents as reticulated (livedoid) erythema and/or subcutaneous nodules usually on the extremities (which is reversible), after 2 or 3 or more years of minocycline use. Serologic Testing has shown pANCA positivity in several cases, suggesting the term ‘drug-induced vasculitis.

5. Hepatotoxicity (Autoimmune)

Minocycline-induced hepatotoxicity can occur early, with a median exposure time of 35 days (DHS), with an average exposure time of 365 days (autoimmune hepatitis or as part of LLS).

6. Other Effects

Immune thrombocytopenia presenting as Schamberg's disease, and neutropenia as a component of LLS, have been reported with minocycline use.

Special Groups

Renal failure prolongs the half-life of most TCNs, except doxycycline, which is excreted primarily by the GI tract in bile and thus is acceptable for use in patients with renal failure. Caution is warranted when prescribing doxycycline for patients with severe liver disease

Pregnancy: Category D

BIBLIOGRAPHY

1. Archer JS, Archer DF. Oral contraceptive efficacy and antibiotic interaction: a myth debunked. J Am Acad Dermatol. 2002;46(6):917-23.
2. Bhambri S, Bhambri A, Del Rosso JQ. Atypical mycobacterial cutaneous infections. Dermatol Clin. 2009;27(1):63-73.
3. Blankenship ML. Gram-negative folliculitis. Arch Dermatol. 1984;120:1301-3.
4. Del RJ. Clinical significance of brand versus generic formulations: focus on oral minocycline. Cutis. 2006;77:153-6.
5. Del Rosso JQ. A status report on the use of subantimicrobial-dose doxycycline: a review of the biologic and antimicrobial effects of the tetracyclines. Cutis. 2004;74(2):118-22.
6. Del Rosso JQ. Update on rosacea pathogenesis and correlation with medical therapeutic agents. Cutis. 2006;78(2):97-100.
7. Dickinson BD, Altman RD, Nielsen NH, et al. Drug interactions between oral contraceptives and antibiotics. Obstet Gynecol. 2001;98(5Pt1):853-60.
8. Elston D. Methicillin-resistant Staphylococcus aureus (MRSA). In: Lebwohl MG, Heymann WR, Berth-Jones J, Coulson I (Eds). Treatment of skin disease: comprehensive therapeutic strategies, 3rd ed. Philadelphia, USA: Mosby Elsevier; 2010. pp. 449-51.
9. Fleischer Jr AB, Dinehart S, Stough D, Plott RT. Safety and efficacy of a new extended-release formulation of minocycline. Cutis. 2006;78:21-31.
10. Fujimoto N, Mitsuru M, Tanaka T. Successful treatment of Morbihan disease with long-term minocycline and its association with mast cell infiltration. Acta Derm Venereol. 2014 Aug 27.
11. Hauser AR. The ABCs of choosing the right antibacterial agent antibiotic basics for clinicians. 2nd edn. Lippincott Williams & Wilkins, a Wolters Kluwer business. 2013.

12. Majmudar V. Mycobacterial (atypical) skin infections. In: Lebwohl MG, Heymann WR, Berth-Jones J, Coulson I, (Eds). Treatment of skin disease: comprehensive therapeutic strategies. 3rd ed. Philadelphia, USA: Mosby Elsevier; 2010. pp. 463-67.
13. Margolis DJ, Hoffstad O, Bilker W. Association or lack of association between tetracycline class antibiotics for acne vulgaris and lupus erythematosus. Br J Dermatol. 2007;157(3):540-6.
14. Miller DM, Helms SE, Brodell RT. A practical approach to antibiotic treatment in women taking oral contraceptives. J Am Acad Dermatol. 1994;30(6):1008-11.
15. Moore A, Ling M, Bucko A, Manna V, Rueda MJ. Efficacy and safety of subantimicrobial dose, modified-release doxycycline 40 mg versus doxycycline 100 mg versus placebo for the treatment of inflammatory lesions in moderate and severe acne: a randomized, double-blinded, controlled study. J Drugs Dermatol. 2015;14(6):581-6.
16. Ocampo-Candiani J, Velazquez-Arenas LL, de la Fuente-Garcia A, Trevino-Gomezharper C, Berber A. Safety and efficacy comparison of minocycline microgranules vs lymecycline in the treatment of mild to moderate acne: randomized, evaluator-blinded, parallel, and prospective clinical trial for 8 weeks. J Drugs Dermatol. 2014;13(6):671-6.
17. Sardana K, Gupta T, Garg VK, Ghunawat S. Antibiotic resistance to Propionobacterium acnes: worldwide scenario, diagnosis and management. Expert Rev Anti Infect Ther. 2015;13(7):883-96.
18. Siadat AH, Zeinali N, Iraji F, Abtahi-Naeini B, Nilforoushzadeh MA, Jamshidi K, et al. Narrow-band ultraviolet b versus oral minocycline in treatment of unstable vitiligo: a prospective comparative trial. Dermatol Res Pract. 2014;2014:240856.
19. Simonart T, Dramaix M, De Maertelaer V. Efficacy of tetracyclines in the treatment of acne vulgaris: a review. Br J Dermatol. 2008;158:208-16.
20. Singh A, Kanwar AJ, Parsad D, Mahajan R. Randomized controlled study to evaluate the effectiveness of dexamethasone oral minipulse therapy versus oral minocycline in patients with active vitiligo vulgaris. Indian J Dermatol Venereol Leprol. 2014;80(1):29-35.
21. Skidmore R, Kovach R, Walker C, et al. Effects of sub-antimicrobial-dose doxycycline in the treatment of moderate acne. Arch Dermatol. 2003;139(4):459-64.
22. Stewart DM, Torok HM, Weiss JS, Plott RT. Solodyn phase 2 study group. Dose-ranging efficacy of new once-daily extended-release minocycline for acne vulgaris. Cutis. 2006;78(4 Suppl):11-20.
23. Sturkenboom MC, Meier CR, Jick H, et al. Minocycline and lupuslike syndrome in acne patients. Arch Intern Med. 1999;159(5):493-7.
24. Tatro DS. Drug interactions facts. St. Louis. Wolter's Kluwer Health. 2006.
25. Toossi P, Farshchian M, Malekzad F, Mohtasham N, Kimyai-Asadi A. Subantimicrobial-dose doxycycline in the treatment of moderate facial acne. J Drugs Dermatol. 2008 Dec;7(12):1149-52.

TIGECYCLINE

Tigecycline is not actually a tetracycline but a member of a structurally related class of antibiotics called the glycylcyclines, of which tigecycline is the only commercially available member. It received FDA approval in June 2005.

Mechanism of Action

The key modification present in glycylcyclines is the addition of a glycyl amide group to the terminal six-membered ring of the core tetracycline. This addition prevents recognition of tigecycline by many bacterial-efflux pumps and makes it insensitive to modifications of the 30S ribosomal subunit that confer resistance to tetracyclines and other antibiotic classes (β-lactams, macrolides, and fluoroquinolones).

Spectrum

Tigecycline has a broad antimicrobial spectrum. It is active against most aerobic gram-negative bacteria, including multidrug-resistant *Acinetobacter* spp. However, *P. aeruginosa* and *Proteus* spp., which produce efflux pumps that do recognize this agent, are usually resistant.

Most aerobic gram-positive bacteria, including methicillin-resistant staphylococci,vancomycin-resistant enterococci, and penicillin-resistant *S. pneumoniae*, are susceptible to tigecycline. It also has good activity against anaerobic bacteria, although it is inferior to carbapenems and piperacillin-tazobactam in this regard. As would be expected of a tetracycline-related agent, tigecycline appears to have excellent activity against atypical bacteria.

Dose

100 mg IV first dose followed by 50 mg BD.
Status: Available in India.

Special Population

Tigecycline is pregnancy category D, with known tetratogenicity and embryolethality, and its safety during lactation is unknown. The safety of tigecycline in pediatric patients younger than 18 years of age has not been established.

LINEZOLID

(Linosept tab, Linospan tab, Lizoforce tab).
Linezolid is a member of a novel class of antibacterial agents called oxazolidinones, which are completely synthetic compounds. Linezolid's structure consists of an oxazolidinone core that has been modified at several sites.

Mechanism of Action

It works by binding to the 23S portion of the 50S ribosomal subunit, owing to a unique binding site, there is no cross-resistance with other antimicrobial agents. It also inhibits protein synthesis by preventing formation of the first

peptide bond of the nascent peptide. As it is a relatively small molecule, it easily enters Gram-positive bacteria. The site of inhibition occurs earlier in the initiation process than other protein synthesis inhibitors (e.g., chloramphenicol, clindamycin, aminoglycosides, and macrolides) that interfere with the elongation process. Because the site of inhibition is unique to linezolid, cross-resistance to other protein synthesis inhibitors has not yet been reported. Linezolid may also inhibit virulence factor expression and decrease toxin production in Gram-positive pathogens.

Spectrum

Linezolid has excellent activity against most aerobic Gram-positive bacteria, including methicillin-resistant staphylococci, penicillin-resistant *S. pneumoniae*, and vancomycin-resistant enterococci. It also has in vitro activity against *some* aerobic Gram-negative, anaerobic, and atypical bacteria, but it currently is *not* used to treat infections caused by these organisms. Interestingly, some aerobic Gram-negative bacilli such as *Escherichia coli* are intrinsically resistant to linezolid because they produce efflux pumps active against this compound.

Pharmacology

100% bioavailability, serum half life of 5-7 hours.

Dosage

600 mg 12 hrly

USSTI: 400 mg BD—14 days

Linezolid is available in both oral and intravenous formulations and achieves similarly high serum levels when given by either route.

Uses

It is the treatment of choice for **CA-MRSA** in patients who have *failed* the first line drugs (tetracycline, TMP-SMX, clindamycin/rifampicin, or vanomycin).

There have been studies that have examined the cost effectiveness of linezolid and vancomycin, for treating skin and soft tissue infections. Skin and soft tissue infections such as impetigo, abscesses, ulcers, and surgical site infections are common infections of the skin. Linezolid and vancomycin are antibiotics that are effective in treating skin and soft tissue infections, particularly infections caused by bacteria that have developed resistance to some antibiotics. A review which identified nine RCTs, with a total of 3,144 participants, and

compared treatment with linezolid against treatment with vancomycin for skin and soft tissue infections, found that linezolid was more effective than vancomycin for treating these infections. It also had fewer skin complications, and those treated with linezolid had shorter lengths of hospital stay than those treated with vancomycin. Importantly most of these trials were funded by pharmaceuticals manufacturing linezolid (Yue J). A study that compared retapamulin ointment 1% (plus oral placebo), twice daily for 5 days or oral linezolid (plus placebo ointment) 2 or 3 times daily for 10 days also found that linezolid had a better response rate (Tanus T).

We feel that in cases of MRSA, it is preferable to first try conventional drugs, like doxycycline, rifampicin or TMP/SMX and use of drugs like linezolid should be reserved for cases that have documented failure to these drugs.

Interactions

1. Linezolid should not be given with monoamine oxidase (MAO) inhibitors.

Adverse Effects

1. GIT: nausea, vomiting, and diarrhea.
2. Thrombocytopenia, anemia, and leukopenia occur relatively frequently but are reversible.
   Platelets should be monitored when linezolid is used for more than 2 weeks.
3. Optic and peripheral neuropathy can be seen and may be rarely progressive.
4. Serotonin syndrome characterized by cognitive dysfunction, hyperpyrexia, hyper-reflexia, and incoordination has been reported in patients receiving linezolid and serotonergic drugs.

Special Populations

- Pregnancy C
- Liver Safe
- Kidney Safe.

BIBLIOGRAPHY

1. Tanus T, Scangarella-Oman NE, Dalessandro M, Li G, Breton JJ, Tomayko JF. A randomized, double-blind, comparative study to assess the safety and efficacy of topical retapamulin ointment 1% versus oral linezolid in the treatment of secondarily infected traumatic lesions and impetigo due to methicillin-resistant *Staphylococcus aureus*. Adv Skin Wound Care. 2014;27(12):548-59.
2. Yue J, Dong BR, Yang M, Chen X, Wu T, Liu GJ. Linezolid versus vancomycin for skin and soft tissue infections. Evid Based Child Health. 2014;9(1):103-66.

NUCLEIC ACID INHIBITION

RIFAMYCINS

The rifamycins consist of rifampin (also called rifampicin), rifabutin, rifapentine, and rifaximin.

Mechanism of Action

Rifamycins act by inhibiting bacterial RNA polymerase. Resistance develops relatively easily and can result from one of several single mutations in the bacterial gene that encodes RNA polymerase. These mutations change only a single amino acid at the site where the rifamycins bind to RNA polymerase but are sufficient to prevent this binding. Because single mutations are sufficient to lead to resistance, rifamycins are usually used in combination with other agents to prevent the emergence of resistant strains.

Spectrum

Although *S. aureus* strains may be sensitive to rifampin in vitro, resistance often develops rapidly when monotherapy is used. Thus, it is advisable to combine it with either clindamycin or trimethoprim-sufamexazole when treating CA-MRSA (Table 1.12).

Table 1.12: Antimicrobial activity of rifamycins

Gram-positive bacteria	Staphylococci
Gram-negative bacteria	*Haemophilus influenzae* *Neisseria meningitidis*
Mycobacteria	*Mycobacterium tuberculosis* *Mycobacterium avium* complex *Mycobacterium leprae* *M. kansasii* *M. marinum*

Pharmacology

Absorption: Rifampin is readily absorbed from the GI tract but an interindividual variation in peak levels is seen. It should ideally be administered empty stomach. After GI absorption, rifampin is quickly hydrolyzed in bile and undergoes enterohepatic circulation.

Metabolism: Liver

Half life: 3 hrs (After a 600 mg dose of rifampin the average serum half-life is 3.35 hours, but this can get shortened to 2–3 hours with repeated dosing as the drug induces its own hepatic metabolism).

Rifampin is a potent inducer of multiple CYP isoforms, which results in increased hepatic metabolism and more rapid clearance of wide variety of drugs.

Rifabutin is a less potent inducer of CYP enzymes Rifapentine is an oral, long-acting analog of rifampin that may be given once weekly for TB treatment. Rifaximin is orally administered and is not used for systemic infections as <0.4% of an oral dose is absorbed systemically.

Indications

FDA: Treatment of tuberculosis (TB) and is best used in combination therapy for the meningococcal carrier state.

Off-label uses: Leprosy, Atypical mycobacterial infections, anthrax, brucellosis, *Legionella neumophila* infections, *Listeria* spp infections, and some infections caused by staphylococci, streptococci and *Rhodococcus* spp.

Rifabutin is favored over rifampin in individuals who are simultaneously being treated for tuberculosis and HIV infection because it inhibits the cytochrome P-450 system to a lesser degree than rifampin or rifapentine and thus can be more easily administered along with the many antiretroviral agents that also interact with this system. *Rifapentine* has a long serum half-life, which has led to its use in once-weekly regimens for immunocompetent patients with tuberculosis. *Rifaximin* is a poorly absorbed rifamycin that is used for the treatment of travelers' diarrhea. Because it is not systemically absorbed, it has limited activity against invasive bacteria, such as *Salmonella* and *Campylobacter* spp.

Dose

Adults 600 mg daily; children 10 mg/kg/day (600 mg maximum).

Special instructions: To be taken with water 1 hour before or 2 hours after a meal, and at least 1 hour before ingestion of antacids. Concomitant antacid administration may reduce GI absorption of rifampin, and so rifampin should be given at least 1 hour before antacid intake.

Clinical Use

A. Infections

1. TB: In combination with other drugs as per the national Program. Cutaneous TB accounts for 0.1 to 2.5 percent of all patients with skin diseases. Several clinical types of cutaneous TB have been described. In those not previously exposed to *M. tuberculosis*, TB of the skin and TB chancre has been described. Previously sensitized hosts develop lupus vulgaris, scrofuloderma and tuberculosis verrucosa

cutis. Other lesions seen are tuberculids which includes lichen scrofulosorum, papulonecrotic tuberculid, erythema induratum and erythema nodosum. Lupus vulgaris is the most common variety seen in India, followed by tuberculosis verrucosa cutis and scrofuloderma. As per the RNTCP most cases of skin TB fall in category III (http://www.tbcindia.nic.in).

Diagnosis and Treatment of EPTB under the RNTCP: The treatment of extrapulmonary TB follows standard RNTCP treatment guidelines depending on categorization, and is consistent with international recommendations by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD).

Categorization is done according to history, and clinical and diagnostic criteria. All RNTCP regimens are given thrice weekly, and Rifampicin-containing regimens given for six to eight months. If patients are seriously ill with extrapulmonary TB, they are treated with the RNTCP Category I regimen consisting of, initially, two months isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) given thrice a week, with each dose given under the direct observation of a DOT provider (Table 1.13). This two-month intensive phase is followed by a four-month continuation phase of isoniazid and rifampicin, given thrice a week, with at least the first of the thrice-weekly doses given under the direct observation of the DOT provider.

2. Leprosy: Rifampicin is given in a monthly dose with adjuvant drugs clofazamine and dapsone depending on the classification of the disease (http://nlep.nic.in) given in Table 1.14.

3. Atypical Mycobacterial Infections: Rifabutin is more effective than rifampin in the treatment of atypical mycobacteria infections, and is used often in combination with clarithromycin and ethambutol.

M. marinum: Rifampin with ethambutol with or without clarithromycin.

Disseminated Atypical Infection: Disseminated atypical mycobacterial infection (including MAC) in HIV/AIDS patients with CD4 counts <50/μL : Rifabutin.

4. Bartonella Infections: *Bartonella henselae* (cat-scratch disease, bacillary angiomatosis, peliosis hepatis).

5. Pyoderma

CA-MRSA: Rifampin should be combined with either clindamycin or trimethoprim-sulfamethoxazole.

6. Other Infections: Cutaneous leishmaniasis and rhinoscleroma, aspergillosis, brucellosis, tularemia, chlamydial infections, and gonorrhea.

Table 1.13: TB treatment requires under RNTCP

Category I	New sputum smear-positive pulmonary TB (PTB) Seriously ill* new sputum smear-negative PTB Seriously ill* new EPTB	$2H_3R_3Z_3E_3 + 4H_3R_3$
Category II	Sputum smear-positive *relapse* Sputum smear-positive *failure* Sputum smear-positive treatment after *default* Others**	$2S_3H_3R_3Z_3E_3+$ $1H_3R_3Z_3E_3+$ $5H_3R_3E_3$
Category III	New sputum smear-negative PTB New EPTB, not *seriously ill*	$2H_3R_3Z_3+4H_3R_3$

The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week. The dosage strengths are as follows: H: Isoniazid (600 mg), R: Rifampicin (450mg), Z: Pyrazinamide (1500 mg), E: Ethambutol (1200 mg), S: Streptomycin (750 mg). Patients who weigh 60 kg or more receive additional Rifampicin 150 gm. Patients who weigh less than 30 kg receive drugs per body weight. Patients in Categories I and II who have a positive sputum smear at the end of the initial intensive phase receive an additional month of intensive phase treatement.

*A patient who is HIV positive

**In rare and exceptional cases, patients who are sputum smear-positive or who have extra-pulmonary disease can have relapse or failure. The diagnosis in all such cases should be made by the MO and should be supported by culture or histological evidence of current active TB. In these cases, the patient should be categorized as 'Others' and given Category II treatment

Table 1.14: Drug therapy of leprosy

Regimens	*Drugs*		*Dosage (adult) ≥15 years*	*Dosage (Children) 10-14 years)#*	*Dosage (Children) <10 yrs**	*Duration*
MB Leprosy	Rifampicin	Once monthly	600 mg	450 mg	300 mg	Completion of 12 monthly pulses in 18 Consecutive months
	Clofazimine		300 mg	150 mg	100 mg	
	Dapsone	OD	100 mg	50 mg	25 mg	
	Clofazimine	Daily for adults (every other day for children)	50 mg	50 mg Alternate day	50 mg Twice a week	
PB Leperosy	Rifampicin	Once monthly	600 mg	450 mg	300 mg	Completion of 6 monthly pulses 9 consecutive months
	Dapsone	OD	100 mg	50 mg	25 mg Or 50 mg alternate day	

*For children below 10 years, doses (as per kg body wt) should be provided loose (capsules/tablets) after opening appropriate BCP

For children between 10–14 yr whose body weight is greater than 35 kg, adult BCP should be given

B. Hidradenitis Suppurativa

Though medical management is useful only in the early stages of the disease, a clindamycin-rifampin combination has been found to be effective (Rambhatla PV).

C. Granuloma Annulare

Once monthly rifampin, ofloxacin, and minocycline for 6 months has been shown to achiere at least a 50% reduction in about 48% of cases, though randomized trials may be warranted to further assess this therapy (Simpson B).

D. Pruritus

In pruritus associated with primary biliary cirrhosis. Rifampicin is helpful by increasing the degradation of pruritogenic bile salt metabolites via induction of hepatic metabolic enzymes.

E. Sarcoidosis

An oral regimen of levofloxacin, ethambutol, azithromycin, and rifampin (CLEAR) for 8 weeks may help in reducing the granuloma burden, size and extent of lesions (Drake WP).

Interactions

Rifampin is a potent inducer of multiple CYP isoforms, including CYP1A2, 2C9, 2C19, 2D6, and 3A4, with a resultant increased drug clearance and loss of efficacy of various drug substrates.

Enzyme induction secondary to rifampin may take a few days to take effect, reaching its maximum effect 3 weeks after treatment initiation, and may persist up to 4 weeks after its discontinuation.

Increase level of rifampicin	Isoniazid concomitant use increasess the risk of hepatotoxicity from rifampin H2 antagonists, proton pump inhibitors, etc; increase absorption of rifampin
Decrease level of other drugs	Antiarrhythmic agents (Digoxin) MAcrolide antibiotics, Anticholinergic agents Anticoagulants (warfarin) Anticonvulsants (Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, valproic acid) Antidepressants—non-selective, tricyclic (buspirone, amitriptyline, imipramine) Antifungal agents (ketoconazole, itraconazole, voriconazole; terbinafine) Antipsychotic agents (olanzapine, pimozide, risperidone) Beta-blockers

	Bronchodilators (theophylline) Corticosteroids Diabetes drugs (sulfonylureas nateglinide, repaglinide) Erectile dysfunction drugs HIV drugs, hormonal contraceptives Cyclosporine Sedatives – benzodiazepines Statins
Increase levels of other drugs	Leflunomide, acetaminophen

Adverse Effects

A. Common

Cutaneous

It can cause a orange-red discoloration of liquid body excretions (i.e. urine, sweat, tears, breast milk).

Rarely linear IgA bullous dermatosis, pemphigus foliaceous, and pemphigus vulgaris have been reported.

CNS

It can cause headache, drowsiness, ataxia, dizziness, and fatigue.

GIT

Epigastric distress, nausea, vomiting, and diarrhea, with antibiotic-associated colitis due to *C. difficile* has been reported.

Liver Toxicity

1. Asymptomatic changes in liver function tests (LFT), especially transaminases, may be associated with rifampin use.
2. In some patients hyperbilirubinemia is seen in the early days after initiation of rifampin, and is believed to be due to competition between rifampin and bilirubin for access to hepatic excretory pathways.

Flu like Syndrome/Immunologic Side effects

When used intermittently and in high doses rifampin has immunogenic properties leading to the formation of rifampin-dependent antibodies, with rare reports of IgE mediated anaphylaxis. The adverse effects mediated by rifampin-dependent antibodies can be minor (cutaneous, gastrointestinal, and influenza-like syndromes) or more severe (thrombocytopenia, hemolytic anemia, respiratory insufficiency, and acute renal failure). This is seen in therapy of leprosy where intermittent therapy is used.

B. Rare Side Effects

1. Deep venous thrombosis
2. Pulmonary fibrosis
3. Ocular toxicity also noted.

Special Populations

Pregnancy: C
Although rifampin crosses the placenta, several reviews of TB treatment during pregnancy have concluded that rifampin is not a teratogen. The drug is known to cause hemorrhagic disease of the newborn and mother, with a need for prophylactic vitamin K_1.

Lactation: Safe
Rifampin is excreted in human breast milk in apparently low concentrations (0.05% of daily dose). No reports of adverse effects in infants have been observed, and the American Academy of Pediatrics (AAP) classifies rifampin as compatible with breastfeeding.

Liver : Dose modification is required.

Kidney: Owing to extensive hepatic metabolism, dosage adjustment of rifampin is not necessary in patients with mild renal failure at doses of ≤600 mg daily; however, dosage adjustments are necessary in patients with a creatinine clearance <50 mL/h. Urinary excretion accounts for approximately 30% of total rifampin elimination, with about 7% of the drug excreted unchanged in the urine.

BIBLIOGRAPHY

1. D rake WP, Oswald-Richter K, Richmond BW, Isom J, Burke VE, Algood H, Braun N. Oral antimycobacterial therapy in chronic cutaneous sarcoidosis: a randomized, single-masked, placebo-controlled study. JAMA Dermatol. 2013;149(9):1040-9.
2. International Union against Tuberculosis and Lung Disease (IUATLD). Management of tuberculosis: a guide for low-income countries. 5th ed. Paris: IUATLD, 2000.
3. Rambhatla PV, Lim HW, Hamzavi I. A systematic review of treatments for hidradenitis suppurativa. Arch Dermatol. 2012;148(4):439-46.
4. Simpson B, Foster S, Ku JH, Simpson EL, Ehst BD. Triple antibiotic combination therapy may improve but not resolve granuloma annulare. Dermatol Ther. 2014;27(6):343-7.
5. World Health Organization (WHO). Treatment of tuberculosis. guidelines for national Programmes, 3rd ed. WHO/CDS/TB 2003.313. Geneva, Switzerland: WHO, 2003.

STREPTOGRAMINS

Streptomyces spp naturally secrete pairs of antibiotics from the streptogramin family that work together to kill other bacteria.

Mode of Action

Streptogramins consist of two different macrocyclic compounds each of which binds to the 50S subunit of the bacterial ribosome to inhibit protein synthesis. Whereas each component alone has moderate antibacterial activity, the two together are quite potent. This synergy is explained by the fact that each compound alone inhibits a different step in the process of protein elongation and that dalfopristin induces a conformational change in the ribosome that enhances binding of quinupristin.

Spectrum

It is the most powerful antibiotic against aerobic gram-positive bacteria, including methicillin-resistant staphylococci, penicillin-resistant *S. pneumoniae*, and some vancomycin-resistant enterococci.

Dosage

7.5 mg/kg IV every 8-12 hourly.

Uses

Pyoderma: Main use in the treatment of multidrug-resistant CSSTI due to gram-positive organisms.

Drug Interactions

Quinupristin-dalfopristin is a potent inhibitor of the CYP3A4 isoform, with the typical interactions including simvastatin, atorvastatin, cyclosporine, and many others.

Adverse Effects

1. If given via a peripheral intravenous catheter it can cause pain, inflammation, and thrombophlebitis. For this reason, it is recommended that this drug be given through a central venous catheter.
2. Arthralgias, myalgias, and hyperbilirubinemia are also common.
3. It can cause anaphylactic shock and angioedema.

4. Quinupristin/dalfopristin inhibits the cytochrome P-450 system and can therefore affect the levels of other drugs (statins and cyclosporine).

ANTIMETABOLITES

TRIMETHOPRIM-SULFAMETHOXAZOLE

Trimethoprim-sulfamethoxazole is actually a combination of two antimicrobial agents: trimethoprim and sulfamethoxazole. Trimethoprim is not a sulfa drug but acts on the same general pathway as these drugs. This popular antimicrobial agent contains a fixed dose ratio of 1 part TMP to 5 parts SMX.

Mechanism of Action

Trimethoprim-sulfamethoxazole inhibits bacterial growth by preventing the synthesis of tetrahydrofolate (THF), the active form of folic acid. THF is an essential cofactor for metabolic pathways that generate deoxynucleotides, which are the building blocks of DNA. Sulfamethoxazole does this by mimicking para-aminobenzoate (PABA) and thereby competitively inhibiting the enzyme dihydropteroate synthase that normally incorporates PABA into the synthesis pathway of THF. Trimethoprim, on the other hand, is a structural analog of dihydrofolate and therefore inhibits dihydrofolate reductase, which is required for conversion of dihydrofolate to THF (Fig 1.14).

Spectrum

Trimethoprim-sulfamethoxazole:

1. **Gram-positive bacteria:** *S. aureus,* CA-MRSA, *S. pyogenes, Enterococcus faecalis*, *Streptococcus viridians*
2. **Gram-negative bacteria:** *H. influenzae* and some *Pseudomonas* spp
3. **Anaerobic:** *Bacteroides* spp. and *Clostridium* spp.
4. *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Pneumocystis jirovecii*
5. *Cyclospora cayetanensis, Isospora belli*
6. Nocardia.

Absorption and Distribution

They are well absorbed orally (70–100%), with half-lives of 8–10 hours and 10–12 hours.

In the presence of marked renal insufficiency, the half-lives of TMP and SMX may be prolonged to 24 hours and 18–50 hours, respectively. They are distributed into breast

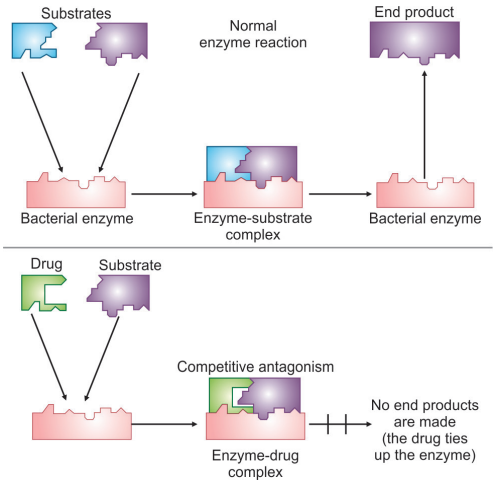


Fig. 1.14: Competitive antagonism: The drug resembles a microbial substrate and competes with that substrate for the limited microbial enzyme. The drug ties up the enzyme and blocks a step in metabolism

milk and cross the placenta. Biotransformation of both TMP and MX is partially via hepatic metabolism. About 30–60% of TMP and 20–40% of SMX is excreted unchanged in the urine.

Uses

Though the drug was used for acne vulgaris, rising resistance to this drug precludes its use in acne. It is thus used for USSTI due to CA-MRSA.Other uses include hidradenitis suppurativa, granuloma inguinale, atypical mycobacterial infections, actinomycetoma, catscratch disease, *Aeromonas* spp infections, and chronic melioidosis (*Burkholderia pseudomallei*).

Dose

A single-strength TMP-SMX tablet contains 80 mg TMP and 400 mg SMX. A double-strength TMP-SMX tablet contains 160 mg TMP and 800 mg SMX. For most disorders, TMP-SMX double strength is administered twice daily, with the duration of therapy dependent on the individual disease state and clinical response. Oral medication should be taken with 8 oz of water 1 hour before or 2 hours after eating.

Drug Interaction

- Drugs that increase effects/toxicity of trimethoprim–sulfamethox-azole: salicylates and other NSAIDs.
- Trimethoprim–sulfamethoxazole increases effects/toxicity of warfarin, dapsone, phenytoin, methotrexate, cyclosporine, ACE inhibitors, digoxin, oral hypoglycemic drugs.

Special Considerations

- Use with caution in patients with possible folate deficiency (chronic alcoholics, elderly), concurrent anticonvulsant therapy, blood dyscrasias, G6PD deficiency, severe allergies, bronchial asthma, AIDS.
- Administer folinic acid if bone marrow depression occurs.

Advice to Patient

- Drink large amounts of fluids (2.5–3 L) per day and maintain adequate fluid intake after discontinuing the drug.
- To minimize possible photosensitivity reaction, apply adequate sunscreen and use proper covering when exposed to strong sunlight.

Side Effects

1. **Common:** anorexia, nausea, vomiting, glossitis, rash.
2. **Serious:** Stevens–Johnson syndrome (rare), pseudomembranous colitis, agranulocytosis, aplastic anemia, megaloblastic anemia, hyperkalemia, hemolysis (patients with G6PD deficiency).
3. **Anaphylaxis:** TMP-SMX-induced cutaneous eruptions may be seen in 4–5% of healthy patients and approximately 15% of HIV-infected patients, usually manifesting within the first 1–2 weeks after starting therapy. These reactions include morbilliform and urticarial eruptions and/or pruritus, and less commonly fixed drug eruption. Sulfonamides, including TMP-SMX, account for up to 30% of all cases of SJS/TEN, with the risk of TEN being more in HIV-infected patients. Patients receiving TMP-SMX should be told to discontinue treatment if they develop flu-like symptoms (fever, malaise, 'swollen glands', muscle aches), arthralgias, 'hives', 'skin rash', 'sore throat', 'mouth or lip sores (erosions, ulcers)', or painful skin. TMP-SMX should be avoided in patients with first-degree relatives who have experienced DHS or SJS/TEN associated with sulfonamide use, and in those that have a prior sulfonamide allergy.
4. **Hematologic Toxicity:** In addition to agranulocytosis mentioned above, other uncommon hematologic reactions with TMP-SMX use are thrombocytopenia, neutropenia, hypoprothrombinemia, aplastic anemia (very rare), and pure red cell aplasia (very rare). Hemolytic anemia may occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Others

Antibiotic-associated colitis due to *C. difficile* has been reported with TMP-SMX, including when given as prophylaxis for *P. jirovecii (P. carinii)* pneumonia. The other side effects include pulmonary infiltrates, and upper respiratory symptoms, pustular skin eruptions, drug-induced Sweet's syndrome, drug fever, cholestatic hepatitis, nephrolithiasis, interstitial nephritis and hyperkalemia. Nail changes seen include Beau's lines, paronychia, partial leukonychia, and photo-onycholysis.

Monitoring

Early signs and symptoms of Stevens–Johnson syndrome:

- CBC and differential, liver enzymes, kidney function. Discontinue drug if there is significant reduction in any formed element.
- Signs and symptoms of renal toxicity. Perform urinalysis with microscopic examination as well as kidney function tests.

Special Groups

- Kidney disease: Creatinine clearance >30 mL/min: usual dose; creatinine clearance 15–30 mL/min: 50% of usual dose; creatinine clearance < 15 mL/min: not recommended.
- Liver disease: None.
- Elderly: Use with caution, particularly in those with liver or kidney disease.
- Pediatric: This drug is contraindicated for use in infants < 2 months.
- Pregnancy: Contraindicated.
- Lactation: Contraindicated.

QUINOLONES

Classification

The quinolones, were discovered consequent to the observation that a byproduct generated during the synthesis of chloroquine, an antimalarial compound, possessed modest activity against Gram-negative bacteria. The subsequent modification of this compound has led to agents with potent activity against aerobic Gram-negative, aerobic Gram-positive, and even some anaerobic bacteria.

They have a broad spectra of activity, high absorbance when given orally, and favorable toxicity profiles and this has helped in making quinolones to one of the most commonly used antibiotics today.

Classification of Quinolones

1st Generation: Narrow spectrum	Nalidixic acid Cinoxacin	Only aerobic gram-negative; *Enterobacteriaceae, Hemophilus* *influenzae, Neisseria gonorrhoeae*, and catarrhalis
2nd Generation: Fluorinated fluoroquinolones	Ciprofloxacin	Excellent Gram-negative activity, the quinolone of choice for *P. aeruginosa;* covers all *Enterobacteriaceae* ■ Good activity against *S. aureus* including MRSA ■ Excellent for atypical pneumonia, (ie, *Legionella, Mycoplasma, C. pneumoniae*) ■ Excellent for genital infections (including prostatitis), *N. gonorrhoeae* (single dose), *Chlamydia trachomatis, M. hominis,* Ureaplasma Also used for acute or chronic sinusitis, otitis media, or skin infections ■ Poor coverage for anaerobic and streptococci
	Norfloxacin	Narrower spectrum; used for UTI, prostatitis, *N. gonorrhoeae*
	Ofloxacin	Similar to ciprofloxacin, but less effective against *P. aeruginosa*
Quinolones with improved gram-positive coverage	Levofloxacin	Levo isomer of ofloxacin with activity against *Streptococcus pneumoniae* and streptococci; some anaerobic activity (not *Bacillus fragilis*)
	Sparfloxacin	Like levofloxacin, but improved activity against *B. fragilis*
	Gatifloxacin	Excellent anaerobic and Gram-positive coverage

	Moxifloxacin	Therapeutically equivalent to cefuroxime axetil and trovafloxacin for acute bacterial sinusitis, to clarithromycin and azithromycin for acute bacterial exacerbations of chronic bronchitis, and to amoxicillin and clarithromycin for community-acquired pneumonia Moxifloxacin is as effective as levofloxacin, sparfloxacin, trovafloxacin, and gatifloxacin Moxifloxacin's has an antistaphylococcal and antistreptococcal activity

Mechanism of Action

Small and hydrophilic, quinolones have no problem crossing the outer membrane. They easily diffuse through the peptidoglycan and the cytoplasmic membrane and rapidly reach their target. Quinolones inhibit DNA synthesis.

All topoisomerases can relax DNA but only gyrase can also carry out DNA supercoiling ('supercoiling' process is necessary to compact the bacterial chromosome which is 1,000 times longer than the bacterial cell). Topoisomerases are also involved in DNA replication, transcription and recombination.

The main quinolone target is the DNA gyrase, which is responsible for cutting one of the chromosomal DNA strands at the beginning of the supercoiling process. The nick is only introduced temporarily and later the two ends are joined back together (i.e., repaired). The quinolone molecule forms a stable complex with DNA gyrase thereby inhibiting its activity and preventing the repair of DNA cuts. They inhibit two topoisomerases, bacterial enzymes that regulate DNA supercoiling. These topoisomerases are named DNA gyrase and topoisomerase IV. These affect the DNA replication machinery, leading to inhibition of DNA synthesis and eventually bacterial death (Fig. 1.15).

Spectrum

The quinolones have broad activity against various bacteria including **anaerobes** (including *P. acnes*). They are also effective against some staphylococci and streptococci, many atypical bacteria, and even some mycobacteria.

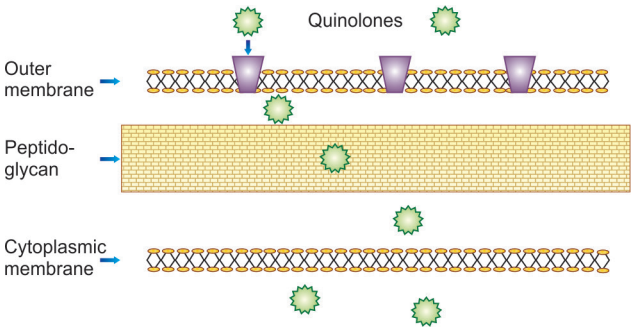


Fig. 1.15: Entry of quinoiones: Small and hydrophilic, quinolones have no problem crossing the outer membrane. They easily diffuse through the peptidoglycan and the cytoplasmic membrane and rapidly reach their target. Target = Topoisomerases, e.g., DNA-gyrase

1. Ciprofloxacin, is the most effective antibiotic against *P. aeruginosa*
2. Levofloxacin and moxifloxacin are reported to be efficacious against *S. aureus and S. pyogenes*.
3. Ciprofloxacin is active against *Bacillus anthrax.*
4. The FQ possess minimal anaerobic activity but are active against *P. acnes* (Moxifloxacin).
5. Ciprofloxacin, ofloxacin, and levofloxacin are active against *Mycobacterium* spp, including *M. tuberculosis, M. fortuitum,* and *M. kansasii*.

Pharmacology

The oral bioavailability of the FQ is excellent and minimally affected by food, except in the presence of antacids, and vitamin/mineral supplements. Half-lives of FQ vary from 3 to 13 hours. They are excreted from the kidney.

Clinical use in Dermatology

1. Pyoderma

They have been used for USSTI caused by Gram-negative bacteria, including those caused by multiresistant organisms such as folliculitis, abscesses, cellulitis, infected ulcers, and wound infections. They are an alternative to penicillins or β-lactams to treat USSTI caused by susceptible organisms in patients allergic or hypersensitive to penicillins or other β-lactams.

Levofloxacin and moxifloxacin are reported to be efficacious against *S. aureus* and *S. pyogenes*. Though these drugs are effective against **MRSA**, including CA-MRSA strains, FQ are *not* considered first-line agents for USSTI caused by

CA-MRSA, but may be used in selected cases when other options are limited by specific circumstances.

They are ideal for Gram-negative toe web-space infections, infected diabetic foot ulcers, and puncture wounds.

2. STD

Fluoroquinolones are effective against donovanosis and chancroid.

3. Anthrax

Ciprofloxacin is a treatment of choice for cutaneous anthrax.

4. Acne

The Japanese dermatologist (Kawada, Murata K) have used levofloxacin in a dose of 500 mg once a day for a short duration of 2 weeks. It can be used for Gram-negative folliculitis and refractory cases of Acne. Prolonged administration of FQ is not suggested in order to preserve the utility of oral FQ for indications where they are regularly dependent upon for efficacy (Amin K).

5. Gram-negative Folliculitis

Oral FQ may be helpful in some cases of Gram-negative folliculitis, including persistent 'hot tub folliculitis' caused by *Pseudomonas* spp. In patients with Gram-negative folliculitis other than the 'hot tub' variety, treatment with oral FQ is sometimes curative, with antibiotic selection optimally based on bacterial culture and sensitivity results. However, treatment with oral isotretinoin may be needed for refractory cases and/or recurrences (Sardana K).

Usage Guidelines

Dose

- Ofloxacin 200–400 mg PO q12h
- Ciprofloxacin 250–750 mg PO q12h
- Levofloxacin 250–750 mg PO/IV q24h
- Moxifloxacin 400 mg PO/IV q24h
- Gatifloxacin 400 mg OD.

Special Considerations

The absorption is reduced by antacids. A practical guideline useful in clinical practice is to instruct patients to take their FQ antibiotic at least 1–2 hours ***before,*** and not within 4 hours after, the ingestion of antacids. The metabolism of caffeine is similarly inhibited, and can cause a 'double espresso-

like' effect. Evening dosing of these agents may minimize phototoxic potential.

Drug Interactions

Some important FQ drug interactions resulting in increased drug levels and toxicity include (Table 1.15):

1. Theophylline metabolism is reduced by ciprofloxacin and norfloxacin, resulting in potential toxicity.
2. The metabolism of caffeine is similarly inhibited, and patients are best warned to consider reducing caffeine intake while taking an FQ, in order to avoid a 'double espresso-like' effect.
3. A decrease in warfarin and cyclosporine metabolism has been documented.
4. Gatifloxacin, and moxifloxacin may increase the risk of torsades de pointes when given along with some antiarrhythmic drugs, and are contraindicated with drugs known to prolong QTc interval.

Adverse Effects

Because human gyrases and topoisomerases are quite dissimilar to the corresponding bacterial enzymes, quinolones are in general well tolerated. Gatifloxacin was withdrawn from the US market in 2006 owing to reports of serious dysglycemia in older adults. The other FQ have *no such issue,* though the gatifloxacin is still marketed in India.

1. Gastrointestinal symptoms are the most common side effect, seen in 5% to 10% of individuals taking these agents. Nausea, vomiting, and diarrhea are commonly reported.

Table 1.15: Summary of the drug interactions

Decrease the efficacy fluoroquinolone	Antacids, nutritional supplements
Fluoroquinolone increase the effect (CYP1A2 inhibition)	Anticoagulants, bronchodilators (Theophylline) erlotinib; caffeine
Risk of QT interval prolongation	Antiarrhythmic agents clarithromycin, erythromycin antidepressants, antipsychotic agents, beta blockers
Cardiac drugs—inotropic agents	Digoxin; may increase serum levels
Diabetic drugs	Metformin, pioglitazone, repaglinide, sulfonylureas; may increase or decrease glucose levels
Immunosuppressive agents	Cyclosporine; may lead to creatinine levels in transplant patients

2. **CNS:** Adverse effects involving the central nervous system such as headache and dizziness occur in approximately 5% of patients. They range from milder reactions such as headaches, dizziness, agitation, and sleep disturbances to more severe reactions including seizures, psychotic reactions, hallucinations, and depression. The mechanism of at least some CNS reactions may relate to FQ antagonism of the inhibitory neurotransmitter γ-aminobutyric acid (GABA).
3. **Musculoskeletal:** Achilles tendon rupture has been reported in the elderly. It may have a delayed onset. *Risk factors* for FQ-induced tendinopathy and tendon rupture include, corticosteroid use, patient age, sports participation, history of renal failure, diabetes mellitus, hyperparathyroidism, rheumatic disease, gout, and a history of tendinopathy.
4. **CVS:** Quinolone use has been associated with prolongation of the QT interval on electrocardiograms. Gatifloxacin and moxifloxacin are associated with QTc interval prolongation. Thus, these agents may predispose to ventricular arrhythmias such as torsades de pointes, especially when they are used in conjunction with other agents that also prolong the QT interval.
5. **Hypersensitivity and photosensitivity reactions:** Hypersensitivity reactions and photosensitivity have also been reported, and photo-onycholysis has been described. The order of decreasing photosensitivity ranges from levofloxacin, ciprofloxacin, norfloxacin, and ofloxacin. Evening dosing of these agents may minimize phototoxic potential. Patients may present with edema of the face, difficulty breathing, hypotension, tachycardia, fever, pruritus, and/or diffuse erythroderma, with the reactions tending to occur up to 3 days following the initial dose of IV or oral ciprofloxacin.
6 **Pigmentation:** Blue-black pigentation of the legs similar to minocycline dyschromia, with demonstration of iron particles within the cytoplasm of dermal macrophages, has been reported with perfloxacin therapy.

Special Groups

Quinolones cause cartilage abnormalities in juvenile animals, so they should be avoided when possible in children younger than 18 years of age and not used at all in pregnant women.

Pregnancy C. Accidental exposure is not a definitive indication for medical abortion

Lactation C

Children:

A retrospective observational study completed through an automated database identified patients <19 years of age, 6,124 of whom were treated with at least 1 of 3 FQ, (ciprofloxacin, levofloxacin, or ofloxacin (active study group) and 15,073 who were treated with azithromycin (Lee et al). Tendon or joint disorders (TJD) occurring within 60 days of a prescription for one of the study antibiotics were identified based on diagnosis coding and were verified. The incidence of verified TJD diagnosed within 60 days of prescribing either an FQ antibiotic or azithromycin was <1% in both study groups. Despite this information, cautious prescribing of FQ in children is wise, particularly when other drug categories are equally effective.

BIBLIOGRAPHY

1. Amin K, Riddle CC, Aires DJ, et al. Common and alternative oral therapies for acne vulgaris: a review. J Drugs Dermatol. 2007; 6(9):873-80.
2. Kawada A, Wada T, Oiso N. Clinical effectiveness of once-daily levofloxacin for inflammatory acne with high concentrations in the lesions. J Dermatol. 2012 Jan;39(1):94-6.
3. Murata K, Tokura Y. Anti-microbial therapies for acne vulgaris:anti-inflammatory actions of anti-microbial drugs and their effectiveness. JUOEH. 2007;29(1):63-71.
4. Sardana K, Gupta T, Kumar B, Gautam HK. Efficacy of a Single Daily Dose of Levofloxacin in Gram-Negative Folliculitis Complicating Acne Vulgaris. Skinmed. 2015;13(6):488-90.
5. Yee CL, Duffy C, Gerbino PG, et al: Tendon or joint disorders on children after treatment with fluoroquinolones or azithromycin. Pediatr Infect Dis. 2002;21(6):525-9.

INHIBITORS OF MEMBRANE FUNCTION

1. Polymyxins
2. Cyclic lipopeptides.

POLYMYXIN

This class of drugs includes, polymyxins that have been around since 1940's and 1950's. This has a narrow spectrum for Gram-negative UTI, blood, CSF and eye infections and is rarely used in dermatology. The other drug is colistin (Colistimethate Sulfate) which has a narrow spectrum for Gram-negatives, especially *Pseudomonas aeruginosa*. It has come into recent use for treating multi-drug resistant Acinetobacter infections.

CYCLIC LIPOPEPTIDES

Daptomycin (Cubicin): Cubicin from CUBIST Pharmaceutical got FDA approval on September 12, 2003

It is a bactericidal drug and resistance rate appears to be low.

Mechanism of Action

Daptomycin is bactericidal. Active against Gram-positive bacteria (MRSA, MSSA) including those resistant to methicillin, vancomycin and linezolid.

It binds to components (calcium ions) of the cell membrane of susceptible organisms and causes rapid depolarization, inhibiting intracellular synthesis of DNA, RNA, and protein. Gram-negatives appear to be naturally resistant.

Uses

FDA approval for skin/skin structure infections:

- *S. aureus* (MSSA and MRSA)
- Beta-hemolytic Streptococci (A,B,C,G)
- *E. faecalis* (Vanco sensitive).

Spectrum

Gram-positive bacteria	streptococcus pyogenes Viridans group streptococci streptococcus pneumoniae staphylococci enterococci
Anaerobic bacteria	Some clostridium spp.

Dose

- Daptomycin is a lipopeptide antibiotic available only in IV form
- Daptomycin should be given cautiously in patients taking medications associated with myopathy, such as HMG CoA reductase inhibitors, but has no CYP-based drug interactions.

Side Effects

1. Neuropathy, primarily paresthesias.
2. Reversible skeletal muscle toxicity (myopathy), which is seen only at higher than approved doses.
3. Eosinophilic pneumonia has been reported to develop during treatment with daptomycin, with potential for respiratory failure.

2

CHAPTER

Antifungal Medications

Surabhi Sinha, Kabir Sardana

INTRODUCTION

Classification of Antifungals

The antifungal drugs have been classified depending on the structure, mode and site of action (see below). As the drugs used in dermatology are used for superficial fungal infections, a summary of the antifungal spectrum of the commonly used drugs is given in Table 2.1. An overview of the efficacy of and some practical tips related to the drugs is given in Box 2.1.

Table 2.1: A summary of the antifungals and their relative efficacy

	Terbinafine	*Itraconazole*	*Fluconazole*
Trichophyton species	Terbinafine = Itraconazole > Fluconazole		
Microsporum species			
Epidermophyton floccosum.			
C. albicans and *C. parapsilosis*	Terbinafine < Itraconazole = Fluconazole		
Non-dermatophyte	Terbinafine = Itraconazole > Fluconazole		
Tinea capitis: Endothrix (Terbinafine); Ectothrix (Azoles, Griseofulvin)			

Box 2.1: Salient features of antifungal drugs

Safest overall: Griseofulvin and Terbinafine

Safest in **Pregnancy**: Griseofulvin and Terbinafine

Safest in **Renal Dysfunction**: Fluconazole

Safest in **Liver dysfunction**: Fluconazole

Maximum **bioavailabilty:** Fluconazole

Newer Antifungals

Voriconazole: Invasive aspergillosis, esophageal candidiasis, *Fusarium* and *Scedosporium infections*

Posaconazole: Broadest spectrum amongst azoles (*zygomycosis and mucormycosis).*

Caspofungin**:** *D*isseminated and mucocutaneous *Candida* infections, *C. glabrata* and *C. krusei* febrile neutropenia patients.

ANTIFUNGAL DRUGS

According to Chemical Structure

1. **Antifungal antibiotics**
   a. Polyenes: amphotericin B, natamycin, nystatin
   b. Heterocyclic benzofurans: griseofulvin
2. **Synthetic antifungal drugs**
   i. Azoles:
      a. Imidazole derivatives: clotrimazole, econazole, miconazole, oxiconazole, ketoconazole
      b. Triazole derivatives: fluconazole, intraconazole
   ii. Allylamines: naftifine, terbinafine
   iii. Thiocarbamate: tolnaftate
   iv. Derivatives of undecyclenic acid
   v. Pyrimidine antagonist: flucytosine
   vi. Echinocandins: caspofungin, micafungin
   vii. Antifungal drugs with other chemical structure:
      a. Iodine drugs: potassium iodide (KI).

According to Mode of Action

1. **Alter cell permeability:** azoles, polyenes, terbinafine
2. **Disrupt microtubule function:** griseofulvin
3. **Ergosterol binding:** amphotericin-B
4. **DNA-RNA inhibitors:** flucytosine
5. **Ergosterol synthesis inhibitors/P450 inhibitors:** azoles
6. **β (1-3) glucan inhibitors:** caspofungin, micafungin, anidulafungin

According to Site of Action

1. **Systemic antifungal drugs**
   i. For systemic mycoses: amphotericin-B, flucytosine, azoles, echinocandins
   ii. For mucocutaneous mycoses: griseofulvin, terbinafine
2. **Topical antifungal drugs**: nystatin, topical azoles, topical allylamines.

Mechanism of Action

Amphotericin B and other polyenes, such as nystatin, bind to ergosterol in fungal cell membranes and increase membrane permeability (Fig 2.1). Amphotericin B is selective in its fungicidal effect because it exploits the difference in lipid composition of fungal and mammalian cell membranes. Ergosterol, a cell membrane sterol, is found in the cell membrane of fungi, whereas the predominant sterol of bacteria and human cells is cholesterol. Amphotericin B binds to ergosterol and alters the permeability of the cell

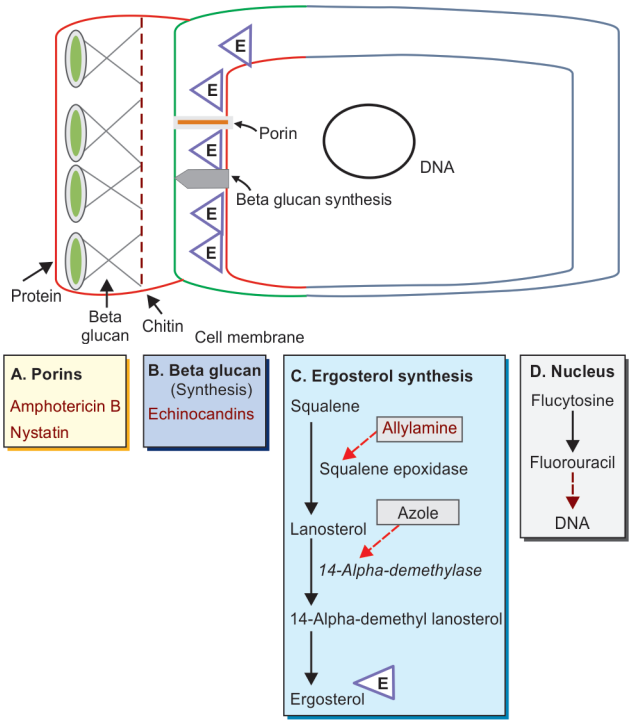


Fig. 2.1: Site of action of antifungal drugs. The diagram in the upper panel is a depiction of the fungal cell wall

by forming Amphotericin-B-associated pores in the cell membrane. As suggested by its chemistry, amphotericin-B combines avidly with lipids (ergosterol) and helps in pore formation which allows the leakage of intracellular ions and macromolecules, eventually leading to cell death. Some binding to human membrane sterols does occur, probably accounting for the drug's prominent toxicity.

The imidazoles and triazoles, such as itraconazole and fluconazole, inhibit 14-α-sterol demethylase, prevent ergosterol synthesis, and lead to the accumulation of 14-α-methylsterols (Figs 2.1 and 2.2). The selective toxicity of azole drugs results from their greater affinity for fungal than for human cytochrome P-450 enzymes. Imidazoles exhibit a lesser degree of selectivity than the triazoles, accounting for their higher incidence of drug interactions and side effects. Resistance to azoles occurs via multiple mechanisms. Once rare, increasing numbers of resistant strains are being reported, suggesting that increasing use of these agents for prophylaxis and therapy may be selecting for clinical drug resistance in certain settings.

Echinocandins act at the level of the fungal cell wall by inhibiting the synthesis of β (1–3)-glucan (Fig. 2.1). This results in disruption of the fungal cell wall and cell death.

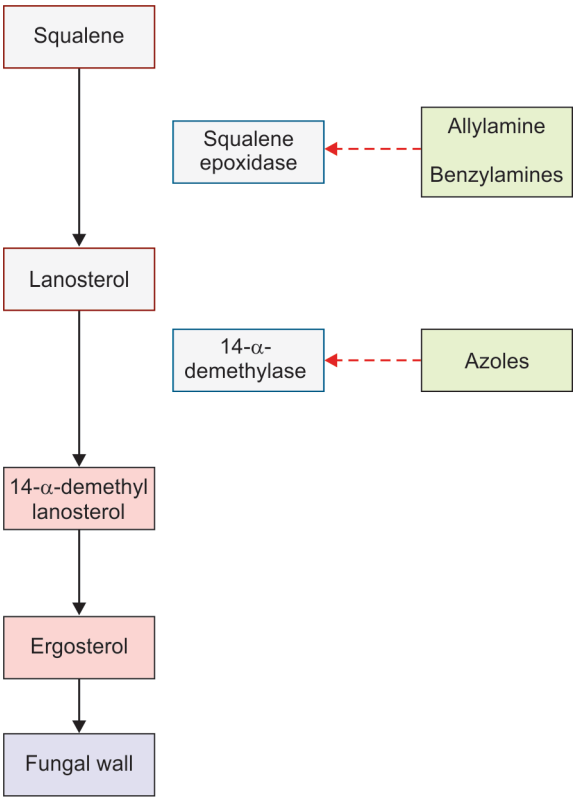


Fig. 2.2: Mechanisms of action of imidazoles, triazoles, benzylamine and allylamines

Like the azole drugs, terbinafine interferes with ergosterol biosynthesis, but rather than interacting with the P450 system, it inhibits the fungal enzyme squalene epoxidase (Figs 2.1 and 2.2). This leads to the accumulation of the sterol squalene, which is toxic to the organism and results in fungal cell death.

BIBLIOGRAPHY

1. Antifungal agents. In: Katzung BG, Masters SB, Trevor AI, (eds). Basic & Clinical Pharmacology, 11th edn. 835.
2. Antifungal Agents. In: Brunton L, Lazo J, Parker K (eds). Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 11th edn. New York: McGraw-Hill Medical; 2008.

AMPHOTERICIN B

The drug was discovered in 1956 by Gold and colleagues and was obtained from a filamentous bacterium, *Streptomyces nodosus.*

Amphotericin B (AmB) is an amphoteric polyene macrolide (polyene = containing many double bonds; macrolide = containing a large lactone ring of 12 or more

atoms). As it is nearly insoluble in water, it is therefore prepared as a colloidal suspension of amphotericin B and sodium desoxycholate for intravenous injection. Several new formulations have been developed in which amphotericin B is packaged in a lipid-associated delivery system.

Classification

Polyene antibiotic.

Category

Fungicidal.

Mechanism of Action

It combines with *ergosterol*, a steroid present in the cell membranes of fungi altering their permeability and causing loss of cytoplasmic contents. It also causes oxidative injury resulting in alteration of metabolic functions that are important for cell survival. AmB also combines with cholesterol in human cell membranes altering them and thus leading to adverse effects. Innate or acquired resistance to amphotericin B is rare. Sensitivity of fungi to amphotericin B is related to the concentration of ergosterol present in the cytoplasmic membrane

Absorption and Distribution

Amphotericin B is poorly absorbed from the gastrointestinal tract. AmB is given by intravenous infusion only. It reaches the highest concentration in liver, spleen, kidney and lungs. The levels of the circulating fraction, approximately 95% of which bind with protein, cholesterol and erythrocytes, decrease slowly. So, it is possible to administer it at 48–72-hour intervals.

The intravenous injection of 0.6 mg/kg/d of amphotericin B results in average blood levels of 0.3–1 μg/mL; the drug is more than 90% bound by serum proteins. Although, it is mostly metabolized, some amphotericin B is excreted slowly in the urine over a period of several days. The serum t1/2 is approximately 15 days.

Uses

Amphotericin B remains the antifungal agent with the *broadest spectrum of action*.

Spectrum: It has activity against the clinically significant yeasts, including *Candida albicans* and *Cryptococcus neoformans*; the organisms causing endemic mycoses,

including *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*; and the pathogenic molds, such as *Aspergillus fumigatus* and *Mucor*. Some species, such as *Pseudallescheria boydii* and *Fusarium*, *Trichosporon, Geotrichum*, and *Scedosporium*, are often resistant or not susceptible to amphotericin B. It can also treat infections caused by the protozoa, *Leishmania braziliensis* and *Naegleria fowleri.*

1. Life-threatening mycotic infections: in the initial induction regimen.
2. Treatment of choice: mucormycosis, initial treatment of cryptococcal meningitis, severe or rapidly progressing histoplasmosis, blastomycosis, coccidioidomycosis, penicilliosis, and in patients not responding to azole therapy of invasive aspergillosis, extracutaneous sporotrichosis, fusariosis, alternariosis, and trichosporonosis.
3. Amphotericin B is given once weekly to prevent relapse in patients with AIDS who have been treated successfully for cryptococcosis or histoplasmosis.
4. The treatment of visceral leishmaniasis in immunocompetent patients, including both adults and children.
5. The empirical treatment of presumed fungal infections in febrile neutropenic patients, where the fever has failed to respond to broad spectrum antibiotics and appropriate investigations have failed to define a bacterial or viral cause.
6. A *topical* formulation has been launched, though its approved indication was for candidiasis while it is being widely used for dermatophytosis.

Dosage

Conventional (Fungizone micelles 1 mg/kg/day)

Liposomal (AmBisome spheres 3–5 mg/kg/day; Amphotec disks 5 mg/kg/day; Abelcet ribbons 5 mg/kg/day)

The role of lipid formulations of amphotericin B in fungal infections remains to be determined. The risk of adverse effects, such as nephrotoxicity is decreased by ~50% with lipid formulations, but they cost 20–50 times more and may be associated with a greater risk of febrile infusion reactions.

As most centers now use the liposomal preparation its dosimetry is given below.

Liposomal amphotericin B (AmBisome) should be administered by intravenous infusion over a 30–60 minute period. For doses greater than 5 mg/kg/day, intravenous infusion over a 2-hour period is recommended. The recommended concentration for intravenous infusion is 0.20 mg/mL to 2.00 mg/mL amphotericin B as AmBisome.

1. Adult patients

Treatment of mycoses:

Therapy is usually instituted at a daily dose of 1.0 mg/kg of body weight, and increased stepwise to 3.0 mg/kg, as required. Data are presently insufficient to define total dosage requirements and duration of treatment necessary for resolution of mycoses. However, a cumulative dose of 1.0–3.0 g of amphotericin B as AmBisome over 3–4 weeks has been typical. Dosage of amphotericin B as AmBisome must be adjusted to the specific requirements of each patient.

Treatment of visceral leishmaniasis:

A total dose of 21.0–30.0 mg/kg of body weight given over 10–21 days may be used in the treatment of visceral leishmaniasis. Particulars as to the optimal dosage and the eventual development of resistance are as yet incomplete. The product should be administered under strict medical supervision.

Empirical treatment of febrile neutropenia:

The recommended daily dose is 3 mg/kg body weight per day. Treatment should be continued until the recorded temperature is normalized for 3 consecutive days. In any event, treatment should be discontinued after a maximum of 42 days.

2. Pediatric patients: Both systemic fungal infections in children and presumed fungal infections in children with febrile neutropenia have been successfully treated with AmBisome, without reports of unusual adverse events. AmBisome has been studied in pediatric patients aged one month to 18 years old. Doses used in these clinical studies were the same as those used in adults on mg/kg body weight basis. AmBisome is not recommended for use in children below 1 month old due to lack of data on safety and efficacy

1. **Preparation (50 mg/powder)**: Prepare a solution of **5 mg** Amp B by adding 10 mL of sterile water to the vial and shake until it is clear. Dilute (1:50) with 5% dextrose (0.1mg/mL)

2. Test dose: A test dose may be given before the first amphotericin B dose.

The greatest utility of a test dose is identification of patients particularly sensitive to infusion-related adverse effects of amphotericin B, or identification of patients with hypersensitivity to an alternative amphotericin B formulation.

Conventional amphotericin B 1 mg (**10 mL of reconstituted solution of 0.1 mg/mL**) in 5% **dextrose 20 mL infused over 10–20 min)** without premedication can be used as a test dose. Monitor patients closely for 30–60 min after the test dose.

3. Administration: To prevent drug-induced hyperkalemia, amphotericin B must be infused over 4–6 hr in patients with renal failure, preexisting hyperkalemia, or markedly reduced potassium clearance.

The preparation of liposomal Amp B is given below:

Vials of AmBisome containing 50 mg of amphotericin are prepared as follows:

1. Add 12 mL of sterile water for injection to each AmBisome vial, to yield a preparation containing 4 mg/mL amphotericin.

2. IMMEDIATELY after the addition of water, SHAKE THE VIAL VIGOROUSLY for 30 seconds to completely disperse the AmBisome. After reconstitution the concentrate is a translucent, yellow dispersion. Visually inspect the vial for particulate matter and continue shaking until complete dispersion is obtained. Do not use if there is any evidence of precipitation of foreign matter.
3. Calculate the amount of reconstituted (4 mg/mL) AmBisome to be further diluted.
4. The infusion solution is obtained by dilution of the reconstituted AmBisome with between one (1) and nineteen (19) parts dextrose solution (5%, 10% or 20%) for infusion by volume, to give a final concentration in the recommended range of 2.00 mg/mL to 0.20 mg/ml amphotericin as AmBisome.
5. Withdraw the calculated volume of reconstituted AmBisome into a sterile syringe. Using the 5 microns filter provided, instill the AmBisome preparation into a sterile container with the correct amount of dextrose solution (5%, 10% or 20%) for infusion.
   An in-line membrane filter may be used for intravenous infusion of AmBisome. However, the mean pore diameter of the filter should not be less than 1.0 micron.

Administration: Slow intravenous infusion at a dosage of 0.5–1 mg/kg/d. It is usually continued to a defined *total dose* (e.g. 1–2 g), rather than a defined time span, as used with other antimicrobial drugs. Cumulative total dosage of amphotericin B is generally 10–20 mg/kg.

Initiate therapy with the full treatment dose for patients with life-threatening fungal disease. Some advocate initiation of amphotericin B at a fraction of the therapeutic dose with daily incremental increases to achieve the desired therapeutic dosage. Although it has not been evaluated in a controlled manner, the intent of this approach is improvement of patient tolerance to infusion-related adverse effects.

Maintenance therapy conventional amphotericin B and amphotericin B lipid complex can be given every alternate day like Monday, Wednesday, and Friday.

Duration of therapy with amphotericin B is not well defined. Patients with life-threatening mycotic disease must receive amphotericin B until resolution of clinical and microbiologic evidence of fungal infection, or until unacceptable drug-induced toxicity occurs.

Alternative Routes of Administration

There are examples of extemporaneously prepared amphotericin B to facilitate drug availability to a sanctuary site or minimize systemic toxicity. Use of alternative routes of amphotericin B administration is based primarily on case reports, and the safety and efficacy of extemporaneously prepared amphotericin B administered by alternative routes have not been evaluated in a controlled manner.

Subsequently, administration of amphotericin B by an alternative route should not replace standard therapy.

Intra-articular for fungal arthritis: **5–50 mg qd 2–7 days**. The dose of intra-articular amphotericin B is determined by the size of the infected joint.

Intracavitary for pulmonary aspergillomas: **5–50 mg in D5W daily or 2–3 times weekly** has been used in patients unable to undergo surgical resection.

Inhalation for prophylaxis against *Aspergillus* sp. after bone marrow transplantation 0.15% in D5W nebulized to deliver 10 mg/day in 2 divided doses.

*Intranasa*l for prophylaxis in bone marrow transplant recipients Amphotericin B 0.5% in sterile water 10 mg/day in divided doses.

Intrathecal administration of conventional amphotericin B 0.5–1 mg 2–3 times/week or 0.3 mg/day has been reported. The Intrathecal dosage of conventional amphotericin B is generally started at 0.025–0.05 mg/dose, with subsequent doses increased at 0.025–0.05 mg/day increments to the desired therapeutic or maximum tolerated dosage.

Drug Interaction

Additive nephrotoxicity can occur with cyclosporine, tacrolimus, aminoglycosides, loop diuretics, or other nephrotoxic agents. Corticosteroids can enhance potassium loss.

Side Effects

A. Infusion-related Toxicity

Fever, chills, muscle spasms, vomiting, headache, and hypotension are the side effect. They can be ameliorated by slowing the infusion rate or decreasing the daily dose. Premedication with antipyretics, antihistamines, meperidine, or corticosteroids can be helpful. When starting therapy, many clinicians administer a test dose of 1 mg intravenously to gauge the severity of the reaction. This can serve as a guide to an initial dosing regimen and premedication strategy.

B. Cumulative Toxicity

Renal damage is the most significant toxic reaction. Renal impairment occurs in nearly all patients treated with clinically significant doses of amphotericin. The degree of azotemia is variable and often stabilizes during therapy, but it can be serious enough to necessitate dialysis. A reversible component is associated with decreased renal perfusion and represents a form of prerenal renal failure. An irreversible component

results from renal tubular injury and subsequent dysfunction. The irreversible form of amphotericin nephrotoxicity usually occurs in the setting of prolonged administration (>4 g cumulative dose). Renal toxicity commonly manifests as renal tubular acidosis and severe potassium and magnesium wasting. There is some evidence that the prerenal component can be attenuated with sodium loading, and it is common practice to administer normal saline infusions with the daily doses of amphotericin B.

Abnormalities of liver function tests are occasionally seen, as is a varying degree of anemia due to reduced erythropoietin production by damaged renal tubular cells. After intrathecal therapy with amphotericin, seizures and a chemical arachnoiditis may develop, often with serious neurologic sequelae.

Monitoring

Monitor infusion-related adverse effects with first 3 doses, then as indicated by severity of reactions.

Baseline	*Follow-up*	*Interval*
Serum Cr, BUN, magnesium, potassium	Yes	At least twice weekly
Hb	Yes	Weekly

Special Groups

Hepatic impairment, renal impairment, and dialysis have little impact on drug concentrations, and therefore no dose adjustment is required. Amphotericin B is rated pregnancy category B.

Liposomal Amphotericin B

Therapy with amphotericin B is often limited by toxicity, especially drug-induced renal impairment. This has led to the development of lipid drug formulations on the assumption that lipid-packaged drug binds to the mammalian membrane less readily, permitting the use of effective doses of the drug with lower toxicity. Liposomal amphotericin preparations package the active drug in lipid delivery vehicles, in contrast to the colloidal suspensions, which were previously the only available forms. Amphotericin binds to the lipids in these vehicles with an affinity between that for fungal ergosterol and that for human cholesterol. The lipid vehicle then serves as an amphotericin reservoir, reducing nonspecific binding to human cell membranes. This preferential binding allows for a reduction of toxicity without sacrificing efficacy and permits use of larger doses. Furthermore, some fungi contain lipases that may liberate free amphotericin B directly at the

site of infection. Three such formulations are now available and have differing pharmacologic properties as summarized in Table 2.2 and Figure. 2.3. Although clinical trials have demonstrated different renal and infusion-related toxicities for these preparations compared with regular amphotericin B, there are no trials comparing the different formulations with each other. Limited studies have suggested at best a moderate improvement in the clinical efficacy of the lipid formulations compared with conventional amphotericin B. Because the lipid preparations are much more expensive, their use is usually restricted to patients intolerant to, or not responding to conventional amphotericin treatment.

GRISEOFULVIN

(Gris OD 375 mg, Grisomed 375 mg, Grisovin FP 250 mg) 125, 250 mg tablet (ultramicrosize); 500 mg tablet (microsize). In India 375 mg is available which is given once a day in adults and is ultramicronized.

Classification

Griseofulvin is a metabolic product of *Penicillium griseofulvum* isolated from culture in 1939 by Oxford and colleagues. It is a heterocyclic benzofuran.

Mechanism of Action

Disrupts fungal mitotic spindle structure, arresting cell division in metaphase.

Pharmacology

Susceptible organisms *in vivo*: Species of *Trichophyton*, *Microsporum*, and *Epidermophyton*.

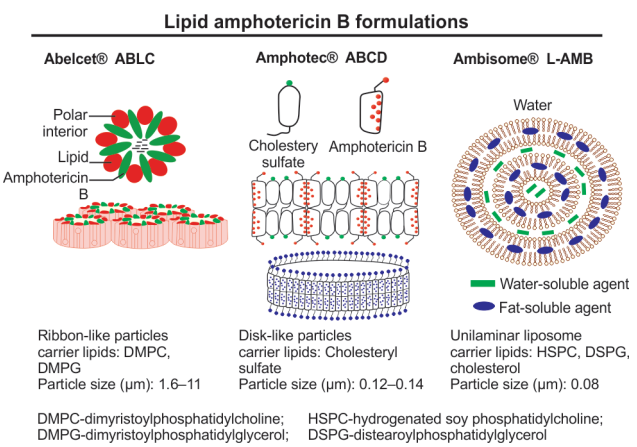


Fig. 2.3: A figurative depiction of the lipid Amph B formulation

Table 2.2: A comparison of various formulation of Amph B

	Fungizone *Amphotericin B*	*Amphotec* *Amphotericin B Cholesteryl Sulfate*	*Abelcet* *Amphotericin B Lipid Complex*	*AmBisome* *Liposomal Amphotericin B*
LIPID CHEMISTRY Size Shape	Deoxycholate 50 nm Micelle	Cholesteryl Sulfate 120–140 nm Discoid	DMPG, DMPC 1600–11,000 nm Ribbon-like	HSPC, DSPC 80 nm Spherical liposome
Vial Temp	50 mg 2–8°C	50, 100 mg 15–30°C	50, 100 mg 2–8°C	50 mg 2–8°C
Daily dosage (mg/kg) Sensitive fungi Less-sensitive fungi	 0.5–1 1–1.5	 3–4 6	 2.5–5 5	 1–3 3–5
Infusion duration (hr)	1–6 (≤50 mg/hr)	2–4	2	1–2
Compatible IV fluids	D5W	D5W	D5W	D5W
Admixture concentration (mg/mL)	0.5–0.25	0.16–0.83	1–2	1–2

Absorption and Distribution

Oral absorption is increased by a fatty meal. The excretion is mostly renal (50%), 1% excreted unchanged in urine; 36% in feces. It is also secreted in the sweat.

Clinical Use in Dermatology

Dermatophytic infections: Tinea corporis, capitis, pedis, onychomycosis.

It is believed that terbinafine is superior for the treatment of *T. tonsurans* infection, while griseofulvin is useful largely for *M.canis* infections. *Trichophyton* infections are usually endothrix (inside the hair shaft thus drug accumulation may help eradicate infection), while *Microsporum* are ectothrix (outside the hair shaft, requiring drug to be secreted to the hair surface via sweat or sebum). As children have little sebum secretion prior to puberty, **terbinafine** may not reach ectothrix infections adequately for treatment, whereas its incorporation into the hair shaft is effective in **endothrix** infections. As **griseofulvin** is secreted in *sweat* they are more effective in **ectothrix** infections.

Usage Guidelines

Microsize: 15–20 mg/kg daily (usual maximum 1 g); use higher range (20–25 mg/kg daily) for tinea capitis

Ultramicrosize: 10–15 mg/kg/d (max 750 mg/d).

It is believed that doses >20 mg/kg/day do not significantly increase the complete cure rate compared to <20 mg/kg/day

Children *13.6–22.7* kg: Microsize: 125–250 mg/d. Ultramicrosize: 82.5–165 mg/d. > *22.7* kg: Microsize: 250–500 mg/d. Ultramicrosize:165–330 mg/d.

A summary of its common uses and dosage in dermatology is given in Table 2.3.

Special Considerations

Avoid concomitant alcohol:

- Use protective clothing and sunscreen to avoid photosensitivity reactions if exposed to strong sunlight
- **Food:** Should be taken with high-fat food (icecream, milk, etc.)
- Pregnancy, history of porphyria, hepatocellular failure, hypersensitivity to griseofulvin.

Drug Interactions

Barbiturates decrease effects/toxicity of griseofulvin.

Griseofulvin increases effects/toxicity of alcohol.

Table 2.3: Uses and dosages of griseofulvin

Indication	*Dose*
Tinea Capitis	Microsize: 15–20 mg/kg daily Ultramicrosize: 10–15 mg/kg/d Duration: 6–12 weeks
Tinea corporis, Tinea cruris	Microsize: 0.5 g/d, single or divided doses. Ultramicrosize:330–375 mg/d Duration: 2–4 weeks
Tinea pedis	Duration: 4–8 weeks
Tinea imbricata	Griseofulvin, 500 mg twice daily for 4–6 weeks
Onychomycosis	Although approved for tinea infection of the nails, its affinity for keratin is low and long-term therapy (at least 9–12 months) is required

Griseofulvin decreases effects/toxicity of oral anticoagulants and oral contraception.

Adverse Effects

Common: Headache, skin rash.

Serious: urticaria, granulocytopenia, hepatotoxicity, proteinuria, renal toxicity.

Special Groups

Kidney disease: None

Liver disease: None

Elderly: None

Pediatric: Safety has not been determined in children <2 years

Pregnancy: Category C

Lactation: No data available. Best to avoid.

AZOLES

Azoles are synthetic compounds that can be classified as either imidazoles or triazoles according to the number of nitrogen atoms in the five-membered azole ring. The imidazoles consist of ketoconazole, miconazole and clotrimazole. The latter two drugs are now used only in topical therapy. The triazoles include itraconazole, fluconazole, voriconazole, and posaconazole.

Azoles work through a common mechanism of action. They are fungistatic but not fungicidal, except at very high concentrations. Azoles selectively inhibit the synthesis of ergosterol, an essential component of fungal cell membrane, by interacting with fungal *lanosterol 14α demethylase*, a cytochrome P-450 dependent enzyme that converts

lanosterol to ergosterol (Fig. 2.2). Depletion of ergosterol and accumulation of 14α-methylated sterols interferes with the function of ergosterol, causes increased permeability and rigidity of fungal cell membrane, and disrupts the enzymes bound to fungal cell membrane, inhibiting fungal growth and replication. As it works via a cytochrome P-450 enzyme, this class has a number of drug interactions some of which are listed in Table 2.4.

The **spectrum** of action of azole medications is broad, including many *Candida* species, *C. neoformans,* the endemic mycoses (blastomycosis, coccidioidomycosis, histoplasmosis), the dermatophytes, and, in the case of itraconazole and voriconazole, even *Aspergillus* infections. They are also useful in the treatment of intrinsically amphotericin-resistant organisms such as *P. boydii*.

Table 2.4: Drugs that have potentially clinically significant pharmacokinetic interactions with systemic itraconazole, ketoconazole, and possibly higher doses of fluconazole (>200 mg/day)

Interaction significance	*Potential effects*
Life-threatening(CI)	
Astemizole Terfenadine Cisapride	May induce torsades de pointes
Major interactions(CI)	
Midazolam/ Triazolam Lovastatin/ Simvastatin/ Atorvastatin	Sedation Myopathy, rhabdomyolysis
Avoid or use with caution	
Rifampicin Protease inhibitors	Antifungal inefficacy Increased effects
Mild or moderate interaction	
Digoxin	Digoxin toxicity
Cyclosporin	Increased nephrotoxicity and neurotoxicity
Methylprednisolone	Increased methylprednisolone effects
Phenytoin	Increased phenytoin levels or antifungal inefficacy
Oral hypoglycemic	Hypoglycemia
Quinidine	Ototoxicity
Calcium channel blockers	Edema formation
Carbamazepine	Antifungal inefficacy
Proton pump inhibitors, H_2 blocker, antihistamines Isoniazid	Antifungal inefficacy

Ketoconazole was the first oral azole introduced into clinical use. It is distinguished from triazoles by its greater propensity to inhibit mammalian cytochrome P-450 enzymes; that is, it is less selective for fungal P-450 than are the newer azoles. As a result, systemic ketoconazole has fallen out of clinical use at least for systemic use.

Itraconazole

Classification

Antifungal.

Category

Synthetic triazole.

Mechanism of Action

Itraconazole inhibits fungal 14α-demethylase, resulting in a depletion of ergosterol and disruption of membrane synthesis by fungi.

Mechanisms of Resistance

Resistance of fungi to azoles appears to develop *slowly* and is often the result of several genetic mutations. Mechanisms that have been described are as follows:

- Over-expression of *ERG11*, the gene that encodes 14α-demethylase (the target enzyme)
- Point mutations in *ERG11* that lead to decreased affinity of 14α-demethylase for itraconazole
- Drug-transporter over-expression resulting in increased efflux of itraconazole from fungal cells (i.e. removal of itraconazole from its target)
- Cross-resistance. Cross-resistance amongst members of the azole class of active ingredients has been observed within *Candida* species though resistance to one member of the class does not necessarily confer resistance to other azoles.

Using CLSI methods, breakpoints for itraconazole have only been established for *Candida* species from superficial mycotic infections. The CLSI breakpoints are susceptible $\leq$0.125 mg/L and resistant $\geq$1 mg/L.

The prevalence of acquired *resistance* may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. An in house study did *not* find any resistance to *dermatophytes*. The *in vitro* susceptibility

of fungi to itraconazole depends on the inoculum size, incubation temperature, growth phase of the fungi, and the culture medium used. A list of species susceptible to the drug is given as follows:

Commonly susceptible and resistant species (Itraconazole)	
Aspergillus spp. *Blastomyces dermatitidis*	**Acquired resistance:** *Candida glabrata, Candida krusei, Candida tropicalis*
Candida albicans, Candida parapsilosis *Cladosporium* spp. *Coccidioides immitis* *Cryptococcus neoformans* *Epidermophyton floccosum* *Fonsecaea* spp. *Geotrichum* spp. *Histoplasma* spp. *Malassezia* (formerly *Pityrosporum)* spp. *Microsporum* spp. *Paracoccidioides brasiliensis* *Penicillium marneffei* *Pseudallescheria boydii* *Sporothrix schenckii* *Trichophyton* spp. *Trichosporon* spp.	**Inherently resistant organisms** *Absidia* spp. *Fusarium* spp. *Mucor* spp. *Rhizomucor* spp. *Rhizopus* spp. *Scedosporium proliferans* *Scopulariopsis* spp.

Absorption and Distribution

Relative oral bioavailability of the capsules compared with an oral solution is >70%. The absorption is better in an ***acidic*** environment, *food increasing* the absorption. Peak serum concentration occurs in 4–5 h. The drug is >99% protein bound, primarily to albumin.

Pharmacokinetics in Skin

1. The delivery is by passive diffusion from the plasma to the keratinocytes.
2. It is strongly adhered to keratin.
3. There is extensive excretion of itraconazole into *sebum*.
4. Itraconazole may persist in the stratum corneum for *3–4 weeks* after discontinuation of therapy.

Pharmacokinetics in Nail

1. Itraconazole is detected in the distal end of the fingernail and toenail within respectively 1 and 2 weeks of starting therapy.
2. The levels are more in the subungual nail material is more than double the corresponding level in the distal nail clippings.

3. On pulse therapy (2 pulses;200 mg twice daily 1 week/3 weeks off) the drug becomes undetectable in fingernail by *9 months* after the initiation of therapy. In the toenail onychomycosis (3 pulses of itraconazole) drug levels have been detected in the nail for *11 months*.

Pharmacokinetics in Hair

1. The route is via the *sebum*, and by incorporation into the hair follicle.
2. With a pulse regimen the concentration was 2.6- and 3.4-fold higher after the second and third pulses.
3. After stopping drug is detectable in hair for up to *9 months.*

Metabolism

Itraconazole is metabolized in the liver and exhibits dose-dependent elimination. One metabolite, hydroxyitraconazole, has antifungal activity, and serum concentrations are double those of itraconazole at steady state. Extensive metabolism in liver is by CYP3A4; active metabolite: hydroxyl-itraconazole. Renal excretion40% inactive metabolites; fecal 3–18%; parent drug $t^{1}/_{2}$ is 24–42 hr.

The absolute oral bioavailability of itraconazole is **55%.** A maximum oral bioavailability is achieved if itraconazole is taken directly **after a meal**.

Uses/Dosages

FDA approved (onychomycosis, dermatophyte infections, oropharyngeal candidiasis, esophageal candidiasis, blastomycosis, histoplasmosis, aspergillosis)

Itraconazole is the azole of choice for treatment of disease due to the dimorphic fungi *Histoplasma, Blastomyces,* and *Sporothrix*. For *Aspergillus* sp, it has been replaced by voriconazole.

A few general principles dictate therapy by Itraconazole:

1. As azoles also tend to be secreted in *sweat* they are more effective in *ectothrix* infections (*T. capitis*).
2. For onychomycosis, though pulse regimen have been tried but better results are achieved by a daily dose regimen.
3. The drug is useful for non-dermatophyte molds and *Candida* species. Itraconazole is effective against *Aspergillus* sp, *S. brevicaulis, Fusarium* sp., S*cytalidium* sp. and *O. canadensis* infections. It is more effective than Terbinafine against *Candida* species, in particular *C. albicans*.

A tabulated list of disorders responsive to the drug are given in Table 2.5.

Table 2.5: Dosimetry of itraconazole

Disorder (FDA approved/ Unapproved)	*Dose/Duration*
Aspergillosis	200 mg PO TDS for 4 days Then 200 mg PO OD X3 months
Blastomycosis	200 mg OD. If there is no improvement or the disease is progressive, the dose may be increased in 100-mg increments. Maximum: 400 mg/d. Children: 100 mg/d
Candidiasis *Oral Thrush* *Stomatitis/Esophagitis/ Vaginitis*	 200 mg PO OD for 7 days (Swish and swallow) 200 mg PO OD for 14 days (Swish and swallow)
Chromomycosis	100 mg PO OD for 18 months (Adjunctive Rx)
Coccidiodomycosis	200 mg PO bd for 3–12 months
DERMATOPHYTE INFECTION *Tinea capitis*	 5 mg/kg daily for 4–8 weeks, or, in the case of pulse therapy, 5 mg/kg daily for 1 week a month, given for 2–4 months
Tinea corporis and tinea cruris	100 mg OD -15 days or 200 mg OD 7 days
Tinea pedis and mannum	100 mg/day for 30 days 200 mg daily for **2–4 weeks** (*Ideal regimen*) 200 mg bid for 7 days
Majocchis's granuloma	200 mg BD for 7 days, then off for 14 days (repeat 3 times total)
Onychomycosis *Fingernail*	 i. 200 mg PO OD for 3 months ii. Pulse: 200 mg twice daily (400 mg daily) for 1 week per month. 2 pulses (**FDA approved**)
Toenail	i. 200 mg daily for 12 weeks ii. **Pulse:** 200 mg twice daily (400 mg daily) for 1 week per month. (3–4 pulses)–**Not Approved by FDA**
Candida onychomycosis	200 mg daily
Phaeohyphomycosis	200 mg PO bid until clinical resolution
Tinea versicolor	***Treatment:*** 200 mg OD 5–7 days or 100 mg daily for 2 weeks Prophylaxis: A single 400 mg dose of itraconazole-6 months
Seborrheic dermatitis	Regimen 1: 200 mg OD for 7 days Regimen 2: 200 mg PO OD for first week of month, then first 2 days of every month for 11 months
Sporotrichosis	100–200 mg PO OD for 3–6 months or until 2–4 weeks after all lesions have resolved

Drug Interaction

Itraconazole inhibits CYP3A3/4 and inhibits metabolism of certain drugs such as cyclosporine and warfarin (Table 2.6 and 2.7).

Itraconazole and its major metabolite, hydroxy-itraconazole, can inhibit the metabolism of active ingredients metabolized by CYP3A4 and can inhibit the transport of active ingredients by P-glycoprotein, which may result in increased plasma concentrations of these active ingredients and/or their active metabolite(s) when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these medicinal products. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7–14 days, depending on the dose and duration of treatment.

Table 2.6: Medicinal products that may decrease itraconazole plasma concentrations

1. Medicinal products that reduce the gastric acidity (e.g. acid neutralizing medicines, such as aluminum hydroxide, or acid secretion suppressors such as H_2-receptor antagonists and proton-pump inhibitors) impair the absorption of itraconazole from itraconazole capsules. It is recommended that these medicinal products be used with caution when coadministered with itraconazole capsules.
2. It is recommended that itraconazole be administered with an acidic beverage (such as non-diet cola) upon cotreatment with medicinal products reducing gastric acidity.
3. It is recommended that acid neutralizing medicines (e.g. aluminum hydroxide) be administered at least 1 hour before or 2 hours after the intake of itraconazole capsules.
4. Administration of potent enzyme inducers of CYP3A4 with itraconazole is not recommended. It is recommended that the use of these medicinal products be avoided from ***2 weeks before and during treatment*** with itraconazole, unless the benefits outweigh the risk of potentially reduced itraconazole efficacy.
   Antibacterials: isoniazid, rifabutin, rifampicin.
   Anticonvulsants: carbamazepine, phenobarbital, phenytoin.
   Antivirals: Efavirenz, nevirapine.
   Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

Table 2.7: Medicinal products that may increase itraconazole plasma concentrations

Potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole.

Antibacterials: Ciprofloxacin, clarithromycin, erythromycin

Antivirals: Ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, indinavir

A detailed list of drug that interact with intraconazole is given in Table 2.8.

Special Considerations

- Absorption of itraconazole in a fasting state, or in individuals with relative or absolute achlorhydria (e.g. those on H_2 inhibitors, antacids, or proton pump inhibitors), may be increased when the itraconazole is administered with at 250 mL of a cola beverage
- Itraconazole capsules can be opened and mixed with fatty foods such as peanut butter for administration in *children*
- Itraconazole should be avoided in patients with ventricular dysfunction or a history of heart failure
- Avoid Co-administration of cisapride, pimozide, lovastatin and simvastatin, midazolam and triazolam, nisoldipine, and CYP3A4 ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)
- Absorption is reduced in AIDS and neutropenia
- Drugs that reduce acid production interfere with its absorption (e.g. antacids, H_2-blockers, omeprazole)
- Patients should be forewarned about signs and of symptoms of jaundice (fatigue, loss of appetite, nausea, vomiting, yellowing of the skin, dark urine, or pale stools).

Side Effects

Common: Nausea, vomiting, diarrhea, hypokalemia, elevated liver enzymes, skin rash, vasculitis, abdominal pain, elevated creatinine levels, headache, fever, hypertension, hypertriglyceridemia.
Skin: Angioedema (1 case) and erythema multiforme (1 case) and rarely Stevens–Johnson syndrome.

Abnormal liver function tests is commoner in the continuous regimen.

Rare: Hepatotoxicity, hepatic failure, congestive heart failure, pulmonary edema, anaphylaxis, peripheral neuropathy, Stevens-Johnson syndrome, toxic epidermal necrolysis, malaise, anorexia, pruritus, dizziness, decreased libido, somnolence, vertigo, impotence, albuminuria, depression, constipation, dyspepsia, stomatitis, sinusitis, pain, fatigue, alopecia, neutropenia.

With intravenous injection hypertension and hyperglycemia.

The excipient hydroxypropyl-β-cyclodextrin, can cause pancreatic adenocarcinomas in rats.

Table 2.8: A list of drugs that interact with intraconazole

Class of active ingredient	*Contraindicated**	*Not recommended**	*Use with caution*
Alpha blockers		Tamsulosin	
Analgesics	Levacetylmethadol (levomethadyl) methadone	Fentanyl	AIfentanil, buprenorphine IV and sublingual, oxycodone
Antiarrhythmics	Disopyramide, dofetilide, dronedarone, quinidine		Digoxin
Antibacterials		Ifabutin*	
Anticoagulants and antiplatelet medicinal products		Rivaroxaban	Coumarms, cilostazol, dabigatran
Anticonvulsants		Carbamazepine*	
Antidiabetic			Repaglinide, saxagliptin
Antihelmintics and antiprotozoals	Halofantrine		Praziquantel
Antihistamines	Astemizole, mizolastine, terfenadine		Ebastine
Antimigraine medicinal products	Ergot alkaloids, (such as dihydroergotamine, ergometrine ergonovine), ergotamine, (methylergometrine methylergonovine)		Eletriptan
Antineoplastics	Irinotecan	Dasatinib nilotinib trabectedin	Bortezomib, busulphan, rabectedin docetaxel, erlotinib, ixabepilone, lapatinib, trimetrexate, vinca alkaloids
Antipsychotics, anxiolytics and hypnotics	Lurasidone, oral midazolam, pimozide, sertindole, triazolam		Alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam, perospirone, quetiapine, ramelteon, risperidone

Contd...

Contd...

Class of active ingredient	*Contraindicated**	*Not recommended**	*Use with caution*
Antivirals			Maraviroc, indinavir, ritonavir, saquinavir
Beta blockers			Nadolol
Calcium channel blockers	Bepridil, felodipine lercanidipine, isoldipine		Other diydropyridine s, including verapamil
Cardivascular medicinal products, miscellaneous	Ivabradine, ranolazine	Aliskiren	
Diuretics	Eplerenone		
Gastrointestinal medicinal products	Cisapride		Aprepitant, domperidone
Immunosuppressants		Everolimus	Budesonide ciclesonide, ciclosporin dexamethasone, fluticasone, Methylprednisolone, rapamycin (also known as sirolimus), tacrolimus, temsirolimus
Lipid regulating medicinal products	Lovastatin, simvastatin		Atorvastatin
Respiratory medicinal products		Salmeterol	
SSRIs, tricyclics and related antidepressants			Reboxetine
Urological medicinal products		Vardenafil	Fesoterodine. imidafenacin, sildenafil, solifenacin, tadalafil, tolterodine
Other	Colchicine, in subjects with renal or hepatic impairment	Colchicine	Alitertinoin (oral formulation), cinacalcet, mozavaptan, tolvaptan

*Contraindicated: Under no circumstances is the medicinal product to be coadministered with itraconazole, and up to *two weeks* after discontinuation of treatment with itraconazole. 'Not recommended': It is recommended that the use of the medicinal product be avoided during and up to two weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects.

Monitoring

As it is metabolized in the liver a 6 weekly, LFT is advised.

Special precaution should be exercised if concomitant therapy is being given like in the case of warfarin.

Special Category

Pregnancy: Category C.

Male: No effect on androgen levels and alteration of male reproduction is unlikely.

Lactation: Appears in breast milk. Avoid breastfeeding.

Pediatric: Safety and efficacy have not been established in children <3 years.

Liver: itraconazole elimination half-life showed a 2-fold increase in liver dysfunction.

Renal dosing: Use with caution.

Itraconazole bioavailability is slightly reduced for subjects with renal insufficiency

Creatinine clearance (CrCl) 10–90 mL/min: 100% of normal dose of; CrCl <10 mL/min: 50% of normal dose. Hemodialysis, continuous ambulatory peritoneal dialysis, continuous arteriovenous hemofiltration: 100 mg IV q12–24 h. Avoid intravenous infusion if eGFR less than 30 mL/min/1.73 m^2.

Fluconazole

Fluconazole, a member of the triazole antifungal family, was approved by the FDA in the early 1990s.

Fluconazole displays a high degree of water solubility and good cerebrospinal fluid penetration. Unlike ketoconazole and itraconazole, its oral bioavailability is high. Drug interactions are also *less common* because fluconazole has the least effect of all the azoles on hepatic microsomal enzymes. Because of *lesser* hepatic enzyme interactions and better gastrointestinal tolerance, fluconazole has the *widest therapeutic index* of the azoles, permitting more aggressive dosing in a variety of fungal infections.

Classification

Antifungal.

Category

Synthetic triazole.

Mechanism of Action

This triazole drugs inhibit the CYP-dependent enzyme, lanosterol 14α-demethlyase with resultant inhibition of

the conversion of lanosterol to ergosterol. It is primarily a fungistatic drug.

Absorption and Distribution

It has a high bioavailability of >90% and undergoes little hepatic metabolism. Its absorption is not affected by food intake and is minimally protein bound (11–12%). This makes it a useful drug that can be used for most dermatological indications.

There is little first-pass hepatic metabolism, much of dose is excreted as unchanged parent drug. The excretion is primarily by the renal route (80% as parent drug, 11% metabolites; 2% feces).

The elimination half-life is long (60–90 hours).

Pharmacokinetics in Skin

1. When two doses of fluconazole (150 mg once weekly) are administered, the drug accumulates in the stratum corneum through *sweat* and by *direct diffusion* through the dermis and epidermis.
2. The pharmacokinetic data suggest that fluconazole 150 mg given once weekly should be effective in the treatment of cutaneous fungal infections.

Pharmacokinetics in Nail

1. It is detectable at the distal end of the nail plate within 1 day of starting treatment with 50 mg.
2. When 150 mg of fluconazole is given once weekly for 12 months, it can be detected in the nail plate for at least 6 months after the discontinuation of therapy in both healthy and diseased nails.

Pharmacokinetics in Hair

1. The route is via the *sebum*, and by incorporation into the hair follicle.
2. With a pulse regimen, the concentration was 2.6- and 3.4-fold higher after the second and third pulses.
3. After stopping, drug is detectable in hair for up to 9 months.

Metabolism

$t^{1}/_{2}$—30 hr.

Uses/Dosages

FDA: Vaginal candidiasis, oropharyngeal candidiasis, esophageal candidiasis, cryptococcal meningitis (Table 2.9).

Table 2.9: Dosimetry of fluconazole

Disorder	*Dose/Duration*
Blastomycosis	400–800 mg PO OD for 8 months
Candidiasis	
1. Cutaneous candidiasis	150 mg once weekly given for 2–4 weeks
2. Systemic candidiasis	400 mg IV OD for 7 days, then 400 mg PO OD for 14 days
3. Thrush (Oral)	200 mg once or 100 mg PO OD for 5–14 days
4. Oropharyngeal/Esophagitis	200 mg PO first day, then 100 mg PO OD for 14 days Children:6 mg/kg on day 1 then 3 mg/kg q24–72 h for 14 days
5. Esophageal	200 mg on day 1 then 100 mg OD for at least 3 weeks Treat for at least 2 weeks after symptoms resolve Children: 6 mg/kg on day 1 then 3–12 mg/kg q24–72 h for 21 days
6. Vaginal	150 mg PO once stat
Cryptococcosis	400 mg PO/IV OD for 2–6 months **Meningitis** 400 mg on day 1 then 200–400 mg OD Continue until 10–12 weeks after spinal fluid is negative **Relapse of cryptococcal meningitis in HIV patients** 200 mg OD

Contd...

Contd...

Disorder	*Dose/Duration*
Dermatophyte Infection Tinea capitis	Continuous regimen: 6 mg/kg daily for 3 weeks can effectively treat tinea capitis Pulse: 8mg/kg/day -4-8 weeks
Tinea corporis and tinea cruris	150–300 mg once weekly X 2–4 weeks 50–100 mg po X 2–4 weeks
Tinea pedis and mannum	150 mg once weekly, administered for 2–6 weeks
Tinea Versicolor	Regimen 1: Fluconazole doses of 300 mg weekly for 1–4 weeks has shown high rates of mycological cure Regimen 2: 400 mg PO once
Onychomycosis	**Dermatophytic molds** Fluconazole 150–300 mg once weekly until the abnormal-appearing nail has grown out. The duration is 3–6 months(fingernails) and 9–12 months for toenail **Non-dermatophyte molds and *Candida* species** *Scopulariopsis brevicaulis*:150 mg daily for 12 weeks *Candida* onychomycosis: 50 mg daily or pulse therapy of 300 mg/week for 6-week for fingernails and 3 months for toenails **Children** Dose 5 mg/kg daily for 1 week (2 and 3 pulses for fingernails and toenails)
Sporotrichosis	400 mg PO OD for 6 months

The high oral bioavailability of fluconazole is an asset, but the narrow spectrum of action limits its use.

Drug Interaction

Increased levels of fluconazole: Amprenavir, protease inhibitors, paclitaxel.

Decreased levels of fluconazole: Barbiturates, rifampins

Increased levels of: Amiodarone, aprepitant, bosentan, budesonide, buspirone, ergotamine, carbamazepine, celecoxib, cyclopsorin, digoxin, statins, imatinib, metformin, sulfonylureas, methadone, mifepristone, phenytoin, quinidine, repaglinide, sildenafil, sirolimus, tacrolimus, theophylline, tolterodine, vinca alkaloids, warfarin.

Increased risk of hypotension: Calcium channel blockers

Increased QT prolongation: Cisapride, pimozide.

Increased hyperglycemia: Pioglitazone.

Increased central nervous system depression: Alfentanil, benzodiazepines, propoxyphene, buprenorphine, fentanyl.

Special Considerations

- Be careful about coadministration with drugs likely to cause QT prolongation and metabolized through CYP3A4
- Use with caution in liver dysfunction; renal dysfunction—may need to adjust fluconazole
- Use with caution in proarrhythmic conditions.

Side Effects

Fluconazole has shown a favorable adverse effects profile.

Common: Nausea, headache, rash, vomiting, abdominal pain, diarrhea, dyspepsia, aguesia, dizziness.

Rare: Hepatotoxicity, Stevens-Johnson syndrome, angioedema, seizures, leukopenia, agranulocytosis, toxic epidermal necrolysis, alopecia, neutropenia, thrombocytopenia, hypercholesterolemia, hypertriglyceridemia, hypokalemia.

Special Category

Pregnancy: Category C.

Male: No effect on androgen levels and that alteration of male reproduction is unlikely.

Lactation: Appears in breast milk. Avoid breastfeeding.

Liver: Safer than other antifungals.

Renal dosing: Safer than other antifungals.

Creatinine clearance 10–50 mL/min: administer 50% of usual dose.

Ketoconazole

Ketoconazole is an imidazole derivative first developed by Janssen Pharmaceutica in 1977 and approved by the FDA in 1981. It is the most widely used and most extensively studied azole antifungal agent.

Mechanism of Action

Like other azoles, ketoconazole selectively inhibits fungal cell cytochrome P-450 enzyme 14α-ademethylase, inhibiting the conversion of lanosterol to ergosterol required in fungal wall synthesis. It also results in increased permeability of fungal cell membranes. The net result is cessation of fungal cell division and growth. Ketoconazole can also inhibit the synthesis of thromboxane and adrenal steroids such as aldosterone, cortisol, and testosterone by inhibiting cytochrome P-450 enzymes.

Absorption and Distribution

Ketoconazole is well absorbed through the gastrointestinal tract. The mean peak plasma levels of ketoconazole reach approximately 3.5 mg/ml within 1–2 hours after oral administration of a single 200-mg dose when it is taken with a meal. It is mainly excreted through the bile into the intestinal tract.

Uses

Ketoconazole is a broad-spectrum synthetic imidazole antifungal agent that inhibits the growth of dermatophytes and yeasts including *Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis, M. audouini, M. gypseum, Epidermophyton floccosum, Candida albicans, C. tropicalis, Malassezia ovale*, and *M. furfur.*

Dose: PO 200–400 mg daily or bid, depending on site and severity of infection.

Drug Interaction

Ketoconazole is a potent inhibitor of CYP3A4. The plasma concentrations of drugs primarily metabolized by CYP3A4 (e.g. terfenadine, midazolam, cyclosporin, cisapride, quinidine, Atorvastatin, simvastatin, lovastatin) can be increased when they are coadministered with ketoconazole.

Likewise, the plasma concentrations of ketoconazole may be elevated when it is administered concomitantly with other inhibitors, potentiating its therapeutic and adverse effects.

Side Effects

Common

The most common adverse effects that have been reported following oral administration of ketoconazole include nausea, vomiting (in approximately 3% of patients), abdominal pain (1.2%), and pruritus (1.5%).

Rare

Less than 1% of patients may experience headache, dizziness, somnolence, fever, chills, photophobia, diarrhea, gynecomastia, impotence, thrombocytopenia, leukopenia, and hemolytic anemia.

More serious adverse effects, such as anaphylaxis, hypersensitivity reactions and hepatic toxicity, suicidal tendencies, and severe depression have been reported in rare cases and warrant special attention and close monitoring.

TERBINAFINE

Classification

Antifungal.

Category

Allylamine.

Mechanism of Action

It interferes with the enzymes involved in the manufacture of ergosterol, leading to an arrest in cell growth.

It is not clear whether the *in vitro* fungicidal or the *in vitro* fungistatic properties of this drug categories translate into similar properties *in vivo*.

Absorption and Distribution and Metabolism

Following oral administration, terbinafine is well absorbed (>70%) and the absolute bioavailability of terbinafine as a result of first-pass metabolism is approximately 50%. Single dose pharmacokinetic studies in patients with renal impairment (creatinine clearance <50 mL/min) or with pre-existing liver disease have shown that clearance may be reduced by about 50%.

Significant first-pass hepatic metabolism; CYP2C9, 1A2, 3A4, 2C8, 2C19 major isozymes; no active metabolites.

Excretion: Renal 70%; clearance decreased 50% in renal impairment or hepatic cirrhosis.

Pharmacokinetics in Skin

1. The delivery is by passive dermoepidermal diffusion, through ***sebum*** and through incorporation of drug from migrating basal keratinocytes.
2. Within 2 days of administering terbinafine 250 mg daily, the drug achieves a high level in the sebum.
3. After administration of terbinafine 250 mg daily for 12 days, drug concentrations above the MIC for most dermatophytes is present for 2–3 weeks after oral therapy is discontinued.

Pharmacokinetics Nail

1. It is detected in the distal end of the fingernail within 1 week of starting therapy.
2. When terbinafine 250 mg daily is administered for 6 or 12 weeks to treat onychomycosis, maximum nail levels of 0.52 and 1.01 μg/g respectively are detectable after 18 weeks of therapy.
3. After completion of 6 and 12 weeks of therapy, terbinafine is detected in the nail for 30 and 36 weeks, respectively. This makes it useful for onychomycosis.

Pharmacokinetics in Hair

1. Early detection in hair may be due to delivery of drug to hair via the sebum. The drug may become incorporated into hair by hair matrix cells.
2. Terbinafine 250 mg daily is administered for 14 days, the drug has been detected in hair for at least 50 days after the start of dosing.
3. Terbinafine may be more effective against tinea capitis caused by *endothrix* organisms (e.g. *Trichophyton tonsurans*) than against ectothrix infections (e.g. *Microsporum canis*), as the drug accumulates preferentially in the hair shaft.

Metabolism

$t^{1}/_{2}$—36 hrs.

Uses/Dosages (Table 2.10)

FDA: Onychomycosis: Dermatophyte, tinea capitis (*granule form* >4 years) Oropharyngeal candidiasis, esophageal candidiasis, blastomycosis, histoplasmosis, aspergillosis.
Some general principles that dictate its use are as follows.

1. US FDA labeling is only for *oral granule* formulation (for 6 weeks) in tinea capitis.
2. It is more useful for *Trichophyton* sp.

Table 2.10: Dosage regimens for Terbinafine

Disorder (FDA approved/ Unapproved)	*Dose /Duration*
Aspergillosis,	5–15 mg/kg/d PO for 3–5 months
Black piedra	250 mg for 6 weeks
Chromomycosis	500 mg PO OD for 8–12 months
DERMATOPHYTE INFECTION 1. Tinea capitis (oral granule is US FDA approved)	**Oral Granule** <25 kg, 125 mg daily; 25–35 kg, 187.5 mg daily; >35 kg, 250 mg daily **Tablet**: 10-20 kg: 62.5 mg; 21-40 kg: 125 mg; 41–50 kg, 250 mg
2. Tinea corporis and tinea cruris	250 mg daily for 4 weeks
3. Tinea pedis and mannum	250 mg daily for **2–6** weeks
4. Onychomycosis	250 mg daily for 6 and 12 weeks for fingernail and toenail onychomycosis,
Seborrheic dermatitis	250 mg -4 weeks

3. It is effective against *Aspergillus* sp, *S. brevicaulis, Fusarium* sp. S*cytalidium* sp. and *O. canadensis* infections.

Drug Interaction

Increased levels of: Aripiprazole, atomoxetine, caffeine, flecainide, propafenone, theophylline, tricyclic antidepressants
Decreased levels of: Codeine, Cyclosporin
Increased levels of terbinafine: Cimetidine,fluconazole
Decreased levels of terbinafine: Rifampins.

Special Considerations

- Not recommended in chronic, active liver disease
- Avoid if creatinine clearance ≤50 mL/min
- Monitor for depressive symptoms
- Look for taste smell dysfunction.

Side Effects

Terbinafine is considered a safe medication for the general population, as well as children, the elderly, transplant patients, diabetics, and HIV patients.
Common: Headache, gastrointestinal symptoms (diarrhea, dyspepsia, abdominal pain, nausea, and flatulence), dermatologic manifestations (rash, pruritus, urticaria), liver enzyme abnormalities greater than or equal to twice the upper limit of normal, taste disturbance and visual disturbance.

Rare: Erythema multiforme, toxic epidermal necrolysis, and Stevens–Johnson syndrome, idiosyncratic hepatobiliary dysfunction (within 4–6 weeks of treatment), precipitate or exacerbate cutaneous and systemic lupus erythematosus, depressive symptoms.

Monitoring

LFT, LFT.

Special Category

Pregnancy: Category B. This makes it the ***safest*** oral antifungal in current practice.
Male: No effect on androgen levels and that alteration of male reproduction is unlikely.
Lactation: Appears in breast milk. Avoid breastfeeding.
Pediatric
Liver: Liver cirrhosis. Terbinafine clearance was reduced by approximately 50%.
Renal dosing (serum creatinine >3.4 mg/dL, or creatinine clearance <50 mL/min), terbinafine clearance is decreased by about 50%.

NEWER ANTIFUNGAL AGENTS

1. Voriconazole

Voriconazole (VFEND; UK-109,495) is a triazole that is similar to fluconazole but has increased activity and an expanded spectrum.

Classification

Azole.

Absorption and Distribution

Oral bioavailability is nearly complete, and unlike itraconazole gastric acid is *not* necessary for absorption. The volume of distribution is high (4.6 L/kg), with extensive tissue distribution; metabolism is by hepatic CYPs, especially 2C19. Less than 2% of native drug but most of the inactive metabolites are secreted in the urine. The oral dose is not adjusted for azotemia or hemodialysis. Plasma elimination t ½ is 6 hours.

Genetic polymorphisms in CYP2C19 can cause up to a fourfold difference in drug exposure; ~20% of Asians are poor metabolizers compared to 2% of Caucasians and African Americans.

The intravenous formulation of voriconazole contains sulfobutyl ether b-cyclodextrin (SBECD), which is excreted by

the kidney. Accumulation of SBECD occurs with a creatinine clearance <50 mL/min; in that setting, oral voriconazole is preferred.

Metabolism

Uses

Voriconazole was approved for the treatment of serious fungal infection by the FDA in 2001.

Voriconazole is a broad-spectrum antifungal agent that has shown *in vitro* activity against ***Aspergillus*** spp. *(A. flavus, A. niger, A.terreus*, as well as itraconazole and amphotericin B resistant *A fumigatus*,), ***Candida*** spp (*C. glabrata, C. parapsilosis,C. tropicalis*, and fluconazole resistant *C. albicans* and *C. krusei*,), ***Scedosporium*** **spp, and** ***Fusarium*** **spp.**

Clinically, voriconazole has been used for serious fungal infections in patients refractory to amphotericin B or other azoles, such as esophageal candidiasis, candidemia, invasive.

1. Voriconazole is the ***treatment of choice*** of invasive aspergillosis.
2. Voriconazole is approved for use in esophageal candidiasis (including fluconazole-resistant species such as C. krusei)
3. Salvage therapy in patients with *P. boydii* and *Fusarium* infections.

Dosage

Treatment usually is initiated with 6 mg/kg every 12 hours for two doses, followed by 4 mg/kg every 12 hours, administered at 3 mg/kg/hour. As the patient improves, oral administration is continued at 200 mg every 12 hours. Patients failing to respond may be given 300 mg every 12 hours. Oral drug should be given either 1 hour before or 1 hour after meals.

Adults

Loading dose (First 24 hrs)

- **Weight > 40 kg:** 400 mg every 12 hr
- **Weight < 40 kg:** 200 mg every 12 hr.

Oral Maintenance Doses

- **Weight > 40 kg:** 200 mg every 12 hr
  - **If no response increase to:** 300 mg every 12 hr
- **Weight < 40 kg:** 100 mg every 12 hr
  - **If no response increase to:** 150 mg everyv 12 hr

Children

Dose: 200 mg every 12 hr
(No loading dose).

Aspergillosis

Voriconazole is used for invasive aspergillosis at 4 mg/kg intravenously every 12 hours or 100 to 200 mg orally every 12 hours. A loading dose of 6 mg/kg intravenously, given twice, 12 hours apart, is administered prior to the intravenous or oral regimen.

Drug Interaction

In decreasing rank order, voriconazole is metabolized by, and inhibits, CYP2C19, CYP2C9, and CYP3A4, as does its major metabolite, voriconazole N-oxide. Inhibitors or inducers of these enzymes may increase or decrease voriconazole plasma concentrations, respectively, while voriconazole may increase the plasma concentrations of other drugs metabolized by these enzymes.

Increase voriconazole metabolism: Rifampicin, rifabutin,, ritonavir, efavirenz and NNRTIs. When given with phenytoin, the voriconazole dose should be doubled.

Increase levels of other drugs: Cyclosporine, tacrolimus, Phenytoin, rifabutin, warfarin, and sirolimus. Omeprazole dose should be reduced by half if 40 mg or more per day is given.

Side Effects

Although the drug is generally well tolerated, hepatotoxicity has been reported and liver function should be monitored. Voriconazole can prolong the QTc interval, which can be significant in patients with other risk factors for torsades de pointes.

Approximately 30% of patients note transient visual changes (e.g., blurred vision, altered color perception, and photophobia) beginning about half an hour after administration and lasting for another half an hour. Activities that require keen vision should be avoided, but no sequelae occur. Uncommonly, confusion or transient visual hallucinations occur.

Patients receiving their first intravenous infusion have had anaphylactoid reactions requiring drug discontinuation. Rash occurs in 6% of patients.

Special Groups

Drug exposure is increased considerably in the elderly and in patients with mild or moderate hepatic insufficiency. Patients with hepatic cirrhosis should receive the same loading dose of voriconazole but half the maintenance dose.

Voriconazole is teratogenic in animals and should not be used in pregnancy (category D).

2. Posaconazole

Posaconazole is the newest triazole to be licensed in the USA.

Absorption and Distribution

Posaconazole is rapidly distributed to the tissues, resulting in high tissue levels but relatively low blood levels.

Dose

It is available only in a liquid oral formulation and is used at a dosage of 800 mg/d, divided into two or three doses. Absorption is improved when taken with meals high in fat.

Uses

Posaconazole is the *broadest spectrum* member of the azole family, with activity against most species of *Candida* and *Aspergillus*. It is the only azole with significant activity against the agents of zygomycosis and mucormycosis.

It is currently licensed for salvage therapy in *invasive aspergillosis*, as well as prophylaxis of fungal infections during induction chemotherapy for leukemia, and for allogeneic bone marrow transplant patients with graft-versus-host disease.

Posaconazole is a 40 mg/mL suspension, given with food. The dosage is 200 mg orally three times daily in patients over 13 years of age. For oropharyngeal candidiasis, it may be given as 100 mg orally twice daily (on the first day) and then 100 mg daily for 12 days. In cases refractory to fluconazole or itraconazole, the dose is increased to 400 mg orally twice daily. Duration of treatment varies according to patient response.

Side Effects

Visual changes have not been reported, but drug interactions with increased levels of CYP3A4 substrates such as tacrolimus and cyclosporine have been documented.

3. Echinocandins

Echinocandins are the newest class of antifungal agents to be developed. They are large cyclic peptides linked to a long-chain fatty acid. Caspofungin, micafungin, and anidulafungin are the only licensed agents in this category of antifungals, although other drugs are under active investigation. These agents are active against ***Candida*** and ***Aspergillus***, but *not* ***C. neoformans*** or the agents causing zygomycosis and mucormycosis.

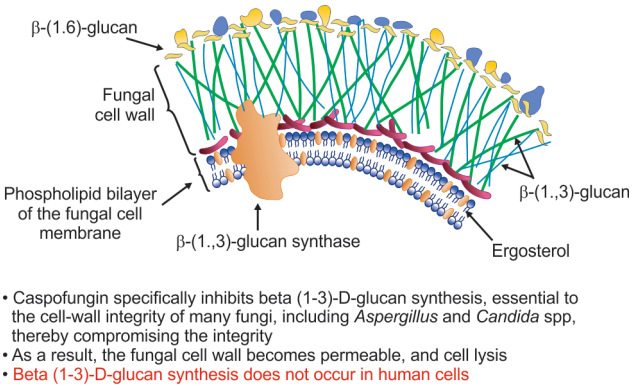


Fig. 2.4: Caspotungin: mechanism of action

Echinocandins exert their antifungal action through noncompetitive inhibition of the synthesis of 1,3-beta-glucans, an essential component of the fungal cell wall (Fig. 2.4).

Dose

The echinocandins are available only in intravenous formulations.

Caspofungin is administered as a single loading dose of 70 mg, followed by a daily dose of 50 mg. Caspofungin is water-soluble and highly protein-bound. The half-life is 9–11 hours, and the metabolites are excreted by the kidneys and gastrointestinal tract. Dosage adjustments are required only in the presence of severe hepatic insufficiency.

Micafungin displays similar properties with a half-life of 11–15 hours and is used at a dose of 150 mg/d for treatment of *Candida* esophagitis, 100 mg/d for treatment of candidemia, and 50 mg/d for prophylaxis of fungal infections.

Anidulafungin has a half-life of 24–48 hours. For esophageal candidiasis, it is administered intravenously at 100 mg on the first day and 50 mg/d thereafter for 14 days. For candidemia, a loading dose of 200 mg is recommended with 100 mg/d thereafter for at least 14 days after the last positive blood culture.

Clinical Use

Caspofungin is currently licensed for *disseminated and mucocutaneous Candida infections*, as well as for *empiric antifungal therapy during febrile neutropenia* and has largely replaced amphotericin B for the latter indication. Note that caspofungin is licensed for use in invasive aspergillosis only as salvage therapy in patients who have failed to respond to amphotericin B, and not as primary therapy.

Micafungin is licensed for mucocutaneous candidiasis, candidemia, and prophylaxis of *Candida* infections in bone marrow transplant patients.

Anidulafungin is approved for use in esophageal candidiasis and invasive candidiasis, including candidemia.

Caspofungin

Absorption and Distribution

The plasma concentrations of caspofungin decline in a polyphasic manner after iv infusions. Immediately after infusion a short a-phase is followed by b-phase with half-life of 9–11 hours, where plasma concentration decreases ten-fold. An additional g-phase, having longer half-life of 40–50 hours, also follows the b-phase. Caspofungin binds to plasma protein (albumin). It is slowly metabolized by hydrolysis and N-acetylation and hence there is little excretion or biotransformation within initial 30 hours of administration through feces and urine.

Dose

For candidemia and invasive aspergillosis:

- **Adult:** Loading dose of 70 mg followed by 50 mg iv daily in adult (<80 kg) or 70 mg daily iv in adult (>80 kg)
- **Children (3 months–17 years):** Loading dose is 70 mg/m^2 and maintenance dose is 50 mg/m^2 daily.
- **Neonates:** 25 mg/m^2 IV daily.

No dose adjustment is required for patients with mild hepatic impairment.

Uses

In vitro activity of caspofungin has been shown to be effective against most strains of *Aspergillus* (*A. fumigatus, A. flavus, A. terreus*) and *Candida* including nonalbicans (*C. albicans, C glabrata, C. guilliermondii, C. krusei, C. parapsilosis, C. tropicalis*). Activity against *C. guilliermondii, C. parapsilosis* and *A. flavus* has been reported to be variable.

1. Caspofungin is approved for patients with *invasive aspergillosis* who are failing or intolerant of drugs such as Amphotericin B or voriconazole and for *esophageal candidiasis.*
2. Caspofungin also is approved to treat persistently febrile neutropenic patients with suspected fungal infections.
3. It is also used to treat serious fungal infections refractory to or intolerant of, other therapy (e.g. amphotericin B, itraconazole).

Dosage

Caspofungin is administered intravenously once daily over 1 hour. In candidemia and salvage therapy of aspergillosis, the initial dose is 70 mg, followed by 50 mg daily. The dose may be increased to 70 mg daily in patients failing to respond. Esophageal candidiasis is treated with 50 mg daily.

Drug Interactions

- Tacrolimus: Caspofungin is known to reduce the circulatory levels of tacrolimus; hence, appropriate monitoring of tacrolimus blood concentration as well as dose adjustments are recommended in case of concomitant use.
- Caspofungin can be used safely with other antifungal drugs like Amphotericin B, itraconazole. Caspofungin given along with mycophenolate has not shown interactions.
- Drugs (e.g. carbamazepine, phenytoin, rifampin, dexamethasone), that induce hepatic enzymes may increase Caspofungin clearance. In such cases 70 mg IV should be considered as daily maintenance dose.

Side Effects

Caspofungin is well tolerated, with the exception of phlebitis at the infusion site. Histamine-like effects have occurred with rapid infusions. Other effects are comparable to those in patients receiving fluconazole.

Special Groups

Mild or moderate hepatic insufficiency increases the AUC by 55% and 76%, respectively. About 97% of serum drug is bound to albumin. Dose adjustment is unnecessary for renal insufficiency or hemodialysis.

3

CHAPTER

Antihistaminics

Kabir Sardana, Usha Ranganathan

INTRODUCTION

The antihistamines have been conventionally classified as first and second generation antihistaminics (Table 3.1). The first generation drugs are sedative but have a long safety record, while the newer drugs are probably more rigorously studied are non-sedative, thus can be "up dosed" in chronic urticaria. The drugs listed in Table 3.1 are according to the chemical classes. It is useful to know the chemical

Table 3.1: Functional classification of antihistamines

Chemical class	*First-generation agents*	*Second-generation agents*
Tricyclic dibenzoxepins	Doxepin	Epinastine
Ethanolamines	Carbinoxamine Clemastine Dimenhydrinate Diphenhydramine Doxylamine Phenyltoloxamine	
Ethylenediamines	Antazoline, pyrilamine, Tripelennamine HCl	
Alkylamines	Chlorpheniramine Dexchlorpheniramine	Acrivastine
Piperazines	Hydroxyzine HCl Cyclizine HCl Meclizine HCl	Cetirizine HCl Levocetrizine
Phenothiazines	Promethazine HCl	
Piperidines	Cyproheptadine HCl Azatadine Ketotifen	Bilastine Desloratadine Ebastine Fexofenadine Loratadine Mizolastine Olopatadine Rupatadine
Phthalazinones		Azelastine HCl

classes specially if a decision is made to administer drugs of different chemical classes, e.g. Loratidine (a piperidine) + hydroxyzine (a piperazine). This is a useful and practical aspect of urticaria management, which has been ratified by a major international guidelines group (Bernstein JA, et al.), even though some experts do not endorse this concept.

Classification

Dibenzoxepin Tricyclics

Doxepin, the only drug in this class, is marketed as a tricyclic antidepressant. It also is a remarkably potent H1 antagonist. Doxepin is much better tolerated by patients who have depression than by those who do not. Its use in urticaria emanates from its potent H1/H2 blocking activity. Its sedative effect is useful in psychogenic pruritus and atopic dermatitis.

Ethanolamines

These drugs possess significant antimuscarinic activity and have a pronounced tendency to induce sedation. About half of those treated with conventional doses experience somnolence. The incidence of GI side effects is low.

Alkylamines

These are among the most potent H1 antagonists. The drugs are less prone than some H1 antagonists to produce drowsiness and are more suitable agents for daytime use, but again, a significant proportion of patients do experience sedation. Side effects involving CNS stimulation are more common than with other groups.

First-generation Piperazines

Hydroxyzine is a long-acting compound that is used widely for skin allergies; its considerable CNS-depressant activity may contribute to its prominent antipruritic action. It is frequently combined with nonsedative antihistaminics.

Second-generation Piperazines

Cetirizine and levocetrizine are the only drugs in this class. They have minimal anticholinergic effects, negligible penetration into the brain but are associated with a somewhat higher incidence of drowsiness than the other second-generation H1 antagonists.

First-generation Piperidines

Cyproheptadine uniquely has both antihistamine and antiserotonin activity. Cyproheptadine and phenindamine

cause drowsiness and also have significant anticholinergic effects.

Second-generation Piperidines

Most of the commonly used non-sedative drugs are in this class and include *loratadine, desloratadine, and fexofenadine*. These agents are highly selective for H1 receptors, lack significant anticholinergic actions, and penetrate poorly into the CNS. Taken together, these properties appear to account for the low incidence of side effects of piperidine antihistamines.

An important note here is that there are drugs in these class, which are not licensed for use in USA or Europe as oral preparations, but are remarkably effective in urticaria and other pruritic disorders. *Ebastine* in doses of 10/20 mg is effective and safe in urticaria and with the latter dose is more effective than other antihistamines (Sastre J). *Olopatidine*, which has been extensively used in Japan, is again more effective than levocetrizine 5 mg (Takeo T) and promethazine, (Kamei H) while like fexofenadine does not cause cognitive or psychomotor impairment (Kamei H). Its action on substance P, bradykinin and its effect of cytokines makes it a useful drug for atopic dermatitis, a condition where most antihistamines are not effective (Ito T, Yamanaka K). Thus, it is important to understand that drugs approved in countries apart from USA or Europe are effective and this is of relevance in countries like India, where both ebastine and olopatadine are available.

HISTAMINE AND ITS RECEPTORS

Histamine is a ubiquitous bioamine that has a variety of physiological functions. First synthesized in 1907, it was recognized as a natural substance in 1910 by Sir Henry Dale and colleagues, who found it in ergot. It is now known that histamine acts via **four** receptors, namely, the histamine H_1 receptor (H_1R), the histamine H_2 receptor (H_2R), the histamine H_3 receptor (H_3R), and the histamine H_4(H_4R) (Box 3.1). Drugs that target the H_1R have been in use since Bovet and Staub showed that the actions of histamine could be blocked by synthetic compounds. This led to the development of the first clinical antihistamine, 2339 RP/phenbenzamine/Antergan. The term "antihistamine" is largely used to describe compounds that block the actions of the H_1R, and predates knowledge of the existence of the other receptors. Thus, the itch in both urticaria and allergic rhinitis is effectively blocked by H_1R antihistamines and can be properly considered to be histamine mediated. Conversely, these drugs are not effective against the itch in either atopic dermatitis or psoriasis; therefore, it has been concluded that

Box 3.1: Types of histamine receptors their role in itching

Receptor	*Role in itch*	*Other uses*
H_1	Mediates itch in urticaria, allergic rhinitis, and allergic conjunctivitis	The treatment of hives, overall allergic symptoms in rhinitis and conjunctivitis, insomnia
H_2	No known role	The treatment of duodenal and gastric ulcers, gastroesophageal reflux disease
H_3	Local antagonist induces itch in preclinical models	Potential indications include excessive daytime sleepiness and attention-deficit hyperactivity disorder
H_4	Antagonist inhibits itch in several preclinical models	Potential indications include atopic dermatitis, psoriasis asthma, and rheumatoid arthritis

the itch in these conditions is not histamine mediated. Since only H_1R and H_2R antagonists are available for clinical use in diseases where they fail to control symptoms, the conclusion that histamine is not involved may not be accurate. The H_4R has been found to be effective in atopic dermatitis and will be discussed later.

Through the H_1 receptor, histamine *increases* antigen-presenting cell capacity, increases release of histamine and other mediators from mast cells and basophils, up-regulates cellular adhesion molecule expression and chemotaxis of eosinophils and neutrophils, up-regulates Th1 priming and Th1 cell proliferation and interferon-γ production, and down-regulates humoral immunity (Fig. 3.1). Most importantly histamine-induced itch is mediated via neuronal activation and has been confirmed by the identification of histamine sensitive C-fibers that transmit the itch response to the spinal cord (Schmelz et al. 1997). These C-fibers can also respond to other nociceptive compounds such as capsaicin and bradykinin in addition to histamine, but do not respond to mechanical stimuli (Schmelz et al. 2003).

Through the H_2 receptor, it suppresses inflammatory and effector functions. Through the presynaptic H_3 receptor on histaminergic and nonhistaminergic neurons in the central and peripheral nervous systems, it is probably involved in control of neurogenic inflammation through mast cell feedback loops.

Through the H_4 receptor, it facilitates some proinflammatory activities (Fig. 3.2). Antagonists to the H_4R have also been shown to inhibit itch induced by other pruritogens such as substance P or H_3R antagonists (Yamaura et al. 2009).

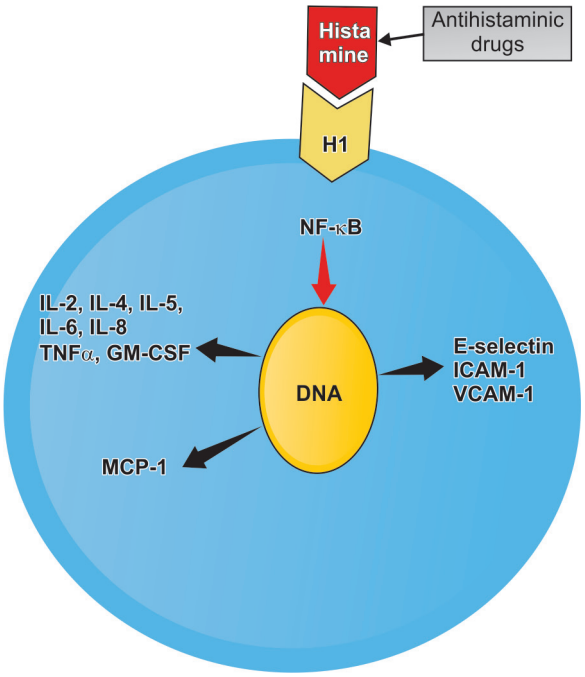


Fig. 3.1: Anti-inflammatory effects of the antihistamines. H_1 receptor inactivity due to interaction with the antihistamine prevents activation of cytoplasmic transcription factors such as Nuclear Factor kB (NF-kB), required for the expression of cytokines, chemokines and adhesion molecules

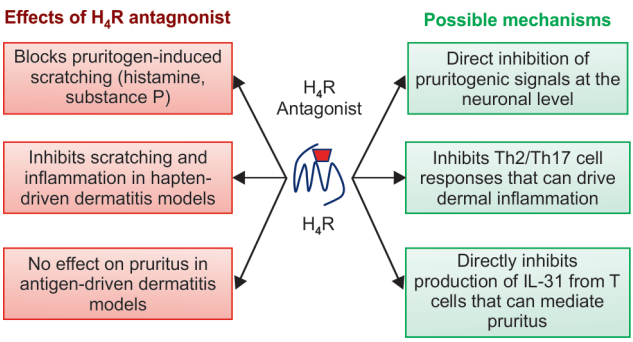


Fig. 3.2: Role of H_4 receptors in the skin and atopic dermatitis

The H_4R also appears to mediate itch driven by allergic responses to haptens. The H_4R antagonist, JNJ 7777120, was able to inhibit the scratching and the inflammation in this model (Cowden et al. 2010). The role of the H_4R in histamine-induced itch in humans and in numerous preclinical models of itch, including some thought to mimic atopic dermatitis, suggests that the H_4R may play a major role in controlling histamine effects in this disease. In addition, there is other evidence for a role of the receptor in mediating the inflammation in atopic dermatitis. The H_4R help in

proliferation of keratinocytes in atopic dermatitis (Glatzer et al. 2013). The receptor also mediates the production of IL-31 by Th2 T cells from atopic dermatitis patients. IL-31 is thought to play a role in mediating both pruritus and inflammation in atopic dermatitis (Sonkoly et al. 2006). In preclinical models, H_4R antagonists reduce the itch of atopic dermatitis.

MECHANISM OF ACTION OF ANTIHISTAMINES

Most of the antihistamines appear to possess anti-inflammatory actions, including the reduction of pre- and neoformed mediators, reductions in cytokine, chemokine and adhesion molecule expression—and thus reduction in inflammatory cell recruitment and inflammation (Walsh GM). These actions may be attributed mainly to two types of mechanisms:

a. Stabilization of the *mast cell and basophil membranes*, and inhibition of the transmembrane flux of calcium and intracellular cAMP (Simons, 2004). The effect is independent of the H_1 receptor, and is considered to be due to drug-membrane ionic interactions (Church MK). This is seen particularly *in vitro* and at experimental concentrations, and induces a decrease in preformed (histamine, tryptase) and neoformed mediators (prostaglandins, leukotrienes) of the mast cells and basophils.
b. Inhibition of *cytoplasmic transcription* factors, such as nuclear factor kappa-B (NF-kB), which activates with H_1 activation and migrates towards the nucleus where it interacts with nuclear DNA-stimulating the transcription of cytokines, chemokines and adhesion molecules, and the generation of nitric oxide (NO) [Leurs R] (Figure 3.1). The inhibition of this phenomenon is linked to interaction of the antihistamine with the H_1 receptor, and is therefore to a certain extent a class effect.

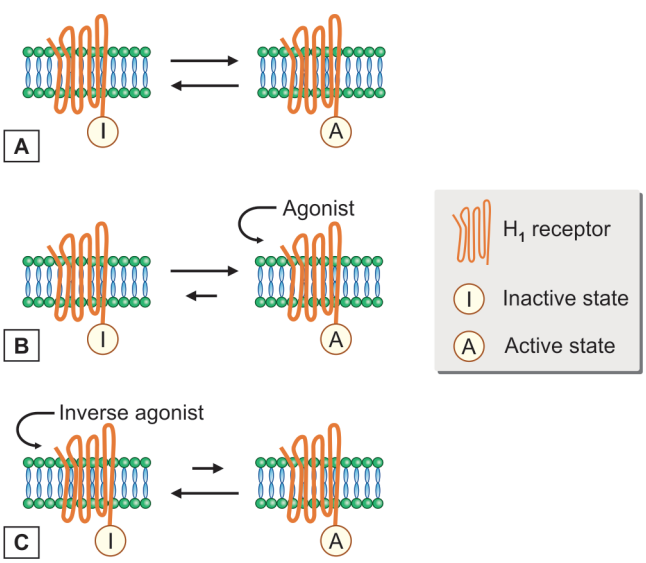
At low concentrations, antihistamines are inverse agonists of histamine at H_1 receptor sites (Simons 2004). The H_1 receptors belong to the superfamily of G protein coupled receptors (GPCRs), and are encoded for by chromosome 3 (Fig. 3.3A to C). The cloning and expression of these elements by recombinant cells has allowed advances in the study of these receptors that have changed our understanding of how they work. We now know that these receptors exhibit spontaneous activation of their intracellular messengers, requiring no binding by an agonist at surface level. This spontaneous activity is referred to as *constitutive activity* and is attributable to the dynamic balance between two conformations of the receptor-activated (characterized by the

production of intracellular second messengers) and inactive (no such intracellular signaling).

This situation has led to reclassification of the drugs that act upon these receptors, according to which of the two receptor conformations are stabilized as a result of their action. In this sense, if the ligand stabilizes the active receptor conformation, making it the predominant form, then the drug is referred to as an **agonist**, while if the inactive conformation is stabilized the drug is said to be a **inverse agonist**. In this way, histamine is an agonist, while the antihistamines are presently considered to be inverse agonists instead of antagonists as previously believed (Figs 3.3A to C). Antagonism results in decreased vascular permeability, reduction of pruritus and relaxation of smooth muscle in the respiratory and gastrointestinal tracts (Simons, 2004).

The other actions include interference with mediator release from mast cells by inhibiting either calcium ion influx across mast cell and basophil plasma membrane or intracellular calcium ion release within the cells, inhibition of the late-phase allergic reaction by acting on leukotrienes or prostaglandins, or by producing an anti–platelet activating factor (PAF) effect.

Almost all the new antihistamines have been subjected to *in vitro* and *in vivo* studies in this sense, though there are obvious differences among the different molecules. Thus, cetirizine and levocetirizine have shown antiallergic and anti-inflammatory action even at therapeutic concentrations [Walsh]—though in cutaneous processes such as CU, the true relevance of these anti-inflammatory properties in terms of



Figs 3.3A to C: The three different states in which the histamine receptor can be found. Case A: balance between the two conformations; B: predominance of the activated conformation via the action of an agonist; and C: predominance of the inactivated conformation via the action of an inverse agonist

the final therapeutic effect is not known (the importance in any case is much less than that of the glucocorticoids).

The anti-inflammatory action of these drugs is the rationale of their "updosing" as they inhibit a number of mediators besides histamine (leucotrienes, prostaglandins, thromboxanes, platelet-activation factor, bradykinin, tachykinins, cytokines, chemokines and adhesion molecules) which are involved in systemic allergic inflammation important in the pathogenesis of urticaria. Some of the antiallergic effects may be explained by mast-cell stabilizing properties. These non-histamine-mediated effects express a different dose-response curve than the antihistamine response for which these drugs were originally developed and on which the regular dose was defined.

OVERVIEW OF PHARMACOKINETICS AND PHARMACODYNAMICS

Curiously, most of the pharmacological aspects of the new antihistamines are difficult to document, and remain largely unpublished—the only source for consultation being the summaries presented by the drug manufacturers at scientific congresses and meetings, or the famous "data on file" that are commonly found in the publicity literature of the different drug products.

Absorption

The absorption of second-generation H_1 receptor antagonists ranges from fairly good to excellent. The peak plasma concentration (C_{max}) is generally reached in 1 to 3 hours; **cetirizine and olopatadine** are the most *rapid* (0.5 hours) and azelastine the most delayed (5 hours). Administration with *food* decreases the total absorption of astemizole by 60%, *increases* the absorption of *ebastine and loratadine*, and appears to have no effect on the total absorption of acrivastine, azelastine and cetirizine (Table 3.2).

P glycoprotein which are located in the cell membrane, and function as active transport systems for ceratin molecules. In some cases, these transport systems act as important elements in drug absorption or clearance, while in other cases they allow tissue detoxification, depending on whether they are located in intestinal cell membranes (in the former case) or at the blood-brain barrier (in the latter case). Some antihistamines behave as substrates for these active transport systems, such as fexofenadine. This has two implications, one is that it helps in tissue detoxification. Secondly for drugs like fexofenadine, variations in bioavailability have been documented when co-administration with foods that serve as substrates for P, such as grapefruit or bitter orange juice.

Table 3.2: Pharmacokinetics of commonly used antihistamines

Drugs /dose	*T_{max} (h)*	*Terminal half-life*	*Onset/ Duration of action (h)*	*Vd (L/kg)*	*F (%)*	*Elimination*	*First-pass metabolism*	*Hepatic metabolism*	*E(R/F)*
Chlorpheniramine (4 mg TDS/SR 12 mg BD)	2.8 ± 0.8	27.9 ± 8.7	3/24 h	3	72	Na	Na	Na	Na
Hydroxyzine (25–50 mg TDS)	2.1±0.4	20.1 ± 4	2/24	13–19	Na	Na	Na	Na	Na
Doxepin (25–50 mg TDS)	2	13	Na	9–33	75–80	75–80	Na	Na	Na
Ketotifen (1–2 mg /12h)	3.6 ± 1.6	18.3 ± .6.7	Na	56	75	Renal	Yes	Yes	59/0
Cetirizine (10 mg /24h)	1 ± 0.5	6.5–10	1–1.5/≥24	0.5	>95	Renal	Limited	<40%	60/10
Levocetirizine (5 mg /24 h)	0.8 ± 0.5	7 ± 1.5	1/≥24	0.4	>95	Renal	Limited	<15%	86/0
Loratadine (10 mg/24 h)	1.2 ± 0.3	7.8 ± 4.2	2/24	120	>95	Renal	Extensive	CYP3A4 CYP2D6	0/0
Desloratadine (5 mg/24 h)	1–3	27	2/≥24	100	87	Renal	Moderate	CYP3A4	0/0
Fexofenadine (120–180 mg/24 h)	2.6	14.4	2/24	5.6	60–70	Bile	Negligible	<8%	12/80
Ebastine (10–20 mg /24 h)	2.6–5.7	10.3–19.3	2/≥24	>100	95	Renal	Moderate	Yes	97/0
Mizolastine (10 mg /24 h)	1.5	12.9	1/24	1.4	95	Renal	Limited	Negligible	0.5/0
Rupatadine (10 mg /24 h)	0.7–1.0	6	2/24	143	95	Bile	Limited	Yes	0/0
Olopatadine (5 mg/24 h)	0.5	7.1–.4	0.25/12 h	Na	Na	Na	Na	Na	Na

Abbreviations: F, Fraction absorbed orally; % Excretion without change (Renal/Fecal); Vd, volume of distribution

Distribution

Although most of the second-generation H_1 antagonists are highly bound to plasma proteins (>90%,), this property does not appear to confer a relative advantage or disadvantage in the selection of a drug for therapy.

In general, these compounds are relatively lipophobic and have a small volume of distribution (Vd) ranging from 0.41 to 14.5 L/kg. The H_1 receptors are widely distributed throughout the body, and are found in smooth muscle, endothelial and epithelial cells, eosinophils or neurons. A sufficiently low distribution volume means that the intracellular receptors remain unaffected. Taking into account that the H_1 receptors are easily accessible from the bloodstream, the H_1 antihistamines do *not* require extensive tissue distribution for correct action.

The advantages of a *low distribution volume* then is that they have *minimum dose-dependent toxicity*, minimum interindividual variations in therapeutic effect, a reduction in undesired drug interactions, and the absence of drug accumulation within the heart or liver. Thus as seen in Table 3.2, *cetrizine, levocetirizine, fexofenadine and mizolastine* which have the lowest Vd that makes them preferred drugs. P-gp plays a role in the transport of certain substances into the CNS including antihistamine thus the higher affinity of the second generation drugs for P-gp as compared to the first-generation drugs accounts for the less CNS side effects of these agents.

Metabolism and Elimination

The activity and/or toxicity of the second generation H_1 receptor antagonists are affected by the following elimination processes: (i) metabolism of the parent drug and active metabolites by the liver; (ii) clearance of the active drug and/or metabolites via the bile duct or kidney.

At the manufacturers' recommended dosages, the serum concentrations of most of the second-generation H_1 receptor antagonists are extremely low because of a high first-pass effect, resulting in metabolism and elimination of the parent compound (*cetirizine, levocetirizine, fexofenadine and mizolastine* are exceptions) (Table 3.2).

Almost all second-generation H_1 receptor antagonists, with *the exception* of fexofenadine (<8%), cetrizine, levocetirizine (<15%), desloratadine and mizolastine, have been reported to be metabolized by the **liver** to active metabolites. In some cases, the metabolites are 2 to 4 times more potent than the parent drug (ebastine and loratadine). In other instances, the active metabolite plays a significant role because the half-life and duration of action exceeds that of the parent compound (terfenadine and fexofenadine; ebastine and carebastine). If liver function is impaired, either by disease or by inhibition of the cytochrome P450 (CYP) 3A system, the

Table 3.3: A summary of the use of antihistaminics in special populations

Drugs	*Pregnancy*	*Lactation*	*Children*	*Elderly*	*Liver*	*Kidney*	*Sun*
Hydroxyzine	Used in 2nd/3rd trimester FDA -C	X	Tablet > 6 years Syrup >2.5 years	Elderly	Dose adjustment is required	√	√
Cyproheptadine	B	X	>6 years	Safe	Caution	Caution	Caution
Dexchlorpheniramine	1st/2nd trimester	X	Tab >6 years Syrup >2 m	Caution	Caution	Caution (40% renal excretion)	√
Chlorpheniramine	1st/2nd trimester FDA-B	X		Caution	Dose adjustment is required	√	√
Cetirizine	2nd/3rd trimester FDA-B	X	Tablet > 6 years Sol >2 years	√	Caution	Caution (60% excretion)	√
Levocetirizine	X	X	Tablet/Syrup >6 years	√	Caution	Caution (85% renal elimination)	√
Ebastine	X	X	>12 years	√	Caution	Caution	
Loratadine	2nd/3rd trimester FDA-B	AAP classifies it as safe	Tablet >12 years Syrup >2 years	√	Caution	Caution	√
Fexofenadine	X FDA-C	AAP considers it safe	Tablet >6 years Syrup >6 months	√	√	Caution ? largely in feces	√

Table 3.4: Doses of common non-sedating antihistaminics

	Adults	*Children/ T1/2*	*Elderly/ T1/2*	*Renal impair-ment/ T1/2*	*Hepatic impair-ment/ T1/2*
Cetrizine	5–10 mg	6–11 years: 5–10 mg /↑ 0.5–5 years: 2.5–5 mg /↓	5–10 mg /↑	5 mg/↑	5 mg/↑
Fexofen-adine	180 mg	6–11 years: 30 mg twice daily/No change	180 mg	60 mg / No change	180 mg/ No change
Loratadine	10 mg	>6 years: 10 mg 2–5 years: 5 mg/↓	↑	10 mg every 48 hours /No change	10 mg every 48 hours/↑
Deslorat-adine	5 mg	>12 years: 5 mg /No change	5mg/↑	5 mg every 48 hours/↑	5 mg every 48 hours

parent compounds may accumulate and/or show toxicity; this occurs with astemizole, ebastine and terfenadine (Tables 3.2 and 3.3).

For most second-generation antihistamines, only 10–20% of the administered dose is eliminated through the kidneys—the *exceptions* being cetirizine (60%) and levocetirizine (85% renal elimination). Caution and/or dosage adjustment is required in patients with renal impairment (Tables 3.3 and 3.4). The first-generation antihistamines like hydroxyzine and chlorpheniramine and second-generation agents like mizolastine are relatively safe in renal impairment.

A summary of doses of 2nd generation antihistamines in various scenarios is detailed in Table 3.4 as a ready reckoner.

Action on Target Organ

In the wheal and erythema test, objective assessment is made of the intensity of the antihistaminic effect by measuring the inhibition of wheal and erythema formation induced by histamine injection into the skin, after oral dosing of the study drug. Practically, all the antihistamines have been studied with this model, inducing significant inhibition of wheal and erythema formation versus placebo, in an intense and constant manner over time.

In one of the most interesting comparative studies made with this model [Grant 1995], showed that **epinastine** to be the *fastest* acting antihistamine according to this model, while **cetirizine** was the most *potent*. The maximum effect on wheal and erythema formation is reached 5–8 hours after oral dosing, unlike the maximum plasma concentration, which is

reached much earlier. In previous cross-over studies (Grant JA 1999, Simons FE 1990) comparing the suppression of skin papule and erythema formation induced by intradermal histamine injection following a single antihistamine dose, cetirizine was found to offer the most significant effect versus other antihistamines—the order of the inhibitory effect being as follows: **cetirizine > epinastine > terfenadine > ebastine > fexofenadine > loratadine > placebo.** In another study, mizolastine showed efficacy similar to that of terfenadine, with significantly less efficacy than cetirizine, and greater efficacy than loratadine (Rosenzwey P). Likewise, a single-dose comparative study found **levocetirizine** to be the most potent of the antihistamines examined, followed by ebastine, fexofenadine and mizolastine, with similar potencies—though ebastine took four hours in eliciting an effect different from that of placebo. Loratadine was again seen to be the least potent molecule. Outside the context of these studies, the antihistamine with the longest skin histamine reaction-suppressing effect (4–6 weeks) was found to be astemizole. Studies have shown olopatadine to be as or more effective than levocetirizine (Takeo et al.), thus the order of potency is **cetirizine/levocetirizine/oloptatidine > epinastine > terfenadine/mizolastine > ebastine > fexofenadine > loratadine > placebo.**

Fexofenadine and cetirizine maintain inhibitory action due to proportionality between the tissue and plasma drug concentrations strongly in favor of skin concentration, while other antihistamines such as loratadine or ebastine maintain a less potent though still considerable effect thanks to the suggested persistence in skin of their active metabolites.

The 'receptor occupation model' arises from the paradoxical observation that antihistamines with a high *in vitro* affinity (Ki) for the receptor and a very long plasma half-life (t1/2) induce less potent and briefer wheal and erythema inhibition than other antihistamines with a priori poorer pharmacokinetic performance. This model proposes receptor occupation (expressed as a percentage) determined 4 and 24 hours after oral administration as pharmacodynamic assessment criterion (Gillard M). The greater receptor occupation, the better the pharmacodynamic behavior of the antihistamine. Such receptor occupation is calculated on the basis of receptor affinity (Ki), the concentration of free antihistamine at the action site (which is close to the free plasma concentration of the antihistamine [C4h and C24h]), and the maximum percentage of binding sites for the antihistamine. Wheal and flare suppression correlates better with tissue H_1-antihistamine concentrations than with plasma H_1-antihistamine concentrations, and correlates best with H_1 receptor occupancy by free unbound drug, where such data are available.

Tachyphylaxis

Second-generation H1 receptor antagonists do not appear to demonstrate a loss of efficacy over time; this was shown in studies lasting 4–12 weeks with terfenadine, loratadine and mizolastine.

A overview of important salient findings of the use of antihistamines is given in the Box 3.2.

OTHER THERAPEUTIC AGENTS WITH ANTIHISTAMINIC ACTIVITY

Tricyclic Antidepressants

Tricyclic antidepressants bind both H1 and H2 receptors. The tricyclic antidepressant most commonly used in dermatology is doxepin. Oral **doxepin** has been used successfully in the treatment of refractory chronic idiopathic urticaria, physical urticaria, and pruritus associated with systemic conditions. Sedation is the most common adverse effect with both the oral form and the topical form, which is absorbed percutaneously, although some patients may develop tolerance with regular use. Oral doxepin has been classified by the FDA as a pregnancy category C drug; topical doxepin is classified as a pregnancy category B drug.

Mirtazapine is a tetracyclic antidepressant with H1 antihistamine properties. Several case series have reported its successful use in reducing pruritus attributable to uremia, cholestasis, and various cancers, but it has not been well studied as a primary dermatologic agent. Patients taking mirtazapine require monitoring of blood counts and lipid levels for hyperlipidemia and the rare but serious adverse effects of agranulocytosis and neutropenia. Mirtazapine carries an FDA black box warning of possible increased risk of suicide, particularly during initiation of therapy, and its concomitant use with monoamine oxidase inhibitors is contraindicated. It is classified as an FDA pregnancy category C drug, and its safety during breastfeeding and in children has not been established.

Ketotifen

Ketotifen, a benzocycloheptathiophene derivative, is an H1-type antihistamine with additional mast cell– and basophil-stabilizing properties.

Ketotifen has been used successfully in the treatment of chronic idiopathic urticaria, physical urticaria, and urticaria pigmentosa. Results of one early open-label trial suggested that ketotifen not only reduces the pruritus and pain of neurofibromatosis but also slows the growth of neurofibromas. The drug has been discussed in the following section.

Box 3.2: Important facts about antihistamine use in clinical practice

Onset of action	Average of 3 hours
Peak action	About 8 hours
Metabolism	In liver *except* cetrizine, levocetirizine, desloratadine, fexofenadine
Plasma protein binding	Least is of fexofenadine
Potency	Cetirizine and olopatadine > epinastine > Mizolastine=terfenadine > ebastine > fexofenadine > loratadine > placebo
Maximum action on skin	Fexofenadine/Cetrizine
Receptor occupation and affinity	Levocetirizine > Fexofenadine > Desloratadine Receptor occupation after 4 h (%) (71/95/90) Receptor occupation after 24 h (%) (43/12/57) Maximum wheal inhibition after 4 h (%) (34/100/100) Wheal inhibition after 24 h (%) (32/15/60) Maximum erythema inhibition after 4 h (%) (19/83/89) Erythema inhibition after 24 h (%) (41/35/74)
Residual effect	Longest with desloratadine and loratadine (7 h)
Vd	Lowest with cetrizine, levocetirizine, mizolastine, fexofenadine
P glycoprotein metabolism	Cetrizine, ebastine, epinastine, fexofenadine, loratadine and desloratadine
CNS effects	Lowest with fexofenadine (receptor occupancy 0%) and cetrizine (30%)
Safe drug in liver dysfunction	Chlorpheniramine, mizolastine, levocetirizine, fexofenadine
Relatively safe drug in kidney dysfunction	Chlorpheniramine, hydroxyzine, doxepin, mizolastine
Relatively safe drug in pregnancy*	FDA B: Chlorpheniramine, loratadine, cetrizine (2nd/3rd trimester), levocetarizine FDA C: Hydroxyzine, ketotifen, desloratadine, fexofenadine, olopatadine
Safe drugs in children	Cetrizine, fexofenadine, ebastine and desloratadine (6 to 11 months of age) Levocetirizine, and loratadine (12–36 months) Hydroxyzine (>6 months), dexchlorpheniramine (>1 year), diphenhydramine, promethazine, cyproheptadine and ketotifen (>2 years)
FAA approved for pilots	Desloratidine, fexofenadine, loratidine

* The AH-1G are considered the drugs of choice, since they offer greater cumulative experience. It is advisable to avoid AH-1G in the third trimester of pregnancy, due to the risk of neonatal seizures. (I Jáuregui et al.)

Lactation: Avoid first generation antihistaminics as they have an anticholinergic effect that reduces milk secretion

ANTIHISTAMINES IN URTICARIA

Urticaria is probably the most common indication and urticaria (of any type) is more common than previously thought and may be increasing in prevalence. At any single time, 0.5%–1.0% of the population are suffering from CSU with a lifetime prevalence of 15%–20%. Our concern is chronic spontaneous urticaria (CSU) where there is a spontaneous appearance of wheals, angioedema, or both >6 weeks due to known or unknown causes. Up to 40% of CSU cases may be autoimmune-associated, where autoantibody-dependent activation of mast cells is believed to be the most common pathogenesis (Fig 3.4).

A host of other autoimmune causes include, antibody directed against FCERI (60%), IgG anti-lgE (10%), histamine-releasing autoantibodies directed against high-affinity IgE receptor (30–40%) or, less frequently, IgE itself (5–10%). A subgroup of patients with IgE have allergen autoantibodies against thyroperoxidase (Fig. 3.5).

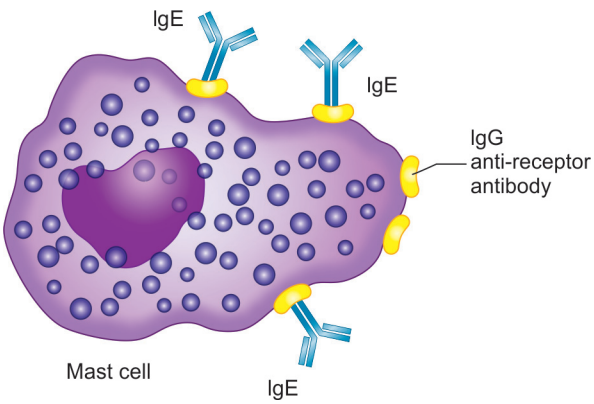


Fig. 3.4: Mechanism of urticaria following the action of IgE on mast cells

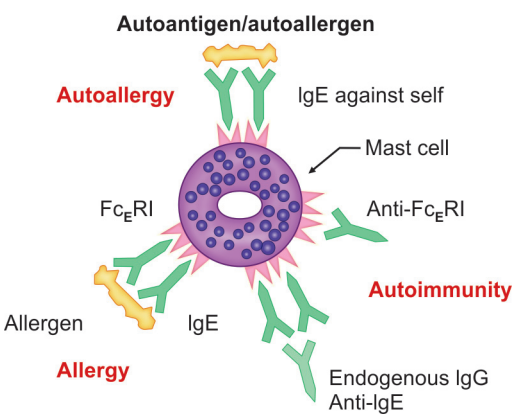


Fig. 3.5: Various autoimmune mechanisms of urticaria

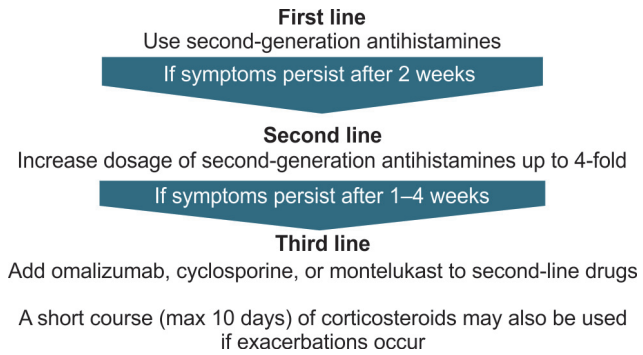


Fig. 3.6: Approach to treatment of urticaria (Zuberbier T et al.)

The prevalent view is of updosing of 2nd generation antihistamines (Zuberbier T, Fig. 3.6) which is diametrically opposite with the prevailing practice where 1st generation and 2nd generation antihistamine are often combined. In realistic terms, the latter is needed as most patients have disturbance of the sleep cycle and a recent guideline (Box 3.3) has included this view (Bernstein JA). In allergic rhinitis where sleep induction is not a priority the concept of updosing has a rationale, without the use of concomitant sedating drug.

First-line treatment options in both the guidelines are non-sedating second-generation antihistamines. The efficacy of standard doses of second-generation antihistamines in CU has been well documented in randomized, placebo-controlled clinical trials of 4–6 weeks' duration (Table 3.1). The present data suggests that a higher proportion of patients responded with clearance of symptoms with cetirizine (52%) than with fexofenadine (4%) after 1 month

Box 3.3: Approach to treatment of urticaria (Bernstein JA et al.)

Step 1
- Monotherapy with second-generation antihistamine
- Avoidance of triggers (e.g. NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present

Step 2
One or more of the following:
- Dose advancement of second-generation antihistamine used in step 1
- Add another second-generation antihistamine
- Add H_2-antagonist
- Add LTRA
- Add first-generation antihistamine to be taken at bedtime

Step 3
- Dose advacement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated

Step 4
- Add an alternative agent
- Anti-inflammatory agent (e.g. dapsone, hydroxychloroquine, sulfasalazine)
- Biologic agent (omalizumab)

of treatment (Handa et al.). A rapid effects was seen with loratadine (10 mg) as compared to cetirizine (10 mg). Also a higher proportion of patients were symptom-free (63%) with loratadine as compared with cetirizine (45%) (Guera et al.). An overview of pharmacology reveal some clear choices for the practicing physician (Tables 3.2 and 3.3). If **potency** is the concern cetrizine, olopatadine and levocetirizine are clear winners. If **rapidity** of action is the need again olopatadine is the ideal drug. Loratadine and desloratadine have the **longest** action, while the **safest** drug with almost no sedation is fexofenadine.

Sedating, first-generation antihistamines have been used as adjunctive therapy for patients whose symptoms have not been completely controlled with non-sedating second-generation antihistamines, particularly when symptoms interfere with sleep at night (Kozel MMA).

Comparative Effectiveness

It must be understood that the efficacy of the second-generation H_1 receptor antagonists is not well correlated with serum concentrations. In addition, the ultimate duration of H_1 receptor antagonism cannot be predicted solely from the metabolic half-lives of these drugs, since tissue distribution, production of active metabolites and poor reversibility of receptor binding contribute to observed clinical effects and are often independent of measured serum concentrations. In addition, the relationship between the pharmacokinetics and observed effects of H_1 antagonists can be linear or nonlinear, making it difficult to derive a comprehensive model for the duration of effect.

We have already detailed previously the order of the inhibitory effect on histamine as follows: **cetirizine > epinastine > terfenadine > ebastine > fexofenadine > loratadine > placebo.**

Head-to-Head Trials Comparing 2nd generation antihistamines

1. Levocetirizine >desloratadine (Potter PC):
   Levocetirizine led to a significantly greater decrease in pruritus severity and CSU composite scores as compared to desloratadine.
2. Cetirizine > desloratadine (Purohit A):
   The activity of cetirizine was found to be superior to desloratadine
3. Cetirizine > fexofenadine (Handa A):
   The symptom-free period of cetirizine (51.9%) was more than fexofenadine (4.4%). The partial improvement with cetirizine (36.5%) was less than fexofenadine (42.2%) and there were less cases of no improvement with cetirizine (11.5%) as compared to fexofenadine (53.3%).

A recent Cochrane review found that cetirizine at 10 mg once daily in the short-term and in the intermediate-term was found to be effective in completely suppressing urticaria. Evidence is limited for desloratadine given at 5 mg once daily in the intermediate-term and at 20 mg in the short-term. Levocetirizine at 5 mg in the intermediate but not short-term was effective for complete suppression. Levocetirizine 20 mg was effective in the short-term, but 10 mg was not (Sharma M).

Combination Therapy with Antihistamines

In cases of urticaria unresponsive to a single drug four options can be tried:

1. Dose advancement of second-generation antihistamine
2. Add another second-generation antihistamine
3. Add H2 antagonist
4. Add LTRA
5. Add first-generation antihistamine to be taken at bedtime.

Updosing: The concept of updosing, wherein doses up to 4X the approved dose are given, has been studied with *levocetirizine, desloratadine, fexofenadine, cetrizine and rupatadine.* Potential anti-inflammatory effects of second-generation anti-histamines may provide an explanation for the effects of antihistamines at high doses. It is important to understand two concepts here, one which *drugs* have been tested in this concept and what is the *dose* studied. The latter is important as often fexofenadine is given in a dose of 240 mg a day by clinicians which actually is of little use as is evidenced by the data that follows:

a. Levocetirizine and desloratadine up to 4 times conventional doses in difficult-to-treat urticaria was studied and it was found that updosing from **5 mg** (levocetirizine/desloratadine) to **10 mg** of levocetirizine and **20 mg o**f desloratadine helped in relieving symptoms in a larger number of patients. Of the 28 patients *nonresponsive* to 20 mg desloratadine, 7 became symptom-free with **20 mg** levocetirizine. Thus, Staevska M et al. showed that updosing is a valid intervention and levocetrizine is better than desloratadine. But it must be remembered that updosing is a off label use, and interestingly a paradoxical decrease in somnolence over time was noted in patients treated with levocetirizine.
b. **Fexofenadine (Nelson HS):** This drug was compared with a placebo and was found to reduce pruritus and number of wheals scores over a 4-week treatment period. Greater reductions was noted in urticaria symptoms in the 60-mg fexofenadine group than in the 20-mg group, while ***similar*** reductions were observed with 60, 120, and 240 mg. Thus

probably the 180 mg dose recommended is sufficient for urticaria and this does not need to be updosed.

One of the biggest issue with updosing is that it is off label and no package insert states this dosing. Thus, it is difficult to convince patients to take, say levocetirizine 4 times a day. Thus, the recommendation of Bernstein JA et al. seems more practical (Box 3.3).

Adding another 2nd generation Antihistamine: This is a practical guideline. There are other molecules in this class that are effective in urticaria, which include ebastine and olopatadine. The former has metabolites, that are more potent than ebastine. Olopatadine 5 mg BD has been found to be more effective than levocetirizine.

Adding an H2 blocker: Clinical studies have demonstrated additional benefits by combining an H1-antihistamine with an H2-antihistamine compared with H1-antihistamine monotherapy. Analysis of the effects of H1-and H2-antihistamines shows that combinations of agents with common liver metabolism exhibit greater efficacy than those with distinct metabolic pathways. Thus, cimetidine 300 mg/4 day significantly (P <0.05) increased mean plasma concentrations of loratadine 10 mg/day but did *not* affect the mean plasma concentrations of a 10-mg dose of cetirizine, which is excreted through the kidneys (Simons et al.). These findings suggest that the potential benefit of combination therapy is likely *pharmacokinetic* in nature, because of an increase in the area under the plasma drug concentration-time curve and subsequent increased effects at the H1-receptor, rather than being a genuine synergistic effect. (Jauregui et al.).

***Adding a 1st Generation Antihistamine*:** A lot of dermatologists use a combination of a sedating and non-sedating H1-antihistamines or combining two different non-sedating H1-antihistamines, which may result in increased plasma concentrations of the H1-antagonist. The logic of this approach is that unlike allergic rhinitis, in urticaria or pruritus the symptoms are intense in the evenings with sleep deprivation. Thus, it makes sense to combine a sedative H1 antihistamine at night, coupled with a low-sedation antihistamine in the morning.

Though it has been shown that the first generation antihistamines are unsafe due to reduction in rapid eye movement sleep and impairment of cognitive function and should not be prescribed for the indication of chronic urticaria and angioedema (Church MK), this is mainly based on data obtained from healthy subjects and patients with hay fever and is not necessarily applicable to patients with severe chronic urticaria suffering profound sleep deprivation (Simons FE. 2004). A recent guidelines has focused on this concept (Bernstein JA) (Box 3.3). Thus it makes clinical

practical sense in cases of failure of a 2nd generation antihistamine to add hydroxyzine 25 mg, oral doxepin 25–75 mg, promethazine 25 mg each night.

Making Sense of Guidelines

There have been two guidelines published with significant differences in their approach. Interestingly one of them has included, sensibly, the use of first generation antihistamines in combination with second generation antihistamines as a second step, which is a useful tool in alleviating the itching at night which affects the sleep quality of patients in urticaria.

One guideline (Zuberbier T, Fig. 3.6) does not mention the combination with a first generation antihistamine, and the second line recommendation is updosing to four times the approved dose. But a more clinically practical approach (Box 3.3) was elucidated by Bernstein JA, where they have recognized the need to use other antihistamines in combination, wherein a sedative drug may be of more use in patients of urticaria. Thus the second step entails, adding another second-generation antihistamine, a H 2 antagonist, LTRA or ***importantly*** **a** first-generation antihistamine to be taken at bedtime.

A step-care approach has been developed for the management of CU (Box 3.3). H1 antagonists are effective in the majority of patients with CU but might not achieve complete control in all patients. Second-generation antihistamines are safe and effective therapies in patients with CU and are considered first-line agents (step 1). For patients not responding to monotherapy with a second-generation antihistamine at US Food and Drug Administration–approved doses, several treatment options can be used (step 2).

Higher doses of second-generation antihistamines might provide more efficacy, but data are limited and conflicting for certain agents. Addition of H2 antagonists or leukotriene receptor antagonists can be considered for patients with CU with unsatisfactory responses to second-generation antihistamine monotherapy. First-generation antihistamines can also be considered in patients who do not achieve control of their condition with higher-dose second-generation antihistamines.

Treatment with hydroxyzine or doxepin can be considered in patients whose symptoms remain poorly controlled with dose advancement of second-generation antihistamines and/or addition of 1 of more of the following: H2 antihistamines, first-generation H1 antihistamines at bedtime, and/or antileukotrienes (step 3). Systemic corticosteroids are frequently used for patients with refractory CU, but no controlled studies have demonstrated efficacy. In some patients short-term use (e.g. 1–3 weeks' duration) might be required to gain control of their disease until other therapies

can achieve control. Because of the risk of adverse effects with systemic corticosteroids, long-term use for treatment of patients with CU should be avoided as much as possible. Patients with CU whose symptoms are not adequately controlled on maximal antihistamine therapy (e.g. step 3 care) might be considered to have refractory CU. A number of alternative therapies have been studied for the treatment of CU; these therapies merit consideration for patients with refractory CU (step 4) like Omalizumab, FDA.

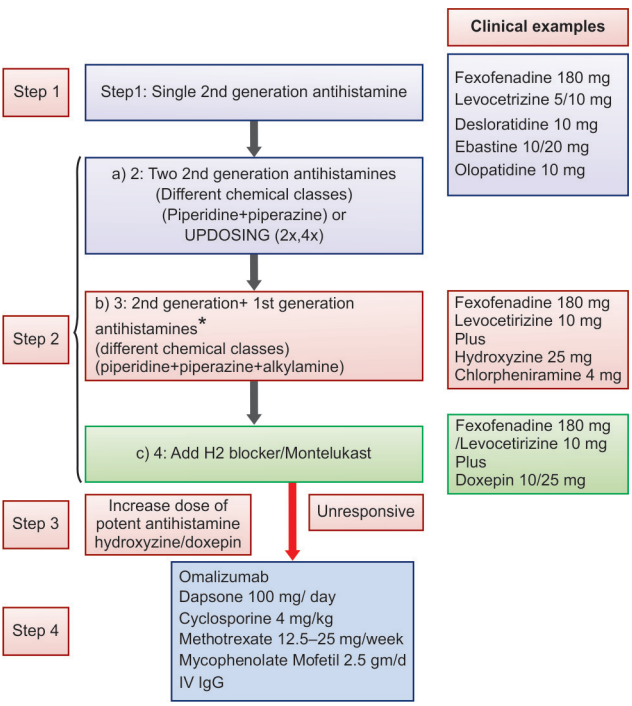
Based on the above guidelines a composite approach is detailed below for the treatment of chronic spontaneous idiopathic urticaria (Flowchart 3.1).

ANTIHISTAMINES IN PRURITUS

Pruritus is a multifactorial condition mediated by multiple primary and secondary mediators and thus antihistamines are not the most effective mode of intervention.

Histamine has emerged as the best-characterized human pruritogen. It is now accepted that certain direct stimuli such as scratching or painful stimuli such as a pin prick, heat, or cold can inhibit the itch response and histamine sensitive C-fibers can transmit the itch response to the spinal cord (Schmelz et al. 1997). The transmission of histamine-induced pruritic signals appears to require TRPV1. Transmission of pruritus to the brain also appears to be mediated via

Flowchart 3.1: A composite clinically useful protocol for treating urticaria



*as urticaria can affect the sleep cycle adding a 1st generation drug is a valid concept

specific spinothalamic tract neurons and these neurons are polymodal and can respond to mechanical stimuli, which may explain why scratching can reduce the histamine-induced activity of these neurons and may provide a mechanism for the inhibition of itch by other stimuli (Thurmond et al.). In the brain, peripheral itch stimuli evoke a complex pattern of regional neuronal activation that contains elements of sensation, emotion, and motivation.

Thus, there is a *central* and *peripheral* component to itch. Amongst the mediators that play a role in the itch pathway are NGF, substance P and PAR-2. Of the conventional 2nd generation antihistamine, two drug that inhibits both these is *olopatadine* (Takeo T, Yoshizaki A) and *cetrizine* (Liu JY). As pruritus has both a central and a peripheral component, most clinicians use either the sedative 1st generation antihistamines, like *hydroxyzine* or *doxepin* in pruritus apart from olopatadin and cetrzine. Interestingly mirtazapine which is an noradrenergic and specific serotonergic antidepressant with an antihistamine action is useful in refractory cases of pruritus (Davis MP, Hundley JL).

ANTIHISTAMINES IN ATOPIC DERMATITIS

Despite the successes in treating itch associated with urticaria, allergic rhinitis, and allergic conjunctivitis, not all pruritic diseases are controlled by H1R antihistamines. One such disease is atopic dermatitis, which is an inflammatory skin disease where pruritus is one of the most common and characteristic symptoms. Despite evidence of elevated histamine levels and increased numbers of mast cells in pruritic skin of atopic dermatitis patients, there is little clinical evidence that H1R antihistamines have any effect. Several clinical studies have been conducted, and reviews of these studies suggest that any effect seen is due to sedation by blocking the central H1R or off-target anti-inflammatory or skin barrier effects.

Atopic dermatitis can be divided into 2 immunologic phenotypes according to the disease condition. The TH2 immune phenotype is predominantly involved in acute exacerbation of the disease, while TH1 immunity plays a pathogenic role in the chronic stage.

Effects of fexofenadine, certizine, olopatadine, and loratadine on cytokine secretion*

T cells	Cytokine	Fexofen-adine	Cetirizine	Olopat-adine	Lorat-adine
TH2	IL-4/IL-5	+		+	+
TH1	IL-12/ IFN-y	+	+	-	-

*TH1 indicates type 1 helper T cell; TH2 type 2 helper T cell; IL, interleukin; IFN, interferon

Fexofenadine had effects on TH2 and TH1 responses, whereas *cetirizine* affected the *chronic* but not the acute stage. Conversely, *olopatadine* and *loratadine* affected the acute but

not the chronic stage. Overall, the findings suggest that these antihistamines, may have immunomodulatory properties, as demonstrated by the downregulation of mRNA and inhibition of IFN- γ and IL-5 in isolated T cells. Therefore in addition to demonstrating, the modulatory impact of antihistamines on cytokine responses, findings suggest that antihistamines have distinct immunologic effects that may allow the choice of treatment to be directed by atopic dermatitis signs and symptoms (Ashenager MS).

Another cytokine that mediates itching in AD is IL-31. Recently, interleukin (IL)-31 was found to play a role in pruritus and skin barrier function in AD. Moreover, serum and tissue IL-31 levels in patients with AD were increased compared with levels in control subjects, and IL-31 levels correlated with both disease activity and severity of AD. Olopatadine may affect local skin lesions by reducing pruritus via decreasing tissue levels of IL-31.

The role of the H4R in histamine induced itch in humans and in numerous preclinical models of itch, including some thought to mimic atopic dermatitis, suggests that the H4R may play a major role in controlling histamine effects in this disease (Yamaura K). In addition, there is other evidence for a role of the receptor in mediating the inflammation in atopic dermatitis.

The H4R is expressed on keratinocytes, fibroblasts, and inflammatory dendritic epidermal cells that are associated with atopic dermatitis (Baumer et al. 2008; Glatzer et al. 2013). Proliferation of keratinocytes from atopic dermatitis has been shown to be increased upon activation of the H4R (Glatzer et al. 2013). The receptor also mediates the production of IL-31 by Th2 T cells from atopic dermatitis patients (Gutzmer et al. 2009). IL-31 is thought to play a role in mediating both pruritus and inflammation in atopic dermatitis (Sonkoly et al. 2006).

In preclinical models, H4R antagonists reduce the production of inflammatory cytokines and the infiltration of inflammatory cells (Ohsawa and Hirasawa 2012). For example, in the mouse fluorescein isothiocyanate-induced dermatitis model, treatment with the H4R antagonist, JNJ 7777120, reduced the tissue accumulation of eosinophils and mast cells (Cowden et al. 2010). Furthermore, reductions in tissue levels IL-4, IL-6, IL-1 β, and TNF were observed (Cowden et al. 2010). Interestingly, as discussed above, the H4R appears to play a stronger role in models driven by ***haptens*** instead of proteins. The difference between hapten and protein models may suggest a relationship to intrinsic versus extrinsic atopic dermatitis. *Intrinsic* atopic dermatitis is characterized by **normal** barrier function and **low IgE** levels compared to *extrinsic* atopic dermatitis where there is **elevated** IgE levels and **impaired** barrier function. It has been speculated that extrinsic atopic dermatitis is driven by

protein antigens whereas in intrinsic atopic dermatitis the antigens are not proteins (Tokura 2010). Thus probably H4R antagonist, JNJ 7777120 may play a role in intrinsic AD.

Ohsawa Y et al. 2014 found that the co-administration of an H1R antagonist and H4R antagonist had potent inhibitory effects that were equal to those of steroids in a chronic allergic dermatitis mouse model, and JNJ 39758979 exhibited anti-pruritic effects in moderate AD patients.

OTHER USES

Antihistamines have been used in allergic rhinitis, asthma and mosquito bites. In mosquito bites ebastine, cetirizine, and levocetirizine decreasing bite pruritus by 60–70%.

ANTIHISTAMINE DRUGS

As a detailed overview has been given previously, in this section, we will detail the properties of each drug.

The guidelines of drug usage and special population data is sourced from US FDA and BNF (British National Formulary)/Martindale Textbook of Pharmacology.

Second Generation Non-sedating Antihistamines

1. Cetirizine (Piperazine)

Classification

It is a low-sedating, long-acting H1-receptor antagonist that is a metabolite of hydroxyzine. At physiological pH, cetirizine exists almost exclusively in zwitterionic form, accounting for a very low volume of distribution (0.5 L/kg,) but skin concentrations of cetirizine have been shown to be relatively high. This property accounts for a low affinity for lean tissues such as myocardium, with a resulting low potential for cardiac effects. Its varied actions are given in Box 3.4.

Absorption and Distribution Metabolism

Cetirizine is rapidly absorbed after oral administration. Peak serum levels are reached within 1 hour. Food does not affect the amount absorbed but might decrease the absorption rate.

Box 3.4: Inhibitory effects on inflammatory cells, cytokines, chemokines and adhesion molecules

In vitro	*In vivo/ex vivo*
Adhesion eosinophils	Recruit. eosinophils-skin
Chemotaxis eosinophils and neutrophils	Recruit. eosinophils-bronchiole
Chemotaxis T lymphocytes and monocytes IL-8, MCP-1/ RANTES NF-κB19	Inhibition ICAM-1 in nasal secretion

Protein binding averages 93%. After a 10 mg dose, 70% of the drug is excreted unchanged in the urine within 72 hours and 10% is excreted in feces.

Onset and Duration: Onset is within 1 hour; duration is 24 hours.
T½. (Adults) 7–10 hours; (children) 6–7 hours; (elderly/renal insufficiency) 18–21 hours.

Uses/Dosages

Urticaria: Adults 10 mg/day; Children: 2–5 years:2.5–5 mg/day; >6 years :adult dose.

Geriatric Dosage: Reducing dosage in geriatric patients might be necessary because of a 50% increase in cetirizine's half-life and a 40% decrease in clearance.

Systemic Dysfunction: In patients with Clcr of 11–31 mL/min, those on hemodialysis, and in hepatically impaired patients, give 5 mg/day.

Drug Interaction

Caution is needed when cetirizine is combined with anticholinergic agents, alcohol, or other CNS depressants. Because most of cetirizine is eliminated renally, cytochrome P450 interactions are not likely. It seems appropriate to monitor patients for increased sedation or other CNS-related side effects when administering theophylline concomitantly with cetirizine.

Special Considerations

Clinically important drug interactions have not been found with cetirizine and azithromycin, pseudoephedrine, ketoconazole, or erythromycin.

Cetirizine does not cause the prolongation of the QT interval seen with some nonsedating antihistamines.

There is increase in sedation/driving impairment with alcohol (ethanol).

Side Effects

The most frequent side effects are sedation, headache, dry mouth, fatigue, and nausea.

A recent review has detailed the side effects in 2034 patients. The notable side effects were drowsiness/somnolence (13.7%), headache (2%), Fatigue (5.9%), Dry mouth (5%), Pharyngitis (2%), Dizziness (29%) and gastrointestinal distress (2%).

Special Category

Kidney disease: Creatinine clearance <31 mL/min: reduce dose to 5 mg/d. Do not use if <6 years old.

Liver disease: Reduce dose to 5 mg/d. Do not use if <6 years old.

Elderly: None.

Pediatric: 6–11 months

Pregnancy: Category B.

Lactation: Appears in breast milk. Avoid breastfeeding.

Summary

Cetirizine, is still the *most potent* antihistamine and as has been discussed, is the ideal drug for CIU. With the influx of a new generation of antihistamines, its use has been curtailed by dermatologists, probably as the industry does not frontic it any longer.

2. Levocetirizine (Piperazine)

Classification

It is the R-enantiomer of cetirizine and is used similarly, as the hydrochloride, for the symptomatic relief of allergic conditions including rhinitis and chronic urticaria.

Absorption and Distribution

Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9 h after dosing. Steady state is achieved after two days.

Elimination: The plasma half-life in adults is 7.9 ± 1.9 hours. The major route of excretion of levocetirizine and metabolites is via **urine,** accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Binding studies revealed that levocetirizine has high affinity for human H1-receptors and has an affinity 2-fold higher than that of cetirizine. Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.

Uses/Dosage

The dose in urticaria is 5 mg once daily. US licensed product information suggests that the dose should be given in the evening, and that a dose of 2.5 mg may be adequate in some patients. Maximum duration 1 year. Note please updosing is a off label indication.

Children: In the **UK**, children (2 to 6 years) 2.5 mg daily in 2 divided doses. > **6 years**: 5 mg daily.

In the **USA**, however, levocetirizine hydrochloride is not recommended for children under 6 years of age. In those

aged 6 to 11 years, a dose of 2.5 mg once daily in the evening may be given, and the adult dose of 5 mg daily only given to children aged 12 years and older.

i. Children aged 6–12 years: The daily recommended dose is 5 mg (10 mL of solution).
ii. Children aged 2–6 years: The daily recommended dose is 2.5 mg to be administered in 2 intakes of 1.25 mg (2.5 mL of solution twice daily).

Even if some clinical data are available in children aged 6 months to 12 years, these data are *not* sufficient to support the administration of levocetirizine to infants and toddlers aged *less than 2 years*).

Kidney

Dosing adjustments for patients with impaired renal function		
Group	*Creatimine clearance (mL/min)*	*Dosage and frequency*
Normal	≥80	1 tablet once daily
Mild	50–79	1 tablet once daily
Moderate	30–49	1 tablet once every 2 days
Severe	<30	1 tablet once every 3 days
End-stage renal disease–Patients undergoing dialysis	<10	Contraindicated

Drug Interaction

In vitro data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes.

Side Effects

In therapeutic studies in women and men aged 15–66 years, 14.7% of the patients in the levocetirizine 5 mg group had at least one adverse drug reaction, compared to 11.3% in the placebo group. Ninety-five percent of these adverse drug reactions were mild to moderate. In therapeutic trials with levocetirizine, dropout rate for adverse drug reaction under levocetirizine 5 mg represented 0.7% of the patients, of the same magnitude of what was observed under placebo (0.8%). In clinical therapeutic trials, adverse events reported at rates of 1% or greater under levocetirizine 5 mg compared to placebo recipients were as follows:

Headache (levocetirizine 8.4% vs. placebo 9.9%), somnolence (6.3% vs. 1.6%), dry mouth (2.8% vs. 1.3%), fatigue (2.6% vs. 1.0%), rhinitis (2.2% vs. 1.8%), pharyngitis (1.9% vs. 2.6%), asthenia (1.3% vs. 1.8%), abdominal pain (1.3% vs. 1.8%), migraine (1.1% vs. 0.8 %). Slightly sedating adverse reactions

such as somnolence, fatigue, and asthenia were thus altogether more common (10.2%) than after placebo (4.4%).

Special Groups

Pregnancy: Category B

Lactation: Levocetirizine is expected to be excreted in breast milk. Therefore use during breastfeeding is *not* recommended and should only be considered if the expected benefit to the mother is greater than any theoretical risk to the child.

Kidney Failure

CC 50–79 mL/minute: 5 mg once daily in the UK; 2.5 mg once daily in the USA.

CC 30–49 mL/minute: 5 mg every other day in the UK; 2.5 mg every other day in the USA.

CC 10–29 mL/minute: 5 mg once every 3 days in the UK; 2.5 mg once every 3 or 4 days in the USA.

CC less than 10 mL/minute and patients undergoing dialysis: contraindicated in both the UK and USA.

Hepatic

Impairment is unlikely to affect the clearance of levocetirizine.

Geriatrics

Clinical trials with levocetirizine have included patients up to the age of 66 years. Elderly patients are more likely to have an age-related decrease in renal function which may necessitate an adjustment of the dose.

Summary

Though this drug is now widely used in CIU, two important features of this drug must be appreciated. Firstly, it is sedative in some patient and though it is less potent that desloratadine, in cases where sedation is an issue, this drug should not be given. Secondly, its use in children from 6 to 12 months is not cleared from US FDA and European FDA. Though remarkably safe there are recent reports of lung damage and FDE in patients on levocetirizine (Gupta LK, Endo S).

BIBLIOGRAPHY

1. Endo S, Yamamoto Y, Minami Y, Okumura S, Sasaki T, Ohsaki Y. Histamine H1 antagonist levocetirizine as a potential cause of lung injury. Respirol Case Rep. 2015;3(2):64-7.
2. Gupta LK, Agarwal N, Khare AK, Mittal A. Fixed drug eruption to levocetirizine and cetirizine. Indian J Dermatol. 2014;59(4):411-3.

3. Ebastine

Piperidine

It is a piperidine derivative, is a non-sedating antihistamine with a long duration of action. Active form is the metabolite carebastine. It does not have significant sedative or antimuscarinic actions.

Absorption and Distribution

It is absorbed rapidly after oral administration and undergoes extensive metabolism to its active metabolite, carebastine. It is highly bound to plasma proteins (> 95%) and has extensive distribution throughout the body. Metabolism of ebastine is principally via cytochrome P450 (CYP) enzymes. Urinary excretion accounts for 66% of the elimination. The terminal elimination half life of carebastine is generally 16 to 25 h.

Uses

It is indicated for the treatment of symptoms of chronic idiopathic urticaria and allergic rhinitis. It is also used with a decongestant such as pseudoephedrine hydrochloride.

Dosage

Ten to twenty mg once daily. It can be administered with or without food and similar levels of anti-allergic activity is achieved.

In controlled clinical trials in adult and adolescent patients with allergic rhinitis, ebastine 10 mg once-daily improved symptoms to a significantly greater extent than placebo and to a **similar** extent as loratadine 10 mg and cetirizine 10 mg (both once-daily), while ebastine 20 mg proved to be **more effective** than these two comparator antihistamines.

It is also useful for *cold urticaria, dermographic urticaria, atopic asthma, mosquito bite*s and (in combination with pseudoephedrine) for common cold.

Drug Interaction

Concomitant use of ketoconazole, itraconazole, clarithromycin or erythromycin may increase plasma levels of ebastine and cause QTc interval prolongation.

Special Considerations

Pregnancy: Category B

Elderly: Generally, there are no clinically relevant differences in the pharmacokinetics of ebastine/carebastine between young adults and elderly patients. Hence, dose modifications are not necessary in elderly patients.

Hepatic and renal impairment: Dose modifications are not necessary in patients with renal or mild to moderate hepatic impairment. The maximum recommended dose for patients with severe hepatic impairment is 10 mg once daily.

Side Effects

Common: Headache, drowsiness, dryness of the mouth.

Rare: Less than 1% incidence—abdominal pain, dyspepsia, epistaxis, rhinitis, sinusitis, nausea and vomiting.

Monitoring

At the recommended doses of 10 and 20 mg daily, ebastine has no clinically relevant effect on the QTc interval.

Co-administration of ebastine with ketoconazole or erythromycin led to small increases in QTc interval of up to around 10 ms above that seen with ketoconazole or erythromycin alone.

At therapeutic doses, ebastine is not sedative and has no clinically relevant effect on cognitive or psychomotor performance, including driving ability.

Children

Dosage in children:

- 6–11 years old: 5 mg once daily
- 2–5 years old: 2.5 mg once daily.

Summary

Ebastine is a once-daily, non-sedating, selective, long-acting, second-generation antihistamine. Though, it is as effective as other second-generation antihistamines, such as cetirizine and loratadine, I use it when the former drugs fail. In fact as this drug is a piperidine in cases where levocetirizine fails it is a great choice. This concurs with the guidelines of Bernstein JA et al. Where a use of another second generation antihistamine is a valid intervention. Even with ebastine 20 mg/day skilled performance does not appear to be impaired. Furthermore, ebastine 5–10 and 2.5 mg, appears to be efficient and can be used safely in children 6–11 and 2–5 years of age, respectively.

BIBLIOGRAPHY

1. Bernstein JA, Lang DM, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133(5):1270-7.
2. Sastre J1. Ebastine in allergic rhinitis and chronic idiopathic urticaria. Allergy. 2008;63 Suppl 89:1-20.

3. Van Cauwenberge P1, De Belder T, Sys L. A review of the second-generation antihistamine ebastine for the treatment of allergic disorders. Expert Opin Pharmacother. 2004;5(8):1807-13.

4. Fexofenadine

Classification (Piperadine)

Fexofenadine is a histamine H1-receptor antagonist that is a metabolite of terfenadine.

It has myriad actions (Box 3.5) apart from its effect on histamine.

Absorption and Distribution

Onset is rapid; peak serum levels occur at 2.6 hours. Food decreases oral absorption. It is 60–70% plasma protein bound and excreted unchanged in urine and feces. Its half-life is about 14 hours in normal renal function and increases to about 19 hours in severe renal impairment.

It undergoes minimal biotransformation in the body. It has been shown to be a substrate for both P-glycoprotein (P-gp), a membrane-bound efflux transporter that inhibits absorption and promotes excretion of drugs.

Grapefruit, orange or apple juice may increase the drugs bioavailability by inhibiting the activity of P-gp thus reducing the rate of efflux from the small intestine. A similar effect is seen with ketoconazole and erythromycin while rifampicin upregulate intestinal P-gp, and decreases the plasma concentration.

Dosage

CIU: 180 mg

The recommended dose of fexofenadine hydrochloride to adults and children 12 years and older is 180 mg once daily.

In Renal Impairment: 60 mg OD.

Special Considerations

Fexofenadine has an excellent safety profile. It does not cause prolongation of the QT interval seen with other non-sedating antihistamines.

Box 3.5: Mode of action of fexofenadine

In vitro inhibition	*In vivo inhibition*
Chemotaxis cosinophils	Inhibition ICAM-1 in nasal secretion
Adherence eosinophils	
Generation of superoxide	
IL-6, IL-8, TNF-α, GM-CSF	

Drug Interactions

- *Decrease fexofenadine levels*
  - Antacids, grapefruit juice, rifampicin
- *Increase fexofenadine levels*
  - Erythromycin, ketoconazole, verapamil.

Side Effects

The side effects seen in a study in 679 patients were; drowsiness/somnolence (1.3%), headache(10.6%), fatigue (1.3%), pharyngitis (3.2%), dizziness(2%) gastrointestinal distress (1.3%) and dysmennorhea in 1.5%.

Special Populations

Kidney disease: Reduce initial dose to 60 mg/d.

Liver disease: None.

Elderly: None.

Pediatric: See above. Safety and efficacy have not been established in children <12 years.

Pregnancy: Category C.

Lactation: No data available. Best to avoid.

Summary

Fexofenadine has some singular advantages, including its lack of sedation and safety in hepatic failure cases. But it is *inferior* to cetrizine and levocetirizine in urticaria (Handa S). So where sedation with these drugs is a issue fexofenadine is the preferred drugs. In cases of resistant CSU (chronic spontaneous urticaria) fexofenadine is not effective (Magen E). As mentioned in the previous section, updosing beyond 180 mg is of no added use, as studies had shown that beyond 120 mg no advantage was noted (Nelson HS).

BIBLIOGRAPHY

1. Handa S, Dogra S, Kumar B. Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. J Dermatolog Treat. 2004;15(1):55-7.
2. Magen E, Mishal J, Zeldin Y, Schlesinger M. Antihistamines do not inhibit the wheal induced by the intradermal injection of autologous serum in resistant chronic idiopathic urticaria. Allergy Asthma Proc. 2012;33(6):531-7.
3. Nelson HS, et al. Ann Allergy Asthma Immunol. 2000;84(5):517-22.

5. Loratidine (Piperidine)

Classification

Second generation antihistaminics.

Category

Loratadine, a piperidine derivative related to azatadine, is a long-acting, non-sedating antihistamine with no significant antimuscarinic activity.

Mechanism of Action

Antagonizes histamine effects on GI tract, respiratory tract, blood vessels.

Absorption and Distribution

The drug is rapidly absorbed and the bioavailability and peak serum levels are increased by about 50% in the elderly (66–78 years) or when taken with food. It is 97% bound to plasma proteins and extensively metabolized to an active metabolite, descarboethoxyloratadine. Approximately 80% of a dose is excreted equally in urine and feces as metabolites after 10 days. The half-lives in healthy adults are 8.4 hours (range 3–20) for loratadine.

Uses

Dosage

Allergic rhinitis or urticaria : 10 mg/day on an empty stomach.
Hepatic impairment: 10 mg every *other* day.
Pediatric dosage: PO (<2 years) safety and efficacy not established:

- (2–6 years) 5 mg/day
- (>6 years) same as adult dosage.

Special Considerations

Desloratadine is the active metabolite of loratadine given in a dose of 5 mg once daily. It might have some advantages such as fewer adverse reactions and drug interactions.

Drug Interaction

Loratadine is metabolized by cytochrome P450 isoenzymes CYP3A4 and CYP2D6. Therefore use with other drugs that inhibit or are metabolized by these hepatic enzymes may result in changes in plasma concentrations of either drug and, possibly, adverse effects.

Drugs known to inhibit one or other of these enzymes include cimetidine, erythromycin, ketoconazole, quinidine, fluconazole, and fluoxetine.

Side Effects

The side effects seen in a study in 1926 include drowsiness/somnolence (8%), insomnia (2%), headache(12%), fatigue

(4%), dry mouth (3%), pharyngitis (2%), dizziness (2%) and gastrointestinal distress (2%).

Special Populations

Kidney disease: Creatinine clearance <10 mL/min: 10 mg alternate day.

Liver disease: 10 mg alternate day.

Pediatric: Not to be given less than 2 years.

Pregnancy: Category B.

Lactation: Appears in breast milk. Should be safe to breastfeed.

Desloratadine

This is the major, active metabolite of loratadine and is a non-sedating antihistamine. The drug was introduced following a lapse in patent protection for loratadine. It is well-tolerated and effective and about 5 times more potent than loratadine in suppressing the histamine wheal. There is little or no anticholinergic activity, minimal sedation, and no cardiac toxicity even at 9 times the licensed dosage. It is also not metabolized via the CYP enzyme pathway, and therefore can be safely administered with macrolides and imidazoles/triazoles.

Dose

Desloratadine is given in an oral dose of 5 mg once daily. It is also used with a decongestant such as pseudoephedrine sulfate.

Children aged 6 to 11 months: 1 mg once

- Those aged 1 to 5 years: 1.25 mg once daily
- Those aged 6 to 11 years: 2.5 mg once daily.

Special Groups

Children: In the UK, desloratadine is licensed for use in children aged 1 year and over.

In the USA, it may be given to those aged 6 months and over for perennial allergic rhinitis and urticaria and to those aged 2 years and over for seasonal allergic rhinitis.

Hepatic/renal

Desloratadine 5 mg orally on *alternate* days.

Breastfeeding

Desloratadine is distributed into breast milk and consequently UK and US licensed product information does not recommend its use during breastfeeding.

Pregnancy

Desloratadine was not teratogenic in animal studies; however, product information recommends it should be used with caution, if at all, in pregnant women.

Summary

As discussed previously, desloratadine and loratadine are inferior in potency to levocetrizine and fexofenadine (Dhanya NB). But both these drugs have the *longest residual action*. Thus in cases where a combination is needed, one of these two drugs in combination with a 1st generation antihistamine, is a sound option to control urticaria (Bernstein JA).

BIBLIOGRAPHY

1. Bernstein JA, Lang DM, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133(5):1270-7.
2. Dhanya NB, Thasleem Z, Rai R, Srinivas CR. Comparative efficacy of levocetirizine, desloratidine and fexofenadine by histamine wheal suppression test. Ind J Dermatol Venereol Leprol. 2008;74(4):361-3.

6. Olopatadine

Classification

It is a piperidine derivative.

Apart from an antihistamine action it also inhibits PAF, substance P and tachykinin.

Absorption and Distribution

The T_{max} with the 5 mg dose is 1.00 ± 0.32 while the T1/2 is 8.75 ± 4.63. For the 10 mg dose, it is 0.92 ± 0.47 and 7.13 ± 2.21.

Urinary excretion rate of the unchanged drug until 48 hours after a single oral dose of 5 mg or 10 mg of olopatadine hydrochloride in healthy adults was 63.0 to 71.8% of the administered dose.

Dosage

Usually, for adults, administer 5 mg as olopatadine hydrochloride **twice** a day orally in the morning and at bedtime. The dose may be increased or decreased according to age and symptoms.

Children: Usually, for children over 7 years of age, administer 5 mg as olopatadine hydrochloride twice a day orally in the morning and at bedtime.

Use

Adults: Allergic rhinitis, urticaria, itching resulting from skin diseases (eczema/dermatitis, prurigo, pruritus, psoriasis vulgaris).

Urticaria: Olopatadine hydrochloride was effective in 80.6% (225/279) of the patients in the study conducted at 39 institutions in Japan.

Pruritus: olopatadine hydrochlride was effective in 74.6% (91/122) of the patients for eczema/dermatitis, 50.8% (31/61) for prurigo.

Olopatadine is known to suppress the release of tachykinins. Because substance p, SP is a representative substance with tachykinin bioactivity, the SP reduction by olopatadine is an anticipated finding. This antiallergic may potentially exert its anti-pruritic effect by virtue of this SP-decreasing capacity as well as by antihistaminic activity.

Children: Allergic rhinitis, urticaria, itching resulting from skin diseases (eczema/dermatitis, pruritus cutaneous).

Special Considerations

It may induce drowsiness, patients should be cautioned against engaging in potentially hazardous activities requiring alertness such as operating machinery or driving a car.

In case, it is administered in the patients who have been under chronic treatment with a steroid, dose reduction of the steroid should be made gradually under careful supervision.

In case, it is administered in the patients with seasonal diseases, it is recommended to initiate administration immediately before the typical season to be continued until the end of the season.

Side Effects

The collective data from clinical trials before approval, drug use-results survey and special survey for long-term use include a total of 1,402 adverse reactions reported from 1,056 patients (11.0%) among 9,620 patients treated. The major adverse reactions were sleepiness 674 events (7.0%), ALT (GPT) increased 68 events (0.7%), malaise 53 events (0.6%), AST (GOT) increased 46 events (0.5%), thirst 36 events (0.4%), etc. (at the end of reexamination).

Children

The collective data from clinical trials in Japan include a total of 78 adverse reactions reported from 62 patients (14.9%) among 417 patients treated. The major adverse reactions were sleepiness 22 events (5.3%), ALT (GPT) increased 18 events

(4.3%), AST (GOT) increased 8 events (1.9%), leukocytosis 7 events (1.7%), γ-GTP increased 3 events (0.7%), etc.

Summary

This drug is underutilized as most of the literature in books is from USA or Europe where only the eye drop is approved. In Japan, the drug has been found to be effective in AD (Murota H) and pruritus (Wang T, Yoshizaki A) apart from urticaria where it is as effective as cetrizine/levocetirizine (Takeo T, Wang T,) and has a psychomotor side effect profile comparable to fexofenadine (Kamei H). It is one my favorite antihistamine in itchy disorders including urticaria.

BIBLIOGRAPHY

1. Kamei H, Isaji A, Noda Y, Ishikawa K, Senzaki K, Yamada K, Sugiura K, Tomita Y, Nabeshima T. Effects of single therapeutic doses of promethazine, fexofenadine and olopatadine on psychomotor function and histamine-induced wheal- and flare-responses: a randomized double-blind, placebo-controlled study in healthy volunteers. Arch Dermatol Res. 2012;304(4):263-72.
2. Murota H, El-latif MA, Tamura T, Katayama I. Olopatadine hydrochloride decreases tissue interleukin-31 levels in an atopic dermatitis mouse model. Acta Derm Venereol. 2014;94(1):78-9.
3. Takeo T, Kasugai C, et al. Evaluation of the antihistamine effects of olopatadine and levocetirizine during a 24-h period: a double-blind, randomized, cross-over, placebo-controlled comparison in skin responses induced by histamine iontophoresis. J Dermatol. 2013;40(12):987-92.
4. Wang T, Liu Y, Yin J, Lian S, Li M, Zheng Z, Zeng F, Zhang S. A multicenter, double-blind, randomized, noninferiority comparison of 14 days' treatment with oral olopatadine 10 mg or cetirizine 10 mg in Chinese adults with cutaneous pruritus. Pharmacology. 2013;91(1-2):117-22.
5. Yoshizaki A, Sato S. Olopatadine hydrochloride inhibits scratching behavior induced by a proteinase-activated receptor 2 agonist in mice. J Dermatol Sci. 2009;56(2):136-9.

7. Mizolastine

Mizolastine is a non-sedating antihistamine with a long duration of action. It does not have significant antimuscarinic actions; it is reported to have mast-cell stabilizing properties.

It is also reported to have anti-inflammatory actions.

Classification

It is a piperidine derivative.

Absorption and Distribution

Mizolastine is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations being reached after

about 1.5 hours. Plasma protein binding is about 98%. It is not significantly affected by concomitant ingestion of food or alcohol. The mean elimination half-life is about 13 hours. Mizolastine is mainly metabolized by glucuronidation although other metabolic pathways are involved, including metabolism by the cytochrome P450 isoenzyme CYP3A4, with the formation of inactive hydroxylated metabolites.

Dosage

The oral dose is 10 mg daily. In the elderly, although the half life is longer, no dose adjustment is necessary.

Drug Interaction

Moderate increases in plasma concentrations of mizolastine have been reported with erythromycin and ketoconazole; use with systemic imidazole antifungals is contraindicated by the manufacturer. They also advise against use of mizolastine with drugs known to prolong the QT interval, such as class I and III antiarrhythmics.

Other potent inhibitors of substrates for the hepatic metabolism of mizolastine include cimetidine, ciclosporin, and nifedipine; caution is advised if given together.

Special Considerations

It is contraindicated in patients with clinically significant cardiac disease or a history of symptomatic arrhythmias and in patients with known or suspected QT prolongation, patients with electrolyte imbalance (particularly hypokalemia), and in those with clinically significant bradycardia.

Mizolastine is also contraindicated in patients taking other drugs that decrease its metabolism, in patients with significantly impaired liver function, and in patients who are hypersensitive to the drug.

Mizolastine should be avoided in pregnancy (particularly the first trimester) and is not recommended during lactation.

Side Effects

Common: Drowsiness and fatigue.

Dry mouth, diarrhea, dyspepsia and increased appetite have been reported.

Rare: Isolated cases of hypotension, anxiety, depression and raised liver enzymes have been reported. Minor changes in blood sugar and electrolytes have been observed rarely.

Monitoring

Most patients taking mizolastine may drive or perform tasks requiring concentration—however, it is advised that

individual response to the drug is checked before driving or performing complicated tasks.

8. Bilastine

Bilastine is a new second generation H1-antihistamine recently approved for the symptomatic treatment of allergic rhinitis (AR) and chronic urticaria (CU) in patients older than 12 years of age.

Classification

It belongs to piperidine derivatives and is not structurally derived from any other currently available antihistamines. Bilastine exerts a potent and specific H1-antihistamine activity.

Mechanism of Action

The affinity for the H1 receptor is 3 and 6 times **higher than** for cetirizine and fexofenadine, respectively. The results of *in vivo* preclinical studies confirmed those obtained from *in vitro* experiments, as in rats bilastine has demonstrated to reduce histamine-stimulated smooth muscular contraction, bronchospasms, endothelial permeability, and microvascular extravasation, providing evidence to possess antiallergic properties, with **similar** potency to **cetirizine** and **superior** potency to **fexofenadine**.

In vitro data have shown that bilastine also exerts anti-inflammatory activity by inhibiting the release of histamine, IL-4 and tumor necrosis factor (TNF)-α from human mast cells and granulocytes.

Absorption and Distribution

The drug is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1 hour following administration and the mean oral bioavailability was found to be about 60%.

Bilastine does **not** undergo any significant hepatic metabolism and approximately 95% is excreted intact in feces (67%) or in urine (33%); bilastine is a substrate for P-glycoprotein which limits its passage across the blood–brain barrier. The mean elimination half-life calculated in healthy volunteers was 14.5 hours.

Dosage: 20 mg.

Use

1. **Allergic rhinitis:** Bilastine 20 mg was more effective than placebo and as effective as cetirizine 10 mg.
2. **Urticaria:** As effective as levocetirizine 5 mg.

Drug Interaction: None.

Side Effects

The most common adverse effects were headache, somnolence and fatigue that were reported less frequently than in patients receiving cetirizine at 10 mg once daily. The frequency of these adverse effects in patients with SAR were comparable with that of desloratadine. The first generation antihistamines cross the blood–brain barrier and bind the H1-receptors on postsynaptic neurons membranes in the central nervous system, causing sedation and impaired mental status, while the second-generation antihistamines usually do not cross the blood–brain barrier and have fewer sedative effects. Bilastine 20 mg histamine H1-receptor occupancy had been evaluated by positron emission tomography (PET) in healthy subjects, confirming that bilastine has objective and PET criteria to be defined as a non-sedating antihistamine.

Conclusion

Bilastine is a new second generation H-1-antihistamine with similar efficacy of desloratadine and cetirizine but with better tolerability, at least compared to the latter.

Several pharmacological properties of bilastine may explain this property.

Selectivity: Binding studies performed in animal tissues with a high density of H1-receptors show that bilastine has a moderate-high affinity for histamine H1-receptors, with values 3 times higher than those of cetirizine and 5 times higher than those of fexofenadine. These studies have also revealed that at a high concentration, bilastine does not show affinity for the 30 other receptors that have been assessed (including muscarinic receptors), nor for the other histamine receptor subtypes H2, H3 and H4. Bilastine binds specifically and selectively to histamine H1-receptor.

CNS penetration: The tissue distribution of bilastine has been examined in three types of mice using whole body autoradiography, no detectable drug levels being seen in the CNS in any of them at the different measured time points. Bilastine may have a limited penetration across the blood-brain barrier because it is a good P-glycoprotein substrate, additionally the relative high molecular weight, the relative lower lipophilicity may play a role.

Metabolism: Bilastine metabolism has been studied by *in vitro* incubation with hepatic microsomes, and human and other species hepatocytes. Bilastine does not induce the enzymatic activity of CYP450 family.

FIRST GENERATION SEDATING ANTIHISTAMINES

1. Chlorpheniramine Maleate

Classification

Sedating first generation antihistaminic.

Mechanism of Action

Chlorpheniramine is a competitive antagonist of histamine at the H1-histamine receptor. It also has anticholinergic and transient sedative effects when used intermittently.

Absorption and Distribution Metabolism

Oral bioavailability is about 34%; 72% is plasma protein bound. Rapidly and extensively metabolized by CYP2D6 to mono- and didesmethyl chlorpheniramine and unidentified metabolites, one or more of which are active. Metabolites and a small amount of parent drug are excreted in urine.

Fast metabolizers have an earlier, greater, and more prolonged antihistaminic response than slow metabolizers because of rapid conversion to active metabolite. In the elderly, duration of action can be ≥36 hours, even when serum concentrations are low.

- Onset is 0.5–1 hour; duration of suppression of wheal and flare response (IgE mediated) to skin tests with allergenic extract is 2 days.
- $t^1/_2$: (Adults) 20 ± 5 hours; (children) 13 ± 6 hours; (chronic renal failure) 280–330 hours.

Uses/Dosages

Adults, children >12 years: 4 mg q 6 hours. Maximum: 24 mg/d.
Children 6–12 years: 2 mg q 6 hours. Maximum: 12 mg/d.
Children 2–6 years: 1 mg q 6 hours.
Extended-release tablets
Adults, children >12 years: 8 mg q 12 hours. Maximum: 24 mg/d.
Children 6–12 years: 4 mg q 12 hours.
Children <6 years: Dosage not established.

Dexchlorpheniramine

Tablet 2 mg SR 4,6 mg

- Adult: PO 2 mg q 4–6 hours, to a max of 12 mg/d
  SR 4–6 mg HS or every 8–10 hours
- Children: PO (2–5 years) 0.5 mg q 4–6 hours (max of 3 mg/d); SR not recommended
- 6–12 years 1 mg q 4–6 hours/**SR** 4 mg HS.

Drug Interaction

MAOIs prolong and intensify the anticholinergic effects of antihistamines. Alcohol or sedative-hypnotics can increase CNS depressant effects.

Special Considerations

SR formulations offer no advantage over syrup or plain, uncoated tablets because the drug has an inherently long duration of action.

Use chlorpheniramine with caution in patients ≥ 60 years.

It might cause paradoxical CNS stimulation in children.

OTC labeling states to avoid in patients with narrow-angle glaucoma, symptomatic prostatic hypertrophy, asthma, emphysema, chronic pulmonary disease, shortness of breath, or breathing difficulties except under physician supervision; however, many studies have shown some bronchodilator effect of H1-receptor antagonists.

MAOIs prolong and intensify the anticholinergic effects of antihistamines. Alcohol or sedative-hypnotics can increase CNS depressant effect.

Side Effects

Frequent drowsiness, dry mouth, dizziness, and irritability occur with intermittent therapy; however, most patients develop tolerance to these side effects during continuous therapy, particularly if the dosage is increased.

Special Category

Kidney disease: Safe.

Liver disease: Safe.

Elderly: Use with caution, at higher risk for toxicity.

Pediatric: Void in neonates, premature infants. Infants and young children are at increased risk of overdose.

Pregnancy: Category B.

Lactation: No data available. Potentially toxic to infant. Avoid breastfeeding.

2. Hydroxyzine Hydrochloride

Classification

First generation antihistaminics.

Category

It is a piperazine.

Mechanism of Action

Competitive antagonist of histamine (H1) receptors. Mechanism of anxiolytic and sedative actions: inhibits subcortical neuronal activity.

Absorption and Distribution

Onset 15–30 minutes after oral administration. Duration of suppression of wheal and flare response to allergenic extract skin test is 4 days.

$t^{1}/_{2}$. (Healthy adults) 20 ± 4 hours; 53 (elderly); 51 (children), 53 (primary biliary cirrhosis).

Uses

Pruritus
Urticaria.

Dosage

Adult: Pruritus: 25 mg tid/qid.

Pediatric Dosage: Pruritus (<6 years) 50 mg/day in 2–3 divided doses; (≥6 years) 50–100 mg/day in divided doses Or 1 mg/kg daily, to a maximum of 2.5 mg/kg daily in children aged 1–6 years, and to a maximum of 2 mg/kg daily in those aged 6 years and over. The pre- or postoperative sedative dose in children is 600 μg/kg.

Geriatric dosage: Pruritus 10 mg tid/qid, increasing to 25 μg tid/qid, if necessary.

Drug Interaction

MAOIs prolong and intensify the anticholinergic effects of antihistamines. Alcohol or sedative-hypnotics can increase CNS depressant.

Special Considerations

Hydroxyzine suppresses wheal and flare response to the *greatest* degree and for the *longest* duration of all antihistamines, including the newer nonsedating antihistamines.

Use with caution in patients with hypertension, thyroid disease, asthma, heart disease, diabetes, prostatic hyperplasia, angle closure glaucoma.

Avoid alcohol and other CNS depressants, such as opiate analgesics, barbituates, sedatives (e.g. diazepam) when taking this drug.

Side Effects

Transient drowsiness and dry mouth occur frequently when the drug is taken intermittently. Most patients develop

tolerance to these effects when the drug is taken continuously, particularly if the dosage is slowly increased over 7–10 days.

Special Populations

Kidney disease: None.

Liver disease: Increase interval (q 24 hours in primary biliary cirrhosis).

Elderly: Dosage reduction may be required.

Pediatric: See above.

Pregnancy: Category C.

Lactation: Probably appears in breast milk. Avoid breastfeeding.

3. Doxepin

Category

It is a tricyclic dibenzoxepins and a tricyclic antidepressant.

Mechanism of Action

Doxepin is probably the ideal agent for the treatment of depressed patients with neurotic excoriations. This is as it has a very powerful H_1 antihistamine action. To stop the excoriating behavior, it is important to treat the patient's depression and to put an end to the 'itch–scratch cycle.' Moreover, the majority of depressed patients who present with excoriations appear to be suffering from an agitated depression, in which they paradoxically become more restless, angry, and argumentative when depressed. For these patients, the most common adverse effect–sedation can actually be beneficial.

Absorption and Distribution

Doxepin is readily absorbed from the gastrointestinal tract after oral doses, and is extensively demethylated by first-pass metabolism in the liver, to its primary active metabolite, desmethyldoxepin. Doxepin is also absorbed through the skin after topical application.

Paths of metabolism of both doxepin and desmethyldoxepin include hydroxylation and N-oxidation. Doxepin is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Doxepin and desmethyldoxepin are widely distributed throughout the body; the plasma protein binding of doxepin is about 76%. Doxepin has been estimated to have a plasma elimination half-life ranging from 8 to 24 hours, which may be considerably extended in overdosage; that of desmethyldoxepin is longer.

Doxepin crosses the blood-brain barrier and the placenta. It is distributed into breast.

Uses

- Depression
- Anxiety
- Insomnia
- Headache
- Urticaria/Pruritus.

Dosage

i. *Mild to moderate anxiety or depression*
   - **Adults:** 25 mg tid or up to 150 mg at bedtime. Maintenance: 75–100 mg/d.
   - **Elderly:** 25–50 mg/d.

ii. *Severe anxiety or depression*
   - **Adults:** Initial: 50 mg tid. Increase to maximum 300 mg/d if needed.

iii. *Urticaria*

Dose; 10–50 mg at night

It has been shown to be an effective oral alternative to conventional antihistamines in the treatment of chronic urticaria, and to be an effective oral treatment for idiopathic cold urticaria.

Special Considerations

Hypersensitivity to doxepin or other dibenzoxepines, concomitant use of MAO inhibitor, glaucoma, urinary retention.

Side Effects

Common

Sedation and prolongation of the QT interval with a decreased threshold to precipitate seizure disorder or manic–depressive disorder.

Other side effects include weight gain, orthostatic hypotension, and anticholinergic adverse effects such as dry mouth, blurry vision, constipation, and urinary retention.

Abrupt discontinuation of TCA may lead to 'discontinuation symptoms' such as transient dizziness, nausea, headache, diaphoresis, insomnia, malaise, and 'REM rebound' with uncomfortably vivid dreams.

Contraindications

Hypersensitivity to doxepin or other dibenzoxepines, concomitant use of MAO inhibitor, glaucoma, urinary retention.

Special Groups

Kidney disease/Liver disease:

None

Pediatric: It is given in children though it is a off label use

Pregnancy

Safety has not been established.

Lactation

Appears in breast milk. American Academy of Pediatrics expresses concern over use when breastfeeding.

4. Promethazine

Classification

Promethazine is a phenothiazine derivative which differs structurally from the antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution. It is thought that this configuration is responsible for its relative lack (1/10 that of chlorpromazine) of dopamine antagonist properties. Promethazine is an H1 receptor blocking agent. In addition to its *antihistaminic* action, it provides clinically useful *sedative* and *antiemetic* effects.

Absorption and Distribution

Promethazine is well absorbed from the gastrointestinal tract. Clinical effects are apparent within 20 minutes after oral administration and generally last four to six hours, although they may persist as long as 12 hours. Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethyl promethazine are the predominant metabolites appearing in the urine.

Uses

Phenergan, is used for numerous indications like perennial and seasonal allergic rhinitis, allergic conjunctivitis, urticaria and angioedema, allergic reactions to blood or plasma, sedative, as an antiemetic and as an active and prophylactic treatment of motion sickness.

Urticaria: The average oral dose is **25 mg** taken before retiring, it is a good adjunct in patients who have difficulty in sleeping because of the severity of symptoms of urticaria.

Motion sickness: The average adult dose is 25 mg taken twice daily. The initial dose should be taken one-half to one hour before anticipated travel and be repeated 8 to 12 hours later, if necessary. On succeeding days of travel, it is recommended that 25 mg be given on arising and again before the evening meal.

Special Considerations

Phenergan tablets and suppositories are **contraindicated** for use in pediatric patients less than two years of age. Phenergan tablets and suppositories are contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to promethazine or to other phenothiazines. Antihistamines are contraindicated for use in the treatment of lower respiratory tract symptoms including asthma.

Drugs having anticholinergic properties should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction.

Phenergan tablets and suppositories should be used cautiously in persons with cardiovascular disease or with impairment of liver function.

The drug can cause marked drowsiness or impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery. The use of alcohol or other central-nervous-system depressants such as sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers, may enhance impairment.

Drug Interactions

CNS Depressants—Phenergan tablets and suppositories may increase, prolong, or intensify the sedative action of other central-nervous-system depressants, such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers.

Epinephrine—Because of the potential for phenergan to reverse epinephrine's vasopressor effect, epinephrine should not be used to treat hypotension associated with phenergan tablets anticholinergics—Concomitant use of other agents with anticholinergic properties should be undertaken with caution.

Monoamine oxidase inhibitors (MAOI)—Drug interactions, including an increased incidence of extrapyramidal effects,

have been reported when some MAOI and phenothiazines are used concomitantly.

Side Effects

1. Central nervous system drowsiness is the most prominent CNS effect of this drug.
2. Cardiovascular—Increased or decreased blood pressure, tachycardia, bradycardia, faintness.
3. Dermatological—Dermatitis, photosensitivity, urticaria.
4. Hematologic—Leukopenia, thrombocytopenia, thrombocytopenic purpura, agranulocytosis.
5. Gastrointestinal—Dry mouth, nausea, vomiting, jaundice.
6. Respiratory—Asthma, nasal stuffiness, respiratory depression (potentially fatal) and apnea (potentially fatal).

Paradoxical reactions: Hyperexcitability and abnormal movements have been reported in patients following a single administration of promethazine HCl. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

Special Populations

Pregnancy: C
Children: >2 years.

KETOTIFEN

Ketotifen is an oral anti-allergic drug developed in 1970 by Sandoz Pharmaceuticals of Switzerland. It is a benzocycloheptathiophene derivative and was initially marketed as an inhibitor of anaphylaxis.

Classification

Ketotifen has a chemical structure similar to some first-generation antihistamines, such as cyproheptadine and azacitidine.

Absorption and Distribution

With regard to the pharmacokinetic properties of ketotifen, it is readily absorbed from the gastrointestinal tract after oral administration and achieves peak plasma concentrations within 2 to 4 hours of administration. Clearance of the drug from plasma is biphasic, with a half-life of distribution of 3 hours and a half-life of elimination of 22 hours in adults.

However, the onset of action of ketotifen is *slow, and it may take 4 to 6 weeks* to achieve full prophylactic value under certain conditions.

Uses

Oral ketotifen has been used in patients with asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, chronic urticaria, cold-induced urticaria, cholinergic urticaria, exercise-induced urticaria, mastocytosis, and food allergy in Canada, Europe, and Mexico. Approval was granted for ocular administration in the United States for allergic conjunctivitis and later the drug became available over the counter.

Most studies published on the use of ketotifen have focused on its benefits in childhood and adult asthma. However, by inhibiting the release of the proinflammatory mediators listed earlier, ketotifen can prevent the vascular permeability changes that are involved in the development of wheals and flare responses. Thus, it can be used in the management of urticaria. However, overall, there is a paucity of literature on this topic, because ketotifen is not an FDA-approved drug in the United States for the management of urticaria.

Dose

For adults and older children: 1 mg twice daily.
For young children 6 months to 3 years old: 0.5 mg twice daily.

Drug Interaction

Ketotifen may potentiate the effects of central nervous system depressants, antihistamines, and alcohol. Concomitant use of oral ketotifen with oral diabetic agents, such as glyburide and metformin, may result in reversible thrombocytopenia.

Adverse Effects and Precautions

Oral ketotifen is usually well-tolerated and relatively safe, with the most frequent side effect of sedation. This is seen in approximately 10% to 20% of patients, especially at higher doses, but the effect decreases within 1 to 2 weeks of use.

Other rarer reactions include dizziness, dry mouth, nausea, and headache, which have been reported in 1 to 2% of patients at initiation of therapy. However, these side effects do not persist in patients on long-term treatment. Weight gain and central nervous stimulation also have been reported in a small number of patients.

Overdosage. Overdoses of ketotifen ranging from 10 to 120 mg were reported in 8 patients. Symptoms included drowsiness, confusion, dyspnea, bradycardia or tachycardia, disorientation, and convulsions. Gastric lavage was performed in 6 patients, and all 8 recovered within 12 hours after supportive treatment.

In an overview of 21 cases of overdosage (including those reported above) the manufacturers stated that no serious signs or symptoms had been reported with doses below 20 mg, and there had been no fatalities. The most serious effects reported had included unconsciousness, convulsions, bradycardia and tachycardia, and a severe hypotensive reaction. Management is essentially supportive and symptomatic.

BIBLIOGRAPHY

1. Ashenager MS, Grgela T, Aragane Y, Kawada A. Inhibition of cytokine-induced expression of T-cell cytokines by antihistamines. J Investig Allergol Clin Immunol. 2007;17(1):20-6.
2. Baümer W, Wendorff S, Gutzmer R, Werfel T, Dijkstra D, Chazot P, et al. Histamine H4 receptors modulate dendritic cell migration through skin—immunomod ulatory role of histamine. Allergy. 2008;63:1387-94.
3. Bernstein JA, Lang DM, et al. The diagnosis and management of acute and chronic urticaria. J Allergy Clin Immunol. 2014;133(5):1270-7.
4. Cowden JM, Zhang M, Dunford PJ, Thurmond RL. The histamine H 4 receptor mediates inflammation and pruritus in Th2-dependent dermal inflammation. J Investig Dermatol. 2010;130:1023-33.
5. Church MK, Maurer M, Simons FER, et al: Risk of first generation H1 antihistamines: a GA2LEN position paper. Allergy. 2010; 65:459-466. Epub 2015 Jan 2. PubMed PMID: 25838101.
6. Davis MP, Frandsen JL, Walsh D, Andresen S, Taylor S. Mirtazapine for pruritus. J Pain Symptom Manage. 2003;25(3):288-91. PubMed PMID: 12614964.
7. Gillard M, Benedetti MS, Chatelain P, Baltes E. Histamine H1 receptor occupancy and pharmacodynamics of second generation H1-antihistamines. Infl amm Res. 2005;54:367-9.
8. Glatzer F, Gschwandtner M, et al. Histamine induces proliferation in keratinocytes from patients with atopic dermatitis through the histamine 4 receptor. J Allergy Clin Immunol. 2013;132:1358-67.
9. Grant JA, Danielson L, Rihoux J-P, et al. A comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine versus placebo in suppressing the cutaneous res-ponse to histamine. Int Arch Allergy Immunol. 1999;118:339-40.
10. Grant JA, Danielson L, Rihoux J-P, et al. A double-blind, single-dose crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine versus placebo: suppression of wheal and flare response for 24h in healthy male subjects. Allergy. 1999;54:700-7.
11. Grant JA, Riethuisen J-M, Moulaert B, et al. A double-blind, randomized, single-dose, crossover comparison of levoce-tirizine with ebastine, fexofenadine, loratadine, mizolastine, and placebo: suppression of histamine-induced wheal-and- flare response during 24 hours in healthy male subjects. Ann Allergy Asthma Immunol. 2002;88:190-7.

12. Guerra L, Vicenzi C, Marchesi E, et al. Loratadine and cetirizine in the treatment of chronic urticaria. J Eur Acad Dermatol. 1994;3: 148-52.
13. Handa S, Dogra S, Kumar B. Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. J Dermatolog Treat. 2004;15: 55-57.
14. Hundley JL, Yosipovitch G. Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. J Am Acad Dermatol. 2004;50(6):889-91.
15. Ito T, Tatsuno K, et al. Antihistaminic drug olopatadine downmodulates T cell chemotaxis toward CCL17 in patients with atopic dermatitis. Allergol Int. 2015;64(2):200-2. doi: 10.1016/j.alit.2014.10.008.
16. Jauregui I, Ferrer M, Montory J, et al. Antihistamines in the treatment of chronic urticaria. J Investig Allergol Clin Immunol 2007;17(Suppl. 2):41-52.
17. Kamei H, Isaji A, et al. Effects of single therapeutic doses of promethazine, fexofenadine and olopatadine on psychomotor function and histamine-induced wheal- and flare-responses: a randomized double-blind, placebo-controlled study in healthy volunteers. Arch Dermatol Res. 2012;304(4):263-72.
18. Kozel MMA, Sabroe RA. Chronic urticaria. Aetiology, management and current and future treatment options. Drugs. 2004;64:2515-36.
19. Leurs R, Church MK, Taglialatela M. H1-antihistamines: Inverse agonism, anti-infl ammatory actions and cardiac effects. Clin Exp Allergy. 2002;32:489-98.
20. Liu JY, Zhao YZ, Peng C, Li FQ, Zhu QG, Hu JH. [Effect of cetirizine hydrochloride on the expression of substance P receptor and cytokines production in human epidermal keratinocytes and dermal fibroblasts]. Yao Xue Xue Bao. 2008;43(4):383-7.
21. Murota H, El-latif MA, Tamura T, Katayama I. Olopatadine hydrochloride decreases tissue interleukin-31 levels in an atopic dermatitis mouse model. Acta Derm Venereol. 2014;94(1):78-9.
22. Nelson HS, et al. Ann Allergy Asthma Immunol. 2000;84(5):517-22.
23. Ohsawa Y, Hirasawa N. The antagonism of histamine H1 and H4 receptors ameliorates chronic allergic dermatitis via anti-pruritic and anti-inflammatory effects in NC/Nga mice. Allergy. 67:1014-22.
24. Ohsawa Y, Hirasawa N. The role of histamine H1 and H4 receptors in atopic dermatitis: from basic research to clinical study. Allergol Int. 2014;63(4):533-42.
25. Potter PC, et al. Allergy. 2009;64(4):596-604.
26. Purohit A. et al. Ann Allergy Asthma Immunol. 2004;92(6):635-40.
27. Rosenzwey P, Caplain H, Chofour S, Iliac N, Cabanis MJ, Thebault JJ. Comparative wheal and flare study of mizolastine vs terfenadine, cetirizine, loratadine and placebo in healthy volunteers. Br J Clin Pharmacol. 1995;40:459-65.
28. Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L, Alenius H, Dieu-Nosjean MC, Meller S, Rieker J, Steinhoff M, Hoffmann TK, Ruzicka T, Zlotnik A, Homey B. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol. 2066;117:411-7.

29. Sastre J. Ebastine in allergic rhinitis and chronic idiopathic urticaria. Allergy. 2008;63 Suppl 89:1-20.
30. Sharma M, Bennett C, Cohen SN, Carter B. H1-antihistamines for chronic spontaneous urticaria. Cochrane Database Syst Rev. 2014;11:CD006137.
31. Schmelz M, Schmidt R, Bickel A, Handwerker HO, Torebjork HE. Specific C-receptors for Itch in human skin. J Neurosci. 1997; 17:8003.
32. Schmelz M, Schmidt R, Weidner C, Hilliges M, Torebjoerk HE, Handwerker HO. Chemical response pattern of different classes of C-nociceptors to pruritogens and algogens. J Neurophysiol. 2003;89:2441-8.
33. Simons FE, Simons KJ. Pharmacokinetic optimisation of histamine H1-receptor antagonist therapy. Clin Pharmacokinet. 1991;21(5):372-93.
34. Simons FE, Sussman GL, Simons KJ. Effect of the H2-antagonist cimetidine on the pharmacokinetics and pharmacodynamics of the H1-antagonists hydroxyzine and cetirizine in patients with chronic urticaria. J Allergy Clin Immunol. 1995;95:685-93.
35. Simons FE. Advances in H1–Antihistamines. N Engl J Med. 2004;351:2203-17.
36. Simons FE, McMillan JL, Simons KJ. A double-blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine versus placebo: suppressive effects on histamine-induced wheals and fl ares during 24 hours in normal subjects. J Allergy Clin Immunol. 1990;86:540-7.
37. Sonkoly E, Muller A, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol. 117:411-7.
38. Staevska M, et al. Allergy Clin Immunol. 2010;125(3):676-82.
39. Takeo T, Kasugai C, et al. Evaluation of the antihistamine effects of olopatadine and levocetirizine during a 24-h period: a double-blind, randomized, cross-over, placebo-controlled comparison in skin responses induced by histamine iontophoresis. J Dermatol. 2013;40(12):987-92.
40. Tokura Y. Extrinsic and intrinsic types of atopic dermatitis. J Dermatol Sci. 2010;58:1-7.
41. Walsh GM. Anti-inflammatory properties of antihistamines: an update. Clin Exp Allergy Rev. 2005;5:21-5.
42. Yamanaka K, Motomura E, ET AL. Olopatadine, a non-sedating H1 Antihistamine, decreases the nocturnal scratching without affecting sleep quality in atopic dermatitis. Exp Dermatol. 2015;24(3):227-9.
43. Yamaura K, Oda M, Suwa E, Suzuki M, Sato H, Ueno K. Expression of istamine H4 receptor in human epidermal tissues and attenuation of experimental pruritus using H4 receptor antagonist. J Toxicol Sci. 2009;34:427.431.
44. Yoshizaki A, Sato S. Olopatadine hydrochloride inhibits scratching behavior induced by a proteinase-activated receptor 2 agonist in mice. J Dermatol Sci. 2009;56(2):136-9.
45. Zuberbier T, et al. Allergy. 2014;69:868-87.

FURTHER READING

1. Antihistamines. In Martindale (ed). The Complete Drug Reference Thirty-sixth edition Edited by Sean C Sweetman. Published by the Pharmaceutical Press, 2009.
2. Histamine, Bradykinin, and their Antagonists. In Brunton L, Lazo J, Parker K (Eds). Goodman & Gilman's. The Pharmacological Basis of Therapeutics, 11th edn. New York: McGraw-Hill Medical, 2008.
3. Golightly LK, Greos LS. Second-generation Antihistamines Actions and Efficacy in the Management of Allergic Disorders Drugs. 2005;65(3):341-84.
4. Slater JW, Zechnich AD. Haxby DG. Second-generation Antihistamines. A Comparative Review Drugs. 1999; 57(1): 31-47.
5. Thurmond et al. Antihistamines and Itch. Robin LA. Cowan, G Yosipovitch (Eds), Pharmacology of Itch, Handbook of Experimental Pharmacology. 226, DOI 10.1007/978-3-662-44605-8-15.
6. Zuberbier T. Pharmacological rationale for the treatment of chronic urticaria with second-generation non-sedating antihistamines at higher-than-standard doses JEADV. 2012;26:9-18.

4

CHAPTER

Antiandrogens

Kabir Sardana, Chanchal Singh

INTRODUCTION

This class of drugs is used primarily in females acne and hirutism; and in males, in male pattern alopecia. As an off label use finasteride and spironolactone are also used in female pattern alopecia.

It is important to understand the basic biosysynthesis of androgens in females and males before addressing the role of various antiandrogens.

Many steroidal and nonsteroidal compounds possess estrogenic activity. The most potent endogenous estrogen is 17 beta-estradiol, followed by estrone and estriol. Steroidal estrogens arise from **androstenedione or testosterone** by aromatization of the A ring, a reaction catalyzed by aromatase (CYP19), an enzyme found in ovarian granulosa cells, testicular Sertoli and Leydig cells, adipose stroma, placental syncytiotrophoblast, preimplantation blastocysts, bone, various brain regions and other tissues.

Ovaries are the principal source of circulating estrogen in premenopausal women (Fig. 4.1). Gonadotropins, acting via receptors that couple to the Gs-adenylyl cyclase–cyclic AMP pathway, increase the activities of aromatase and the cholesterol side-chain cleavage enzyme. The ovary contains the type I isoform of *17 beta-hydroxysteroid dehydrogenase*, which favors the production of *testosterone and estradiol from androstenedione and estrone, respectively*. In the liver, the type II isoform oxidizes circulating estradiol to estrone, which then is converted to estriol. In postmenopausal women, the principal source of circulating estrogen is adipose tissue stroma, where estrone is synthesized from dehydroepiandrosterone (DHEA) secreted by the adrenals.

In males (Fig. 4.2), Leydig cells in the testes synthesize testosterone. LH, secreted by the pituitary gonadotropes is the principal stimulus of testosterone secretion in men, perhaps potentiated by follicle-stimulating hormone (FSH), also secreted by gonadotropes. LH secretion is stimulated by hypothalamic gonadotropin-releasing hormone (GnRH), while testosterone directly inhibits LH secretion in a negative

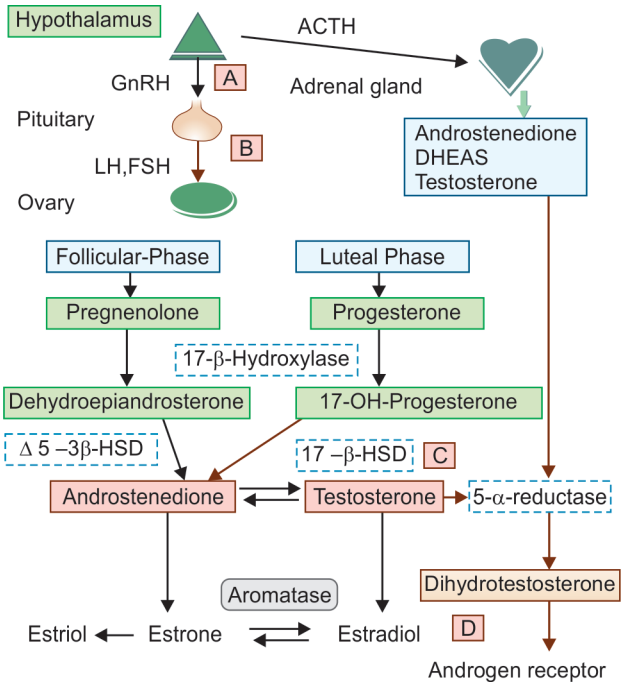


Fig. 4.1: Androgenic pathway and mode of action of various anti-androgen in females. (A) GnRh Agonist (leuprolide, triptrorelin, metformin), (B) OCP, danazol, cyproterone acetate (C) ketoconazole, spironolactone (D) flutamide, cyproterone, spironolactone, drospirenone, cimetidine

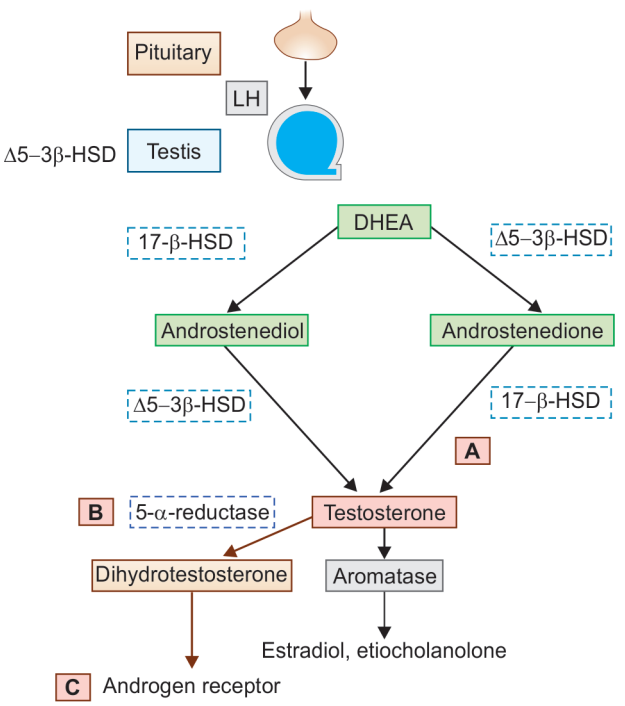


Fig. 4.2 Androgenic pathway in males and site of action of antiandrogen. (A) Ketoconazole, spironolactone, (B) finasteride, (C) flutamide, cyproterone, spironolactone, drospirenone, cimetidine

feedback loop. Testosterone secretion is likewise pulsatile and diurnal, with the highest plasma concentrations occurring at about 8 AM and the lowest at about 8 PM. The morning peaks diminish as men age. Sex hormone–binding globulin (SHBG) binds about 40% of circulating testosterone with high affinity, such that testosterone bound to SHBG is unavailable for biological effects. Albumin binds almost 60% of circulating testosterone with low affinity, leaving approximately 2% unbound or free. In some testosterone assays, the latter two components are considered as "bioavailable" testosterone.

Testosterone has many different effects in tissues, both directly and after its metabolism to two other active steroids, dihydrotestosterone and estradiol. The enzyme 5α-reductase catalyzes the conversion of testosterone to dihydrotestosterone. Although testosterone and dihydrotestosterone both act via the androgen receptor (AR), dihydrotestosterone binds with higher affinity and activates gene expression more efficiently. Two forms of 5α-reductase have been identified: Type I, found predominantly in nongenital skin, liver and bone, and type II, found predominantly in urogenital tissue in men and genital skin in men and women. The enzyme complex aromatase (CYP19), which is present in many tissues, converts testosterone to estradiol. This conversion results in approximately 85% of circulating estradiol in men; the remainder is secreted directly by the testes. Testosterone is metabolized in the liver to androsterone and etiocholanolone.

Recent studies evaluating variants in the androgen receptor (AR) gene in men revealed a positive association between the variant associated with increased androgen sensitivity and finasteride response to treat AGA. Androgen sensitivity on the AR gene is determined by repeat sequences of the amino acid glutamine which is formed from a sequence of three nucleotides, known as CAG, on the DNA backbone that makes up the gene. This variant is often referred to as the number of CAG repeats on the AR gene. **Fewer** CAG repeats are associated with ***increased androgen sensitivity.***

The AR gene is located on the X-chromosome, and women carry two X chromosomes in each cell; therefore, all women have two copies of the AR gene. That means that each gene has an opportunity to influence the androgen sensitivity of the cell. Within a single cell, only one AR gene copy is active, while the second AR gene copy is inactivated through the process of X-chromosome inactivation (XIA). By measuring the percentage activation of each AR gene copy, it is possible to weight the contribution to a patients androgen sensitivity. A patient with a shorter weighted average number of CAG repeats in their AR gene is more androgen sensitive. Based on previous published studies evaluating AR CAG repeats in

women/girls, it is expected that patients with the androgen sensitive genotype are more likely to respond to anti-androgenic therapies when treating androgenic conditions like AGA(Keene S).

The antiandrogens can inhibit the production of the hormones and can act at various levels (Figs 4.1 and 4.2). They have been divided into two types those that block the androgen receptors and androgen inhibitors that affect the synthesis.

Alopecia

When indicated in females oral antiandrogens, minoxidil or a combination of both is often indicated. In males 5α-reductase inhibitor and minoxidil are the mainstay of therapy. An average of 4 months are required for a response and therapy should be continued for 12 months. Subtle fluctuations often occur specially on account of seasonal variations (variations in the melatonin), stress and dietary issues and thus patient interpretation is uniformly unreliable.Serial 6 monthly photographs should be used to monitor therapy.

It is unlikely that either spironolactone or cyproterone acetate will ever show more efficacy than minoxidil, which is the current standard of treatment for hair loss in women. In the event that spironolactone is used, recall that it is pregnancy category D. Patients should ideally be on birth control, and they should be reminded that the drug may elevate potassium levels. Recently, finasteride has been used in females, both normoandrogenic pre- and postmenopausal women with FPHL, in a dose of 5 mg, with a reasonable efficacy (Yeon S).

Acne

Acne is associated with increased sebum secretion and proliferative activity of sebaceous glands. Much effort has therefore gone into developing treatments for acne that reduce sebaceous gland activity. Possible mechanisms include reducing the circulating levels of serum androgens through an effect on the pituitary, adrenal or gonads, or by affecting the transport of androgens. Alternatively, the pharmacological/physiological suppression of androgens could be achieved through a direct effect on sebocyte metabolism. Such mechanisms include blocking enzyme activity (5α-reductase type 1, Δ 5 –3β-HSD, cytochrome P-450), or by a block of androgen or retinoid receptors (Figs 4.1 and 4.2).

Clinical benefit does not occur until sebum suppression achieves a *minimum* of **30%**. An OCP (Dianette® and Estelle 35®), which contains 35 μg ethinyl estradiol and 2 mg

cyproterone acetate (CPA), reduces sebum excretion by 28%. When combined with additional CPA (100 mg/day) from the 5th to the 14th days of cycle, the sebum suppression rises to 68%. Inocoterone, another nonsteroidal recepor blocker, reduces sebaceous gland activity when applied topically to rat and hamster sebaceous glands and lacks any systemic effects.

Spironolactone, given systemically, has been shown to inhibit the hamster flank organ, and, given topically, to block androgen activity in sebaceous glands of the hamster pinna. However, there was no effect on sebum excretion when applied topically to humans. In contrast, spironolactone given orally significantly reduces sebum excretion in humans in a dose-dependent manner; there is a reduction of around 30% with 100 mg/day, and a reduction of 60–70% with 200 mg/day.

Certain derivatives of vitamin A, in particular isotretinoin (13-cis-RA), have marked effects on the sebaceous glands when given systemically. They have been shown to reduce the size of the hamster flank organ and human sebaceous glands, in which they profoundly inhibit sebum excretion. Isotretinoin reduces 5α-reductase activity in human liver and skin, and has been shown to reduce the binding capacity of the androgen receptor in back skin. Isotretinoin reduces the synthesis of DNA and the incorporation of a lipid precursor 14 C-acetate in human sebaceous glands *in vitro*. Topical retinoids, in contrast to certain oral retinoids, have no effect in reducing sebum production or excretion.

Although androgens are a major causative factor in AV, most adult women with AV do not have elevated circulating hormone levels or clinical evidence of hyperandrogenism. Thus, ***end-organ sensitivity*** of the pilosebaceous unit to androgens may be a factor. Persistent and/or treatment resistant AV, or AV of sudden onset, are clinical clues suggestive of abnormal androgen excess. The possibility of an ovarian or adrenal tumor must be considered in this scenario, especially if other signs of hyperandrogenism have emerged, even if subtle. Signs of hyperandrogenism in women include androgenic alopecia, seborrhea (i.e. new onset "oily skin"), AV, hirsutism, cushingoid features, increased libido, clitoromegaly, deepening of the voice, hyperhidrosis, and acanthosis nigricans. Women experiencing these abnormalities should be screened for underlying endocrine disorders, and preferably referred to an endocrinologist.

The two most common causes of excess circulating androgen levels in women are PCOS and congenital adrenal hyperplasia (CAH). The overall prevalence of PCOS is estimated to be 3–6%, with approximately 23–35% of women with PCOS exhibiting acne vulgaris clinically.

If an endocrine abnormality is suspected, screening tests to help diagnose excess circulating androgens are

suggested. These tests include dehydroepiandrosterone sulfate (DHEAS), total testosterone, free testosterone, and the luteinizing hormone/follicle-stimulating hormone (LH/FHS) ratio. The optimal time for checking these laboratory values is during the *luteal* phase of the menstrual cycle, that is right before the onset of menses. Patients should be instructed to stop any oral contraceptives at least one month before testing these laboratory values to optimize the accuracy of the results. It is important to consider that a hormone-releasing intrauterine device (IUD) may also affect testing results. It is prudent to repeat testing of hormonal laboratory abnormalities before starting therapy to establish an accurate baseline for comparison, if needed at a later date.

1. A good intial test is to measure the total testosterone and or SHBG levels. If the latter is low there could be a raised level of free testosterone. Thus the FAI (free androgen index; testosterone/SHBG X100) is a good way of eliciting this problem and a value >5 is a sign of increased free testosterone level.

   Elevation of the testosterone level >150 ng/dL coupled with an LH:FSH ratio of >2:3 is suggestive of PCOS. If the testosterone level is elevated >200 ng/dL, the source may be an androgen-secreting ovarian tumor.
2. If DHEAS levels are markedly increased (level >8000 ng/dL), an adrenal tumor is an important diagnostic consideration, and an endocrinologist should be consulted for further workup. Levels in the 4000–8000 ng/dL range can indicate CAH.
3. If 17-hydroxyprogesterone is elevated >200 ng/dL, late-onset CAH may be the cause. The most common cause of CAH that is noted in 95% of cases is deficiency of the enzyme 21-hydroxylase.

Lastly, the clinician should keep in mind that oral spironolactone has a role in the treatment of adult women with AV, even when test results that evaluate androgenic status are *normal*.

When adrenal hyperplasia is suspected, the usual corticosteroid regimen is prednisone, 5–10 mg/d, or dexamethasone, 0.25–0.5 mg/d given in the evening on a daily or every other day basis. An overview of the treatment options is given in Table 4.1.

Hirsutism

There are certain important prerequisites that must be addressed to before initiating medical therapy for hirsutism.

1. All medications have potential side effects and they may need monitoring by blood tests and other measures. This is specially a issue as therapy can continue for 6–12 months.

Table 4.1: Treatment options for hormonal acne

Drug	*Indication*	*Mode of Action*
Oral contraceptives	Failed antibiotics No response to dexamethasone or prednisone fT elevated/ FAI>5 *	1. Inhibit ovarian androgen secretion 2. Increase level of SHBG
Spironolactone	Failed antibiotics	Androgen receptor blockade
Dexamethasone or prednisone	DHEAS elevated DHEAS normal but fails prescription with antibiotics or isotretinoin Not responsive to oral contraceptives or spironolactone	An evening dose helps suppress adrenal gland activity Stop when DHEAS level of 70 μg/dL is achieved (in case of NCCAH)

fT, free testosterone; FAI, free androgen index

2. Pregnancy is contraindicated with these drugs, and a pregnancy prevention plan is required for the duration of therapy—which may be long-term. Thus it is useful specially in women in childbearing age group to intiate OCPs with the therapy.
3. Not everyone will respond to treatment and therefore some semiobjective measure of efficacy and timescale for assessment need to be discussed, e.g. frequency of use of depilatory agents at outset and 6 months, or photographs.
4. At what point is it envisaged that the treatment will be stopped is a issue though a minimum of 6–12 months to one is advisable.
5. Who will take responsibility for long-term prescribing and monitoring, where medication is being used outside the licensed indication?

When the hirsute woman has PCOS, prescribing may cross boundaries with treatment of other aspects of the disease and care may be shared with other clinicians. When the woman is otherwise completely healthy, the issues of using unlicensed medication in the absence of disease have to be weighed against the loss of function arising from the hirsutism.

Though OCP containing an antiandrogen is a excellent option a more useful combination is a combination of OCP, like Diane 35 alone (2 mg of cyproterone acetate and 35 μg of ethinyl estradiol) with finasteride 5 mg (Sahin Y et al.). A comparison of the various commonly used agents (cyproterone acetate (12.5 mg/d for the first 10 days of the cycle), finasteride (5 mg/d), or spironolactone (100 mg/d) for 12 months) found that though all are equally effective long- term results were better with spironolactone (Lumachi F, et al.). Another study that examined 5 mg of finasteride or

Table 4.2: Drugs therapy for various types of hirsutism

Adrenal Suppression	Steroids	Deflazacort	30 mg od for 1 month. Maintenance dose of 6 mg daily for up to 2 years.
	Antiandrogen therapy (Androgen receptors)	Cyproterone acetate (Blocks 5-α-DHT effect on the androgen receptor and inhibits the secretion of FSH and LH) Spironolactone Drospirenone (progestagenic, antiandrogenic and antialdosteronic) Flutamide	50–100 mg/day from the 5th–15th days of the menstrual cycle for a 6-month period 50–200 mg/day for at least 6 months Doses of 3 mg/day over 21-day cycle along with 30 µg ethinyl estradiol. 62.5–125
	5-α-Reductase Inhibitors	Finasteride Dutasteride Isotretinoin	2.5 mg daily for 2 years 0.5 mg daily dose of dutasteride/0.5 twice a week
Ovarian	OCP		↑ SHBG ↓ Testosterone
	GnRH-a	leuprolide Metformin	A dose of 20 µg/kg per day in combination with 2 mg EE and 5 mg medroxyprogesterone acetate for 6 months 500 three times daily
	Antiandrogens	Cyproterone acetate Flutamide Finasteride	100 mg/day 125–500 mg/day 2.5–5 mg/day

Table 4.3: Evidence based summary of drugs used for hirsutism (Duration 6–12 months)

First-line treatment	Estrogen plus progestin contraceptives (EPP) CPA, 50 mg/day, 20 days out of 28 or Finasteride 5mg can be combined with OCP	Bachelot A, Beigi A
Second line	Option 1. Spironolactone 100 mg* Option 2. Finasteride 2.5/5 mg* Option 3. Flutamide 250 mg * (All are equally affective)	Moghetti P et al. Fruzzetti F
Third Line	Spironolactone+Finasteride*	

*Unapproved but should be combined with OCP

100 mg of spironolactone for 9 months in hirsutism found that spironolactone group responded significantly better (Erenus M). If for whatever reason a patient cannot be administered a OCP, an option is spironolactone (100 mg/day) plus finasteride (5 mg/day) which was found to better than (51.3%) spironolactone alone (Kelestimur F). Moghetti P et al. though found that finasteride is as affective as other antiandrogens. Amongst the various OCP a study has compared the OCP containing cyproterone acetate and drospirenone and found that to be equally effective for hirsutism (Kelekci KH).

Metformin is a biguanide originally used in the treatment of type 2 diabetes mellitus. It has found a place in the treatment of hirsutism associated with hyperinsulinemia and insulin resistance. In this setting, it can reduce levels of insulin, increase insulin sensitivity and, particularly when associated with a low-calorie diet, result in weight loss. In many, this will be part of PCOS, where it has also been shown to assist in normalization of menstruation and improvement in lipid profiles. These broader metabolic effects can make it a useful therapy where hirsutism is *not* the only problem. A summary of the various agents that can be used for hirsutism are summarized in Table 4.2.

A review of the available literature on the medical therapy of hirsutism (given in Table 4.3) reveals that apart from OCP (with newer antiandrogens), finasteride and spironolactone are good alternatives for treating the condition.

BIBLIOGRAPHY

1. Bachelot A, Chabbert-Buffet N, Salenave S, et al. Anti-androgen treatments. Ann Endocrinol (Paris). 2010;71(1):19-24.
2. Beigi A, Sobhi A, Zarrinkoub F. Finasteride versus cyproterone acetate-estrogen regimens in the treatment of hirsutism. Int J Gynaecol Obstet. 2004;87(1):29-33.
3. Fruzzetti F, Bersi C, Parrini D, Ricci C, Genazzani AR. Treatment of hirsutism: comparisons between different antiandrogens with central and peripheral effects. Fertil Steril. 1999;71(3):445-51.

4. Moghetti P, Tosi F, Tosti A, Negri C, Misciali C, Perrone F, et al. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. J Clin Endocrinol Metab. 2000;85(1):89-94.
5. Swiglo BA, Cosma M, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, et al. Clinical review: Antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. J Clin Endocrinol Metab. 2008;93(4):1153-60.

SPIRONOLACTONE

Classification

Antiandrogen

Chemical Class

Steroidal competitive aldosterone antagonist that acts from the interstitial side of the distal and collecting tubular epithelium to block sodium–potassium exchange, producing a delayed and mild diuresis.

Mechanism of Action

It is a weak antiandrogen that blocks the AR and inhibits androgen biosynthesis. The drug decreases steroid production in adrenal and gonadal tissue. In women, total serum testosterone concentration decreases and dehydroepiandrosterone sulfate level either is decreased or remains unchanged. Free testosterone levels are unchanged or decreased.

1. The metabolites reversibly inhibits adrenal and ovarian cytochrome P-450 (CYP) enzymes, with a decrease in testosterone and DHT production.
2. The progestational activity of spironolactone is variable. The drug influences the ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) by reducing the response of LH to GnRH.
3. Like CPA, long-term therapy is associated with a reduction in cutaneous 5α-reductase activity.

PK, Absorption and Distribution

Onset of action 1–2 days, peak 2–3 days with continued administration; duration 2–3 days after cessation of therapy. Bioavailability is about 90%. Food promotes absorption and possibly decreases first-pass effect. It undergoes rapid and extensive metabolism to canrenone (active metabolite), 7α-thiomethylspironolactone (major metabolite), and other sulfur-containing metabolites. Metabolites are eliminated

primarily renally, with minimal biliary excretion. Little or no parent drug is excreted unchanged in urine.

Clinical Use in Dermatology

Off-label Use: Hirsutism, Acne vulgaris, Androgenetic alopecia, Hidradenitis suppurativa.

Usage Guidelines (Table 4.4)

1. Hirsutism

50 and 200 mg daily, with 100 mg daily being the normal dose.

Initial dose: 50 mg/day, which is enough in adrenal SAHA.

Increase: Monthly increase the dose by 50 mg.

Final dose: 200 mg/day.

Another schedule is administration 3 out of 4 week, which results in a withdrawal bleeding in the fourth week, which is similar to that seen with the oral contraceptive. In case of *menstrual problems* the dose may be *reduced* to 50–75 mg daily or a OCP maybe added.

Comparison with Other Agents

The drug has been found to be variably as effective as finasteride and CPA.

1. Spritzer et al. compared the relative benefits of a combination of CPA 50 mg/day and ethinylestradiol 35 μg/day with spironolactone 200 mg/day over 12 months. Both groups were stratified for those with PCOS and idiopathic hirsutism. In both groups, those with idiopathic hirsutism did equally well. However, those with PCOS did significantly better with the CPA/ethinylestradiol combination.

Table 4.4: Spironolactone in dermatology

Disorder	*Dose*	*Comments*
Acne Vulgaris	50 to 100 mg (combination with OC /Antibiotic) 50 mg BD days 5 through 21of the cycle	33% cleared with low doses 33% had marked improvement 27% showed a partial improvement 7% showed no improvement (Shaw JC,2005) All had improvement of acne (Lubbos HG)
Androgenetic alopecia	200 mg each day	The high dose may cause menstrual problems
Hirsutism	200 mg each day	With OCP the efficacy is better and can ensure contraception

2. When compared with finasteride 5 mg, spironolactone 100 mg had a equivalent efficacy, but long-term results were better with spironolactone.

2. Acne Vulgaris

a. **Initial dose: 25–50 mg:** This should be increased gradually as a proportion of patients experience menstrual problems
b. **Maintenance dose: (25–200 mg)** There is a reduction of sebum excretion in humans in a dose-dependent manner. The reduction is around 30% with 100 mg/day, and 60–70% with 200 mg/day. At a lower dosage range of 50–100 mg/day, spironolactone has been shown to reduce sebum excretion rate by 30–50% with a favorable adverse effect people. After a desired endpoint has been reached, maintenance doses of spironolactone typically ranges from 25–50 mg daily. This low dose of spironolactone is sufficient for some women with sporadic outbreaks of inflammatory or isolated cystic lesions.

Another dose regimen is to start on the fifth day of the menstrual cycle with 100 mg/day of spironolactone divided into morning and evening doses, each dose 50 mg, for 16 days. Almost 85% of patients responded with a decrease in the DHEAS level (Yemisci A).

In adult women with AV, especially those with a hormonal pattern clinically, who do not exhibit androgen excess on laboratory evaluation, or in many with hyperandrogenism associated with endocrine disorders, such as polycystic ovary syndrome (PCOS), oral spironolactone may be an ideal therapy because of its ability to block systemic androgen production and diminish the effects of peripheral androgens on target end organs.

A guide to choose hormonal acne patients who can be initiated on spironolactone is given below.

How to Suspect and when to Treat as a Case of Hormonal Acne

Women with acne flares that cycles with menstruation
Women not responding to conventional therapy and not wanting to use oral isotretinoin or who are not candidates for oral isotretinoin. Repeated recurrence of AV after oral isotretinoin use with short periods of remission (often less than 6–9 months after stopping oral isotretinoin)
Women with late-onset AV, or persistent-recurrent AV past the teenage years, even in the absence of clinical signs of hyperandrogenism and with normal results on hormonal level testing
Women with late-onset AV (acne tarda) or sudden onset of AV
Clinical signs of hyperandrogenism, such as hirsutism, androgenic alopecia, and/or increased sebum production with AV
Abnormal hair growth if not evident, may be elicited by asking the patient if she uses hair-removal techniques especially on the face

Acne involving the chin, mandible, peripheral face and lower face, and neck (Beard Area of men)

Seborrhea

Mild-to-moderate hirsutism.

Combination with OCP

There are certain advantages in combining spironolactone with OCP, apart from the obvious fact that being an antiandrogen conception should be avoided.

1. It helps reduce the menstrual-related side effects, such as dysmenorrhea, irregular menses, and breast tenderness, all of which can occur with spironolactone monotherapy, especially at higher doses.
2. Also, the combination of an OC with spironolactone may in some cases allow women with AV to be on a lower daily dose of spironolactone without a sacrifice in efficacy.
3. OCs can play a significant role in treatment of AV in women because they reduce free serum androgen levels by increasing sex hormone-binding globulin (SHBG) regardless of the type of progestin or concentration of estrogen.

A study (Krunic A) where oral contraceptive containing 30 μg of ethinyl estradiol and 3 mg of drospirenone (Yasmin) was combined with spironolactone 100 mg taken daily given as a single morning dose found that 85% of the subjects were entirely clear of acne lesions or had excellent improvement at the end of the 6-month period.

Of the OCP approved (FDA) to be used in acne EE 20 μg and DROSP 3 mg is available in India. While it has certain advantages(counteracts the weight gain of estrogen), it must be remembered that drospirenone is a 17-alpha spironolactone derivative with antimineralocorticoid activity and a potassium-sparing diuretic effect. This OCP in combination with spironolactone may cause hyperkalemaia.

Combination with Antibiotics

In acne often oral antibiotics are administered. There are reports of hyperkalemia with concomitant TMP/SMX, specially in HIV positive cases thus this should be avoided if spironolactone is prescribed.

Special Considerations

Avoid: In case of anuria, acute renal insufficiency, rapidly deteriorating renal function, severe renal failure, serum potassium >5.5 mEq/L or development of hyperkalemia while taking the drug.

Family or personal history of estrogen-dependent malignancy.

Give potassium supplements only to patients with demonstrated hypokalemia who are taking a proximally acting diuretic and a corticosteroid concurrently with spironolactone.

The patient should be asked to change position slowly, in particular from recumbent to upright to minimize orthostatic hypotension. Sit at the edge of the bed for several minutes before standing, and lie down if feeling faint or dizzy.

Avoid hot showers or baths and standing for long periods.

Male patients should sit on the toilet while urinating rather than stand.

Avoid excessive intake of high-potassium foods (bananas, citrus fruits, peaches, dates) and potassium-containing salt substitutes.

Drug Interactions

Drugs that increase effects/toxicity of potassium-sparing diuretics: ACE inhibitors, cimetidine.

Drugs that decrease effects/toxicity of potassium-sparing diuretics: NSAIDs.

Potassium-sparing diuretics increase effects/toxicity of digoxin,lithium.

Potassium-sparing diuretics decrease effects/toxicity of oral hypoglycemics.

Adverse Effects

The majority of adverse effects associated with spironolactone are dose-dependent. Low-dose therapy using 25–50 mg daily is generally very well tolerated, and even 100 mg daily is not problematic in most cases.

Most side effects are dose-dependent, *except* central nervous system (CNS) symptoms (lethargy, headache, lightheadedness, dizziness), which do not appear to always be dose-related.

Common

1. Menstrual irregularities have been reported to be as high as 18% on low-dose spironolactone (50–100 mg daily) as opposed to 70% in patients on 200 mg daily. Breast tenderness has been reported in 5% of patients on low-dose spironolactone compared to 30% on 200 mg daily. If menstrual abnormalities do not improve within *three months* of monotherapy, the clinician may consider the following options: (i) decrease spironolactone to a dosage

range of 50–75 mg daily if applicable, (ii) add an OC to reduce menstrual dysfunction, or (iii) "cycling" of the spironolactone with 21 consecutive days of therapy followed by seven days off.
2. Hyperkalemia can occur, most frequently in patients with renal function impairment (especially those with diabetes mellitus) and those receiving potassium supplements or concomitant ACE inhibitors.

Rare

1. Hypotension, bradycardia, heart failure, acidosis, dehydration, hepatorenal syndrome (cirrhosis).
2. Agranulocytosis is a rare but serious adverse effect and is of greater concern in patients of advanced age and with hepatic or renal impairment. Drug dosage and duration of use as well as concurrent medications are additional risk factors that may predispose patients taking spironolactone to agranulocytosis.
3. In patients receiving high dosages, frequent estrogen-like side effects, such as gynecomastia, decreased libido, and impotence in males occur; menstrual irregularities and breast tenderness occur in females. These effects are reversible after drug discontinuation.
4. The FDA gives a warning in the package insert that tumors were found in chronic toxicity studies of rats, in which 25–250 times the usual human dose (on a body weight basis) was given to rats. These doses resulted in benign adenomas of the thyroid and testes, malignant mammary tumors, and proliferative changes in the liver.

Cutaneous

Pruritus, xerosis, maculopapulous eruptions, urticaria, facial-pigmentations-type melasma, contact dermatitis, erythema annulare centrifugum, vasculitis, erythema multiforme, Raynaud's phenomenon, alopecia, lupus type eruption and lichenoid eruption.

Monitoring

Laboratory monitoring of the abnormal circulating androgen (testosterone or DHEA-S) every **3–4** months is recommended to ensure successful androgen suppression which may take upto 4–12 months of spironolactone therapy (Table 4.5).

Monitor serum electrolytes, in particular potassium, periodically, especially early in the course of therapy.This is specially needed if combined with a OCP containing drosperinone. Monitor BUN and/or Cr periodically.

Table 4.5: Monitoring protocol for spironolactone

Baseline	*Follow-up*	*Interval*
Serum electrolytes	Yes	First at 7 days then monthly If the level reaches 5–5.9 mEq/L withhold drug, then decrease dosage by 50% or use alternative drug
BUN and/or S. Creatinine	Yes	Monthly then 3 monthly
BP	Yes	Monthly
DHEAS, Free testosterone	Yes	At end of therapy

Observe for clinical signs of fluid or electrolyte depletion such as dry mouth, thirst, weakness, lethargy, muscle pains or cramps, hypotension, oliguria, tachycardia, and GI upset.

Special Groups

Pregnancy

Category B.

Children

Safety and efficacy have not been established.

Lactation

Metabolite appears in breast milk. Considered compatible by American Academy of Pediatrics.

Renal

Creatinine clearance 10–50 mL/min: dose q12–24h; creatinine clearance <10 mL/min: do not use.

Hepatic

None

Elderly

None

DROSPIRENONE

Drospirenone 3 mg, ethinyl estradiol 0.02 mg (Dronis 20)
Drospirenone 3 mg, ethinyl estradiol 0.03 mg (Dronis 30).

Classification

This is a synthetic progestational compound which is a spironolactone analogue with 3 mg dose comparable to a 25 mg dose of spironolactone.

Mechanism of Action

It has antiandrogenic activity.

Clinical use in Dermatology

Acne, hirsutism, female pattern alopecia.

Usage Guidelines

Drosperinone is FDA approved for use as an oral contraceptive and is available in two combinations (3 mg DRSP and 0.02 mg ethinyl estradiol [EE]) and (3 mg DRSP and 0.03 mg of EE). They are given for 24 or 28 days respectively. It is FDA approved for moderate acne vulgaris in women of at least 14 years of age desiring oral contraception who have no known contraindications to OC therapy and have achieved menarche.

Acne

RCT have found that after *6 cycles* a marked decrease in lesions can be achieved. Nodular lesions may be somewhat more treatment resistant.

Hirsutism

Uncontrolled studies have noted a decline in hirsutism scores with DRSP/EE treatment over *6–12 months*, and a comparative randomized study found *similar efficacies* between DRSP/EE and CPA/EE combinations.

Doses of 3 mg/day over 21-day cycle along with 30 μg ethinyl estradiol is currently the normal choice in the treatment of SAHA, because drospirenone does not cause fluid retention and consequently the patient does not gain weight.

Monitoring

Same as spironolactone.

Special Considerations

DRSP/EE tablets are contraindicated in patients with hepatic dysfunction, adrenal insufficiency and renal insufficiency.

Serum DRSP levels are higher in those with moderate renal impairment and the potential exists for hyperkalemia to occur.

As with spironolactone, drospirenone may increase potassium levels, which should be checked during the first month of therapy.

Patients taking these pills may experience hyperkalemia if the drug is taken with other therapies that increase potassium levels (see spironolactone drug interactions, above).

Drug Interactions

Similar to spironolactone.

CYPROTERONE ACETATE

Classification

Cyproterone acetate (CPA) is a synthetic progestogen that acts as both an antiandrogen and an inhibitor of gonadotropin secretion.

Mechanism of Action

1. Cyproterone acetate (CA) acts by interfering with the binding of 5α-DHT to the androgen receptor and by inhibiting the secretion of FSH and LH through its progestogen action
2. It also reduces androgen production and increases the metabolic clearance of testosterone
3. Long-term therapy is associated with a reduction in the activity of cutaneous 5α-reductase.

Clinical Use in Dermatology

Off-label uses include AGA, hirsutism, and virilizing syndromes.

Usage Guidelines

Dose: 50–100 mg/day from 5th to 15th days of the menstrual cycle for 6-months Maintenance: 1 tablet daily for 21 days starting on day 1 of menstrual cycle and repeated after a 7-day interval, usually for several months; withdraw 3–4 months after acne or hirsutism completely resolved (repeat courses may be given if recurrence); long-term treatment may be necessary for severe symptoms.

Acne

The OCP which contains 35 μg ethinyl estradiol and 2 mg cyproterone acetate (CPA), reduces sebum excretion by 28%. When combined with additional CPA (100 mg/day) from the fifth to the 14th days of cycle, the sebum suppression rises to 68%.

Hirsutism

Uncontrolled studies have noted a decline in hirsutism scores with DRSP/EE treatment over 6–12 months, and a comparative randomized study found similar efficacies between DRSP/EE and CPA/EE combinations. This drug is one of the best treatment for the alopecia of SAHA syndrome,

but it has less effect in the treatment of hirsutism in SAHA and adrenal hirsutism

Low-dose therapy (Dianette) is an oral contraceptive pill containing 35 μg ethinylestradiol and 2 mg CPA, taken daily for 21 in every 28 days. However, many of the dose-ranging and efficacy studies have been performed using the preparation that contained 50 μg ethinylestradiol; this may be relevant, as only the higher dose of oestrogen increases SHBG. Current dosage recommendations for CPA usually advise that 50 mg or 100 mg CPA should be administered for 10 days/cycle (e.g. day 1–10 or 5–15). However, there have now been many dose-ranging studies that suggest that there is no such dose effect. Objective studies comparing Dianette with and without extra-CPA found no difference in the reduction of overall hirsutism grades, although the rate of onset of benefit was *faster* with the additional cyproterone.

Monitoring

Blood counts initially and throughout treatment; monitor hepatic function regularly (liver function tests should be performed before treatment), monitor adrenocortical function regularly and look for blood sugar derangements.

Special Considerations

Contraindications: severe diabetes (with vascular changes), sickle-cell anaemia, liver-disease including Dubin-Johnson and Rotor syndromes, previous or existing liver tumors, malignant or wasting diseases, meningioma or history of meningioma, severe depression, history of thromboembolic disorders; children under 18 years (may arrest bone maturation and testicular development).

Adverse Effects

Fatigue and lassitude, breathlessness,weight changes, changes in hair pattern, gynecomastia (rarely leading to galactorrhea and benign breast nodules); rarely hypersensitivity reactions, rash and osteoporosis; inhibition of spermatogenesis; hepatotoxicity reported (including jaundice, hepatitis and hepatic failure usually in men given 200–300 mg daily for prostatic cancer).

FINASTERIDE

Classification

This is a potent nonsteroidal antiandrogen that acts by inhibiting the type 2, 5α-reductase isoenzyme, blocking the conversion of testosterone to 5α-DHT.

Mechanism of Action

The drug inhibits the local level of DHT in the hair follicle. The drug does not directly bind to the AR and is therefore not a traditional antiandrogen. The drug may have secondary effects on the AR by suppressing DHT and via feedback mechanisms that affect AR levels.

After 1 mg the serum concentration of DHT decreases by 65% within 24 hours while the serum concentrations of testosterone and estradiol increase about 15%, but remain within normal limits. Prostate concentrations of testosterone increase about sixfold.

Absorption and Distribution

Finasteride is well absorbed in the gastrointestinal tract, metabolized in the liver, and excreted in urine and feces. The serum half-life is 5–6 hours. Minute quantities (nanogram levels) of the drug are detectable in human semen, but the drug is **not** thought to have any adverse consequences in female partners of men.

The level of finasteride reach *normal levels* after **a month** of stopping therapy.

Clinical Use in Dermatology (Table 4.6)

FDA: Male pattern alopecia (≥18 years)

Off-label: Female pattern alopecia, hirsutism, acne vulgaris, hidradenitis suppurativa.

An overview of the use in MAGA, it is given in Table 4.6.

Usage Guidelines

1. **Male pattern alopecia:** Finasteride in pattern alopecia
Age: 18–41 years of age (Table 4.7).

Site/Severity: Mild-to-moderate AGA predominantly in the vertex and frontal area.

Dose: 1 mg

Some patients find taking the 5 mg tablet cheaper and break the tablets into quarters, taking one quarter of one pill daily. If a patient forgets a pill, taking the double dosage the next day is *not* recommended. In case of adverse events a dosage of 0.2 mg/daily or a dosage of 0.5–1 mg every other day can be given, although no clinical studies are available for this of lebel dose.

Results: Early hair growth starts at 6–9 months and is maximum by 1 year. On therapy, it is maintained up to 24 months on continuation. After 2 years, there is a gradual decline in results As compared to placebo there is a 93%

Table 4.6: Finasteride in dermatology

Disorder (FDA approved/ Unapproved)*	*Dose /Duration*	*Results*
Male Pattern Alopecia*	1 mg - lifelong	Over 30 years old with higher AGA grades demonstrated more improvement. Side effects were reported in 6% of patients (decreased libido and erectile dysfunction). Persistence of hair growth was not significantly less after 10 years versus after 5 years of therapy.(Rossi A)
Hirsutism	2.5–5 mg	A combination with OCP or spironolactone gives better results, though the drug is also effective as a monotherapy Forty hirsute female subjects were randomized to receive either spironolactone 100 mg daily, flutamide 250 mg daily, finasteride 5 mg daily, or placebo. All treatment groups revealed similar reduction in hair diameter.(Moghetti P)
Female Pattern Alopecia	5 mg daily for 12 months.	Of the 87 normoandrogenic, pre and post-menopausal women with FPHL given the drug over 12 months 87% showed improvement (Yeon JH)

Table 4.7: Factoids on finasteride use in male pattern alopecia

Type of alopecia	Primarily vertex type Also frontal, parieto-occipital in some cases
Results	Initial results appear in *6-9 month* By *6 months* (Reduce hair loss) By *12 months* (Regrowth)
Duration of Therapy	12 months If continued effects peaks at 24 months
Efficacy	Age :18-41 years 50% in 1 yr; 60% in 2 yrs At 5 year: Maintains the effect and slows hair loss
Reversal	On stopping effect reverses in 12 month
Females	Normoadrenergic: 1, 2.5, 5 mg (with OCP) Hyperandrogenic: 1, 2.5 mg

decreased risk of further visible hair loss over 5 years (placebo 26.3% decline in hair density).

A new study has shown that the drug can be used for up to 5 years and the drug can improve androgenetic alopecia with sustained effect among Japanese patients. Younger age

and less advanced disease at start of treatment were the key predictors of higher finasteride efficacy (Yoshitake T).

2. **Female pattern alopecia:** Finasteride is *not* generally indicated in women and is contraindicated in pregnant women, because of the risk of feminization of a male fetus. But in *select* cases the drug has been found to be useful both in premenopausal and postmenopausal age group and in both hyper and normoadrenergic women. The latter is explained by the fact that some women may have excessive activity of the 5α reductase enzyme inspite of being normoadreneregic. This explains why they would not benefit from systemic antiandrogen treatments but would benefit from finasteride. The dose used is variable ranging from 1 mg to 5 mg, with a *lower* dose being used for cases where *hyperandrogenic* abnormalities can be demonstrated.

There have been anecdotal reports of finasteride being effective in *postmenopausal* women without hyperandrogenism at 1 or 2.5 mg doses and in women with *hyperandrogenism* at 2.5 mg of finasteride daily in conjunction with the oral contraceptive Yasmin®

One study from Italy demonstrated an increased hair growth in 23 of 27 *premenopausal* women who were given finasteride 2.5 mg in combination *with* an OCP containing both drospirenone and ethinyl estradiol. (Iorizzo et al.). The patients were normoandrogenic. Other *normoandrogenic* women have also benefited from increased doses of oral finasteride (5 mg) (Kohler et al.). Oliveira-Soares R in a recent study in *normoadrenergic post menopausal* women used the drug in a dose of 5mg a day. A recent study by Yeon JH found that the drug was useful in both pre and post menopausal age groups in a dose of 5 mg.

Thus in select cases a dose of 2.5–5 mg can be used, with the proviso that in premenopausal age groups a OCP should be concomitantly administered.

3. **Hirsutism:** The dose used has been either 2.5 mg or 5 mg, but a study, found that the hirsutism scores decreased significantly at 6 and 12 months with both dosages. Thus *low-dose* (2.5 mg/day) finasteride is safe and cost effective in the treatment of hirsutism and may be used instead of high-dose finasteride (5 mg/day) therapy (Bayram F). Moghetti P et al. have shown that the drug is as effective as spironolactone though some clinicians prefer finasteride as it has less menstrual issues than other antiandrogens.

Adrenal hirsutism: Dose of 2.5 mg daily for 2 years, lead to a 93% reduction of facial hirsutism and a 73% reduction of corporal hirsutism.

Ovarian hirsutism: Dose of 2.5 mg/day (PCOS 5 mg/day). It works best in combination with cyproterone acetate 2 mg and EE 35 μg. This combination is also the preferred therapy in constitutional hirsutism.

Special Considerations

1. Women who may become pregnant should not come in contact with crushed tablet. The manufacturers (Merck) warn that women who are, or who may become, pregnant should not take finasteride or handle crushed or broken tablets. Though unless there is a cutaneous barrier abnormality in women handling crushed or broken tablets, significant percutaneous absorption is unlikely.
2. Blood donation is also contraindicated for those taking finasteride for **1 month** after the last dose of medication. The purpose of this deferral period is to prevent blood donation to a pregnant female transfusion recipient which may harm a male fetus.
3. There have been reports of secondary infertility and they remind us to inquire whether the man and his partner are having difficulty getting pregnant. Stopping finasteride in these situations *may* improve semen parameters and help the couple avoid more invasive fertility treatments.

Drug Interactions

No significant drug interactions have been demonstrated with finasteride, with the exception of nevirapine, which may reduce finasteride levels and efficacy

Finasteride is extensively metabolized in the liver, primarily by the CYP3A4 enzyme subfamily. Given the drug's wide therapeutic index, there are *no* important interactions as a result of this CYP metabolism.

Adverse Effects

Mondaini et al. describes a **"nocebo"** phenomenon when an adverse side effect is not a direct result of the pharmacologic action of the drug but rather of the patient knowing that it is a side effect. They tested this hypothesis in 120 patients on finasteride for benign prostatic hypertrophy (BPH) who were randomly assigned to groups that were informed or not informed of the side effects. After 6 and 12 months, the informed group reported a significantly higher incidence (43%) of sexual side effects than did the uninformed group (15%). While these results do not mean that we can intentionally withhold information from our patients. They do suggest that the sexual side effects can sometimes have a **psychological,** rather than a pharmacologic, cause. This is relevant to finasteride.

1. **Sexual dysfunction:** Clinical trials have shown a small increase in sexual dysfunction (e.g. impotence) in men taking finasteride for male balding (4.2% versus 2.2% for placebo in young men, 8.7% versus 5.1% in older men).

These side effects resolve on discontinuation of the drug. Interestingly "right handed "people developed these side effects more commonly (Motofei IG).

Importantly, Irwig MS et al. studied the effect of persistent sexual dysfunction and noted that in most men who developed persistent sexual side effects (≥3 months) despite the *discontinuation* of finasteride, this sexual dysfunction continued for many months or years. In their clinical series, 20% of subjects with male pattern hair loss reported persistent sexual dysfunction for ≥6 years, suggesting the possibility that the dysfunction may be permanent. Prescribers of finasteride and men contemplating its use should be made aware of such potential adverse medication effects.

2. Decreased volume of ejaculate.
3. **Effects on sperm:** At present, there is little evidence that finasteride has a negative effect on sperm count or morphology (Overstreet JW, et al.). This is as testosterone—and not DHT—is the primary androgen regulating spermatogenesis, sperm maturation, and seminal fluid production in the testis, epididymis, and seminal vesicle. But it is important to know about the reported effects of the drug. One recent study, did find a significant drop in sperm count by 34% after 26 weeks of once-daily finasteride 5 mg, but the change became smaller and then was insignificant by week 52 and again on the 24-week follow-up (Amory JK, et al.). One very small study recruited three men who had been on finasteride 1 mg/day for 5 years for sperm analysis. Using a transmission electron microscope, researchers found altered sperm morphology consistent with necrosis (Collodel G). There have also been two case reports of severe azoospermia resulting in impaired fertility (Liu KE). But by and far the drug has no profound effect on sperm in larger study groups.
4. **Prostrate cancer:** There is a 25% overall reduction in the incidence of prostatic cancer in those taking finasteride (5 mg) but a small increase in the frequency of high-grade prostatic cancer. This is largely based on a Cochrane review of men with a mean age of 64 years and a mean PSA of 2.1 ng/mL. In younger individuals and at 1 mg the significance of this is at present unknown. A recent article has found that these fears are unfounded and the concern for the induction of high-grade prostate cancer should be discarded (Lynn R).
5. Though finasteride has teratogenic effects in animals, the meager amounts detected in the semen of men are safe. In pregnant monkeys, oral administration of finasteride at dosages 100 times the recommended human dose of

1 mg/day resulted in external genital abnormalities in male fetuses.

Rare Side Effects

1. Disorders, such as mastalgia, were reported in 0.4% of patients, and did not occur until later in the treatment period.
2. Exfoliative dermatitis, perioral numbness, and swollen glands, all of which resolved with drug cessation and returned with rechallenge have been reported.
3. Isolated reports of depression have also occurred in patients taking finasteride.
4. The drug may alter immune surveillance against cancer in aging men as androgens increase the level of Th1 cells, which are decreased on finasteride therapy.

Monitoring

No specific laboratory monitoring guidelines are required for following patients taking finasteride for male pattern AGA. Men taking finasteride should be aware that PSA levels will be reduced.

A baseline PSA value is appropriate for men 50 years and older, *before* receiving finasteride. Studies from Merck revealed that men aged 50 years taking finasteride for BPH had a 50% reduction in PSA levels, whereas younger men, aged 18–41, taking finasteride for AGA had a 20–30% reduction. The package insert suggests 'doubling' the PSA value for all males at least 41 years of age without BPH if the test is ordered while taking finasteride.

Special Groups

Pregnancy

X

Children

CI

Lactation

X

Renal

Safe

Hepatic

Use with caution.

Elderly

Safe.

Finasteride and Minoxidil

Only few data comparing finasteride 1 mg daily and minoxidil solution is available. Most of the studies showed superiority for finasteride over minoxidil at 12 months.

Working mechanisms of minoxidil and finasteride are different. Thus, association of both drugs is possible and can be considered in motivated patients.

If a patient intends to *switch* from minoxidil to finasteride, a combination therapy for at least 3 but preferably 6 months before discontinuing minoxidil is advisable in order to avoid significant hair loss while finasteride action can take over.

DUTASTERIDE

Mechanism of Action

Dutasteride is a potent nonsteroidal antiandrogenthat acts by inhibiting 5α-reductase isoenzymes 1 and 2 in humans, lowering serum and scalp 5α-DHT levels. As both (types I and II isoenzymes) are located in the pilosebaceous unit, thus inhibiting DHT formation from both enzymes may be important in reversing the miniaturization process that occurs in AGA.

Pharmacology

The longer half-life than finasteride (4 weeks versus 6–8 hours of finasteride) with serum concentrations that remain detectable (0.1 ng/mL) for up to 4–6 months after discontinuation of treatment makes it a drug that can be used in a weekly or a monthly mode, but should be avoided in women in the reproductive age group.

The drug inhibits serum DHT levels by by 90% within 24 hrs and as there is more type 1 isoenzyme systemically it is more effective in reversing alopecia.

Clinical Use in Dermatology

Recent trials comparing dutasteride to the standard dosage of finasteride 1 mg daily have shown that dutasteride is a better drug.

A meta-analysis reiterated the efficacy and safety of 5α-reductase inhibitors for the treatment of AGA and supported the use of dutasteride 0.5 mg as an additional treatment option, in pattern alopecia (Gupta AK). It is essential to understand though that the most effective dosage of dutasteride is 2.5 mg, which is 5 times higher than the standard dosage in the treatment of benign prostatic

hyperplasia (dutasteride 0.5 mg corresponds to finasteride 5 mg).

Off-label Use

Male pattern alopecia,Female pattern alopecia, Hirsutism, Acne vulgaris, Frontal fibrosing alopecia, Hidradenitis suppurativa.

Usage Guidelines

Dutasteride has *not* yet been approved by the FDA for the treatment of hair loss

Dose

1. 0.5 mg daily for 2 weeks (loading) then 0.5 mg twice weekly thereafter
2. 0.5 mg daily.

Male Pattern Alopecia

A comparison of dutasteride (0.02, 0.1, or 0.5 mg/d), finasteride (1 mg/d), or placebo for 24 weeks. revealed that dutasteride 0.5 mg was superior to finasteride at 24 weeks (Gubelin HW et al). Dutasteride can be *combined* in cases which do not respond to finasteride in a low-dose of 0.5 mg/week (Boyapati A).

A recent study examined dutasteride in 35 Korean men with AGA who had not shown significant clinical improvement when treated with finasteride 1 mg/d for at least six months and received dutasteride at a dose of 0.5 mg/d for six months. It was found that with dutasteride more than 78% of cases responded and thus this drug could be a option for patients who do *not* respond to finasteride (Jung JY).

Female Pattern Alopecia

The use of dutasteride in females is restricted to short studies and case reports and should be used *only in* severe cases, unresponsive to minoxidil and finasteride and preferably in postmenopausal females.A case of FAGA who had been treated unsuccessfully with cyproterone acetate and ethinyl estradiol, showed significant improvement after dutasteride treatment. A total of 25 *postmenopausal* women with FAGA (FAGA.M) degree II–III Ebling (III–V Norwood/Hamil-ton) were treated with 0.25 mg/day of dutasteride, demonstrating an improvement in 60% at 1 year of treatment rising to 80% at 2 years. The alopecia was localized to the frontotemporal region followed by the vertex and frontal areas..A combination of 0.5 mg daily dose of dutasteride and 2.5 mg/day finasteride for 6 months was used in 14 *postmenopausal women* with FAGA.M

and 5 women with FAGA.M (central hirsutism degree 9 and nodulo-cystic acne), corresponding to persistent adrenarche syndrome with a improvement of alopecia in all cases, and of hirsutism and acne in 4 cases (80%).

Special Considerations

1. Women who are or may be pregnant should not handle dutasteride. If contact is made with a leaky capsule, the contact area should be washed immediately with soap and water.
2. Blood donation is also contraindicated for those taking dutasteride for at least **6 months** after the last dose of medication.

Drug Interactions

Dutasteride is metabolized by CYP 3A4; thus, its blood concentrations may increase in the presence of CYP3A4 inhibitors, such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, isoniazid, rifampicin and ciprofloxacin.

Adverse Effects

1. A greater number of sexual side effects, particularly decreased libido, occurred with the 2.5 mg dose of dutasteride (9%) than with finasteride 5 mg (3%).
2. There is a relative risk reduction of 22.8% in the number of detected prostate cancers in the dutasteride group versus placebo though the tumors if they develop are of high-grade.
3. As the half-life of dutasteride is 5 weeks, compared with 6–8 hours for finasteride it can have long standing effects that can be difficult to reverse.

DANAZOL

Classification

Antiestrogen, androgen, antiinflammatory.

Mechanism of Action

Suppresses pituitary–ovarian axis and is a gonadal inhibitor. Inhibits ovarian output of FSH and LH; decreases growth of abnormal breast; increases level of C4 complement.

Uses/Dosage

This drug has two dermatological indications. The first is autoimmune progesterone dermatitis which can present

occasionally as recurrent urticaria with a premenstrual flare. In this the use of danazol in a pulse fashion is virtually diagnostic. The other indication is hereditary angioedema.

1. Autoimmune progesterone dermatitis: Successful prophylactic treatment with danazol in two patients at a dose of 200 mg twice daily, starting one to 2 days before menstruation and continuing for 3 days thereafter has been reported by Shahar et al.
2. Hereditary angioedema: For prophylaxis(Cicardi M) a run-in period of 400–600 mg daily of danazol for 1 month is followed by a slow tapering to 100–200 mg daily to determine the minimum dose that will maintain remission (C1-INH level around 50% of normal; C4 within normal range; complete remission of angioedema).

   Danazol (600 mg daily) or stanozolol (6–8 mg daily) has been used from five to 10 days preoperatively to 3 days postoperatively to prevent flare of the attack.
3. Cholinergic pruritus: 200 mg TDS for 1 month.
4. Livedoid vasculitis: 200 mg OD.

Drug Interaction

Danazol increases effects/toxicity of oral anticoagulants.

Danazol decreases effects/toxicity of carbamazepine, oral anticoagulants, insulin, cyclosporine.

Special Considerations

Use with caution in patients with the following conditions: migraine headaches; seizure disorders; cardiac, hepatic, renal dysfunction; hereditary angioedema.

This drug is strongly associated with hepatotoxicity (females, patients > 35 years are at higher risk).

Perform mammography and breast cyst biopsy before and during treatment as clinically indicated.

To minimize possible photosensitivity reaction, apply adequate sunscreen and use proper covering when exposed to strong sunlight.

Examine breasts regularly. Notify treating physician if you notice enlargement of breast, nodules.

Side Effects

Common

Weight gain, vaginal bleeding, menstrual irregularities, emotional instability, hirsutism, decreased breast size, vaginal dryness, deepening voice.

Rare

Hepatic dysfunction, pericarditis, respiratory depression, cholestatic jaundice, hepatitis, hepatic adenoma, peliosis hepatis, benign intracranial hypertension.

Monitoring

- Liver enzymes
- Signs of virilization, menstrual irregularities, persistent erection, GI symptoms, e.g. vomiting, nausea, visual disturbances
- Signs and symptoms of hepatotoxicity.
- Signs of undiagnosed vaginal bleeding, noting frequency and precipitating factors
- Symptoms of pseudotumor cerebri: e.g. headache, nausea, vomiting, visual disturbances.

Special Groups

Pregnancy category X.

FURTHER READING

1. Amory JK, Wang C, Swerdloff RS, Anawalt BD, Matsumoto AM, Bremner WJ, et al. The effect of 5alpha reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men. J Clin Endocrinol Metab. 2007;92:1659-65.
2. Blumeyer A, Tosti A, Messenger A, Reygagne P, Del Marmol V, Spuls PI, et al.; European Dermatology Forum (EDF). Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men. J Dtsch Dermatol Ges. 2011;9(Suppl 6):S1-57.
3. Camacho-Martínez FM. Hirsutism. In Blume-Peytavi U, Tosti A, Whiting DA. Trüeb RM, editors. Hair Growth and Disorders. Berlin Heidelberg: Springer-Verlag; 2008.
4. Cicardi M, Zingale L. How do we treat patients with hereditary angioedema?. Transfus Apheresis Sci. 2003;29:221-7.
5. Collodel G, Scapigliati G, Moretti E. Spermatozoa and chronic treatment with finasteride: a TEM and FISH study. Arch Androl. 2007;53:229-33.
6. De Villez RL. Topical minoxidil therapy in hereditary androgenetic alopecia. Arch Dermatol. 1985;121:197-202.
7. Erenus M, Yücelten D, Durmuşoğlu F, Gürbüz O. Comparison of finasteride versus spironolactone in the treatment of idiopathic hirsutism. Fertil Steril. 1997;68(6):1000-3.
8. Farkas H, Gyeney L, Gidofalvy E, Füst G, et al. The efficacy of short term danazol prophylaxis in hereditary angioedema patients undergoing maxillofacial and dental procedures. J Oral Maxillofac Surg. 1999;57:404-8.
9. Finasteride Male Pattern Hair Loss Study Group. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. Eur J Dermatol. 2002;12(1):38-49.

10. Gubelin Harcha W, Barboza Martínez J, Tsai TF, Katsuoka K, Kawashima M, Tsuboi R, et al. A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with androgenetic alopecia. J Am Acad Dermatol. 2014;70(3):489-98.
11. Gupta AK, Charrette A. The efficacy and safety of 5α-reductase inhibitors in androgenetic alopecia: a network meta-analysis and benefit-risk assessment of finasteride and dutasteride. J Dermatolog Treat. 2014;25(2):156-61.
12. Iorizzo M, Vincenzi C, Voudouris S, et al. Finasteride treatment of female pattern hair loss. Arch Dermatol 2006;142:298-302.
13. Irwig MS. Persistent sexual side effects of finasteride: could they be permanent? J Sex Med. 2012;9(11):2927-32
14. Jung JY, Yeon JH, Choi JW, Kwon SH, Kim BJ, Youn SW, et al. Effect of dutasteride 0.5 mg/d in men with androgenetic alopecia recalcitrant to finasteride. Int J Dermatol. 2014;5.
15. Kelestimur F, Everest H, Unluhizarci K, et al. A comparison between spironolactone and spironolactone plus fi nasteride in the treatment of hirsutism. Eur J Endocrinol. 2004;150:351-4.
16. Kim GK, Del Rosso JQ. Oral Spironolactone in Post-teenage Female Patients with Acne Vulgaris: Practical Considerations for the Clinician Based on Current Data and Clinical Experience. J Clin Aesthet Dermatol. 2012;5(3):37-50.
17. Kohler C, Tschumi K, Bodmer C, Schneiter M, et al. Effect of finasteride 5 mg (Proscar) on acne and alopecia in female patients with normal serum levels of free testosterone. Gynecol Endocrinol. 2007;23:142-5.
18. Krunic A, Ciurea A, Scheman A. Efficacy and tolerance of acne treatment using both spironolactone and a combined contraceptive containing drospirenone. J Am Acad Dermatol. 2008;58(1):60-2.
19. Liu KE, Binsaleh S, Lo KC, et al. Propecia-induced spermatogenic failure: a report of two cases. Fertil Steril. 2007; Dec 3.
20. Lumachi F, Rondinone R. Use of cyproterone acetate, fi nasteride, and spironolactone to treat idiopathic hirsutism. Fertil Steril. 2003;79: 942-6.
21. Lynn R, Krunic A. Therapeutic hotline. Treatment of androgenic alopecia with finasteride may result in a high grade prostate cancer in patients: fact or fiction? Dermatol Ther. 2010;23(5):544-6.
22. Mondaini N, Gontero P, Giubilei G, Lombardi G, Cai T, Gavazzi A, et al. Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon? J Sex Med. 2007;4:1708-12.
23. Motofei IG, Rowland DL, Georgescu SR, Baconi DL, Dimcevici NP, Paunica S, et al. A pilot study on the sexual side effects of finasteride as related to hand preference for men undergoing treatment of male pattern baldness. BJU Int. 2013;111(4 Pt B):E221-6.
24. Oliveira-Soares R, E Silva JM, Correia MP, et al. Finasteride 5 mg/day Treatment of Patterned Hair Loss in Normo-androgenetic Postmenopausal Women. Int J Trichology. 2013;5(1):22-5.
25. Olsen EA, Hordinsky M, Whiting D, Stough D, Hobbs S, Ellis ML, et al.; Dutasteride Alopecia Research Team. The importance

of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride. J Am Acad Dermatol. 2006;55(6):1014-23.
26. Olsen EA, Messenger AG, Shapiro J, Bergfeld WF, Hordinsky MK, Roberts JL, et al. Evaluation and treatment of male and femalepattern hair loss. J Am Acad Dermatol. 2005;52(2): 301-11.
27. Overstreet JW, Fug VL, Gould J, Howards SS, Lieber MM,Hellstrom W, et al. Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men. J Urol 1999;162:1295-300.
28. Rogers NE, Avram MR. Medical treatments for male and female pattern hair loss. J Am Acad Dermatol. 2008;59(4):547-66; quiz 567-8. doi:
29. Sahin Y, Dilber S, Keleştimur F. Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. Fertil Steril. 2001;75(3):496-500.
30. Shahar E, Bergman R, Pollack S. Autoimmune progesterone dermatitis: effective prophylactic treatment with danazol. Int J Dermatol. 1997;36:708-11.
31. Sinclair R, Patel M, Dawson TL Jr, Yazdabadi A, Yip L, Perez A, et al. Hair loss in women: medical and cosmetic approaches to increase scalp hair fullness. Br J Dermatol. 2011;165 (Suppl 3):12-8.
32. Spritzer PM, Lisboa KO, Mattiello S, et al. Spironolactone as a single agent for long-term therapy of hirsute patients. Clin Endocrinol (Oxf). 2000; 52: 587-94.
33. Yemisci A, Gorgulu A, Piskin S. Effects and side-effects of spironolactone therapy in women with acne. J Eur Acad Dermatol Venereol. 2005;19(2):163-6.
34. Yeon JH, Jung JY, Choi JW, Kim BJ, Youn SW, Park KC, et al. 5 mg/day finasteride treatment for normoandrogenic Asian women with female pattern hair loss. J Eur Acad Dermatol Venereol. 2011;25(2):211-4.

SERENOA REPENS

Saw Palmetto.

Constituents

- Fatty acids: capric, caprylic, lauric, cis-linoleic, myristic, palmitic and stearic acid
- Steroids: beta-sitosterol, campesterol, cycloartenol, lupeol, lupenone and stigmasterol
- Aliphatic alcohols
- Polyprenic compounds: arabinose, flavonoids, galactose, glucose and uronic acid
- Anthranilic acid
- Carotenes
- Lipase
- Tannins.

Classification

Botanical DHT inhibitor.

Mechanism of Action

Studies with a liposterolic extract of saw palmetto berries showed that it reduced the uptake by tissue specimens of both testosterone and dihydrotestosterone (DHT) by more than 40% suggesting antiandrogenic activity. Further, the extract inhibited binding of DHT to its receptor and blocked the conversion of testosterone to DHT by inhibiting the activity of 5α-reductase. The berries also inhibit cyclooxygenase and 5-lipoxygenase pathways, thereby preventing the biosynthesis of inflammation-producing prostaglandins and leukotrienes.

Pharmacokinetics

Analysis of saw palmetto components including lauric acid, oleic acid, and beta-sitosterol in rats revealed wide distribution. Highest concentrations were found in abdominal fat, prostate, and skin, while lesser amounts were found in bladder and liver.

Uses

Saw palmetto is a small, slow-growing palm native to southeastern United States. The fruits are a rich source of fatty acids and phytosterols and have been used to promote urination, reduce inflammation, and for treatment of prostatic conditions, such as benign prostatic hyperplasia (BPH). Saw palmetto has been studied in many controlled clinical trials. Whereas data from some studies indicate that it improves lower urinary tract symptoms in patients with benign prostatic hyperplasia conflicting data suggest no such effects.

In dermatology it has been used as a agent for pattern alopecia.

Dosage

Disorder (Unapproved)	*Dose*
Pattern Alopecia	160 mg OD/BD

The use of this drug for alopecia is consequent to a study by Prager et al. The dose recommended is 160 mg a day. A recent study (Rossi et al.) compared its results with finasteride in clinically diagnosed cases of mild to moderate AGA. One group received Serenoa repens 320 mg every day for 24 months, while the other received finasteride 1 mg every day for the same period. The results showed that *only* 38% of patients treated with serenoa repens had an increase in hair

growth, while 68% of those treated with finasteride noted an improvement. Thus, while serenoa repens could lead to an improvement of androgenetic alopecia, finasteride is better and acts in both the frontal area and the vertex, while serenoa repens is effective in the vertex area.

Drug Interaction

- **Anticoagulants:** Saw palmetto may have additive anticoagulant effect
- **UGT (Uridine 5'-diphospho-glucuronosyltransferase) substrates:** Saw palmetto inhibits UGT enzymes in vitro and can increase the side effects of drugs metabolized by them
- **CYP 450 substrates:** Saw palmetto inhibits cytochrome P450 3A4, 2D6, and 2C9 and may interfere with the actions of drugs metabolized by these enzymes.

Special Considerations

In a recent study, of the 37 saw palmetto-containing supplements tested using DNA barcoding, 6% contained related species that cannot be legally sold as herbal dietary supplements in the US. The identity of 9% supplements remains inconclusive. This purity of the product is an issue.

Side Effects

- Although infrequent, saw palmetto may cause intraoperative hemorrhage, GI complaints, nausea, vomiting, and diarrhea. It may also have additive anticoagulant effects and prolong bleeding time
- A case of severe intraoperative hemorrhage following consumption of saw palmetto has been reported
- Hematuria and coagulopathy,acute pancreatitis, liver damage and hot flashes have been reported.

BIBLIOGRAPHY

1. Bayne CW, Donnelly F, Ross M, Habib FK. Serenoa repens (Permixon): a 5 alpha-reductase types I and II inhibitor-new evidence in a coculture model of BPH. Prostate. 1999;40(4):232-41.
2. El-Sheikh MM, Dakkak MR, and Saddique A. The effect of Permixon on androgen receptors. Acta Obstet Gynecol Scand. 1988;67(5):397-9.
3. Little DP, Jeanson ML. DNA barcode authentication of saw palmetto herbal dietary supplements. *Sci Rep.* 2013;3:3518.
4. Prager N, Bickett K, French N, Marcovici G. A randomized, double-blind, placebo-controlled trial to determine the effectiveness of botanically derived inhibitors of 5-alpha-reductase in the

treatment of androgenetic alopecia. J Altern Complement Med. 2002;8(2):143-52.
5. Rossi A, Mari E, Scarno M, Garelli V, Maxia C, Scali E, Iorio A, Carlesimo M.Comparitive effectiveness of finasteride vs Serenoa repens in male androgenetic alopecia: a two-year study. Int J Immunopathol Pharmacol. 2012;25(4):1167-73.
6. Saw palmetto. Natural Medicines Comprehensive Database Web site. Accessed at www.naturaldatabase.com on August 7, 2009.

ORAL CONTRACEPTIVES

There are some excellent texts on the use of OCP in gynecology but our focus will be largely on dermatological indications. A brief overview is provided of OCP to understand the dose, effects and adverse effects of the preparation. In dermatology these drugs are increasingly being used for acne and hirsutism and we will be focusing largely on the two OCPs with antiandrogens, that, i.e. cyproterone and drospirenone.

Mode of Action

OC work by suppression of the midcycle LH surge occurs alongside a decrease in gonadotropin-releasing hormone pulse frequency, suppression of LH and steroidogenesis, and suppression of folliculogenesis and follicle-stimulating hormone (FSH). OCs suppress ovulation, formation of the corpus luteum, and progesterone.

Combination OCs contain an estrogen and a progestin. The estrogen suppresses FSH, which in turn suppresses follicle growth. Thus, the estrogen component exerts its main effect on FSH. In the normal menstrual cycle, as estrogen levels increase during the follicular stage, FSH levels are suppressed. The progestin in the OC suppresses LH by decreasing gonadotropin-releasing hormone pulse frequency and possibly also by exerting a direct effect on the pituitary gland.

The progestin suppresses steroidogenesis, the LH surge, and as a result, ovulation. In a low percentage of patients, a follicle can grow without a mild elevation in progestin. Thus, the only way to judge the efficacy of an OC is to observe how effective it is in preventing pregnancy.

Contraceptive Dosing

When sequential OCs were first introduced in the 1960s, the intent was to provide estrogen in a manner that would mimic the natural menstrual cycle. This form of contraception had more adverse events associated with its use, due more likely to high dosing of estrogen than to the sequential nature of the OCs.

The fixed combination (21 active pills, 7 inert pills) that eventually was derived remains the most popular type of OC. During the 7 hormone-free days, folliculogenesis occurs, which is what had been intended with the original sequential OCs. During the hormone-free interval, FSH and LH levels remain suppressed; however, by the third or fourth day, these levels start to increase, along with estrogen levels. At the end of the 7-day period, the active component of the OC is reintroduced, once again suppressing FSH and LH levels.

High estrogen levels have been the main cause of serious side effects from OCs. The dose of progestin also has been lowered from the first formulations. The original progestins were derived from testosterone. Newer 19-nortestosterone derivatives have been structurally modified to reduce androgenic activity. In the 1970s, the high estrogen content of the pill was found to be associated with serious vascular side effects. Thrombosis, both venous and arterial, appeared to be related to higher estrogen doses in early formulations. Consequently, doses were lowered and the shift was made to phasic preparations, which reduced the risk of thromboembolism associated with OC use.

Androgenicity was believed to be the cause of some of the side effects. The newer formulations appeared to be less androgenic and to possibly have less impact on carbohydrate and lipoprotein metabolism. Cycle control was similar to that of older products. Changes in coagulation-promoting and antithrombotic factors were minor.

The fixed combination followed by unopposed estrogen was eventually derived. Theoretically, this formulation lessens withdrawal symptoms such as headaches and mood changes. Recently, a fixed-combination OC was developed with 24 days of active pills and 4 days of inert pills. In addition, a unique progestin, drospirenone—which is closest in pharmacokinetics to progesterone itself and similar in structure to spironolactone—was developed.

A list of common OCP in India are given in Table 4.8 with their androgenic activity.

Risks Associated with OCPs

The most serious risks associated with modern OC use are vascular—venous and arterial. Venous thrombosis is a risk faced to some extent by all women who are using OCs. In fact, the estrogen component of OCs increases the risk for deep venous thrombosis and pulmonary embolism 3- to 4-fold. Even rarer are arterial complications, which appear to be related, at least epidemiologically, to the estrogen component. However, predicting who will have these problems with estrogen doses lower than 35 μg is difficult. Risk for arterial events associated with OCs was first publicized in the early

Table 4.8: Common OCP in India with their androgenic potential

Brand Name	*Composition*	*Androgenic Activity**
BANDHAN	Ethinylestradiol 0.03 mg, Levonorgestrel 0.15 mg	Levonorgestrel 1 mg = 8.3
MALA-D TAB	Ethinylestradiol 0.03 mg, Norgestrel 0.30 mg	Norgestrel 1 mg = 8.3
OVARAL-L TAB	Ethinylestradiol 0.03 mg, Levonorgestrel 0.15 mg	Levonorgestrel 1 mg = 8.3
FEMILON TAB	Ethinylestradiol 0.02 mg, Desogestrel 0.15 mg	Desogestrel 1 mg = 3.4
NOVELON TAB	Ethinylestradiol 0.02 mg, Desogestrel 0.15 mg	Desogestrel 1 mg = 3.4
DRONIS-20	Ethinylestradiol 0.03 mg, Drospirenone 3 mg	Drospirenone 1 mg = 0
DRONIS-30/ Yasmin	Ethinylestradiol 0.03 mg, Drospirenone 3 mg	Drospirenone 1 mg = 0

* Relative to 1 mg of norethindrone

1970s. Preventing these complications rests not so much on changing the OCs themselves but on monitoring women who are taking the pill. These events are more likely to occur in high-risk patients, such as smokers older than 35 years. A list of conditions that are CI to OC use are listed below.

Contraindications to using OCP

Atherosclerosis
Biliary disease
Breast cancer
Deep venous thrombosis or pulmonary embolism (history)
Diabetes mellitus with end-organ disease
Heart disease, prior myocardial infarction, or stroke
Hypertension (uncontrolled)
Immobilization (prolonged)
Liver disease
Migaine with focal neurologic symptoms
Pregnancy
Smoking, especially in women age > 35 years

Adverse Effects

a. Mild Adverse Effects

1. *Nausea, mastalgia, breakthrough bleeding, and edema* are related to the amount of **estrogen** in the preparation. These effects can often be alleviated by a shift to a preparation containing smaller amounts of estrogen or to

agents containing progestins with more androgenic effects.

2. Changes in serum proteins and other effects on endocrine function (see above) must be taken into account when thyroid, adrenal, or pituitary function is being evaluated. Increases in sedimentation rate are thought to be due to increased levels of fibrinogen.
3. Headache is mild and often transient. However, migraine is often made worse and has been reported to be associated with an increased frequency of cerebrovascular accidents. When this occurs or when migraine has its onset during therapy with these agents, treatment should be discontinued.
4. Withdrawal bleeding sometimes fails to occur—most often with combination preparations—and may cause confusion with regard to pregnancy. If this is disturbing to the patient, a different preparation may be tried or other methods of contraception used.

b. Moderate Adverse Effects

Any of the following may require discontinuance of oral contraceptives:

1. Breakthrough bleeding is the most common problem in using progestational agents alone for contraception. It occurs in as many as 25% of patients. It is more frequently encountered in patients taking **low-dose** preparations than in those taking combination pills with higher levels of progestin and estrogen.
2. Weight gain is more common with the combination agents containing androgen-like progestins. It can usually be controlled by shifting to preparations with less progestin effect or by dieting.
3. Increased skin pigmentation may occur, especially in dark-skinned women. It tends to increase with time, the incidence being about 5% at the end of the first year and about 40% after 8 years. It is thought to be exacerbated by vitamin B deficiency. It is often reversible upon discontinuance of medication but may disappear very slowly.
4. Acne may be exacerbated by agents containing androgen-like progestins, whereas agents containing large amounts of estrogen usually cause marked improvement in acne.
5. Hirsutism may also be aggravated by the "19-nortestosterone" derivatives, and combinations containing nonandrogenic progestins are preferred in these patients.
6. Ureteral dilation similar to that observed in pregnancy has been reported, and bacteriuria is more frequent.

7. Vaginal infections are more common and more difficult to treat in patients who are receiving oral contraceptives.
8. Amenorrhea occurs in some patients. Following cessation of administration of oral contraceptives, 95% of patients with normal menstrual histories resume normal periods and all but a few resume normal cycles during the next few months. However, some patients remain amenorrheic for several years. Patients who have had menstrual irregularities before taking oral contraceptives are particularly susceptible to prolonged amenorrhea when the agents are discontinued.

c. Severe Adverse Effects

1. Vascular disorders: Thromboembolism was one of the earliest of the serious unanticipated effects to be reported and has been the most thoroughly studied.

The risk for this disorder is increased during the **first month** of contraceptive use and remains constant for several years or more. The risk returns to normal within a month when use is discontinued. The risk of venous thrombosis or pulmonary embolism is increased among women with predisposing conditions, such as stasis, altered clotting factors such as antithrombin III, increased levels of homocysteine, or injury. The incidence of venous thromboembolism appears to be related to the estrogen but not the progestin content of oral contraceptives and is not related to age, parity, mild obesity, or cigarette smoking.

2. Myocardial infarction: The use of oral contraceptives is associated with a slightly higher risk of myocardial infarction in women who are obese, have a history of preeclampsia or hypertension, or have hyperlipoproteinemia or diabetes. There is a much higher risk in women who smoke. The progestational component of oral contraceptives decreases HDL cholesterol levels, in proportion to the androgenic activity of the progestin. The net effect, therefore, will depend on the specific composition of the pill used and the patient's susceptibility to the particular effects.

3. **Cerebrovascular disease:** The risk of stroke is concentrated in women over age 35. It is increased in current users of oral contraceptives but not in past users. However, subarachnoid hemorrhages have been found to be increased among both current and past users and may increase with time.In summary, available data indicate that oral contraceptives increase the risk of various cardiovascular disorders at all ages and among both smokers and nonsmokers. However, this risk appears to be concentrated in women 35 years of age or older who are heavy smokers.

OCP IN HYPERANDROGENIC STATES

Approximately 1–2% of serum testosterone is active and unbound; the remainder is bound to 1 of 2 proteins, either albumin or sex hormone–binding globulin (SHBG). Albumin has a high capacity but low affinity for testosterone, so it readily dissociates from testosterone. SHBG, on the other hand, has a high affinity but low capacity for testosterone and binds to testosterone preferentially over estrogen.

Women with acne, hirsutism, or irregular menses (symptoms of hyperandrogenism) may have higher free testosterone levels—due to lower levels of SHBG, higher levels of total testosterone, or both. Higher free testosterone then results in increased sebum production and hair growth. Studies have shown that Cyproterone acetate or drospirenone containing combined oral contraceptives are both equally good for hisrustism (Kelekci KH).

Free testosterone is the primary androgen associated with acne. Testosterone is produced directly by the ovaries and the adrenal glands. Free testosterone levels are determined by both total testosterone and SHBG levels. In susceptible skin cells, free testosterone is then converted to DHT by the 5α-reductase enzyme. DHT in turn acts on the glands' androgen receptors to promote sebum production. Sebum production is lessened when free testosterone levels are decreased.

Mode of Action

1. First, they decrease **testosterone production** by the ovaries, adrenal glands, and peripheral sources and suppress production of luteinizing hormone from the pituitary gland, which in turn decreases androgen (testosterone, androstenedione) synthesis by the ovaries.
2. They also reduce **adrenal production** of dehydroepiandrosterone sulfate (DHEAS) and androstenedione. Peripherally, OCs decrease **3 alpha-androsterone glucuronide**, a DHT metabolite that correlates highly with 5 alpha -reductase activity.
3. They decrease testosterone bioavailability by **increasing SHBG.** Their ethinyl estradiol (EE) component increases SHBG to bind testosterone and thereby lower free testosterone levels. Estrogen and progestin work synergistically to decrease unbound testosterone by a mean of 45%.
4. They inhibit conversion of free testosterone to DHT. Their progestin component directly inhibits the enzymatic activity of 5α-reductase in the hair follicles and skin.

Measuring Androgen Levels

Many studies have shown *clinical improvement* in acne after OC treatment, but *few* studies have shown correlating changes in androgen levels. Use of serum androgen assays comes with many challenges. Assays are often designed to measure androgen levels in males, which are much higher than those in females. Assays and techniques used vary by study and laboratory. Thus, there are no absolute numbers that can be used for reference ranges or for posttreatment targets. Hormone levels also vary substantially throughout the treatment cycle. Serum measurements, therefore, are likely to be unreliable.In addition, there are no reliable data on optimal timing of these measurements in patients with acne. Most important, androgen trends across the population cannot predict an individual's clinical course. Therefore, measurement of testosterone levels usually is not helpful in the clinical management of women with acne.

OCPs Use for Acne

Three OCs have received approval from the US Food and Drug Administration for the treatment of acne, even though many others have been used in various trials in acne (Table 4.9) EE 20 μg plus drospirenone 3 mg is indicated for treatment of moderate acne vulgaris in females who are at least 14 years old, have reached menarche, and require or request an OC for contraception. Though Diane 35 is not available in the US it is available in India but is not approved for acne.

Van Vloten et al. had compared EE 30 μg/drospirenone 3 mg with EE 35 μg/cyproterone 2 mg over **9** treatment cycles. Though both were found to be effective the former was better at 9 months. The inflammatory and noninflammatory lesions were reduced by 73.5% and 50%, respectively, in the EE 30 μg/drospirenone 3 mg group and by 75% and 60%, respectively, in the EE 35 μg/cyproterone 2 mg group. The logic of using the various dosed pills (24/4 Vs 21/7) is discussed in the following sections.

Who Qualifies and Does Not Qualify for Acne Treatment with OCs Containing Drospirenone?

1. Healthy nonsmoking women.
2. Recalcitrant lower face, jawline, and neck acne.
3. Women with hyperandrogenic conditions (hirsutism, alopecia).
4. Women who have had difficulty adhering to an OC schedule because of untoward side effects from high estrogen levels but who are now willing to take a low-dose OC.

Table 4.9: Oral contraceptive with anti-acne benefits

	Ethinyl estradiol (μg)	*Progestin*
FDA Approved for Acne*		
Estrostep	20/30/35	Norethindrone 1 mg
Ortho Tri-Cyclen	35	Norgestimate 180/215/250 μg
Yaz	20	Drospirenone 3 mg
Acne benefits examined in studies		
Alesse	20	Levonorgestrel 100 μg
Yasmin	30	Drospirenone 3 mg
Microgynon	30	Levonorgestrel 150 μg
Nordette	30	Levonorgestrel 150 μg
Levlen	30	Levonorgestrel 150 μg
Femodene	30	Gestodene 75 μg
Femovan	30	gestodene 75 μg
Ortho-Cept	30	Desogestrel 150 μg
Unavailable in United States		
Diane-35	35	Cyproterone 2 mg

*FDA indicates US Food and Drug Administration

5. Women who have acne and premenstrual dysphoric disorder.
6. Teenagers who have failed oral therapy.

Patients who do *not* qualify include women with a contraindication to OC therapy, including thromboembolic disorders, severe or uncontrolled hypertension, migraine with focal neurologic symptoms, some malignancies, and pregnancy; heavy smokers (≥15 cigarettes per day), patient older than 35 years.

OC vs Antibiotics

A recent metanalysis has shown that although antibiotics may be superior at 3 months, OCPs are equivalent to antibiotics at 6 months in reducing acne lesions and, thus, may be a better first-line alternative to systemic antibiotics for long-term acne management in women (Koo et al.).

Prescription Logic of 24/4 and 21/7 Cycle Pills

The contraceptive pill has been a revolution of the last 40 years. Although reduction in the concentration of ethinyl estradiol (EE) has reduced the incidence of negative systemic side effects such as water retention, edema and swollen breasts, the *low estrogen* dose may be associated with *spotting* and *hypomenorrhea* or amenorrhea in the long term, as well as *dyspareunia* due to reduced vaginal trophism, which may induce women to suspend use of the

drug. The choice of progesterone therefore involves not only its effect on the endometrium in synergy with estrogen, but also possible residual androgenic activity which may have negative metabolic repercussions. Indeed, addition of a progesterone, especially androgen-derived, attenuates the positive metabolic effects of estrogen. Two new monophasic oral contraceptives are in use. They contain 30 μg or 20 μg EE and a new progesterone, drospirenone, derived from spironolactone, which has antiandrogenic and antimineral ocorticoid activity similar to endogenous progesterone. In women with mild to moderate acne, the formulation with 30 μg EE has been found to be as effective as 2 mg cyproterone acetate combined with 35 μg EE (Diane-35). The latter pills again have two pill packs depending on the amount of estrogen.

It is important to understand the logic of these two packs and how to use them in clinical practice.

1. **Overweight women:** They may benefit from the formulation with 20 μg EE, whereas the formulation with at least 30 μg EE should be more appropriate for underweight women. This as estrogen pills are known to cause weight gain.
2. **Menstrual cycle characteristics:** This is the most important factor that determines the choice of formulation. Randomised control studies comparing the new formulation with others containing second or third generation progesterones have found similar efficacy in cycle control and incidence of spotting. But in clinical practice if a women has *normal* cycles,30 μg EE is enough. In cases of *hypomenorrhea and/or amenorrhea* at least this dose of EE plus drospirenone may be used. Women with *hypermenorrhea* run the risk of spotting if an inappropriate drug is chosen. A solution is to use 30 μg EE/drospirenone from day 5 of the cycle. Thus a higher dose of estrogen 30 μg vs 20 μg can help reduce spotting
3. **Premenstrual tension:** A dose of at least 30 μg EE associated with drospirenone reduces or even prevents symptoms.
4. **Headache:** This is consequential to the estrogen and thus a lower dose of estrogen is needed (20 μg). Although the progesterone component is not considered to affect headache, good results have been obtained with drospirenone, the antimineralocorticoid effects of which reduce blood pressure and improve symptoms.
5. **Mastodynia:** Formulations with 20 μg EE and drospirenone are particularly indicated in women with preexisting mastodynia, fibrocystic breast manifestations or who develop mastodynia as a side effect of oral contraceptive use. Since high plasma concentrations of androgens have been recorded in these women, a progesterone with

antiandrogen and antiedema activity can be beneficial. Thus the use of drospirenone based OCP is justified in such cases.

Finally, it is worth recalling that monophasic pills with low estrogen doses, such as the formulations mentioned above (3 mg DRSP/20 μg EE-24/4), ensure good mood control, reducing the depressive symptoms often associated with oral contraceptive use. In conclusion, formulations containing drospirenone are a valid alternative to conventional oral contraceptives for the personalization of these drugs.

COMBINATION OCP

Though the use of OCP is largely restricted to gynecologist we will focus on a commonly prescribed OCP which has 24 active pills with a low dose of EE with drosperinone. This has been used both in acne and hirsutism.

Between 1973 and 1974, the US Food and Drug Administration first approved several low dose pills. By 1975, no pill recommended for contraception had more than 50 μg of estrogen, with most containing estrogen levels in the range of 20–30 μg. A decrease in the progesterone component to 1 mg or less as well as different progestins were also introduced into the oral contraceptive pill (OCP) formulations. Today, newer OCPs have not only altered estrogen and progestin levels, but also have varied the number of active pills. These changes in OCP have had the goal of acceptable contraceptive efficacy with minimal side effects and risks.

Drospirenone/ethinyl Estradiol

24 light pink tablets, each containing 3 mg drospirenone (DRSP) and 0.02 mg ethinyl estradiol (EE) as betadex clathrate.

Mechanism of Action

The basic mechanism has been delineated above. The addition of *drospirenone* which has both antimineralocorticoid and antiandrogenic effects, minimizes the potentially negative effect that progestins can have on acne. This also binds to the renin-angiotensin-aldosterone system, blocks the aldosterone receptor on the kidney, and promotes excretion of sodium and water, thus decreasing bloating, breast tenderness, and water weight gain. The 24/4 regimen with EE 20 μg/drospirenone 3 mg extends the antimineralocorticoid and antiandrogenic activity by 3 days, and the 30-hour half-life of drospirenone extends the progestogenic effect through the 4 days with hormone-free pills.

Using the formulation of drospirenone 3 mg/ethinyl estradiol 20 μg (3 mg DRSP/20 μg EE-24/4) in women with

PMDD is desirable as the progestin may ameliorate physical symptoms and the shortened hormone-free interval (4 hormone-free days) will provide greater suppression of follicle development and a more stable level of exogenous hormones throughout the cycle.

The only other DRSP containing OCP that is currently marketed is the OCP with DRSP 3 mg and EE 30 μg. The difference between 3 mg DRSP/20 μg EE-24/4 and 3 mg DRSP/30 μg EE-21/7 is that each tablet in the prior formulation contains a lower dose of EE (20 vs 30 μg) and has a shorter hormone-free interval (4 days vs 7 days). The *shorter* hormone-free interval leads to a *greater suppression* of follicle development and a more *stable* hormone time frame than the traditional regimens of 21-day hormone containing pill and 7 days placebo. As expected, greater pituitary and ovarian suppression are seen with the shorter hormone-free interval.

Because of this effect, the 24/4 regimen should better alleviate symptoms, such as pelvic pain, headaches, bloating and breast tenderness that are commonly reported during the 7 days of placebo pills by women taking a regimen of 21 days of active pills followed by seven hormone free pill days (21/7 regimen). Extending the days on active treatment reduces hormone withdrawal effects in most women since the fluctuations in hormone levels is minimal.

Uses

Common indication and duration of use are listed in Box 4.1
Acne: Acne vulgaris is a skin condition with a multifactorial etiology including androgen stimulation of sebum production. While the combination of EE and DRSP increases sex hormone binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been conclusively established.

Dosage

We are detailing the use of the 24 pill preparation as this is FDA approved for acne.

Instruct the patient to begin taking the OCP either on the first day of her menstrual period (day 1 start) or on the first Sunday **after** the onset of her menstrual period (Sunday start).

Day 1 Start

During the first cycle, instruct the patient to take one pill, beginning on day 1 of her menstrual cycle. (The first day of menstruation is day 1). After taking one pill for 24 consecutive

Box 4.1: Common uses of OCP's in medicine

Disorder (FDA approved/Unapproved)	*Dose/Duration*
Moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control (Maloney JM)	6 cycles
Hisrustism EE/DRSP plus spironolactone 100 mg	6–9 cycles
Treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception	12 cycles

days, 4 days break is to be ensured after which a new packet can be started. Time to take is preferably after the *evening* meal or at bedtime with some liquid, as needed.

It is not effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start

Here the patient takes the pill from the first Sunday after the onset of the menstrual cycle.

Drug Interaction

Medications that decrease serum concentrations of hormonal contraception

Anticonvulsants
Anti-infective agents
Barbiturates
Carbamazepine
Phenytoin
Rifampin
Topiramate
Vigabatrin

Drug Increasing the Plasma Concentrations of COC

Atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors, such as itraconazole or ketoconazole may increase plasma hormone concentrations. Non-nucleoside reverse transcriptase inhibitors can also increase levels of OC.

Combined Oral Contraceptives on Other Drugs

Decrease plasma concentrations of lamotrigine.

Special Considerations

1. Women over 35 years old who smoke should not use this drug.
2. Avoid in Renal impairment, adrenal insufficiency, a high risk of arterial or venous thrombotic diseases, undiagnosed abnormal uterine bleeding, breast cancer or other estrogen- or progestin-sensitive cancer, liver tumors or liver disease and Pregnancy.
3. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding.
4. **Management of missed tablets:** If the user is **less than 12 hours** late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.
   If she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:
   i. Tablet-taking must never be discontinued for longer than 7 days.
   ii. Seven days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic–pituitary–ovarian axis.

Side Effects

Common

The most common side effects are nausea, breast tenderness, headache and irregular cycles.

Rare

1. Thromboembolic disorders and other vascular problems: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, retinal thrombosis, myocardial infarction and stroke), hypertension.
2 Hyperkalemia: As it contains 3 mg of the progestin DRSP which has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone, it should not be used in patients with conditions that predispose to hyperkalemia (that is, renal impairment, hepatic impairment,and adrenal insufficiency).

3. Carcinoma of the breasts and reproductive organs
4. Liver disease
5. High blood pressure
6. Gallbladder disease
7. Carbohydrate and lipid metabolic effects: Hyperkalemia, hypertriglyceridemia, changes in glucose tolerance or effect on peripheral insulin resistance (including diabetes mellitus).
8. Headache
9. Bleeding irregularities (8–25%): Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first *three* months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy.Some may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from contraception trials for up to 13 cycles, **6–10%** of women experienced cycles with no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existing.
10. Depression
11. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs.
12. Skin and subcutaneous tissue disorders: Chloasma, angioedema, erythema nodosum, erythema multiforme.

CONCLUSION

Together with the safety and efficacy evidence from clinical trials, it is evident that 3 mg DRSP/20 μg EE-24/4 provides therapeutic efficacy that corresponded to 99% contraceptive protection.

Improving the tolerability of OCPs without affecting their efficacy or safety has been a big challenge over the years. Reduction of hormone-free days in 3 mg DRSP/20 μg EE-24/4 reduces the incidence of hormone withdrawal adverse effects and decreases the incidence of ovulation. It has a high overall user satisfaction rating, and provides a close to physiological bleeding pattern. Because it is well tolerated with a lower incidence of adverse effects, we can extrapolate this to increased compliance.

Additional medical benefits were seen with PMDD and moderate acne vulgaris (the most common form of acne which is considered to decrease the quality of life in many young women). DRSP in this particular regimen offers extended days of acne treatment because of its long half-life

compared to that of traditional OCPs. The antiandrogenic effects are stronger because DRSP is a fourth-generation progestin. It has more direct antiandrogenic effects compared to other progestins, contributing to an overall decrease in androgen synthesis and therefore a decrease in acne formation.

In the near future, DRSP may prove to be of some benefit for postmenopausal women in that it may be cardio protective. Menopausal hormone therapy containing DRSP may cause blood pressure reduction in hypertensive post menopausal women through rapid activation of endothelial nitric oxide synthase.

BIBLIOGRAPHY

1. Kelekci KH, Kelekci S, Yengel I, et al. Cyproterone acetate or drospirenone containing combined oral contraceptives plus spironolactone or cyproterone acetate for hirsutism: randomized comparison of three regimens. J Dermatolog Treat. 2012;23:177-83.
2. Koo EB, Petersen TD, Kimball AB. Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris. J Am Acad Dermatol. 2014;71(3):450-9.
3. Maloney JM, Dietze P Jr, et al. A randomized controlled trial of a low-dose combined oral contraceptive containing 3 mg drospirenone plus 20 microg ethinylestradiol in the treatment of acne vulgaris: lesion counts, investigator ratings and subject self-assessment. J Drugs Dermatol. 2009;8(9):837-44.
4. Murphy A, Cropp CS, Smith BS, et al. Effect of low-dose oral contraceptive on gonadotropins, androgens, and sex hormone binding globulin in nonhirsute women. Fertil Steril. 1990;53:35-9.
5. Pye RJ, Meyrick G, Pye MJ, et al. Effect of oral contraceptives on sebum excretion rate. BMJ. 1977;2:1581-2.
6. Thiboutot D, Knaggs H, Gilliland K, et al. Activity of 5-alpha-reductase and 17-beta-hydroxysteroid dehydrogenase in the infrainfundibulum of subjects with and without acne vulgaris. Dermatology. 1998;196:38-42.
7. Thorneycroft H, Gollnick H, Schellschmidt I. Superiority of a combined contraceptive containing drospirenone to a triphasic preparation containing norgestimate in acne treatment. Cutis. 2004;74:123-30.
8. van Vloten WA, van Haselen CW, van Zuuren EJ, et al. The effect of 2 combined oral contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. Cutis. 2002;69(suppl 4):2-15.

5

CHAPTER

Antiparasitic/Antiprotozoal Agents

V Ramesh, Kabir Sardana

DRUGS FOR TROPICAL PARASITIC INFECTIONS

Though parasitic infections and infestations are an important problem, most of the prescriptions in dermatology are focused around the use of drugs for scabies and leishmaniasis. Nematode infections, also constitute an important problem and will be discussed briefly.

A classification of drugs used for parasitic infection is given below (Table 5.1), though only a few (bold) are used in dermatology (Table 5.2).

Table 5.1: Classification of drugs used in parasitic infections

Antimony compounds	***Meglumine antimonate*** ***Sodium stibogluconate***
Aromatic diamidines	**Pentamidine**
Arsenicals, pentavalent	Acetarsol Tryparsamide
Arsenicals, trivalent	Melarsoprol
Dichloroacetamides	Diloxanide
Halogenated hydroxyquinolines	Diiodohydroxyquinoline
Nitrofurans	Furazolidone Nifuratel Nifurtimox
5-Nitroimidazoles	Metronidazole Nimorazole Ornidazole Secnidazole Tinidazole
Miscellaneous	Atovaquone Benznidazole Dehydroemetine **Eflornithine** Mepacrine Paromomycin Suramin

Table 5.2: Uses of antiprotozoal drugs in dermatology

Disease	*Drug*	*Dose*
Cutaneous leishmaniasis (Oriental sore) (*L. tropica, major, aethiopica*) Visceral leishmaniasis (*L. donovani*, infantum)	DOC Sodium stibogluconate, or meglumine antimonite Alternative Pentamidine isothionate	20 mg/kg/day IM/IV—20 days 2–3 mg/kg/day IV/IM 4–5 days
Visceral leishmaniasis	Amphotericin B	0.5–1 mg/kg IM/IV day/alt day—8 weeks
	Liposomal	3 mg/kg day 1–42
	Miltefosine	2.5 mg/kg/day 28 days
PKDL	Amphotericin B deoxycholate	1 mg/kg per day 60–80 doses Over 4 months
	Miltefosine	100 mg ODX12 weeks (>25 kg) 50 mg OD X12 wks (<25 kg)
	Liposomal amphotericin B	5 mg/kg/d; 2/weekly × 3 weeks (Total dose: 30 mg/kg)
Onchocercosis	Within endemic area	Ivermectin (150 µg/kg)

Contd...

Contd...

Disease	*Drug*	*Dose*
	Outside endemic area	Doxycyline 100 mg for 6 weeks Followed by Ivermectin (150 µg/kg) after 4–6 weeks
Cutaneous larva migrans	>2 years	Albendazole 400 mg OD × 3 days Ivermectin 12 mg single dose (>15 kg)
Scabies	First Line	Permethrin 5% cream Malathion 0.5% lotion Benzyl benzoate Lindane
	Second Line	Sulfur Crotamiton Ivermectin
Pediculosis	First Line	Permethrin 5 %/1% Malathion 0.5%
	Second Line	Lindane 1% Ivermectin(oral)

SODIUM STIBOGLUCONATE

Sodium stibogluconate is an antimony compound. For centuries, antimony and its compounds were hailed as a valuable remedy for syphilis, febrile illness, skin ulcers and eruptions and sleeping sickness.(Sneader W) After the Brazilian physician Gaspar de Oliveira Vianna reported in 1912 that injections of antimony potassium tartarate cured cutaneous leishmaniasis, (Vianna GO) antimony potassium tartarate remained the standard treatment for cutaneous leismaniasis till it was superseded by its less irritant analogs sodium stibogluconate, which was synthesized by Schmidt in Germany. Sodium stibogluconate is a pentavalent antimonial in which gluconicacid replaces tartaric acid (Schmidt H).

Pharmacology: Absorption, Distribution and Metabolism

Sodium stibogluconate is not absorbed orally. It can be administered intramuscularly or intravenously which is then distributed in a mean total apparent volume of ~0.22 L/kg with high concentrations achieved in the plasma, liver and spleen. In the liver, it biotransforms to its more toxic trivalent form and most of the antimony is excreted in urine in 24 hours. It has a short t1/2 of 2 hours, but a second much slower elimination is seen which probably reflects the conversion to and slow release of the trivalent form from tissues (Brunton LL et al.).

More than 80% of the pentavalent antimony is excreted with the urine within the first 6 hours. Only small amounts are excreted with the feces.

Mechanism of Action

Pentavalent antimonials are effective against *Leishmania* (L) *tropica* and *L. mexicana* (cutaneous leishmaniasis), *L. braziliensis* (mucocutaneous leishmaniasis) and *L. donovani* (Kala-azar or visceral leishmaniasis).

The exact mechanism of antileishmanial action of sodium stibogluconate is not known to date. It probably depends on the in vivo conversion to the trivalent state within the phagolysosomes, which is more toxic to the parasite. Initial studies suggest that sodium stibogluconate interferes with the parasite glycolysis, fatty acid beta oxidation and ADP phosphorylation. However, the specific targets in these pathways have not been identified. It has also been reported to bind to SH groups of amastigote proteins and inhibit DNA topoisomerase (Chakraborty AK et al.). The most recent evidence suggests that following reduction, the drug interferes with the trypanothione redox system, inducing a rapid efflux of trypanothione and glutathione from the cells, and inhibiting trypanothione reductase to deplete the

thiol reduction potential. It thus renders the parasite more susceptible to oxidative stress (Wyllie S et al.).

Uses

- First line drug for visceral leishmaniasis in most parts of the world (>90% overall cure rates) except in drug-resistant areas like Bihar in India and Nepal
- Post Kala-azar dermal leishmaniasis
- Cutaneous leishmaniasis
- Mucocutaneous leishmaniasis.

Dosage

For systemic use, sodium stibogluconate is given by intramuscular or intravenous injection as a solution containing the equivalent of pentavalent antimony 100 mg/mL.

1. **Visceral Leishmaniasis**: The standard course is 20 mg/kg/day for 20 days for cutaneous disease and for 28-30 days for visceral disease and mucocutaneous leishmaniasis (Brunton LL et al.).
   Sodium stibogluconate is given intramuscularly or slowly by the intravenous route. The intramuscular route is preferred for the ease of administration and avoidance of complications, specially when the drug needs to be continued for longer periods. Clinical improvement in patients who respond to therapy favorably, is seen within 1–2 weeks of initiation of therapy.
   In areas with >90% response rates to antimonials, generic SSG remains the most effective option for visceral leishmaniasis treatment owing to its low cost (Schenkel K et al.). Amphotericin B is the recommended alternative for treatment of visceral leishmaniasis in India and Nepal, where increased resistance to SSG has compromised its efficacy. In Bihar unresponsiveness to SSG in visceral leishmaniasis has reached up to 60%.
2. **Cutaneous Leishmaniasis (except *L. braziliensis* and *L. aethiopica*):**
   Adults and children: Local therapy—injection of 1–3 mL (containing 100 to 300 Sb) into the base of the lesion, repeated once, or twice if no response is apparent, at intervals of 1–2 days.
   Systemic therapy—10–20 mg Sb/kg IM or IV daily until a few days after a clinical cure and skin smears are negative.
3. **Cutaneous Leishmaniasis (*L. braziliensis*)**
   Adults and children: 20 mg Sb/kg daily IM or IV until the lesion is healed for at least 4 weeks. Should a relapse occur, pentamidine should be used instead.

4. **Mucocutaneous Leishmaniasis (*L. braziliensis*)**
   Adults and children: 20 mg Sb/kg daily IM until-slit-skin smears are negative and for at least 4 weeks. In the advent of toxicity or inadequate response, 10–15 mg Sb/kg should be administered every 12 hours for the same period. Patients who relapse should be retreated for at least twice as long. Those who are unresponsive should receive amphotericin B or pentamidine.
5. **Diffuse Cutaneous Leishmaniasis (*L. amazonensis*)**
   Adults and children: 20 mg Sb/kg daily IM for several months until clinical improvement occurs.
6. **PKDL:** In Sudan SSG is used to treat patients with PKDL wherein lesions have persisted for more than 6 months or are severe and disfiguring. In cases when 20 mg/kg SSG per day for 30 days does not yield satisfactory results, a longer duration of treatment similar to that in Indian PKDL can be resorted to. As Indian PKDL does not heal spontaneously, an accepted therapy includes SSG at a dose of 20 mg/kg per day for 4 months. Cure rates vary from 64–92% (Ganguly S et al.).

Studies on intralesional injection of SSG in cutaneous leishmaniasis showed promising results. A dose of 0.5–5 mL is injected into the base and margins of the lesion to produce complete blanching. Daily, alternate or weekly infiltrations until healing of the lesion (1–8 injections) was found to be effective (Tallab TM et al.). The cure rates improve when this therapy is combined with cryotherapy.

Contraindications and Precautions

The drug should not be given to patients with kidney failure or with cardiomyopathy. Available data suggest that dosage reductions should be proportional to the reduction in glomerular filtration rate. Slow intravenous injections (over 5–10 minutes) are necessary to avoid acute reactions, such as nausea, vomiting, or substernal pain.

Side Effects

Common: Pain at the injection site, anorexia, nausea, vomiting, abdominal pain, malaise, myalgia, headache, metallic taste and lethargy. Raised pancreatic enzymes is commonly seen but clinical pancreatitis is rare.(Thakur CP, Roychoudhury J et al.) ECG changes are dose-dependent and most commonly include T-wave inversion and prolonged QT interval.
Rare: Elevation of serum hepatic transaminases and bone marrow suppression manifested by decreased red cell, white cell, and platelet counts in the blood (Roychoudhury J et al.).

Serious side effects like atrial arrhythmia, atrial fibrillation, ventricular arrhythmia, tachycardia and fibrillation are rare and are dose and duration dependent (At dosages above 20 mg/kg) (Thakur CP, Berman JD et al.). Neurological side effects reported include cerebellar ataxia and reversible polyneuropathy (Khalil EA). Hemolytic anemia, renal damage, shock and sudden death may occur but are rare manifestations of toxicity.

Drug Monitoring

Patients should be monitored by serum chemistry for liver enzymes and pancreatic enzymes. Complete blood counts should be done to monitor bone marrow suppression. Anemia, leukopenia and thrombocytopenia indicate bone marrow toxicity.

Electrocardiography should be done to monitor cardiotoxicity. The commonest ECG changes are T-wave inversion, prolonged Q-T interval and arrhythmia. Prolongation of a corrected Q-T interval (>0.5 sec) signals the likely onset of serius and fatal cardiac arrhythmia.

Severe alterations in blood chemistry, blood counts and ECG warrant drug discontinuation.

Special Groups

Pregnancy and Lactation

Pentavalent antimonials should not be withheld from patients suffering from visceral leishmaniasis. Small amounts of sodium antimony gluconate have been reported to be excreted in breast milk. Because of the poor absorption of the drug from the gut and the insignificant amounts reaching the breast milk, nursing can however be regarded safe, particularly in areas where the possibility of bottle feeding is not feasible.

Children

Children usually tolerate the drug well, and the dose per kilogram is the same as for adults.

BIBLIOGRAPHY

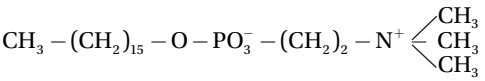
1. Berman JD. Human leishmaniasis: clinical, diagnostic, and chemotherapeutic developments in the last 10 years. Clin Infect Dis. 1997;24:684-703.
2. Brunton LL, Parker KL, Blumenthal DK, Buxton ILO. Goodman and Gilman's Manual of Pharmacology and Therapeutics. New York: McGraw-Hill Medical. 2008;693.
3. Chakraborty AK, Majumder HK. Mode of action of pentavalentantimonials: specific inhibition of type I DNA

topoisomerase of Leishmaniadonovani. BiochemBiophys Res Commun. 1988;152:605-11.
4. Ganguly S, Das NK, Barbhuya JN, Chatterjee M. Post kalaazar dermal leishmaniasis—an overview. Inte J Dermatol. 2010;49: 921-31.
5. Khalil EA, Ahmed AE, Musa AM, Hussein MH. Antimony-induced cerebellar ataxia. Saudi Med J. 2006;27:90-2.
6. Roychoudhury J, Ali N. Sodium stibogluconate: Therapeutic use in the management of leishmaniasis. Indian Journal of Biochemistry & Biophysisics. 2008;45:16-22.
7. Schenkel K, Rijal S, Koirala S, Vanlerberghe V, Bander Stuyft P, Gramiccia M, et al. Visceral leishmaniasis in southeastern Nepal: A cross-sectional survey on Leishmaniadonovani infection and its risk factors. Trop Med Int Hlth. 2006;11:1792-9.
8. Schmidt H, Peter FM. Advances in the Therapeutics of Antimony. Leipzig: Thieme; 1938.
9. Sneader W. Drug Discovery. A History. John Wiley and Sons Ltd. 2005;58
10. Tallab Tm, Bahamdam KM, Ibrahim K, Hameed el Sherbini A, Karkashan E, Khare AK, et al. Cutaneous Leishmaniasis: Schedules for intralesional treatment with sodium stibogluconate. Int J Dermatol. 1996;35(8):594-7.
11. Thakur CP, Sinha GP, Pandey AK. Do the diminishing efficacy and increasing toxicity of sodium stibogluconate in the treatment of visceral leishmaniasis in Bihar, India, justify its continued use as a first-line drug? An observational study of 80 cases. Trans Ann Trop Med Parasitol. 1998;92:561-9.
12. Vianna GO. Anais do 70 CongressoBrasileiro de Medicina e Cirurgia. 1912;4:426.
13. Wyllie S, Cunningham ML, Fairlamb AH. Dual action of antimonial drugs on thiol redox metabolism in the human pathogen Leishmaniadonovani. J Biol Chem. 2004;279:39925-32.

MILTEFOSINE

Miltefosine is the only orally active drug available against leishmaniasis. It was developed as a novel drug against breast cancer and was approved only as a topical formulation for dermal metastases because of severe gastrointestinal toxicity (Dummer R et al.). The antileishmanial activity of this compound was first described in vitro and in vivo in 1987 and the oral activity in mouse models of visceral leishmaniasis was reported in 1992 (Arfanul Bari, Kuhlencord A et al.). The first reports on clinical trials for the treatment of visceral leishmaniasis (VL) in India, came in 1998 with cure rates up to 98% (Sundar S, Engel J et al.). In 2002, miltefosine was registered to be used in visceral leishmaniasis cases in immunocompetent patients from India and in 2004, it was approved in Germany for use in VL in both immunocompetent and immunocompromised patients.

Miltefosine belongs to the class of alkyl phosphocholine drugs, which are phosphocholine esters of aliphatic long-chain alcohols.



Metabolism: Absorption, Fate, and Excretion

Miltefosine is well absorbed orally and distributed throughout the body.

Due to the hemolytic nature of miltefosine no study in humans with intravenous administration can be performed to assess the bioavailability after oral use. In rats and dogs, however, an absolute bioavailability of 82% and 94%, respectively, has been shown with t_{max} values ranging from 4 to 48 hours.

Miltefosine is widely distributed in the body, however, without evidence of melanin binding in pigment containing tissues. Placental transfer and excretion into milk have not been investigated but can be assumed.

Plasma concentrations are proportional to the dose. It has a long half-life of about 8 days. In a study miltefosine was detectable in human plasma samples taken 5–6 months after the end of treatment (Dorlo Thomas PC, et al.).

It has not been adequately studied in children.

Mechanism of Action

Miltefosine modulates cell membrane permeability, membrane lipid composition, phospholipid metabolism, and mitogenic signal transduction primarily by interfering with cellular membranes and resulting in inhibition of cell growth and apoptosis (Verma NK et al.). Miltefosine was shown to possess antiproliferative activity against *Leishmania donovani* promastigotes and amastigotes (Azzouz S et al.). Miltefosine inhibits glycosomal alkyl-specific acyl CoA acyl transferase in a dose dependent manner and thus inhibits leishmanial surface ether lipid synthesis (Lux H et al.). It also strengthens the cytotoxicity of macrophages and consequently lead to death of parasite within the infected cell. It has been demonstrated that it stimulates the oxidative burst of macrophages which results in production of reactive oxygen metabolite (Azzouz S et al.).

Miltefosine also stimulates (*in vitro*) T cells and macrophages to secrete activating cytokines, including interferon (IFN)-gamma.

Spectrum of Activity

Leishmania donovani was the most sensitive species in promastigote and amastigote test systems, with the ED50 concentrations around 1 μmol/L.

For *promastigotes* the sensitivity decreased in the following order: *Leishmania donovani* > *Leishmania aethiopica* > *Leishmania tropica* > *Leishmania panamensis* >*Leishmania mexicana* > *Leishmania major*.

For amastigotes the ranking was:

Leishmania donovani >*Leishmania aethiopica* > *Leishmania tropica* > *Leishmania mexicana* > *Leishmania panamensis* >*Leishmania major*.

Uses

1. **Visceral Leishmaniasis:** Miltefosineis a treatment option in areas in which resistance to pentavalent antimonial drugs is widespread. Miltefosine has been hailed as a novel oral drug for treatment of VL, in both immunocompetent and immunocompromised patients (Sundar S et al.).

   In experimental models of cutaneous leishmaniasis topical miltefosine was seen to be effective in reducing the parasite load (Schmidt-Ott R et al.). However, some studies have demonstrated the insensitivity of Leishmania species from the New World; including: *L. braziliensis, L. guyanensis* and *L. mexicana* (Yardley V et al.). In Ethiopia, miltefosine was seen to havea higher initial treatment failure rate (8%) over all compared with 1% of the sodium stibogluconate (SSG). There was also a higher rate of initial treatment failure and higher rate of relapse in HIV-positive patients who received miltefosine (Ritmeijer K et al.).
2. As an anticancer agent: 6% miltefosine cream has been used to treat skin metastasis of breast cancer (Konstantinov SM et al.).
3. **Other potential indications:** Cutaneous leishmaniasis: Miltefosine has shown relatively high efficacy rates in treatment of New World cutaneous and mucocutaneous leishmaniasis (Soto J et al. 2004; Soto J et al. 2001; Soto J et al. 2007). The response of *L. brasiliensis* and *L. mexicana* to miltefosine treatment is not impressive however, some geographical variation in response *of L. brasiliensis* has been observed. Miltefosine has been found to be effective for the treatment of *L. brasililiensis* infection in Bolivia. Only a little information has become available on miltefosine for treatment of Old World cutaneous leishmaniasis.

   PKDL: Data on treatment of Indian PKDL is limited but demonstrate miltefosine as an effective choice (Sundar S et al.; Ramesh V et al. 2008).

Dosage

The dosage of miltefosine required for treatment of VL is far less than that required in cancer patients. Therefore, adverse effects are much reduced. The capsules should be taken with meals.

1. **Visceral leishmaniasis:** *Children aged 2-11 years:* 2.5 mg/kg/day (50 mg daily once a day)
   Adults >12 years:
   - 50 mg/day for 28 days if body weight <25 kg.
   - 100 mg/day (50 mg BD) for 28 days if body weight 25-50kg
   - 150 mg/day for 28 days if body weight >50 kg
2. **PKDL:** The dose in adults is 50 mg twice daily for 3 months or thrice daily for 2 months depending on patients' tolerability.
   Wt> 25 kg: 100 mg X 12 weeks
   Wt>25 kg: 50 mg X 12 weeks
3. **Cutaneous and mucocutaneous leishmaniasis:**
   (2.5 mg/kg/day for 28 days).
   Children >12 years (weight of at least 30 kg,) and adults (body weight lower than 45 kg) 100 mg miltefosine (2 capsules 50 mg).
   Body weight > 45 kg (150 mg miltefosine daily (3 capsules 50 mg).

Contraindications

It is contraindicated in women with child-bearing potential because of its teratogenic effects as seen in animal studies. (Sundar S et al.; Schmidt-Ott R et al.). *Three months* of contraceptive cover after the end of treatment might be adequate for the standard 28 day miltefosine regimen (Dorlo Thomas PC et al. 2012). Miltefosine is also contraindicated during lactation as it is assumed that it is secreted in breast milk.

- Hypersensitivity to the active substance or any of the excipients.
- Pre-existing severe damage of liver or kidney function
- Sjögren-Larsson-Syndrome.
- Pregnancy and women of child-bearing potential who do not use a reliable contraception during and up to 3 months after treatment.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

HIV/VL coinfection: Miltefosine was reported to be less efficacious in the treatment of HIV/VL coinfection as compared to SSG, however, with a better safety profile (Ritmeijer K et al.). The incidence of relapse in these patients was also high with miltefosine.

Drug Interaction

In vitro investigations have shown that interactions are unlikely with medications that are metabolized by cytochrome P450 or glucuronized or conjugated otherwise. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

Side Effects

Common: Nausea, vomiting, anorexia, elevation of LFT and KFT.

Rare: Abdominal pain, thrombocytopenia, SJS

Miltefosine is well tolerated with considerably fewer adverse effects as compared to antimonials and amphotericin. The compound cannot be given intravenously because of hemolysis.

Loss of appetite, nausea and vomiting were found to bedose-limiting side effects seen in cancer treatment. In the treatment of VL, the primary and most severe side effects encountered with miltefosine were vomiting and diarrhea, which were most prominent in the first week of treatment but reduced significantly over the last week (Bhattacharya SK et al.). The gastrointestinal side effects are most probably directly related to the oral intake of the drug and the detergent-like properties of miltefosine affecting the gastrointestinal lining (Dorlo Thomas PC et al. 2011). Intake of (fatty) food together or just before miltefosine intake drastically reduces the gastrointestinal side-effects (Dorlo Thomas PC et al. 2011; van Thiel PPAM et al.). Gastrointestinal symptoms could be significant in severely-ill patients such as those who are malnourished and dehydrated.

Elevated serum creatinine levels during treatment is possibly related to occasional dehydration by severe vomiting/diarrhea (Sindermann H et al.). Severe nephrotoxicity caused by miltefosineis, however, rare. Serum levels of both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) tend to increase mildly in the first week of miltefosine treatment in VL patients, possibly due to immediate necrosis of pre-damaged hepatocytes (Sindermann H et al.). This generally normalizes in the subsequent weeks together with the resolving infection. Miltefosine though used as an antineoplastic agent is devoid of hematological toxicity.

Monitoring

- Treatment may lead to an increase in serum creatinine and liver enzymes.
- Liver and kidney function must be controlled in weekly intervals.

- In patients with clinically significant abnormality in kidney-function monitoring should be continued until normalization.

Special Groups

Pregnancy: X

Liver and Kidney Failure

Patients with severe damage of liver and kidney functions were not investigated. Sufficient data of patients with mild and moderate impairment of liver and kidney function are not available. Patients with liver values (GOT, GPT, alkaline phosphatase) 3 times and kidney values (serum creatinine, BUN) 1.5 times above the normal range, were excluded from the clinical study.

BIBLIOGRAPHY

1. Azzouz S, Maache M, Garcia RG, Osuna A. Leishmanicidal activity of Edelfosine, Miltefosine and Ilmofosine. Basic Clinic Pharmacol Toxicol. 2005;96:60-5.
2. Bari A. Miltefosine: a breakthrough in treatment of Leishmaniasis. J Pak Assoc Dermatol. 2006;16:225-30.
3. Bhattacharya SK, Sinha PK, Sundar S, et al. Phase 4 trial of miltefosine for the treatment of Indian visceral leishmaniasis. J Infect Dis. 2007;196:591-8.
4. Dorlo Thomas PC, Balasegaram M, Lima MA, et al. Translational pharmacokinetic modelling and simulation for the assessment of duration of contraceptive use after treatment with miltefosine. J Antimicrob Chemother. 2012;67:1996-2004.
5. Dorlo Thomas PC, Manica Balasegaram, Beijnen JH, de Vries PJ. Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. J Antimicrob Chemother. 2012;67:2576-97.
6. Dorlo Thomas PC, Thiel PPAM van, Huitema Alwin DR, Keizer RJ, de Vries HJC, Beijnen JH, et al. Pharmacokinetics of miltefosine in old world cutaneous leishmaniasis patients. Antimicrob Agents Chemother. 2008;52(8):2855-60.
7. Dorlo Thomas PC, van Thiel PPAM, Schoone GJ, et al. Dynamics of parasite clearance in cutaneous leishmaniasis patients treated with miltefosine. P LoS Negl Trop Dis. 2011;5:e1436.
8. Dummer R, Krasovec M, Roger J, et al. Topical administration of hexadecyl phosphocholine in patients with cutaneous lymphomas: results of a phase I/II study. J Am Acad Dermatol. 1993;29: 963-70.
9. Engel J. Miltefosine, the story of a successful partnership: disease endemic country–TDR–pharmaceutical industry (Zentaris). TDR News. 2002;68:5.
10. Konstantinov SM, Eibl H, Berger MR. BCR-ABL influences the antileukaemic efficacy of alkyl phosphocholine. Br J Haematol. 1999;107:365-80.

11. Kuhlencord A, Maniera T, Eibl H, et al. Hexadecyl phosphocholine: oral treatment of visceral leishmaniasis in mice. Antimicrob Agents Chemother. 1992;36:1630-4.
12. Lux H, Heise N, Klenner T, Hart D, Opperdoes FR. Ether-lipid (alkyl phospholipid) metabolism and the mechanism of action of ether-lipid analogs in visceral leishmania. Mol Biochem Parasitol. 2000;111:1-14.
13. Paladin Labs Inc. Application for inclusion of miltefosine on who model list of essential medicines. 2010. http://www.who.int/selection_ medicines/committees/expert/18/applications/Miltefosine_application.pdf.
14. Ramesh V, Ansari NA, Jain RK, Salotra P. Oral miltefosine in the treatment of post-kala-azar dermal leishmaniasis. Clin Exp Dermatol. 2008;33:103-5.
15. Ramesh V, Katara GK, Verma S, Salotra P. Miltefosine as an effective choice in the treatment of post-kala-azar dermal leishmaniasis. Br J Drmatol. 2011;165:411-4.
16. Ritmeijer K, Dejenie A, Assefa Y, Hundie TB, Mesure J, Boots G, et al. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. Clin Infect Dis. 2006;43:357-64.
17. Schmidt-Ott R, Klenner T, Overath P, Aebischer. Topical treatment with hexadecyl phosphocholine (miltex) efficiently reduces parasite in experimental cutaneous leishmaniasis. Trans R Soc Trop Med Hyg. 1999;93:85-90.
18. Sindermann H, Engel J. Development of miltefosine as an oral treatment for leishmaniasis. Trans R Soc Trop Med Hyg. 2006;100:S17-20.
19. Soto J, Arana BA, Toledo J, Rizzo N, Vega JC, Diaz A, et al. Miltefosine for new world cutaneous leishmaniasis. Clin Infect Dis. 2004;38:1266-72.
20. Soto J, Toledo J, Gutierrez P, Nicholls RS, Padilla J, Engel J, et al. Treatment of American cutaneous leishmaniasis with miltefosine; an oral agent. Clin Infect Dis. 2001;33:57-61.
21. Soto J, Toledo J, Valda L, Balderrama M, Rea I, Parra R, et al. Treatment of Bolivian mucosal leishmaniasis with miltefosine. Clin Infect Dis. 2007;44:350-6.
22. Sundar S, Jha TK, Thakur CP, et al. Oral miltefosine for indian visceral leishmaniasis. N Engl J Med. 2002;347:1739-46.
23. Sundar S, Kumar K, Chakravarty J, et al. Cure of antimony-unresponsive Indian post-kala-azar dermal leishmaniasis with oral miltefosine. Trans R Soc Trop Med Hyg. 2006; 100:698-700.
24. Sundar S, Rosenkaimer F, Makharia MK, et al. Trial of oral miltefosine for visceral leishmaniasis. Lancet. 1998;352:1821-3.
25. Thakur CP, Sinha PK, Singh KR, et al. Miltefosine in a case of visceral leishmaniasis: and rising incidence of this disease in India. Trans R Soc Trop Med Hyg. 2000;94:696-7.
26. van Thiel PPAM, Leenstra T, Kager PA, et al. Miltefosine treatment of Leishmania major infection: an observational study involving Dutch military personnel returning from northern Afghanistan. Clin Infect Dis. 2010;50:80-3.
27. Verma NK, Dey CS. Possible mechanism of miltefosine-mediated death of Leishmania donovani. Antimicrob Agents Chemother. 2004;48:3010-5.

28. Yardley V, Croft SL, De Doncker S, et al. The sensitivity of clinical isolates of Leishmania from Peru and Nepal to miltefosine. Am J Trop Med Hyg. 2005;73:272-5.

AMPHOTERICIN B

Amphotericin B is amacrolide polyene antifungal antibiotic agent, discovered in 1956, from the bacterium *Streptomyces nodusus* obtained from the soil of Orinoco River in Venezuela (Singh S et al.). It has the broadest spectrum of antifungal activity. Similar effects of on the sterol cell membrane of leishmania as seen on that of fungi provided the rationale for the use of amphotericin B in the treatment of leismaniais (Ramos H, et al.).

Drug Formulations

Amphotericin B is complexed with deoxycholate (C-AMB) and marketed as a lyophilized powder containing 50 mg of amphotericin B that forms a colloid in water. It is administered intravenously in 5% glucose solution.

Three lipid formulations of amphotericin B are available:

a. Amphotericin B colloidal dispersion contains equimolar amounts of amphotericin B and cholesteryl sulfate.
b. Liposomal amphotericin B, Ambisome is a small, unilamellar vesicle formulation that combines amphotericin B (50 mg) with 350 mg of lipid (phosphatidyl choline, cholesterol, and distearoyl phosphatidyl glycerol, in molar ratio of 10:5:4).
c. Amphotericin B lipid complex (ABLC) contains dimyristoyl phosphatidyl choline and dimyristoyl phosphatidyl glycerol in a 7:3 mixture with ~35 mol% of amphotericin B.

Pharmacology: Absorption, Distribution and Metabolism

Gastrointestinal absorption of amphotericin B is negligible and intravenous delivery is used. Amphotericin B is >90% plasma protein bound. Biliary and renal excretion are both insignificant. The metabolic pathways followed by amB in humans are not known. The plasma half-life is 24–48 h, but the elimination half-life is approximately 15 days (Daneshmend TK et al.).

The lipid formation of amphotericin B, namely ABCD and ABLC are rapidly taken up by the reticuloendothelial system, resulting in low maximal plasma concentrations and a high volume of distribution as compared to the conventional form. Tissue concentrations are high in the liver, spleen, and bone marrow but many folds lower in the kidney, lung, and brain (Janknegt R et al.).

The pharmacokinetic behavior of liposomal amB is different. It has a high plasma concentration as the small, rigid, spherical liposomes are taken up less rapidly by the reticuloendothelial system (De Marie S et al.). In mice, the highest concentration of the drug was seen in the liver and spleen, while pulmonary and renal concentrations were lower than with conventional am B (Proffitt RT et al.).

Mechanism of Action

AmB has strong affinity for ergosterol, the principal sterol of fungal membranes as well as of leishmania cell membrane while exhibiting less affinity for cholesterol, the principal sterol of mammalian cell membranes (Bolard J et al.). It selectively inhibits the membrane synthesis of the parasite and causes holes in the membrane, leading to leakage of ions and other cellular components finally culminating into the death of the organism (Brajtburg J et al. Vertut-croquin A et al.). Other mechanisms of action include proton-pump inhibition in *Candida albicans*, and induction of membrane lipid peroxidation (Brajtburg J et al., Surarit R et al.).

Uses

Leishmaniasis

Amphotericin B has good leishmanicidal activity and constitutes an effective treatment option in patients with VL and CL that show resistance to treatment with antimonials. Liposomal amphotericin B has been approved by the US-FDA for the treatment of VL (Dupnik KM et al.). It is also an effective alternative for antimony-resistant PKDL (Ramesh V). Successful treatment of leishmania recidivans with intralesional amphotericin B has also been reported (Ganor S).

Dosage

Infusion fluids must be freshly prepared by dissolving 50 mg amphotericin B in 10 mL of sterile water and making up to 500 mL with 5% glucose to give a final concentration of 100 µg/mL solution. For adults, a starting dose of 5–10 mg is incremented by 5–10 mg daily to a maximum of 0.5–1 mg/kg. This is then infused (6–8 hours) on alternate days to a total of 1–3 g (**Caution:** do not mix amphotericin with saline solutions, i.e. sodium chloride 0.9%, as precipitate will form).

Some centers infuse a test dose of 1 mg of amphotericin B over periods of 20 minutes to 4 hours before starting treatment. In case of intolerable toxicity with conventional amphotericin B, liposomal amphotericin B can be given by intravenous infusion (over 30–60 minutes) at a dosage of

1 mg/kg/day initially, increased gradually to 3 mg/kg/day for up to 21 days.

a. Visceral leishmaniasis:

- Amphotericin B deoxycholate: 0.75–1.0 mg/kg per day by infusion, daily or on alternate days for 15–20 doses
- Liposomal amphotericin B: 3–5 mg/kg over 3–5 days up to a total dose of 15 mg/kg by infusion or 10 mg/kg as a single dose by infusion.

b. PKDL:

- In East Africa: In patients with severe disfiguring disease or in cases where disease persists >6 months: liposomal amphotericin B: 2.5 mg/kg per day by infusion for 20 days.
- In India: Amphotericin B deoxycholate 1 mg/kg per day by infusion up to 60–80 doses over 4 months (dose for liposomal forms has not been finalized).

  Liposomal amphotericin B: 5 mg/kg per day by infusion two times per week for 3 weeks for a total dose of 30 mg/kg.

c. Cutaneous leishmaniasis:

- Amphotericin B deoxycholate: 0.75 mg/kg per day by infusion, daily or on alternate days for 25–30 doses
- Liposomal amphotericin B: 2–3 mg/kg per day by infusion up to 20–40 mg/kg total dose

d. Mucocutaneous leishmaniasis:

- Amphotericin B deoxycholate: 0.7–1.0 mg/kg by infusion every other day for 25–45 doses
- Liposomal amphotericin B: 2–3 mg/kg per day by infusion up to 40–60 mg/kg total dose.

Contraindications and Precautions

Amphotericin B should be administered under close medical supervision. Blood urea nitrogen (BUN), hemoglobin and potassium values should be regularly monitored. During treatment with amphotericin, other nephrotoxic and potassium depleting agents should be avoided.
Because of the wide range of incompatibilities reported with amphotericin B (see below), it is generally advisable not to mix it with any other drug.

Side Effects

Infusion related adverse effects: Infusion-related adverse events occur in 70–90% of patients, and include nausea, vomiting, fever, chills, pain at the injection site, gastrointestinal disorders, thrombophlebitis, bronchospasm, hypotension, and cardiac arrhythmia (Gallis HA et al.). Tolerance to

infusion-related reactions usually develops during therapy. The major acute reaction to intravenous amphotericin B is fever and chills, which typically end spontaneously in ~30 minutes and often abate with subsequent infusions. Tachypnea and modest hypotension may occur, but true bronchospasm or anaphylaxis is rare. Patients with preexisting cardiac or lung disease may become hypotensive or hypoxic. Pretreatment with oral acetaminophenor intravenous glucocorticoids decreases reactions, while meperidine may shorten the duration of established reactions (Goodwin SD et al.).

Renal toxicity: Transient azotemia occurs in 80% of patients who receive C-AMB. Toxicity is dose-dependent and increased by concurrent therapy with other nephrotoxic agents (e.g. aminoglycosides, cyclosporine) (Goodwin SD et al.). Permanent impairment is uncommon in adults with normal renal function unless the cumulative dose is >3–4 gram. Renal tubular acidosis (due to drug induced renal vasoconstriction) and wasting of K^+ and Mg^{2+} also may occur during and for several weeks after therapy, often requiring repletion. Administration of 1 L of normal saline intravenously prior to C-AMB administration is recommended for adults who can tolerate the Na^+ load (Heidemann HT et al.).

Hematological side effects: Hypochromic, normocytic anemia is usual with C-AMB and reverses slowly following cessation of therapy. It likely reflects decreased production of erythropoietin and often responds to erythropoietin.

Headache: Arachnoiditis, manifested by fever and headache, can occur with intrathecal injection of CAMB;it may be decreased by intrathecal administration of 10–15 mg of hydrocortisone.

Patients treated with liposomal amB experience less fever, fewer chills, less nephrotoxicity (doubling of serum creatinine) and need less premedication than patients treated with amB (Leenders AC et al.).

Monitoring

Regular renal function and serum electrolyte monitoring is recommended with the use of amphotericin B deoxycholate.

Special Groups

Amphotericin B, both liposomal and deoxycholate preparations are well tolerated and effective in the treatment of leishmaniais in children (Thakur CP et al.). It is also found to be effective in pregnant women at a dosage of 1 mg/kg for 20 days, without apparent harm to the fetus (Thakur CP et al.).

Liposomal amphotericin B,is currently the preferential treatment for VL-HIV coinfection according to World Health Organization (WHO) recommendations (World Health Organization).

BIBLIOGRAPHY

1. Bolard J. How do the polyene macrolide antibiotics affect the cellular membrane properties? Biochim Biophys Acta. 1986;864:257-304.
2. Brajtburg J, Bolard J. Carrier effects on biological activity of amphotericin B. Clin Microbiol Rev. 1996;9:512-31.
3. Brajtburg J, Elberg S, Schwartz DR, et al. Involvement of oxidative damage in erythrocyte lysis induced by amphotericin B. Antimicrob Agents Chemother. 1985;27: 172-6.
4. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal drugs. Clin Pharmacokinet. 1983;8:17-42.
5. De Marie S, Janknegt R, Bakker woudenberg IA. Clinical use of liposomal and lipid-complexed amphotericin B. J Antimicrob Chemother. 1994;33:907-16.
6. Dupnik KM, Nascimento EL, Rodrigues-Neto JF, Keesen T, Fernandes MZ, Duarte I, et al. New Challenges in the epidemiology and treatment of visceral leishmaniasis in periurban areas. Drug Development Research. 2011;72:451-62.
7. Gallis HA, Drew RH, Pickard W. Amphotericin B: 30 years of clinical experience. Rev Infect Dis. 1990:12: 308-29.
8. Ganor S. The treatment of leishmaimiasis recidivans with local injections of Amphotericin B. Internation J Dermatol. 1967;6(3):141-3.
9. Goodwin SD, Cleary JD, Walawander CA, Taylor JW, Grasela Th JR. Pretreatment regimens for adverse events related to infusion of amphotericin B. Clinic Infect Dis. 1995:20:755-61.
10. Heidemann HT, Gerkens JT, Spickard WA, Jackson EK, Branch Ra. Amphotericin B nephrotoxicity in human decreased by salt repletion. Am J Med. 1983:75:476-81.
11. Janknegt R, De Marie S, Bakkerwoudenberg IA, Crommelin DJ. Liposomal and lipid formulations of amphotericin B. Clinical pharmacokinetics. Clin Pharmacokinet. 1992;23:279-91.
12. Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (Am Bisome) compared with amphotericin B both followed by oral fluconazole in the treatment of invasive treatment of AIDS-associated cryptococcal meningitis. AIDS. 1997;11:1463-71.
13. Proffitt RT, Satorius A, Chiang SM, Sullivan L, Adler-moore JP. Pharmacology and toxicology of a liposomal formulation of amphotericin B lipid complex therapy of (Am Bisome) in rodents. J Antimicrob Chemother. 1991:28(Suppl B):49-61.
14. Ramesh V. Treatment of post-kala-azar dermal leishmaniasis. Int J Dermatol. 1994;33 (3):153-6.
15. Ramos H, Valdivieso E, Gamargo M, Dagger F, Cohen BE. Amphotericin B kills unicellular Leishmaniaby forming aqueous pores permeable to small cations and anions. J Membr Biol. 1996;152:65-75.
16. Singh S, Sivakumar R. Challenges and new discoveries in the treatment of leishmaniasis. J Infect Chemother. 2004;10:307-15.

17. Surarit R, Shepherd MG. The effects of azole and polyene antifungals on the plasma membrane enzymes of Candida albicans. J Med Vet Mycol. 1987;25:403-13.
18. Thakur CP, Sinha GP, Sharma V, Pandey AK, Sinha PK, Barat D. Efficacy of amphotericin B in multi-drug resistant kala-azar in children in first decade of life. Indian J Pediatr. 1993;60:29-36.
19. Vertut-croquin A, Bolard J, Gary-bobo CM. Transfer of amphotericin B from gel state vesicles to mycoplasma cells: biphasic action on potassium transport and permeability. Antimicrob Agents Chemother. 1985;28:167-71.
20. World Health Organization. Control of the leishmaniasis: report of a meeting of the WHO Expert Committee on the control of leishmaniases; Geneva. 22–26 March 2010. Geneva, Switzerland: World Health Organization;2010.

IVERMECTIN

Classification

Antihelminthic.

Mechanism of Action

Ivermectin belongs to a class of substances known as the avermectines. These are macrocylic lactones produced by fermentation of an actinomycete, *Streptomyces avermitilis*.

Ivermectin is a broad spectrum agent active against nematodes and arthropods in domestic animals and is thus widely used in veterinary medicine. The drug was first introduced in man in 1981. It has been shown to be effective against a wide range of nematodes, such as *Strongyloides sp., Trichuris trichiura, Enterobius vermicularis, Ascaris lumbricoides, hook worms and Wuchereria bancrofti.*

Ivermectin binds selectively to glutamate-gated chloride ion channels found in invertebrate nerve and muscle cells. Binding results in increased permeability of cell membranes to chloride ions, with hyperpolarization of the nerve or muscle cells resulting in death of the parasite. Ligand-gated ion channels represent the primary ivermectin targets in invertebrates. Ivermectin positively modulates CNS ATP-gated purinergic P2X4 receptors and is believed to act in the same region as ethanol.

Absorption and Distribution

The absolute oral bioavailability of the drug is not known. After administration the time to peak serum levels is about 4 hours, and the half-life is about 18 hours. Metabolism is primarily hepatic, with excretion in feces over an estimated 12 days. Ivermectin is metabolized primarily by CYP3A4. Bioavailability is increased when the drug is administered with a high-fat meal.

P-glycoprotein restricts the entry of ivermectin across the blood–brain barrier by an ATP-driven efflux mechanism, and deficiencies have been implicated as a risk factor for neurotoxicity. In dogs with a homozygous mutation, ivermectin accumulates in the brain, producing neurotoxicosis and even death. In this animal model, selamectin is safer than ivermectin. In knockout mice, both drugs have been shown to be substrates of P-glycoprotein, but selamectin accumulates to a much lesser degree than ivermectin in the absence of P-glycoprotein.

Dosage

The dosages are based on the weight as depicted in the Table 5.3. In the treatment of scabies, 200 μg/kg is commonly given as a single dose, and repeated in a week to 10 days. This drug has been found to be superior to most topical agents including lindane (Mohebbipour A), though it is still *not* superior to permethrin (Mounsey KE 2013). Ivermectin is generally well tolerated in infants. The 80% rate of healing observed in infants who had failed to respond to at least two other topical treatments suggests that ivermectin could be considered for treatment of infants with recalcitrant or relapsing scabies. (Bécourt C).

In the setting of crusted scabies (common in immunocompromised patients), ivermectin should generally be used in conjunction with keratolytics and topical therapy, but dosing is otherwise the same as in immunocompetent patients. In a recent report of *crusted scabies*. The Centers for

Table 5.3: Weight-based drug dosage of Ivermectin

FDA Approved	• Strongyloidiasis 15-25 kg: 3 mg PO; may repeat in 3 mo 26-44 kg: 6 mg PO; may repeat in 3 mo 45-64 kg: 9 mg PO; may repeat in 3 mo 65-84 kg: 12 mg PO; may repeat in 3 mo >80 kg: 200 mcg/kg PO once
	• Onchocerciasis 5-25 kg: 3 mg PO; may repeat in 3 mo 26-44 kg: 6 mg PO; may repeat in 3 mo 45-64 kg: 9 mg PO; may repeat in 3 mo 65-84 kg: 12 mg PO; may repeat in 3 mo ≥85 kg: 150 mcg/kg PO; may repeat in 3 mo
Off Label	• **Demodex folliculorum:** 200 mcg/kg PO repeat after 7 days • **Filariasis due to Mansonella Ozzardi:** 6 mg PO as single dose • **Pediculosis Capits:** 200 mcg/kg PO once; may require 1-2 additional doses repeated after 7 days • **Rosacea:** 200 μg/kg. • **Scabies:** Immunocompromised patients: 200 mcg/kg as single dose; may repeat in 14 days if necessary

Disease Control and Prevention suggested a 7-dose regimen of ivermectin and the patient started to improve remarkably after the third dose and was completely cured by the 7 dose (Ortega-Loayza AG).

For lice, a single 400 μg/kg dose has been given on day 1 and day 8. A recent study suggests that both topical and oral ivermectin demonstrate high efficacy and tolerability in treatment of pediculosis capitis. However, a single treatment with topical ivermectin provides significantly higher cure of infestation and faster relief of pruritus than oral ivermectin (Ahmad HM).

Uses (Approved/Unapproved)

Ivermectin is the drug of choice against intestinal strongyloidiasis caused by Strongyloides stercoralis and onchocerciasis caused by *Onchocerca volvulus*.

The role of ivermectin in lymphatic filariasis is not yet well investigated. It should be noted that FDA-reviewed trials have only established that ivermectin is active against the microfilaria of *Onchocerca volvulus* and the intestinal forms of *Strongyloides stercoralis*.

It has also been used been used to treat infestations caused by *Ascaris lumbricoides, Enterobius vermicularis* (pinworm), *Mansonella ozzardi, Gnathostomia spingerum, Mansonella streptocera*, and *Trichuris trichiura* (whipworm), as well as both bancroftian and brugian filariasis.

Resistance

Resistance has been largely seen in onchocercosis and may be related to single nucleotide polymorphisms of P-glycoprotein-like protein.

Scabies mites are also becoming resistant to oral ivermectin, thus alternatives are been discovered, including piperonyl butoxide, S,S,S-tributyl phosphorotrithioate and diethyl maleate as synergists for pyrethroids (Pasay C). Ivermectin-resistant scabies mites have been identified in heavily endemic areas and in a report from Netherlands was seen to both lindane and ivermectin, suggesting clinically significant resistance to these drugs (van den Hoek JA). Sarcoptes scabiei var. hominis mites from scabies-endemic communities in northern Australia have shown increasing resistance to both 5% permethrin and oral ivermectin, based on increased drug metabolism and efflux mechanisms (Mounsey KE). Ivermectin-resistant ticks are also emerging, posing a problem for cattle farmers.

Drug Interaction

There are no reports of harmful drug interactions, but theoretically, the drug may potentiate the effects of

other drugs that are agonists of the GABA receptors (e.g. benzodiazepines and sodium valproate). Rifampicin and phenobarbital enhanced CYP3A activity, and alter ivermectin gastrointestinal disposition via enhanced P-glycoprotein-mediated intestinal transport.

Side Effects

Side effects reported include fever, itching, dizziness, edema, mild Mazzotti reaction, and minimal ocular inflammation in patients with eye involvement. The side effects usually occur during the first 3 days after treatment and are dose dependent. Cutaneous and systemic reactions in patients with onchocerciasis are termed Mazzotti reactions and may include rash, systemic symptoms, and ophthalmological reactions. These may be due to allergic and inflammatory responses to the death of microfilariae or to microorganisms within the worms. Doxycycline can eliminate endo symbiotic bacteria within filarial worms, reducing the incidence of Mazzotti reactions.

Less frequent reactions include tachycardia, facial edema, orthostatic hypotension, diarrhea, and nausea. CNS symptoms and Stevens–Johnson syndrome are rare. Liver function test abnormalities have been reported.

The reported incidences of side effects vary. In one review (De Sole G), which covered 50,929 patients who had been treated with ivermectin, around 9% were reported to have suffered from side effects. The most frequent reaction was symptomatic postural hypotension. The authors reported that the incidence of side effects was directly proportional to the microfilarial density in the skin (De Sole G). In hyperendemic areas, a much higher incidence of adverse reactions may be seen.

Special Groups

Pregnancy

Ivermectin can be given after the first trimester.

Lactation

The drug is excreted into breast milk and may attain concentrations of around 30% of that in plasma. Less than 10% of what goes into breast milk has been estimated to be taken up by the infant, which has been regarded as clinically insignificant.

BIBLIOGRAPHY

1. Ahmad HM, Abdel-Azim ES, Abdel-Aziz RT. Assessment of topical versus oral ivermectin as a treatment for head lice. Dermatol Ther. 2014;27(5):307-10.

2. Bécourt C, Marguet C, Balguerie X, Joly P. Treatment of scabies with oral ivermectin in 15 infants: a retrospective study on tolerance and efficacy. Br J Dermatol. 2013;169(4):931-3.
3. De Sole G, Remme J, Awadzi K, Accorsi S, Alley ES, Ba O. Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined study from eight community trials. Bull WHO. 1989;67:707-19.
4. Mohebbipour A, Saleh P, Goldust M, Amirnia M, Zadeh YJ, Mohamad RM, et al. Comparison of oral ivermectin vs. lindane lotion 1% for the treatment of scabies. Clin Exp Dermatol. 2013;38(7):719-23.
5. Mounsey KE, Holt DC, McCarthy JS, et al. Longitudinal evidence of increasing in vitro tolerance of scabies mites to ivermectin in scabies-endemic communities. Arch Dermatol. 2009;145(7): 840-1.
6. Mounsey KE, McCarthy JS. Treatment and control of scabies. Curr Opin Infect Dis. 2013;26(2):133-9.
7. Ortega-Loayza AG, McCall CO, Nunley JR. Crusted scabies and multiple dosages of ivermectin. J Drugs Dermatol. 2013;12(5):584-5.
8. Pasay C, Arlian L, Morgan M, Gunning R, Rossiter L, Holt D, et al. The effect of insecticide synergists on the response of scabies mites to pyrethroid acaricides. PLoS Negl Trop Dis. 2009;3(1):e354;27(5):307-10.
9. van den Hoek JA, van de Weerd JA, Baayen TD, et al. A persistent problem with scabies in and outside a nursing home in Amsterdam: indications for resistance to lindane and ivermectin. Euro Surveill. 2008;13(48):5-14.

ALBENDAZOLE

Category

Albendazole is a benzimidazole carbamate derivative, which is structurally related to mebendazole. It was originally introduced as a veterinary drug in 1975 and later as a human anthelmintic drug. It has a wide spectrum of activity against intestinal nematodes (hook worm, *Ascaris lumbricoides, Enterobius vermicularis, Strongyloides stercoralis, Trichuris trichiura* and *Capillaria philippinensis*), systemic nematodes (*Trichinella spiralis* and cutaneous larva migrans) and cestodes (*Echinococcus granulosis*, *E. multilocularis* and *neurocysticercosis*). Albendazole is active against both larval and adult stages of intestinal nematodes and ovicidal against *Ascaris lumbricoides* and *Trichuris trichiura*. Its main metabolite, albendazole sulfoxide, may largely be responsible for the pharmacological effects of the drug.

Absorption and Distribution

The parent drug is rapidly converted to a sulfoxide metabolite before reaching the systemic circulation. The systemic antihelminthic activity has been attributed to this primary

metabolite, albendazole sulfoxide. Oral bioavailability is enhanced when albendazole is taken with a fatty meal. Its main metabolite, the sulfoxide, attains maximum concentration after approximately 2.5 hours. The half-life of the major metabolite in the plasma is 8 hours. Urinary excretion of the metabolite albendazole sulfoxide is minor, with less than 1% of the dose recovered in the urine. Albendazole sulfoxide is 70% bound to plasma protein and achieves excellent distribution throughout the body. Therapeutic levels can be detected in urine, bile, liver, cyst fluid, and cerebral spinal fluid.

Metabolism

Uses (Approved/Unapproved)

Single or mixed infections caused by *Ascaris lumbricoides, Enterobius vermicularis*, *Ancylostoma duodenale*, *Trichuris trichiura*. Albendazole may be effective against cutaneous larva migrans and *Strongyloides stercoralis*, but controlled studies are needed to confirm its advantage over thiabendazole. Limited data indicate that albendazole is useful in neurocysticercosis. Albendazole seems to be the drug of choice for the treatment of inoperable hydatid cases, but its long term benefit needs further assessment.

Cutaneous disease and granulomatous amebic encephalitis caused by *Balamuthia mandrillaris* has been reported to respond to a combination of miltefosine, fluconazole, and albendazole. Ivermectin is often combined with albendazole in the treatment of bancroftian filariasis. Albendazole has a potent anti-angiogenic effect, inhibiting endothelial cell migration, lumen formation, vasopermeability, VEGF receptor-2 expression and retinal neovascularization. The anti-angiogenic effect suggests a potential role in treating cutaneous tumors.

Dosage of Albendazole

Ascariasis, enterobiasis, ancylostomiasis and cutaneous larva migrans	A single dose of 400 mg. Re-infection is common with **enterobiasis;** a further dose may be required after 2 to 4 weeks
Trichuriasis	A single dose of 400 mg is usually sufficient. For heavier infections the treatment can be continued for 3 days
Strongyloidiasis	A single dose of 400 mg daily for 3 days
Hydatid disease	Four 28-day courses of 10–15 mg/kg daily in three divided doses separated by 14 days rest periods. The treatment duration, however, is governed by the disease and patient tolerance
Neurocysticercosis	15 mg/kg daily in three divided doses for 28 days

Drug Interaction

Although single doses of albendazole have been shown not to inhibit theophylline metabolism, albendazole does induce CYP1A2. Therefore, plasma concentrations of theophylline should be monitored. Praziquantel, cimetidine, and dexamethosone have been reported to increase the plasma levels of the active metabolite. The AUC of albendazole and mebendazole are reduced after long-term use of ritonavir.

Side Effects

1. After a single dose treatment of albendazole 400 mg, minor and transient side effects such as epigastric pain and diarrhea were seen. Less than 6% of treated patients experience these effects.
2. During the treatment of hydatid disease, where higher doses are used for longer time periods, side effects were more common and severe.
3. Albendazole can cause bone marrow suppression, aplastic anemia, and agranulocytosis. Bone toxicity may occur in patients with and those without underlying hepatic dysfunction.

Monitoring

The manufacturer recommends a CBC at the beginning of each 28-day cycle of therapy, and every 2 weeks while on therapy; periodic liver function tests would also be wise. Patients with liver disease, including those with hepatic echinococcosis, appear to be at increased risk for bone marrow suppression.

Special Groups

Liver Failure

Biliary elimination is presumed to be the major route of excretion, so biliary obstruction will affect blood levels, but renal failure is unlikely to affect levels.

Kidney Failure

Children.

6

CHAPTER

Antiviral Agents

Pooja Arora, Kabir Sardana

INTRODUCTION

Viruses are obligate intracellular parasites that contain either double- or single-stranded DNA or RNA enclosed in a protein coat called a capsid. Some viruses also possess a lipid envelope that, like the capsid, may contain antigenic glycoproteins. Most viruses contain or encode enzymes essential for viral replication inside a host cell, and they usurp the metabolic machinery of their host cell.

Though there are differences in the replicative cycle of a DNA virus and an RNA virus a summary is given of the major action of antiviral agents in Figure 6.1. Although many compounds show antiviral activity *in vitro*, most affect some host cell function and are associated with unacceptable toxicity. Our focus is primarily agents that work against Herpes virus though a list of other agents is given in Table 6.1, including agents for HIV and hepatitis which will not be covered in this chapter.

Clinical Application

Herpes Genitalis

The majority of people who are seropositive for HSV-2 are asymptomatic, and thus probably asymptomatic viral

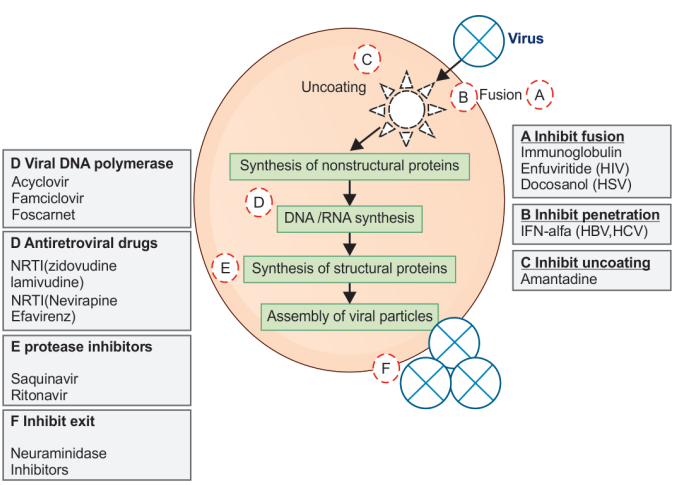


Fig. 6.1: A depiction of the mode of entry of a virus and its replication and the site of action of antiviral drugs

Table 6.1: Classification of antiviral agents

Antiherpesvirus agents	Acyclovir Cidofovir Famciclovir Foscarnet Penciclovir Valacyclovir
Anti-influenza agents	Amantadine Oseltamivir Rimantadine Zanamivir
Antihepatitis agents	Interferon-alfa Lamivudine
Other antiviral agents	Ribavarin Imiquimod

shedding leads to most of the transmission of genital herpes. The decision to treat on an episodic basis or in a continuous suppressive fashion depends on various factors namely, the number of outbreaks per year, the severity of outbreaks, a lack of prodromal symptoms, and an HSV-seronegative sexual partner.

Suppression with acyclovir 400 mg twice daily can decrease recurrences by 80–90% and asymptomatic shedding by 95% (Wald A et al.). A year-long, double-blind, placebo controlled study demonstrated that 1 g of valacyclovir taken daily reduced recurrence rates by 78% (Reitano M et al.). It has also been shown that daily valacyclovir significantly lowered the risk of transmission of genital herpes in heterosexual, immunocompetent, monogamous, HSV-2 discordant couples (Corey L et al.).

Other Herpetic Infections

Acyclovir, valacyclovir and famciclovir are all effective against herpes labialis, when used intermittently or suppressively, and they are all effective in treating herpes zoster. Treatment of varicella in children is controversial, but it does not alter antibody production at 28 days or at 1 year. Oral therapy is recommended for healthy adolescents and adults as well as children with chronic skin or lung disease or on long-term salicylates; intravenous administration is indicated for immunocompromised individuals, including those receiving chronic systemic corticosteroid therapy.

A summary of the doses in various indications is given in Table 6.2, the details will follow in the section that follows.

Comparative Efficacy

Acyclovir, valacyclovir and famciclovir are considered equivalent in safety and efficacy (time to healing, duration of pain, and viral shed ding) for initial episodes of genital

Table 6.2: Overview of dosimetry of antiviral agents against HSV infection

Primary genital herpes	Acyclovir 200 mg 5 times a day for 10 days or 400 mg tds for 10 days	Valacyclovir 1 g po bd for 10 days	Famciclovir 250 mg po tds for 10 days
Recurrent genital herpes	Acyclovir 400 mg tds for 5 days or 800 mg po tds for 2 days	Valacyclovir 500 mg po bd for 3 days or 1 g po od for 5 days	Famciclovir 125 mg po bd for 5 days or 500 mg po × 1 dose then 250 mg bd for 2 days
Chronic suppression of herpes	Acyclovir 400 mg po bd	Valacyclovir 500 mg (if <10 outbreaks/year)\Or 1 g (if ≥10 outbreaks/year) po od	Famciclovir 250 mg po bd
Recurrent orolabial herpes	400 mg BD	Valacyclovir 2 g po bd × 1 day	Famciclovir 1500 mg po once
Herpes zoster	Acyclovir 800 mg po 5 times a day for 7–10 days Disseminated herpes Zoster Acyclovir 5–10 mg/kg iv q8 h for 7–10 day	Valacyclovir 1 g po tds for 7 days	Famciclovir 500 mg po tds for 7 days
Varicella	Acyclovir >2years,>40 kg: 800 mg po 5 times a day for 5 days >2years,<40 kg: 20 mg/kg (800 mg max) po 4 times a day for 5 days	Valacyclovir 20 mg/kg (1 g max) po tds for 5 days	
Mucocutaneous herpes simplex	Acyclovir 5 mg/kg (if age ≥10 years) or 10 mg/kg (if age <10 years) iv q8 h for 7 days Acyclovir 400 mg po 3–5 times a day for 14–21 days	Valacyclovir 1 g po bd–tds for 7 days	Famciclovir 500 mg po bd for 5–10 days

herpes. Famciclovir and valacyclovir have the advantage of greater oral bioavailability and more convenient dosing. Valacyclovir is at least as effective as acyclovir in decreasing the duration of pain in herpes zoster.

Acyclovir Resistance

Frequent use of ACV for the treatment and suppression of HSV infections has led to the emergence of ACV-resistant HSV strains. In immunocompromised patients, especially in those with HIV or who have undergone bone marrow transplantation or are on immunosuppressive therapies, the prevalence of ACV-resistant infections may be as high as 7%. Intravenous foscarnet or cidofovir may be used in such cases. Both work through inhibition of viral DNA polymerase and do not require phosphorylation by thymidine kinase.

Pregnancy

Systemic antiviral drugs should not be used during pregnancy unless the benefit justifies the potential risk to the fetus. Systemic acyclovir is FDA pregnancy category C and crosses the placenta and is mutagenic at high doses *in vitro*. However, it has not been shown to be teratogenic in animal studies, and a prospective registry of 756 pregnant patients who took acyclovir showed an incidence of birth defects similar to that in the general population

Use of acyclovir in pregnancy is indicated in the following scenarios (i) first clinical episode of genital herpes, (ii) life threatening maternal HSV, (iii) near term to avoid cesarian section. Routine use for recurrent herpes is not recommended. Acyclovir has not been shown to prevent neonatal sequelae and that should not guide therapeutic decision for administration of the drug . Acyclovir is the drug of choice for primary genital herpes in pregnant women because it has been used safely more often than other antivirals. Recurrent herpes simplex during pregnancy is generally not an indication for acyclovir.

Varicella in pregnant women should be treated with acyclovir due to the high risk of maternal mortality from varicella pneumonia as well as fetal death or premature delivery. It is not known, however, whether acyclovir prevents congenital varicella syndrome. Acyclovir is excreted in breast milk, but no data is available regarding the risk to nursing infants. There are no adequate human studies of valacyclovir (pregnancy category B) in pregnancy or lactation. Systemic famciclovir (pregnancy category B) and penciclovir have not been shown to be teratogenic in animal studies.

BIBLIOGRAPHY

1. Comprehensive Dermatologic Drug Therapy Third Edition Stephen E. Wolverton, Copyright © 2013 Elsevier.
2. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk Gerald G. Briggs, Roger K. Freeman, Sumner Jason Yaffe Lippincott Williams & Wilkins, 2011.
3. Martindale The Complete Drug Reference Thirty-sixth edition Sean C Sweetman Published by the Pharmaceutical Press; 2009.

JOURNALS

1. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004;350:11-20.
2. Reitano M, Tyring S, Lang W, et al. Valacyclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. J Infect Dis. 1998;178:603-10.
3. Shrim A, Koren G, Yudin MH, Farine D; Maternal Fetal Medicine Committee. Management of varicella infection (chickenpox) in pregnancy. J Obstet GynaecolCan. 2012;34(3):287-92.
4. Su CW, McKay B. Treatment of HSV infection in late pregnancy. Am Fam Physician. 2012;85(4):390-3.
5. Wald A, Zeh J, Barnum G, et al. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. Ann Intern Med. 1996;124:8-15.

ACYCLOVIR

Classification

Acyclovir is an acyclic guanine nucleoside analog that lacks a 3 α-hydroxyl on the side chain.

Mechanism of Action

Acyclovir's selective inhibition of viral DNA synthesis depends on interaction with two distinct viral proteins: HSV thymidine kinase (TK) and DNA polymerase (Fig. 6.2). Cellular uptake and initial phosphorylation are facilitated by TK. The affinity of acyclovir for HSV TK is ~200 times greater than for the host enzyme. Cellular enzymes convert the monophosphate to acyclovir triphosphate, which is present in 40–100-fold higher concentrations in HSV-infected than in uninfected cells and competes for endogenous deoxyguanosine triphosphate (dGTP). Acyclovir triphosphate competitively inhibits viral DNA polymerases and, to a much smaller extent, cellular DNA polymerases. Acyclovir triphosphate also is incorporated into viral DNA, where it acts as a chain terminator because it lacks a 3-alpha-hydroxyl group. By suicide inactivation, the terminated DNA template containing acyclovir binds the viral DNA polymerase and leads to its irreversible inactivation.

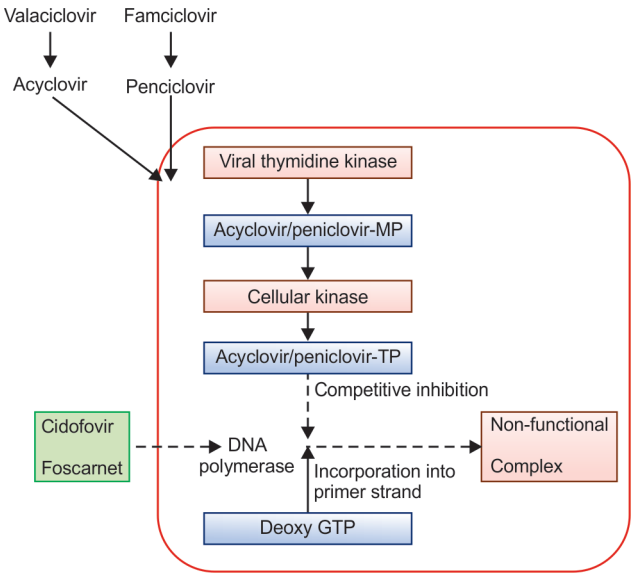


Fig. 6.2: Mode of action of common antiviral drugs (herpes family)

Acyclovir resistance results from three mechanisms: absence or partial production of viral TK, altered TK substrate specificity or altered viral DNA polymerase. The most common resistance mechanism in clinical HSV isolates is *absent or deficient* viral TK activity; viral DNA polymerase mutants are rare. Resistance typically is defined by inhibitory concentrations of >2–3 μg/mL and can predict failure of therapy in immunocompromised patients. Similarly, acyclovir resistance in VZV isolates is caused by mutations in its TK or polymerase.

Absorption and Distribution

Peak level 1.5–2.0 h

Bioavailability: 15–30%.

Orally active prodrugs such as valacyclovir have been developed to overcome this poor absorption.

After intravenous dosage as acyclovir sodium, it is widely distributed to body tissues and fluids including the CSF where concentrations achieved are about 50% of those achieved in plasma. Protein binding is reported to range from 9 to 33%.

Acyclovir is excreted largely unchanged in the urine, by glomerular filtration and some active tubular secretion, with up to 14% appearing in the urine as the inactive metabolite.

Metabolism

No hepatic microsomal metabolism. Roughly equal urine and fecal excretion.

Uses

Though most conditions merit oral dosages, intravenous acyclovir is used in immunocompromised patients with disseminated HSV or VZV and in patients with severe herpes zoster.

Disorder (FDA approved/ Unapproved)	*Dose /Duration*
Herpes simplex infections	
Primary HSV infection	400 mg tds X7 d
Recurrent genital HSV infection	400 mg tds X 7 d
Recurrent oral labial HSV infection	400 mg 5x/day X 5 d
Chronic suppression of HSV infection	400 mg bd X 1 yr
Perinatal HSV infection	10–20 mg/kg q8h X10-21 d
Mucocutaneous herpes simplex in immunocompromised patient	Acyclovir 5 mg/kg(age≥10yr) or 10 mg/kg (age<10 yr) iv q8 h for 7 days. Acyclovir 400 mg 3–5 times a day for 14–21 days.
HSV encephalitis	Acyclovir 10 mg/kg iv q8 h for 10 days.
Varicella	**Patients>2 years; >40 kg:** Acyclovir 800 mg 5 times a day X-5 days **Patients>2 years;<40 kg:** Acyclovir 20 mg/kg (800 mg max) po qid for 5 days
Herpes zoster: normal host	800 mg 5 times a day X 7 days
Herpes zoster: severe disease	10–12 mg/kg 8h IV X 7–14 days

FDA Approved

1. Herpes Simplex Infections

Primary: Dosing should begin as early as possible after the start of an infection; for recurrent episodes this should preferably be during the prodromal period or when lesions first appear.

Suppression of herpes simplex infections in immunocompetent patients: Therapy should be interrupted periodically at intervals of six to twelve months, in order to observe possible changes in the natural history of the disease.

2. Varicella-zoster Infections

Treatment of varicella and herpes zoster infections: Dosing should begin as early as possible after the start of an infection. Treatment of herpes zoster yields better results if initiated as soon as possible after the onset of the rash. Treatment

of chickenpox in immunocompetent patients should begin within 24 hours after onset of the rash.

3. Dosage in Children

Treatment of herpes simplex infections, and prophylaxis of herpes simplex infections in the immunocompromised: Children aged two years and over should be given adult dosages and children below the age of two years should be given half the adult dose.

For treatment on neonatal herpes virus infections, intravenous acyclovir is recommended.

Treatment of varicella infection in children

6 years and over:	800 mg Acyclovir four times daily	5 days
2–5 years:	400 mg Acyclovir four times daily	
Under 2 years:	200 mg Acyclovir four times daily	

Dosing may be more accurately calculated as 20 mg/kg bodyweight (not to exceed 800 mg) four times daily.

No specific data are available on the suppression of herpes simplex infections or the treatment of herpes zoster infections in immunocompetent children.

4. Dosage in Renal Impairment

Caution is advised when administering acyclovir to patients with impaired renal function. Adequate hydration should be maintained.

In the management of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of acyclovir above levels that have been established safe by intravenous infusion. However for patients with severe renal impairment (creatinine clearance less than 10 ml/minute) an adjustment of dosage to 200 mg acyclovir twice daily at approximately twelve-hourly intervals is recommended.

In the treatment of herpes zoster infections it is recommended to adjust the dosage to 800 mg acyclovir twice daily at approximately twelve–hourly intervals for patients with severe renal impairment (creatinine clearance less than 10 ml/minute), and to 800 mg acyclovir three times daily at intervals of approximately eight hours for patients with moderate renal impairment (creatinine clearance in the range 10–25 mL/minute)

Unapproved

Off-label uses of acyclovir are prevention of recurrent herpes-associated erythema multiforme and treatment of eczema herpeticum, primary herpes gingivostomatitis, herpetic

whitlow and neonatal herpes. It has been seen that high-dose ACV in patients with HIV infection, can actually offer a modest survival benefit. Although the mechanism is unclear as ACV has no antiretroviral activity, suppression of bursts of HIV replication during active HSV infections may contribute to prolonged survival.

Dosage

1. Genital HSV

First-episode genital HSV: 200 mg five times daily for 10 days/400 mg TDS 7–10 days

Recurrent: 200 mg five times daily for 10 days/400 mg TDS -5 days

Suppressive: 400 mg twice daily reduces recurrence of genital HSV by 80–90%, and reduces asymptomatic viral shedding of HSV-2 by 95%.

2. *Herpes Labialis*

ACV 200 mg 5 times daily for 5 days, expedites crusting, but does not appear to reduce healing time significantly. Ideally to be started in the prodrome. Acyclovir minimally affects symptoms or viral shedding in recurrent herpes labialis and is not generally used for this disease. However, in a dose of 400 mg twice daily, it is effective in preventing recurrent herpes labialis in those with frequent relapses and in preventing sun-induced relapses.

Suppressive therapy: >2 outbreaks/year or a history of ocular HSV disease.

(400 mg BD reduces the frequency of HSV labialis and ocular HSV recurrence by 50–78%).

3. Chickenpox

Acyclovir should be started within the first 24 hours

Adult: 800 mg 5 times daily for 7 days.

In adults treated within 24 hours, oral acyclovir (800 mg five times daily for 7 days) reduces the time to crusting of lesions by ~2 days, the maximum number of lesions by 50%, and duration of fever.

Children: 20 mg/kg 4 times daily (up to a maximum of 800 mg per dose) for children.

The use of acyclovir in children can help to reduce fever and new lesion formation by ~1 day. Such use should be considered in those at risk of moderate-to-severe illness (persons >12 years old, secondary household cases, those with chronic cutaneous or pulmonary disorders, or those receiving glucocorticoids or long-term salicylates). The

disadvantage though is that active therapy interferes with natural immunity against the VZV.

Prophylaxis

Oral acyclovir (10 mg/kg four times daily) given between 7 and 14 days after exposure may reduce the risk of varicella.

4. Herpes zoster (HZ)

Acyclovir should be started within the first 24–72 hours. The drug has ***no*** effect on establishment of latency, frequency of recurrence, or incidence of post herpetic neuralgia.

Dose: 800 mg of ACV to be taken 5 times daily for 7–10 days

Severe trigeminal nerve distribution: Intravenous ACV (10 mg/kg three times daily for 7–10 days).

Immunocompromised Host

HSV Primary: 200–400 mg 5×/day for 10 days or 5 mg/kg IV q8h for 7–10 days.

HSV Recurrent: 400 mg TID for 7–10 days

HSV Suppressive: 400 mg BID

HZ adults: 800 mg 5×/day for 7–10 days

HZ children: 10 mg/kg IV q8h for 7–10 days.

Drug Interaction

Drugs that increase effects/toxicity of acyclovir: MAO inhibitors, probenecid, ziduvine, CNS depressants.
Drugs that decrease effects/toxicity of acyclovir: β blockers, guanethidine.

Special Considerations

Caution and in reduced doses in patients with renal impairment.

Elderly patients with existing renal impairment should be closely monitored for neurological adverse effects.

Adequate hydration should be maintained in patients given parenteral or high oral doses of acyclovir. Intravenous doses should be given by infusion over one hour to avoid precipitation of aciclovir in the kidney; rapid or bolus injection should be avoided.

Side Effects

Common: nausea, vomiting, diarrhea, headache, malaise, dizziness, rash, lethargy, confusion, phlebitis and infusion site reactions with IV form.

Rare: Seizures, coma, leukopenia, thrombocytopenia, renal dysfunction, reversible renal impairment due to crystalline nephropathy and elevated creatinine with IV form.

Monitoring

- Serum blood urea nitrogen (BUN) and creatinine, complete blood count (CBC) with differential and platelets, liver enzymes
- Signs and symptoms of ocular herpetic infection as this may cause blindness
- **Serum creatinine level:** If this increases during therapy, adjust dose, increase hydration or discontinue drug.
- Signs and symptoms of hepatotoxicity.
- Signs and symptoms of renal toxicity.
- **Signs and symptoms of drug-induced psychologic disturbances:** Changes in mood, behaviour or orientation of patient, agitation, hallucinations, suicidal tendencies, sleep disturbances, lethargy.
- Intake of fluids and urinary and other fluids. Closely monitor electrolyte levels.

Special Groups

Pregnancy: C

The use of acyclovir therapy during pregnancy has not been conclusively proven to prevent transmission to the fetus and thus the primary aim is to prevent complications in the mother. As far as possible if acyclovir is given it should be avoided in the first trimester.

HSV Infection

Pregnant women with a primary or recurrent episode of genital HSV infection who are later than *36 weeks* of gestation should be treated with acyclovir for *viral suppression*. Suppressive therapy at the time of delivery can reduce the rate of recurrence, the risk of asymptomatic viral shedding, and the number of cesarean deliveries because of active HSV infection.

The effect of antiviral prophylaxis on neonatal HSV infection cannot be estimated because of a low incidence rate. Antiretroviral prophylaxis starting at 36 weeks of gestation has been shown to be more cost-effective than expectant management with cesarean delivery for active lesions at the time of delivery.

The American College of Obstetricians and Gynecologists and the Society of Obstetricians and Gynaecologists of Canada (SOGC) recommend that women with active recurrent genital HSV infection be offered suppressive viral therapy with acyclovir or valacyclovir at or beyond 36 weeks of gestation. Both organizations advocate for cesarean delivery in women with active genital lesions or prodromal

symptoms, such as vulvar pain or burning at delivery. The risk of transmission is more in case HSV-1 is isolated .

SOGC also recommends that women with primary genital HSV infection in the third trimester of pregnancy be offered a cesarean delivery regardless of the presence or absence of active lesions at delivery because of the high risk (30–60%) of vertical transmission.

Varicella

Maternal infection in the first 20 weeks may lead to *congenital varicella syndrome*, abortion, preterm labour and fetal death . Women with significant (e.g. pneumonitis) varicella infection in pregnancy should be treated with oral antiviral agents (e.g. acyclovir 800 mg 5 times daily). In cases of progression to varicella pneumonitis, maternal admission to hospital should be seriously considered. Intravenous acyclovir can be considered for severe complications in pregnancy (oral forms have poor bioavailability). The dose is usually 10–15 mg/kg of BW or 500 mg/m^2 IV every 8 h for 5–10 days for varicella pneumonitis, and it should be started within 24–72 h of the onset of rash. In other cases acyclovir can be given but it should be used in caution in the first trimester.

In the case of a possible exposure to varicella in a pregnant woman with unknown immune status, serum testing should be performed. If the serum results are negative or unavailable within 96 hours from exposure, varicella zoster immunoglobulin should be administered. Varicella zoster immunoglobulin should be administered to neonates whenever the onset of maternal disease is between 5 days before and 2 days after delivery.

Lactation: American Academy of Pediatrics considers that its use is usually compatible with breastfeeding.

Kidney failure: Administration in renal impairment. Doses of acyclovir should be reduced in renal impairment according to creatinine clearance (CC) and licensed product information gives the following guidance:

	Acyclovir	
Indication	*Creatinine clearance (mL/min)*	*Adjusted dose*
Primary genital herpes	<10	200 mg po bid
Recurrent genital herpes		
Chronic suppression of herpes		
Herpes zoster	10–25	800 mg po tid
Immunocompromised patients with mucocutaneous herpes; for acyclovir also herpes encephalitis and disseminated zoster	25–50 10–24 <10	5–10 mg/kg iv q12h 5–10 mg/kg iv q24h 2.5–5 mg/kg iv q24h

VALACYCLOVIR

Mechanism of Action

Same as acyclovir.

Absorption and Distribution

Bioavailabiliy: 54%

This 1-valyl ester of ACV has a bioavailability 3–5 times greater than that of oral ACV. In the oral form, it is nearly as potent as intravenous ACV.

Metabolism

- No hepatic microsomal metabolism
- Roughly equal urine and fecal excretion.

Uses

Disorder (FDA approved/Unapproved)	*Dose/Duration*
Herpes simplex infections	
Primary HSV infection	1000 mg BD X 10 d
Recurrent genital HSV infection	500 mg BD X 3 d
Recurrent oral labial HSV infection	2000 mg BD X 1d
Oral labial HSV infection, immunocompromised host	500 mg BD x 3-5 d
Suppressive therapy: >4 outbreaks/year:	500 mg OD
Chronic suppression of HSV infection	Valacyclovir 500 mg (if <10 outbreaks/year) or 1 g (if ≥10 outbreaks/year) od
Mucocutaneous herpes simplex in immunocompromised patient	Valacyclovir 1 g po bd–tds for 7 days.
Varicella Herpes zoster: normal host	Valacyclovir 20 mg/kg (1 g max) po tds X 5 days Valacyclovir 1 g po TDS for 7 days

FDA Approved

- Herpes simplex infections
- Varicella-zoster infections

Herpes Zoster (HZ)

1 g TDS for 7 days.

As effective as ACV in its effect on the appearance of new lesions, time to crusting, and time to 50% healing. *More* efficacious than ACV in ameliorating PHN. VACV patients had a median duration of 40 days of pain after lesion resolution compared to 60 days of pain after lesion resolution for ACV recipients. Thus, in herpes zoster-related discomfort amelioration is 25% greater than ACV making it a *better* choice than acyclovir.

Unapproved

- Recurrent erythema multiforme
- Other subsets of herpes simplex infections

Immunocompromised Host

HSV Recurrent: 500 mg BD for 7 days
HSV Suppressive: 500 mg BD
HZ adults: 1 g TDS 7–10 days

Drug Interaction

Decreased rate of conversion valacyclovir to acyclovir: Cimetidine, probenicid.

Side Effects

Rare: TTP/HUS has been reported in HIV patients and in transplant patients receiving >8 g/day of the medicine. Mononeuritis multiplex due to vasculitis has been reported.

The basis for and causal relationship to valacyclovir of these occurrences have not been established, and TTP/HUS has not been reported in patients taking conventional dosages (up to 3 g/day) of valacyclovir.

Special Groups

Pregnancy: B

Lactation

Compatible with breastfeeding.

Kidney Failure

Indication	*Valacyclovir*	
	Creatinine clearance (ml/min)	*Adjusted dose*
Primary genital herpes	10–29 <10	1g od 500 mg od
Recurrent genital herpes	<30	500 mg od
Chronic suppression of herpes	<30	500 mg/48h or od
Herpes zoster	30–49 10–29 <10	1g bid 1g od 500 mg od
Recurrent orolabial herpes (2 g bid × 1 day)	30–49 10–29 <10	1g bid × 1 day 500 mg bid × 1 day 500 mg once a day

FAMCICLOVIR

Absorption and Distribution

Bioavailabiliy: 77%

Famciclovir is converted to penciclovir and the triphosphate form has a much longer intracellular half-life (10–20 hours in HSV-infected cells and 7 hours in VZV-infected cells) than ACV triphosphate (<1 hour in HSV- and VZV-infected cells). This accounts for its twice a day dosage.

Metabolism

No hepatic microsomal metabolism; conversion to penciclovir. Roughly equal urine and fecal excretion 73% urine, 27% fecal; mostly penciclovir, also 6-deoxypenciclovir.

Uses

FDA Approved

- Herpes simplex infections
- Varicella-zoster infections.

Unapproved

- Recurrent erythema multiforme
- Other subsets of herpes simplex infections.

Disorder (FDA approved/Unapproved)	*Dose /Duration*
Primary HSV infection	250 mg tds X 7–10 d
Recurrent genital HSV infection	125 mg bd (X 5 d) or 1000 mg bd (X1d)
Recurrent oral labial HSV infection	500 mg bd X 7 d/1500 mg OD -1 d
Chronic suppression of HSV infection	250 mg BDX1yr
Mucocutaneous herpes simplex in immunocompromised patients	Famciclovir 500 mg bd X 5–10 d
Herpes-zoster varicella	500 mg TDS X7d

Dosage

Genital HSV

First-episode genital HSV: 250 mg TDS for 10 days (As good as acyclovir).

Recurrent: 125 mg BID for 5 days/1 g BD 1 days (The dose of 1000 mg BD for 1 day was similar in both safety and efficacy to Valaciclovir 500 mg BD for 3 days, which makes it the *most convenient treatment* regimen for recurrent herpes genitalis).

Suppressive: 250 mg BID

Herpes Labialis

Recurrent orofacial HSV: Single 1500 mg dose
UV Induced: 250 and 500 mg TDS for 5 days.

Chickenpox

Adult: 500 mg TDS 5 days; Children: 20 mg/kg/day.

Herpes Zoster (HZ)

500 mg TDS for 7 days.

Immunocompromised Host

HSV Recurrent: 500 mg BD for 7 days
HSV Suppressive: 500 mg BD
HZ adults: 500 mg TDS 7-10 days.

Drug Interaction

Increased Levels: probenicid, theophylline, cimetidine.

Special Groups

Pregnancy: *B*

Lactation: Unknown

Kidney Failure:

Indication	*Famciclovir*	
	Creatinine clearance (mL/min)	*Adjusted dose*
Primary genital herpes	20–39 <20	125 mg bid 125 mg qd
Recurrent genital herpes	40–59 20–39 <20	500 mg bid × 1 day 500 mg once 250 mg qd
Chronic suppression of herpes	20–39 <20	125 mg bid 125 mg qd
Herpes zoster	40–59 20–39 <20	500 mg bid 500 mg qd 250 mg qd
Recurrent orolabial herpes (2 g bid × 1 day)	40–59 20–39 <20	750 mg once 500 mg once 250 mg once
Immunocompromised patients with mucocutaneous herpes; for acyclovir, also herpes encephalitis and disseminated zoster	20–39 <20	500 mg qd 250 mg qd

7

CHAPTER

Biologicals

Kabir Sardana[1], Trilok Raj Tejasvi[1], Deepika Pandhi[2], Rahul Arora[2], Roshni Menon[3], Sujay Khandpur[4], Kiran Godse[5], Aayushi Mehta[5]

BIOLOGICALS IN DERMATOLOGY[1]

Biologics are organic molecules that are made in a living system like an animal or a plant cell. These target molecules are derived from a combinatorial effect of advancement in our understanding of disease pathophysiology and advances in bioengineering technology. These molecules work in a number of autoimmune disorders, including psoriasis and work by targeting mechanisms that include altering T-cell activation and differentiation (e.g. affecting the development of Th1 or Th17 cells), blocking cytokines and eliminating pathogenic B cells. Though most of the drugs were initially discovered for rheumatoid arthritis (RA) they are now being used for other dermatological disorders mostly psoriasis and urticaria. Interestingly some have serendipitously been used for conditions like alopecia areata (JAK inhibitors. ruxolitinib) [Xing L et al.].

A brief overview of the commonly indication is given below.

BIOLOGICALS FOR PSORIASIS

The exact antigen in psoriasis is not established but the basic interplay between T cells, antigen presenting cell (APC) and cytokines is well established and one needs to understand these interactions before initiating biologic therapy. Of the plethora of compounds, only a few have received FDA approval for psoriasis (Box 7.1)

Box 7.1: FDA approved biologicals for psoriasis

Alefacept : T cell inhibition
Etanercept: Fusion protein combined with human igG1 to antagonize TNF-α
Infliximab: Chimeric monoclonal antibody to TNF-α
Adalimumab : Recombinant human monoclonal antibody to TNF-α
Ustekinumab : Monoclonal antibody to common p40 subunit of IL-12/23
Secukinumab : Inhibits IL-17 A
Apremilast :Inhibits PDIE-4

1. T Cell/APC Interaction

To initiate cell mediated immunity, two signals must be delivered between APCs and T cells for activation to occur (Fig. 7.1). The first signal occurs when the major histocompatzibility complex on an APC (bound to a specific peptide antigen) interacts with the T-cell receptor. The second costimulatory signal can be one of a number of interactions between APCs and T cells, as shown in the Figure 7.1. Biologicals that block these interactions were the earliest drugs to be discovered for psoriasis.

Alefacept binds to CD2 on T cells, preventing its interaction with LFA-3 on APCs and the resultant T-cell activation. CD2 is maximally expressed in activated Protein tyrosine phosphatase, receptor type, C short isoform (CD45RO$^+$) T memory cells. In addition to the interaction between the LFA-3 portion of alefacept and CD2 on CD45RO$^+$ T cells, the Fc portion of alefacept binds to receptors on the surface of natural killer cells, which leads to a reduction in the number of CD45RO + T memory cells in the circulation.

The first biologics approved for psoriasis (such as efalizumab and alefacept) were primarily directed against receptors involved in T cell transmigration or activation. Both of these drugs have since been discontinued.

A list of the common drugs in this category including Alefacept (not used) are given in Table 7.1 with their listed uses.

2. Cytokine Production

It is speculated that innate signals first activate antigen-presenting cells within the skin, followed by a CD4 T cell

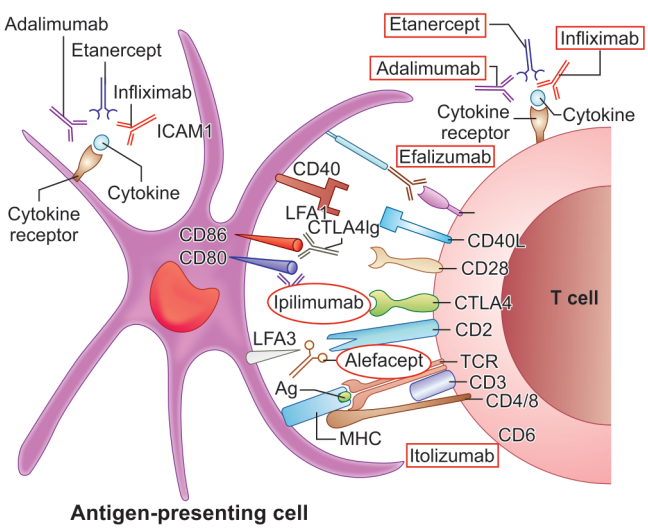


Fig. 7.1: A depiction of APC/T cell interactum and the site of action of common biological drugs

Table 7.1: Activation-blocking therapies and their uses

Drug	*Site of action*	*Uses*
Teplizumab	CD3	Psoriasis
Abatacept	Prevents B7- CD28 binding	Rheumatoid arthritis Psoriatic arthritis Systemic lupus erythematosus Chronic urticaria Diffuse scleroderma Psoriasis
Ipilimumab	CTLA4	Metastatic melanoma Melanoma
Alefacept	CD2	Psoriasis
Itolizumab	CD6	Psoriasis

response. Psoriasis was thought to be primarily due to an enhanced Th1 type response, characterized by the presence of IL-12-expressing DC and Th1 cells, which secrete interferon (IFN) - γ, tumour necrosis factor(TNFα) and IL-2. Now the focus has shifted to IL-12 and IL-23 (Fig. 7.2).

Recent studies demonstrate the role of Th17 (as it produces interleukin17) cells in the evolution of the psoriasis disease. The role of IL-12 which activates Th1 cells and its complex interaction within the IL-23/Th17 axis is also the focus of unique targeted therapies.

The differentiation, survival and expansion of the Th17 cells is mainly by IL-23, other cytokines include IL6 and TGF beta, and in the absence of IL-6, TGF beta with IL21, TNF and IL-1beta (Fig. 7.3). These cells produce proinflammatory cytokines, such as IL-17 (A-F) and IL-22, leading to the recruitment of neutrophils and dysregulation of keratinocyte proliferation. The cytokines IL-22 and IL-20, share a common receptor complex (IL-22R1). **IL-22** effects keratinocyte terminal differentiation, resulting in epidermal hyperplasia and acanthosis, the well-known psoriatic phenotype. **IL-20,** produced by keratinocytes, further perpetuates epidermal hyperplasia, through activation of IL-22R1. Thus, the IL-22R1 receptor appears to be a novel driver of inflammation through positive autoregulatory loops. Some clinical studies, have shown elevated serum levels of IL-20 and IL-22 and the levels correlated with Psoriasis Assessment Severity Index (PASI).

Both **IL-12** and **-23** are structurally similar (heterodimers) as they share a common **p40** subunit that is covalently linked to either a p35 subunit (IL-12) or a p19 subunit (IL-23). The p40 subunit of both interleukins binds the transmembrane IL-12 receptor β1 (IL-12Rβ1) on the surface of T cells and NK cells. **IL-23** probably has more influence over the induction of autoimmune-mediated inflammation than the IL-12/Th1 axis (Figs 7.2 and 7.3).

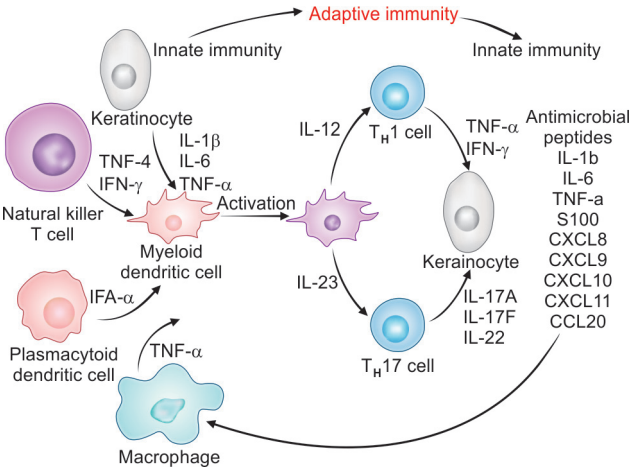


Fig. 7.2: Overview of the immune response and the cytokines involved in the skin

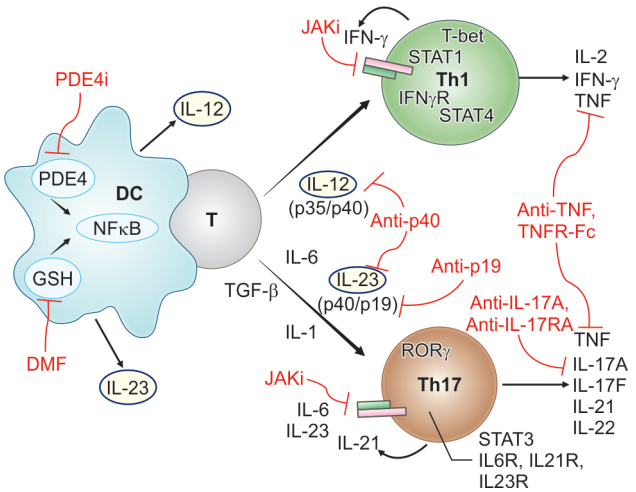


Fig. 7.3: Interaction of T cell with Th1, Th17 cell and the site of action of novel biological drugs

Ustekinumab is a monoclonal antibody approved to treat moderate to severe psoriasis binds to the **p40 subunit** common to IL-12 and IL-23 and prevents their interaction with the IL-12 receptor β1 subunit of the IL-12 and IL-23 receptor complexes.

The Th17 cells mainly produce cytokines of the **IL17** family. IL-17A is a prototype proinflammatory cytokine which belongs to family of six ligand members (A-F), which bind to five receptors (RA-RE). These dimeric glycoproteins exist in the circulation as homodimer of two IL-17A or heterodimer of 17A and F. These cytokines require binding to IL-17 receptors, (IL17-RA and RC) to induce inflammation. Newer monoclonal antibodies like *secukinumab* (recently approved by the FDA for treating moderate to severe

psoriasis) and *ixekizumab* (phase III completed), directly bind and neutralize the action of IL-17A. *Brodalumab* (phase II, completed) exerts its action by binding to the IL-17RA (receptor A). All of these monoclonal antibodies achieved 50-70% PASI 90 in the clinical trials.

TNF-α, produced by both activated dendritic cells and T cells, including Th1, Th17, and Th22, is often elevated in inflammatory conditions including psoriasis, as evidenced by increased levels found in the serum and blister fluid of patients with the disease. TNF antagonists revolutionized the therapy of psoriasis and psoriatic arthritis with impressive response rates. The majority of patients treated with anti-TNF antibodies such as *etanercept*, *adalimumab* or *infliximab* show at least a 50–75% improvement in the clinical psoriasis area and severity index (PASI-75) score.

Based on the present research the biologicals that work in psoriasis via cytokine modulation are detailed in Table 7.2 and Figure 7.3.

3. Small Molecular Weight Inhibitors (SMIs)

Phosphodiesterases (PDE) are a group of enzymes that hydrolyze and degrade cyclic adenosine monophosphate, PDE4 influences the immune and inflammatory processes by controlling the cAMP levels and downstream protein kinase A (Fig. 7.3). *Apremilast* (PDE4i) modulates cytokine expression in activated DCs. It decreases the release of pro-inflammatory cytokines (such as IL-12, IL-23,TNF, CXCL9 and 10) and induces anti-inflammatory cytokines like IL-10 (Fig. 7.3). It is FDA approved for treatment of psoriasis and psoriatic arthritis.

Janus kinase (JAK) inhibitors prevent cytokine receptor signaling. These small molecules inhibit the signal transduction of type I and type II cytokine receptors (receptors for IL-2, IL-6, IL-22, IL-23, IFN- γ and TNF– α (Fig. 7.3). The signal transmission of these receptors requires association with JAK. JAK inhibitors interfere with cytokine signalling and thus suppress immune cell activation and inflammation. Two of the JAK inhibitors, *tofacitinib* and *baricitinib*, are under clinical trial to treat psoriasis and psoriatic arthritis.

Oral Antipsoriatic Biologicals

Modern biologics have helped establish new targeted therapies with dramatic efficacy in psoriasis, even in patients who failed to respond to traditional oral therapies. Yet, more recently, there has been a trend to introduce additional oral anti-psoriatic compounds that specifically interfere with intracellular metabolic processes, with key proteins or with signaling pathways relevant to psoriasis. Apart

Table 7.2: Summary of agents that modulate various cytokines

Th1 cells	Releases inflammatory cytokines	Alefacept (T cell inhibition)
TNF-α	Proinflammatory cytokine released by activated DCs and T cells	Etanercept (TNFR fusion protein) Infliximab(Antibody neutralizing TNF) Adalimumab Golimumab Certolizumab pegol
IL-12 IL-23	Promotes differentiation of Th1 cells Promotes differentiation of Th17 cells	Ustekinumab (Antibody neutralizing IL-12/IL-23p40) Briakinumab STA-5326 (Apilimod) MK-3222 (Antibody neutralizing IL-23p19) Tildrakizumab and guselkumab‡ Dimethyl fumarate
IL-17	Produced by Th17 cells	• Secukinumab (Antibody neutralizing IL-17A) • Ixekizumab (Antibody neutralizing IL-17A) • Brodalumab (Antibody binding IL-17 receptor A(IL-17RA)) • LY-2439821 • AMG-827
IL-17A		AIN457A
IL-22	Produced by Th17 cells induces epidermal hyperplasia and acanthosis Prevents epidermal terminal differentiation	ILV-094
IL-20	Autoactivation of keratinocytes	NN8226
JAK*	Initiates the transduction of key inflammatory cytokines induces Th17 differentiation	Tofacitinib (CP-690, 550) VX-509 R348 INCB-018424
P38 kinase	Activates cytokine production	BMS-582949
PKC	T cell activation	AEB071(Sotrastaurin)
Calcineurin		Voclosporin
Adenosine	Promotes production of inflammatory cells and cytokines	CF-101
PDE 4	Signaling pathway produces inflammatory cytokines	Apremilast (increase of cAMP, inhibition of IL-12, IL-23, TNF and IFN- γ, inhibition of IL-10)

*ruxolitinib (drug is currently in phase II development for psoriasis, myelofibrosis, acute leukemia, polycythemia vera, and essential thrombocytosis) and tofacitinib
‡(IL-23–specific mAbs)

from *Apremilast* and *tofactinib* two more molecules have a potential use as oral agents.

One of these is to use the compound derived from an anti-psoriatic formulation containing FAE. *Dimethyl fumarate* (DMF) is considered to be the important active compound among other FAEs and this compound has been tested in psoriasis and other inflammatory diseases [Bovenschen HJ, Kreuter A]. DMF seems to interact with nuclear factor kappa B (NF k B) activation and inhibits the expression of IL-12 and IL-23 by macrophages and DCs. Notably, DMF is the first modern therapeutic that is clinically effective in psoriasis and multiple sclerosis, unlike established biologics.

The second compound is *voclosporin*. Voclosporin (ISA-247, Isotechnika Pharma, Edmonton, Canada) is similar to cyclosporine in that it is also a calcineurin inhibitor; however, this new drug differs by having an amino acid modification resulting in increased binding to calcineurin and faster elimination of metabolites. In turn, it appears the overall effect is a greater physiologic response with fewer adverse events, especially in regards to renal toxicity. Initial Phase II studies showed that orally administered voclosporin was superior to placebo after 12 weeks of treatment, with a PASI 75 achieved by 66.7% of drug-treated patients versus none of the placebo-treated patients (Kunynetz R). Voclosporin had significant improvements when compared with cyclosporine in rates of hypertension and hyperlipidemia, and had fewer reported adverse events.

New Third Generation Biologicals

The *first generation* of biological therapies for psoriasis (alefacept and efalizumab) was suboptimal, possibly because of their cell surface receptor costimulatory molecule targets, but more likely because their clinical profile and administration challenges impeded broad and sustained use. The *second biological generation* that focused on the targeting of TNF- α included etanercept, infliximab, and adalimumab. Although these biologics were already approved for the treatment of the arthritides and inflammatory bowel diseases, they nevertheless offered dermatology dramatically increased efficacy and a highly favorable benefit/risk reward. *The third generation* of biologic drugs involved the serendipitous discovery of the importance of IL-12/23 blockade.

Secukinumab is a fully human, anti–IL-17A IgG1, monoclonal antibody, which is in development for moderate to severe plaque psoriasis and to date.

Dose (subcutaneous): 1X 25 mg, 3X 25 mg, 3 X 75 mg or 3 X 150 mg at weeks 0, 4, and 8 ,after 12 weeks of treatment, PASI-75 response rates were seen in 82% and 57% for the 150 mg and 75 mg doses, respectively. Similar to the currently

approved biological therapies for psoriasis, the PASI-75 responses gradually declined during the follow-up period. (Papp KA) The PASI-90 response rate was significantly higher in the 150 mg dose group at 52% at week 12, and this remained higher during the follow-up period. Patients weighing less than 90 kg displayed better responses versus patients in the greater-than-90 kg group.

Secukinumab phase 3 data, revealed that at the week 12 primary end point for the controlled part of the FIXTURE phase 3 trial, 67.0% and 77.1% of patients achieved PASI-75 for the 150-mg and 300-mg doses, respectively, when that were administered subcutaneously at weeks 0, 1, 2, 3, 4, and 8.(Langley R).

SE: The most frequently reported AEs were worsening of psoriasis, nasopharyngitis, and upper respiratory tract infection. Rare SAEs of special interest were noted, including candida infections (2.6% and 4.7% for the 150 mg and 300 mg dose groups, respectively).

Overall secukinumab demonstrated a positive benefit/risk profile consisting of rapid onset with high and sustained effectiveness in patients in psoriasis.

Brodalumab is a human, anti–IL-17 receptor antagonist monoclonal antibody that binds with high affinity to the human IL-17 receptor, thus blocking the action of IL-17A as well as IL-17E and F.

Dose: In the AMAGINE-1 study (Amgen and AstraZeneca), patients were randomized to receive 210 mg of brodalumab, 140 mg of brodalumab, or placebo every 2 weeks by subcutaneous injection. The results at the primary end point at 12 weeks demonstrated that 83.3% of patients in the 210 mg group and 60.3% of patients in the 140 mg group achieved PASI-75 responses. Moreover, 70.3% of patients in the 210 mg group and 42.5% of patients in the 140 mg group achieved PASI-90 responses compared with placebo (0.9%). PASI-100 responses were observed in 41.9% of patients in the 210 mg group and 23.3% of patients in the 140 mg group relative to placebo (0.5%).

SE: The most common AEs occurring in the controlled portion of the trial for the brodalu mab group (ie, more than 5% of participants) were nasopharyngitis, upper respiratory tract infection, and headache. SAEs occurred at a rate of 1.8% in the 210 mg group, 2.7% in the 140 mg group, and 1.4% in the placebo group.

Ixekizumab is a humanized anti–IL-17A mono-clonal antibody that similarly has to date been evaluated in a 142-patient, phase 2 clinical trial for moderate to severe chronic plaque psoriasis.

Dose: The trial consisted of 4 dose groups of 10, 25, 75, and 150 mg compared with placebo and administered at weeks 0, 2, 4, 8, 12, and 16. (Leonardi C). At the primary end point

of 12 weeks, the 25, 75, and 150 mg dose groups yielded a statistically significant proportion of patients who reached PASI-75. The percentage of patients with a PASI-90 was 71.4% (150 mg), 58.6% (75 mg), and 50.0% (25 mg). PASI-100 was achieved in the 150 mg group (39.3%) and the 75 mg group (37.9%). Additionally, significant improvements were also reported in nail and joint involvement.

SE: The most common AEs were nasophar yngitis, upper respiratory infection, injection site reaction, and headache.

Guselkumab is an IL-23–specific monoclonal antibody (mAb) that has demonstrated clinical and molecular response in a small phase 1, first-in-human study in patients with moderate to severe psoriasis (Sofen H). Twenty-four patients received a single subcutaneous dose of 10, 30, 100, or 300 mg of guselkumab or placebo with the primary end point for the trial at week 12. The results demonstrated that neutralization of IL-23 improved the clinical manifestations of psoriasis. At week 12, elevated PASI-75 responses were observed in those patients who receive 10 mg (50%), 30 and 100 mg (60%), and 300 mg (100%) of guselkumab, respectively, as compared with 0% of placebo treated patients. It was noted that these improvements in PASI score were maintained through the week-24 course of the trial for those patients.

SE: From a safety perspective, the proportion of patients experiencing an AE was comparable between the combined guselku mab (13 of 20 [65.0%]) and placebo (2 of 4 [50.0%]) groups through week 24.

Tildrakizumab is a humanized anti–IL-23–specific monoclonalantibody that has been studied in phase 2 clinical trials. Tildrakizumab specifically binds to the p19 subunit of IL-23 but does not bind to the p40 subunit that is a component of both the IL-23 and IL-12 cytokines.

In the controlled phase 2b trial that was performed in 355 adult patients with psoriasis, tildrakizumab was dosed at 5, 25, 100, or 200 mg by subcutaneous injection at weeks 0 and 4 and every 12 weeks thereafter through the yearlong study. The proportion of patients, who improved their psoriasis at the week 16 end point, as measured by PASI-75, was 35.0, 65.5, 67.1 and 76.2 in the dose groups of 5, 25, 100, and 200 mg, respectively (Leonardi CL).

SE: No dose-dependent increase in AEs was observed across treatment groups. However, 4 SAEs were reported in the 16-week placebo-controlled portion of the trial consisting of bacterial arthritis (reported as possibly related to the 25 mg dose tildrakizumab); death (unlikely related to the 100 mg dose); ovarian cyst (unlikely related to the 200 mg dose); and lymphedema (possibly related to the 200 mg dose of tildrakizumab).

Certolizumab pegol (CZP) is a pegylated anti-TNF agent that is composed of a TNF- α–targeting Fab' portion of an antibody that has been pegylated to preserve stability of the therapy (Reich K).

CZP has been studied in a controlled phase 2 trial of 176 patients with moderate to severe psoriasis. (Reich K,) Patients received either placebo or 400 mg CZP at week 0 followed by placebo or CZP (200 or 400 mg) every other week dosed subcutaneously through week 10. At the week 12 primary end point for the study, 75% and 83% of patients in the 200 mg and 400 mg groups, respectively, achieved PASI-75.

Serious AEs (SAEs) occurred in 3%, 5%, and 2% of CZP 200 mg, CZP 400 mg, and placebo patients, respectively.

Monitoring of Patients Receiving Biologic Therapy

Given that there are adverse events associated with biologic therapy, it is necessary to prescreen patients prior to initiation and to continue monitoring patients during and after treatment (Box 7.2).

A report of results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) suggests that treatments with adalimumab and infliximab are associated with a higher risk for serious infections than nonmethotrexate and nonbiologic therapies (Kalb RE) (Table 7.3). The registry found no increased risk from treatment with ustekinumab and etanercept. The cumulative incidence rate of serious infections was 1.45 per 100 patient years across all treatment groups. The investigators note that the results are consistent with previous studies that have documented an association between the use of tumor necrosis factor (TNF) inhibitors and serious infection. Other factors that were significantly associated with infection included increasing age, diabetes mellitus, history of significant infection, and the use of

Box 7.2: Monitoring of biologicals for psoriasis

CBC at baseline and every 3–6 months
Hepatitis and HIV screen at baseline if risk factors present or if symptoms develop
LFTs before each infliximab infusion or with signs and symptoms of liver injury
CD4 + T cell count at baseline and every 2 weeks for alefacept
Full body screen for skin cancer and signs of systemic disease (lymphoma) every 3–6 months
Standard vaccinations prior to initiation of biologic therapy influenza, pneumococcal, and/or hepatitis vaccination to high-risk individuals prior to initiation of biologic therapy. Avoidance of live and/or live-attenuated vaccinations while on biological therapy (MMR, nasal spray influenza, varicella, herpes zoster, yellow fever, rabies, BCG, typhoid)

Table 7.3: Cumulative incidence rate of serious infection by treatment group (Kalb RE)

Treatment	*Serious infection per 100 patient-years*
Ustekinumab	0.83
Etanercept	1.47
Adalimumab	1.97
Infliximab	2.49
Nonmethotrexate/nonbiologics	1.05
Methotrexate	1.28

tobacco. Presence of psoriatic arthritis was not significantly associated with serious infection risk.

The reason for this possibly depends on the mechanism of action as between the anti-TNF agents and ustekinumab. Ustekinumab targets the common p40 subunit, which is shared between interleukin 12 and interleukin 23 cytokines, which are specifically involved in psoriasis pathogenesis. TNF, on the other hand, is a more global cytokine, which is involved in many pathways of inflammation, including pathways of arthritis and atherosclerosis. Also etanercept is a low-affinity TNF receptor fusion protein. Adalimumab and infliximab are high-affinity anti-TNF monoclonal antibodies. Differences between adalimumab and infliximab may be result from differences in affinity or more subtle differences in the interaction of the constant portion of the antibodies with other immune cells.

What is the Ideal Biological in Psoriasis?

The treatment response rates of conventional biologicals in psoriasis is given in Table 7.4.

The efficacy and long-term remissions and intergroup comparisons of biologicals is rarely the focus of research articles. A meta-analyses by Lucka TC et al. showed that in a 24 week treatment period; *infliximab* and *ustekinumab* 90 mg every 12 weeks was found to be the **most efficacious** treatment agents. Adalimumab was similar to etanercept efficacy over different range of dose regimens (50 mg once weekly; 25 mg twice weekly; 50 mg twice weekly and 50 mg twice weekly until week 12, then 25 mg twice weekly). After 24 weeks a decrease in efficacy was observed in patients treated with inflximab, adalimumab and etanercept. In another meta-analysis by Puig et al. on differences in onset of action, induction phase and primary failure during therapy, found that *infliximab* (at week 10) had the ***fastest*** response. At the end of induction phase (week 24), *ustekinumab* 45 mg, was the best at achieving PASI 75 response, followed by

Table 7.4: Doses and efficacy of FDA approved biologicals

	Mode of Usage	*PASI 75*
Etanercept	SC, 25 mg	32, 32
	SC, 50 mg	46, 47
Infliximab	IV, 3 mg/Kg	70
	IV, 5 mg/Kg	75, 80
Adalimumab	SC, 40 mg	71, 78
Ustekinumab	SC, 45 mg	67, 67
	SC, 90 mg	66, 76

ustekinumab 90 mg, infliximab, adalimumab and etanercept. The study also showed that ustekinumab 45 mg (at week 28) had the greatest probability of achieving PASI 50 response. Thus, in moderate to severe psoriasis, *ustekinumab* was the most ***efficacious*** therapeutic alternative followed by infliximab, adalimumab and etanercept. Future studies comparing the newer anti-17 monoclonal antibodies are underway.

Future Concepts

The concept of general and nonspecific immunosuppression as a first-line therapy for psoriasis should be revised in the light of modalities targeting single cytokines or intracellular key proteins implicated in psoriasis pathogenesis (Fig. 7.3). These new modalities have helped us improve our understanding of disease pathogenesis and of common pathways in psoriasis, psoriatic arthritis or rheumatoid arthritis.

Ustekinumab was the first anticytokine biologic used exclusively for psoriasis and is now being established for psoriatic arthritis. Biologicals targeting IL-23, without affecting IL-12 and Th1 responses are necessary, as the later responses are required to control tumor proliferation and viral infections. Targeting IL-23a, the p19 unit forming IL-23 together with p40, is currently under investigation. This experience will help decipher the importance of IL-23/Th17 and IL-12/ Th1 responses in psoriasis and may end an old dogma concerning the relevance of Th1 cells in this disease. Neutralizing antibodies targeting IL-17 or blocking IL-17R will most likely be the first choice in a biologic approach to treat moderate to severe psoriasis. SMIs like *Apremilast* and *JAK inhibitors* would be oral alternatives in treatment of psoriasis.

There is a need for comparative trials of IL-17/23 inhibitors Vs TNFα biologicals, combination therapy instead of monotherapy and interventions in difficulty phenotypes, like palmoplantar variants,so that biological can become more applicable in clinical practise.

BIOLOGICALS AGAINST B CELLS

B cells arise from stem cells in the bone marrow, where they acquire an antibody receptor bearing a unique variable region. A number of maturation and activation steps take place as the B cells migrate from the marrow compartment, through blood, and to perifollicular germinal centers and memory compartments in lymphoid tissue, before returning to the marrow as mature plasma cells. Successful maturation and survival of cells are tightly regulated and dependent on a number of trophic signals delivered via cell surface ligands, such as vascular cell adhesion molecule-1 (VCAM-1) and soluble factors such as B lymphocyte stimulator.

B cell depletion strategy would remove the autoreactive B cell clones and their antibody products. Targeting CD20 is an ideal strategy because of its high expression on a range of B lineage cells including pre-B cells, immature B cells, activated cells, and memory cells and its *lack* of internalization and expression on stem, dendritic, or *plasma cells* (Fig. 7.4).

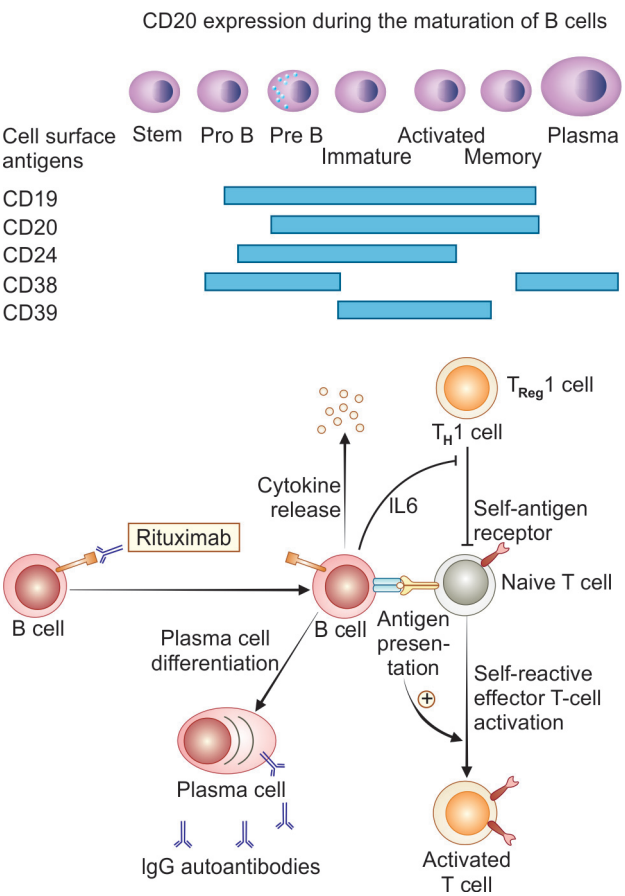


Fig. 7.4: Maturation of B cell and its role in immunology with a depiction of the site of action of rituximab

Rituximab

The primary mode of action for rituximab is through the depletion of CD20+ B cells. CD20 is a highly specific antigen expressed during B-cell differentiation, beginning at the pre-B-cell stage through the mature and memory B-cell stages (Fig. 7.4). Hematopoietic stem cells and plasma cells do not express CD20, and are therefore spared from depletion.

Rituximab is able to deplete B cells through three known mechanisms, antibody-dependent cellular cytotoxicity, complement-mediated cytolysis and inhibition of signaling and apoptosis. Whereas CD20+ B cells are depleted via the above mechanism , CD20– plasma cells of the bone marrow are spared and continue producing immunoglobulin.

It is therefore somewhat surprising that rituximab treatment leads to a significant decline in circulating disease-causing autoantibodies. This paradoxical finding is reconciled by studies suggesting that whereas protective antimicrobial antibodies are produced by long-lived CD20– plasma cells in the bone marrow, auto reactive antibodies are primarily made by short-lived CD20+ plasma cells found in peripheral compartments. Exploitation of this distinction may allow rituximab to be effective at limiting autoimmunity while preserving long-term host defense mechanisms. In addition to the reduction in circulating autoantibodies, B-cell depletion leads to a number of secondary effects; like decreased co-stimulatory molecules on CD4+ T cells, decreased numbers of memory T cells, and increased numbers of regulatory T cells. These data suggest that rituximab may have immunomodulatory effects that extend into compartments outside B cells.

Ofatumumab is a second-generation antibody that recognizes a different CD20 epitope than rituximab and has demonstrated promising efficacy in trials for RA. In addition to the B-cell surface markers CD20 and CD22, it also targets the B-cell survival factors, BAFF and APRIL (Fig. 7.5). Future studies will be necessary to determine whether these B-cell-targeting antibodies are effective in the same and/or different clinical scenarios as described for rituximab. A list of other agents that work on B cells are listed in Table 7.5 and shown in Figure 7.5.

Table 7.5: Summary of agents that act on B cells and their receptors

B-cell targeting therapies	*Receptor*	*Indication*
Abatacept	BAFF, APRIL	Systemic lupus erythematosus Rheumatoid arthritis
Belimumab	BAFF	Systemic lupus erythematosus Rheumatoid arthritis
Rituximab/ Ocrelizumab	CD20	Pemphigus, Rheumatoid arthritis
Epratuzumab	CD22	Rheumatoid arthritis

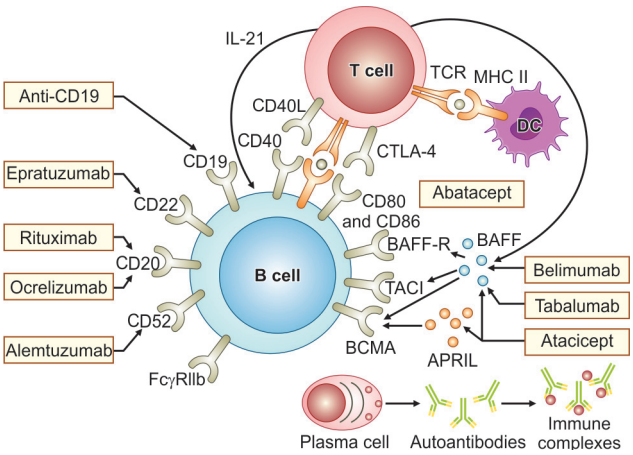


Fig. 7.5: Site of action of various biological drugs on B cell

BIBLIOGRAPHY

1. Amgen and AstraZeneca (THOUSAND OAKS, Calif. and LONDON, UK.) Positive results from phase 3 study Of brodalumab (AMG 827) in patients with moderate-to-severe plaque psoriasis study evaluating novel investigational IL-17 receptor antibody meets all primary and secondary endpoints, 2014/PRNewswire/Press Release.
2. Bovenschen HJ, Langewouters AMG, van de Kerkhof PCM: Dimethylfumarate for psoriasis: Pronounced effects on lesional T-cell subsets, epidermal proliferation and differen- tiation, but not on natural killer T cells in immunohisto- chemical study. Am J Clin Dermatol. 2010;11:343-50.
3. Kalb RE, Fiorentino DF, Lebwohl MG, Toole J, Poulin Y, Cohen AD, Goyal K,Fakharzadeh S, Calabro S, Chevrier M, Langholff W, You Y, Leonardi CL. Risk of Serious Infection With Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol. 2015;May 13.
4. Kreuter A, Knierim C, Stücker M, Pawlak F, Rotterdam S, Altmeyer P, Gambichler T: Fumaric acid esters in necrobiosis lipoidica: results of a prospective noncontrolled study. Br J Dermatol. 2005;153:802-7.
5. Kunynetz R, Carey W, Thomas R, Toth D, Trafford T, Vender R. Quality of life in plaque psoriasis patients treated with voclosporin: a Canadian Phase III, randomized, multicenter, double-blind, placebo- controlled study. Eur J Dermatol. 2011;21(1):89-94.
6. Langley R, Reich K, Griffiths C, et al. Secukinumab compared with placebo and etanercept: a head-to-head comparison of two biologics in a phase 3 study of moderate-to-severe plaque psoriasis (FIXTURE) [poster]. Presented at the 22nd European Academy of Dermatology and Venereology Congress. Istanbul, Turkey, October. 26, 2013.
7. Leonardi C, Matheson R, Zachariae C, et al. Anti- interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012;366(13):1190-9.
8. Leonardi CL, Gordon KB. New and emerging ther apies in psoriasis. Semin Cutan Med Surg. 2014;33(2 Suppl 2):S37-41.

9. Lucka TC1, Pathirana D, Sammain A, Bachmann F, Rosumeck S, Erdmann R, Schmitt J, Orawa H, Rzany B, Nast AEfficacy of systemic therapies for moderate-to-severe psoriasis: a systematic review and meta-analysis of long-term treatment. J Eur Acad Dermatol Venereol. 2012 Nov;26(11):1331-44. doi: 10.1111/j.1468-3083.2012.04492.x. Epub. 2012 Mar 9.
10. Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moder ate to severe plaque psoriasis: a randomized, double- blind, placebo-controlled phase II dose-ranging study. Br J Dermatol. 2013;168:412-21.
11. Puig L1, López A, Vilarrasa E, García I.Efficacy of biologics in the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis of randomized controlled trials with different time points. J Eur Acad Dermatol Venereol. 2013 Aug 19. doi: 10.1111/jdv.12238.
12. Schmitt J1, Zhang Z, Wozel G, Meurer M, Kirch W.Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Dermatol. 2008 Sep;159(3):513-26. doi: 10.1111/j.1365-2133.2008.08732.x. Epub 2008 Jul 9.
13. Sofen H, Smith S, Matheson RT, et al. Guselkumab (an IL-23–specific mAb) demonstrates clinical and molec ular response in patients with moderate-to-severe psoriasis. J Allergy Clin Immunol. 2014;133:1032-40.
14. Xing L, Dai Z, Jabbari A, Cerise JE, Higgins CA, Gong W, de Jong A, Harel S,DeStefano GM, Rothman L, Singh P, Petukhova L, Mackay-Wiggan J, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med. 2014;20(9):1043-9.

ANTI-TNFα AGENTS[2]

ETANERCEPT

Classification

It is a 150 kDa, fully human, dimeric fusion protein with p75 TNF receptor linked to Fc IgG and binds TNF-alfa and lymphotoxin A in the circulation; and prevents interaction with the cell surface receptor.

Category

TNF α antagonist:

Mechanism of Action

In general, TNF-α inhibitors bind to TNF- α thus preventing its proinflammatory actions by:

1. Decreasing proinflammatory cytokines and chemokines
2. Decreasing the expression of adhesion molecules
3. Decreasing the release of vascular endothelial growth factor (VEGF).

4. Decreasing pro-inflammatory cytokine release by keratinocyte.
5. Preventing activation of dendritic cells and their production of IL-23.

Absorption, Distribution and Metabolism

The peak plasma levels are reached in approximately in 2 days and the biological half-life of the drug is 4.8 days. The overall bioavailability is 58%. The drug undergoes proteolysis in blood and is excreted in urine and bile.

Uses

Etanercept was FDA approved for use in psoriasis arthritis in 2002 and for psoriasis in 2004. A number of trials have been carried out demonstrating efficacy of biologics in psoriasis and psoriatic arthritis.

In a study by Gordon et al on a total of 1187 patients from 3 blinded treatment groups: etanercept 50 mg weekly (equivalent to 25 mg twice weekly) subcutaneously, etanercept 50 mg twice weekly subcutaneously, and placebo, a statistically significant dose-dependent improvements was seen in PASI 75 at 12 weeks with etanercept 50 mg weekly (33%) and 50 mg twice weekly (49%), compared with the placebo group (3%; $P < 0.05$).

Uses of etanercept

FDA approved – plaque psoriasis – psoriatic arthritis *Off label* Neutrophilic Dermatosis Behcets disease Pyoderma gangrenosum Apthous ulcers Bullous dermatoses Pemphigus vulgaris Bullous pemphigoid Cicatricial pemphigoid Connective tissue disease Dermatomyositis Relapsing polychondritis Scleroderma Granulomatous dermatoses Generalized GA Sarcoidosis	*Dosage and formulation* ■ Sterile, preservative free, lyophilized powder containing 25 mg etanercept. ■ Prefilled, single use syringe containing either 25 or 50 mg etanercept. ■ Single use Sureclick Autoinjector *General Principles of Use* ■ The FDA approved recommended adult dosage for the treatment of plaque psoriasis is 50 mg twice weekly for 12 weeks, followed by 50 mg weekly thereafter. For psoriatic arthritis the dosing is 25 mg twice weekly or 50 mg once a week. ■ The monoclonal antibodies show a slightly greater efficacy at the onset as compared to the receptor blocker etanercept ■ There is a tendency for all of the TNF-α inhibitors to demonstrate some loss of efficacy with time ■ In case of etanercept; options available in case of loss of efficacy are (i) increase dosing to twice-weekly injections (ii) add ultraviolet light (iii) short-term potent topical steroids (iv) addition of another systemic agent (e.g. low-dose methotrexate, or acitretin).

OTHERS GVHD Hidradenitis suppurativa SAPHO syndrome Pityriasis rubra pilaris	■ Neutralizing antibody response in has been documented with infliximab and etanercept. ■ Once reconstituted is to be stored in refrigerator and stable for 14 days. Product sterility and stability cannot be assured after 14 days. ■ 1 inch gap between injection sites to prevent injection site reactions

Special Considerations (For All Anti-TNF Biologics)

Contraindications

Absolute

- Known hypersensitivity to drug
- Concurrent administration of anakinra
- Active infections
- Chronic localized infections including TB.

Relative

- Congestive heart failure (most important for infliximab in dosage >5 mg/kg)
- Family history of demyelinating conditions like multiple sclerosis.

Hepatitic C

There are many reports of patients with hepatitis C being treated with TNF-α inhibitors.(mainly etanercept) These patients do well and have decreased viral load and normal liver function.

Hepatitis B

There is a risk of reactivation of Hepatitis B virus, hence certain countries like Canada, warn their patient population on etanercept need a close monitoring of their liver functions.

Tuberculosis

- Anti-TNF agents predispose patients to develop active TB in patients with latent TB infection (LTBI). Screening for LTBI is very important for patient planned for all anti TNF therapy including etanercept, adalimumab and infliximab therapy.
- In a resource limited country endemic for TB, most importantly, active TB must first be excluded by history and chest radiograph.

- Screening for LTBI should include checking for a history of untreated or partially treated TB, risk-stratification for exposure to cases of active TB and searching for evidence of residual changes indicative of untreated prior TB infection on a chest radiograph (e.g. calcified granulomas, Gohn focus or complex, apical scarring).
- In addition, given the apparent diagnostic superiority of Interferon gamma release assays (IGRAs) over Tuberculin skin test (TST), one or the other of the new blood tests like QuantiFERON Tb-GOLD or T-SPOT test should be performed.
- Due to the vulnerability of these patients to develop severe and disseminated forms of TB on TNF blockade, it may be prudent to perform TST in parallel with IGRA to maximise the diagnostic sensitivity of screening.
- Since some patients with LTBI may have false-negative IGRA results and true-positive TST results, while others will have true-positive IGRA results and false-negative TST results, a dual-testing strategy should enable physicians to offer all patients with LTBI preventative treatment in the form of INH.
- Moreover, in population with high TB risk and limited availability of IGRA, recommendation that a finding of ≥5 mm on the TST should be an indication for treatment with INH.
- In populations in which background TB rates are lower, other strategies have been proposed, including more stringent criteria regarding TST results (for example, a cut-off of >10 mm) prior to initiating treatment with INH. Furthermore, the benefit of INH should be balanced against the risk of developing toxicity-related hepatitis.

Side Effects

1. **Malignancy risk**: Patients with psoriasis are at increased risk for malignancy, with a relative risk for developing lymphoma(Hodgkin's lymphoma and CTCL) at nearly three times more than an average population.
2. **Skin cancer**: Increased risk of Non melanoma skin cancer (NMSC) has been reported from multiple cohort studies, meta-analysis and controlled trials and the risk doubled if there was concomitant use of methotrexate in patients with rheumatoid arthritis.
3. **Infections**: Postmarketing reports of infliximab,etanercept and adalimumab report an increased risk of serious infections and fatalities. Close monitoring of the patient

and temporary withdrawal of therapy in case of active infection appears to be a reasonable approach.
- Latent tuberculosis reactivation: discussed above
- Invasive fungal infection: histoplasmosis, candidiasis and aspergillosis.
- Reactivation of Hepatitis B: discussed above
- Pneumonia, septic arthritis, erysipelas, phlegmonous infections, diverticulitis and pyelonephritis

4. **Neurological disease**: So far there are three case series of 15 patients or more reporting neurological episodes and around 50 case reports of multiple neurological conditions like multiple sclerosis, optic neuritis, Guillain Barre syndrome and pure sensory neuropathies have been reported in patients taking either of the three anti TNF agents.
5. **Congestive heart failure (CHF)**: Although post marketing surveillance reported new onset CHF and worsening of previous CHF, the evidence to support TNF neutralization leading to worsening CHF is still speculative. Use of infliximab is relatively contraindicated in patients with unstable congestive heart failure
6. **Autoimmunity**: A positive ANA and induction of anti-ds DNA antibodies has been seen with all TNF inhibitors. Infliximab reports higher induction of these antibodies (63.8% and 13 %) as compared to etanercept (11% and 15% respectively) and adalimumab (12.9% and 5.3% respectively). Concomitant immunosuppression can reduce autoantibody formation, and withdrawal of anti-TNF-α therapy usually leads to resolution of symptoms. Steroids and/or immunosuppressive therapy may be required in severe cases.
7. **Hematologic toxicity**: rare reports of leucopenia, thrombocytopenia, neutropenia and pancytopenia.
8. **Injection site reactions**; Most common side effect are the injection site reactions. They occur with the use of etanercept, adalimumab and certolizumab pegol. Signs and symptoms include redness, itching, bruising, pain, swelling and/or irritation at the site of injection. They usually appear after second injection.

Monitoring

There are no FDA mandated guidelines for lab monitoring for initiation of TNF inhibitor therapy. But certain tests should be done at baseline, the most important one is screening for TB. (either TST or Quantiferon Gold/TB spot) The other tests are

complete blood counts, liver function tests at the baseline. It is reasonable to consider repeating the CBC and LFT every 3 months for the first 12 months on therapy. If the labs are stable after 12 months repeating them every 6-12 months may suffice. TB testing should be performed annually. Serologic testing of ANA and double stranded DNA antibodies should be performed in patients who show signs of autoimmune disease to help establish a diagnosis.

Special Groups

Pregnancy Category

All TNF-α inhibitors are pregnancy category – B.

Lactation

Absent from breast milk and serum of infants of nursing mothers.

INFLIXIMAB

Classification

Infliximab is chimeric (75% human and 25% mouse) monoclonal antibody against TNF-a with MW 150 kDa comprising IgG1k. Binds TNF-α only, inhibits its binding to soluble and transmembrane receptor.

Category

TNF- α inhibitor

Mechanism of Action

Similar to etanercept, it also can fix complement and cause apoptosis of cells in addition can. This second action of infliximab (of causing lysis of TNF bearing T lymphocytes) probably explains its effect in granulomatous diseases.

Absorption, Distribution and Metabolism

A large size of the molecule hinders oral absorption of the TNF-α inhibitors. Hence, it is administered parentally. The plasma levels peak immediately as it is given in an infusion form, hence resulting in faster onset of action and a bioavailability of 100%. The biological half life is 7–9 days based on the dosing. It is metabolized by proteolysis and undergoes excretion via bile and urine.

Uses

Infliximab was FDA approved for use in psoriasis in 2006 and psoriatic arthritis in 2005.

Infliximab	
FDA Approved – plaque psoriasis – psoriatic arthritis	Dosage and formulation ■ It is supplied as lyophilized concentrate containing 100 mg of infliximab in a 20 mL vial ■ To be reconstituted with 10 mL sterile water and then injected in 250 mL of 0.9% normal saline ■ Intravenous infusion is to be administered over at least 2 hours; patient to be monitored for infusion reactions during and one hour after administration
	■ Recommended adult dosage is 3-5 mg/kg ■ Maintenance dosage is to be given at 2, 6 weeks and 8 weekly thereafter
Off label **Neutrophilic dermatoses** Pyoderma gangrenosum Behcets disease **Vasculitis** Systemic vasculitis Wegner's granulomatosis **Granulomatous dermatoses** Sarcoidosis Sarcoidosis Granuloma annulare Necrobiosis lipoidica **Bullous dermatoses** Cicatricial pemphigoid Bullous pemphigoid **Connective tissue disease** Dermatomysositis Relapsing polychondritis Scleroderma SLE	*General principles of use* Similar to etanercept; ■ Regulated administration of infusions is critical to maintain the efficacy of infliximab as irregular need based dosing of infliximab has shown greatest loss of response and is not recommended ■ Addition of low dose methotrexate increases the availability of infliximab by decreasing its clearance thereby maintaining its efficacy
Others GVHD TEN Hidradenitis suppurativa Pityriasis rubra pilaris Reiters disease SAPHO syndrome	

Special Consideration

Similar to etanercept.

Contraindications

Same as etanercept.

Side Effects

Similar to as detailed for etanercept.

Infusion-related Reaction with Infliximab

Infusion reactions during the infusion or in the first 24h afterwards are defined as acute reactions. The majority occur during or in the first 2h after the infusion. Symptoms include 'flushing', chest tightness, dizziness, shortness of breath, headache, hypo/hypertension, nausea, sweating, and rise in temperature and (other) symptoms of anaphylaxis, like urticaria and bronchospasms.

Mild reactions are self limiting after temporary cessation of therapy. Adjunctive treatment with acetaminophen and antihistamines further decrease the symptoms. Serious reactions require epinephrine with corticosteroids.

Antidrug Antibodies

It correlates with reduced blood level of the anti-TNF drug and with loss of response and/or increased rate of infusion reactions. An antibody response to the drug often appears between the third and sixth month. When the endogenous production of antibodies exceeds the amount of drug in the serum, the latter is cleared from the circulation and the therapy is rendered ineffective.

Hepatotoxicity: Anecdotal reports of acute liver failure, jaundice and cholestasis following infliximab therapy.

Monitoring Guidelines

Similar to as detailed for etanercept.

ADALIMUMAB

Classification

It is a fully human, 148 kDa, monoclonal antibody of IgG1 type which binds TNF-α only inhibiting its binding to p55 and p75 transmembrane receptor.

Category

TNF-α inhibitor.

Absorption, Distribution and Metabolism

The average absolute bioavailability of adalimumab following a single 40 mg dose is 64%. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 mL/h, the distribution volume ranged from 5 to 6 L. A weight-dependent decrease of treatment efficacy has been reported with adalimumab

in clinical trials. The peak onset of action is in approx 6 days and a half-life of 14 days. It is metabolized by proteolysis and is excreted in bile and urine.

Uses

Adalimumab was FDA approved for psoriatic arthritis in 2005 and psoriasis in 2008.

Adalimumab	
FDA approved – plaque psoriasis – psoriatic arthritis	Dosage and administration ■ Recommended initial regimen in 80 mg subcutaneous injection at week 0 followed by 40 mg at week 1, no dose at week 2 and alternate week injections thereafter ■ Therapy should be reconsidered in case of no response within 16 weeks of treatment
Off label **Neutrophilic dermatoses** Pyoderma gangrenosum Aphthous stomatitis SCPD	General principles of use ■ Similar to othe TNF-α agents as detailed above ■ It comes as a preservative-free sterile solution in prefilled syringes containing 40 mg of adalimumab
Vasculitis ANCA- associated vasculitis **Granulomatous dermatoses** Sarcoidosis Granuloma annulare **Connective tissue disease** Relapsing polychondritis **Others** SAPHO Pityriasis rubra pilaris	■ Prefilled single use pen (1 mL) containing 40 mg (0.8 mL) of drug ■ Adult use carton has 4 single use pen or a single use prefilled syringe whereas for pediatric use a prefilled syringe carton containing two 20 mg (0.4 mL) syringes in available ■ It is to be kept in refrigerator away from light and to be warmed to room temperature for 15 minutes before use

Special Considerations

Similar to as explained above.

Side Effects

Similar to other anti-TNF-α agents.

Monitoring Guidelines

As explained above.

ITOLIZUMAB[3]

Category

Immunoglobulin G1, humanized recombinant anti-CD6 monoclonal antibody (Menon R, Aira LE, Anand A, Krupashankar DS, et al.).

Chemistry

It is a dimer consisting of human-mouse monoclonal T1h heavy chain with human-mouse monoclonal T1h light chain bonded by disulfide linkage.

There are 449 amino acids in the heavy chain and 214 amino acids in the light chain. It has an apparent molecular weight of approximately 148 kilodaltons. (Aira LE, Alzumab TM, et al.).

Structural formula: $C_{4402}H_{6834}N_{1166}O_{1346}S_{32}$ - Heavy Chain dimer

$C_{2034}H_{3184}N_{552}O_{680}S_{12}$ – Light Chain dimer

Mechanism of Action

The suggested mechanisms of action for itolizumab are listed below however most of them need further explanation

1. Main mode of action is modulating CD6 co-stimulation (Figs 7.6 and 7.7). CD6 is a costimulatory molecule required for optimal T cell stimulation by the antigen presenting cells. This step is crucial in T cell proliferation to form Th1 and Th17 cells. This leads to interference with T cell activation and proliferation without interfering the binding of CD6 to ALCAM (activated leukocyte -cell adhesion molecule) (Menon R, Aira LE, Alzumab TM, Beck A, Rodriguez PC, et al.).
2. Negatively affects the intracellular signaling pathways triggered by CD6 by inhibiting intracellular phospho-proteins like MAPK (mitogen activated protein kinase) and STAT-3 (signal transducer and activator of transcriptor 3). (Menon R, Aira LE, Alzumab TM, et al.).
3. Down regulating the gene transcription of pro inflammatory

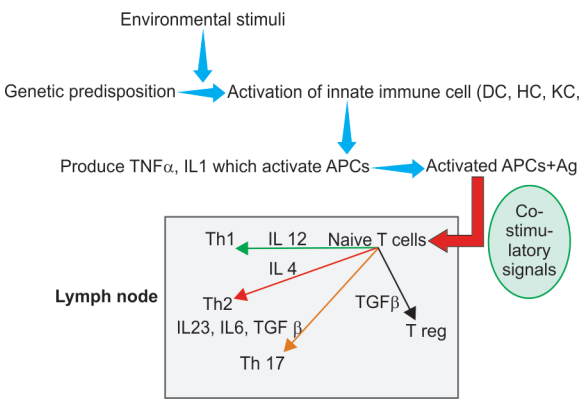


Fig. 7.6: A figure showing the activation of naieve T-cells in the lymph node to different types of T cells by the APCs in the presence of costimulatory signals. *Abbrevation:* DC, dendritic cells; HC, histiocytes; KC, keratinocytes; N, neutrophils; M, monocytes; APCs, antigen presenting cells

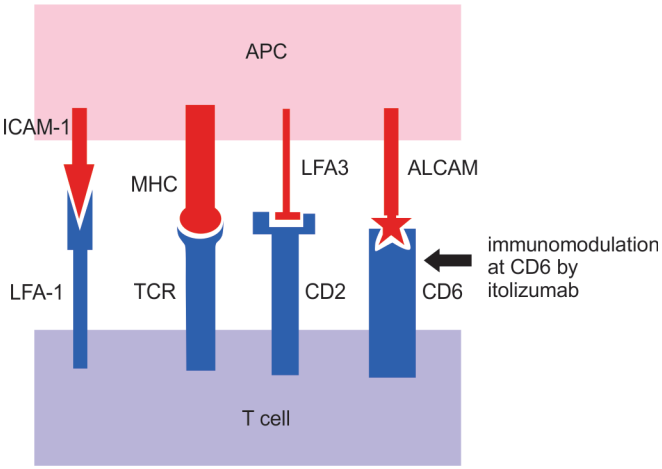


Fig. 7.7: Costimulatory signals between APC and T cells and modulation at the level of CD6

cytokines there by reducing levels of IFN-γ, IL-6 and TNF-α (Menon R, Beck A, et al.).

Uses of Itolizumab

Treatment of moderate to severe psoriasis requiring systemic therapy (Anand A, Krupashankar DS, Jayaraman K, et al.) (Marketing approval given by Drug Controller General of India) (Menon R, Jayaraman K, et al.).

Other uses for which it is being proposed are Rheumatoid arthritis, Sjogren's syndrome and Multiple sclerosis (Menon R, et al.).

Effect on Psoriasis

Statistically significant reductions in PASI 75 (psoriasis area severity index) scores were noted at 12 weeks in phase II and III trials. (Anand A, Krupashankar DS et al.) Histopathological evidence of improvement, such as decrease in epidermal thickness and parakeratosis and development of well defined granular layer is reported after eight treatment sessions (Aira LE et al.).

At present no comparison studies with other biological agents are available for itolizumab. However, based on the available data, Itolizumab is found to have less incidence of infections and better safety profile but lesser efficacy when compared to the other biological agents used for psoriasis. (Menon R, et al.)

Pharmacokinetics and Dynamics

Increased frequency of administration was associated with increased accumulation of the drug. (Alzumab TM 2015). The

T½ of the drug was found to range between 11.72 to 18.51 days across different dose schedules (Krupashankar DS et al.).

Dosage

The recommended dose of itolizumab for plaque psoriasis is 1.6 mg/kg - IV infusion/2 weeks for 12 weeks, followed by 1.6 mg/kg every 4 weeks up to 24 weeks (Alzumab TM 2015). It should be administered as slow IV infusion by mixing it with 250 mL of sterile normal saline. Monitoring of the patient should be done for few hours post administration for any untoward effects.

Drug Interactions

As drug interaction studies have not been performed with Itolizumab, coadministration with other biological agents and mixing with any other drug is not recommended. (Alzumab TM 2015) Live/attenuated vaccines are not to be recommended along with itolizumab as it may affect the efficacy of vaccinations.

Special Considerations

It is better to avoid Itolizumab in pregnant and nursing mothers, children <18 years and in patients with hepatic and renal impairment as the safety of Itolizumab is not established in these conditions. It can cross the placental barrier (Menon R 2015).

The development of antidrug antibodies is found to be less with Itolizumab and not interfering with the efficacy or safety profile of the drug compared to the other biological agents used. The low anti-idiotype antibody response is suggested to be the probable cause for longer duration of action compared to its murine predecessor (Rodriguez PC 2013).

Contraindications

Active infections and known hypersensitivity to the components of Itolizumab injection or murine proteins (Alzumab TM).

Monitoring

Before starting therapy, patients should be screened for all active and latent infections including HIV infection, tuberculosis, hepatitis B and C and conditions causing neutropenia and lymphopenia (Menon R, et al.).

Side Effects

Safety data on itolizumab is derived mostly from the two multicenter clinical trials done on patients with chronic

plaque psoriasis and a study done on rheumatoid arthritis patients (Anand A, Krupashankar DS, Rodriguez PC et al.).

Common

Infusion-related reactions usually occur in the first cycle and tend to decrease in frequency and severity with subsequent cycles of therapy. Symptoms include nausea, rash, urticaria, flushing, cough, wheezing, dyspnea, dizziness and headache (Krupashankar DS, et al.).

Diarrhea, pyrexia, head ache, nausea, upper respiratory tract infections, pruritus (Alzumab TM 2015).

Uncommon

Reactivation of latent infections like lymph node tuberculosis, septic arthritis,abscess, folliculitis, gastroenteritis (Alzumab TM 2015). The other serious side effects were erythrodermic psoriasis, exfoliative dermatitis and adjustment reaction with anxiety noted in single patients in phase III trial (Krupashankar DS et al.). Small and transient decrease in mean absolute lymphocyte count was noted in phase III trial which was not associated with any clinical effects (Krupashankar DS et al.).

BIBLIOGRAPHY

1. Aira LE, López-Requena A, Fuentes D, et al. Immunological and histological evaluation of clinical samples from psoriasis patients treated with anti-CD6 itolizumab. mAbs. 2014;6(3):782-92.
2. AlzumabTM (Itolizumab)solution for iv infusion [prescribing information]. India: Biocon, Inc; 2014. Available from : http://www.biocon.com/docs/prescribing_information /immunotherapy/alzumab_pi.pdf. Accessed on April 3,2015.
3. Anand A, Assudani D, Nair P, et al. Safety, Efficacy and pharmacokinetics of T1h, a humanized anti-CD6 monoclonal antibody, in moderate to severe chronic plaque psoriasis - Results from a randomized phase II trial. J Immunol 2010. (abstract);184:96.13.
4. Beck A, Wurch T, Reichert J M. 6th Annual European Antibody Congress 2010 November29-December 1. Geneva, Switzerland. mAbs. 2011;3(2):111-132.
5. Jayaraman K. Biocon's first -in-class anti CD6 mAb reaches the market. Nat Biotechnol. 2013;31(12):1062-1063.
6. Krupashankar D S, Dogra S, Kura M et al. Efficacy and safety of itolizumab, a novel anti- CD6 monoclonal antibody, in patients with moderate to severe chronic plaque psoriasis: Results of a double- blind, randomized, placebo- controlled, phase-III study. J Am Acad Dermatol. 2014;71(3):484-92.
7. Menon R, David B G. Itolizumab – a humanized anti-CD6 monoclonal antibody with a better side effects profile for the treatment of psoriasis. Clin Cosmet Investig Dermatol. 2015;8:215-22.doi:10.2147/CCID.S47784.eCollection 2015.

8. Rodriguez P C, Torres- Moya R, Reyes G et al. A clinical exploratory study with itolizumab, an anti CD-6 antibody, in patients with rheumatoid arthritis. Results in Immunology. 2012;2:204-211.

RITUXIMAB[4]

Classification

Anti CD-20 monoclonal antibody.

Category

Biological agent.

Mechanism of Action

Rituximab is a chimeric murine/human immunoglobulin G1 (IgG1) kappa monoclonal antibody. It is composed of a murine variable region (Fab portion) that is fused on to a human constant region (Fc portion).

Rituximab binds to the antigen CD20 present on the surface of pre-B, mature and malignant B lymphocytes in the blood, bone marrow, thymus, spleen and lymph nodes through the Fab portion and regulates the activation process for cell cycle initiation and differentiation. It activates the complement cascade (complement-mediated cytotoxicity) and immune effector cells (antibody-dependent cell-mediated cytotoxicity), causing depletion of circulating and tissue-based B cells. Antibody-dependent cell-mediated cytotoxicity recruits other immune mediators to cause cell destruction and apoptosis. Rituximab also sensitizes malignant B cells to the effects of chemotherapy synergistically, enhancing cell lysis.

There is rapid and sustained fall in B-cell population with 3 doses (3 weeks) and the effect is sustained for 6–9 months after treatment. Recovery of B-cells starts after 6 months and is complete by 12 months. A parallel decrease in IgG and IgM also occurs. Rituximab decreases memory B-cells also; hence there is sustained improvement even after stopping therapy.

CD20 antigen is not expressed on the surface of hematopoietic stem cells or pro-B cells; thus, the capacity of these precursor cells to regenerate the B lymphocyte population remains intact. As majority of plasma cells fail to express the CD20 antigen, plasma cells are generally spared and serum immunoglobulin levels do not fall dramatically.

Absorption and Distribution

Rituximab is administered as slow intravenous infusion. A steady state concentration is reached after 6–8 weekly infusions. CD-20 binding capacity of rituximab remains

stable over 96 hours. The drug is detectable in serum 3–6 months after treatment completion. It is degraded into amino acids (similar to natural immunoglobulins (antibodies)). Age and gender had no effect on the pharmacokinetics of rituximab. It has a terminal half-life of 20–32 days.

Uses

FDA Approved Uses

1. Non-Hodgkin's lymphoma (nodal disease)
   Primary Cutaneous B-cell Lymphoma (Primary Cutaneous Marginal Zone Lymphoma, Primary Cutaneous Follicle Center Lymphoma, Diffuse large B cell lymphoma leg-type)—as a single agent in relapsed or refractory cases or during maintenance therapy after achieving complete or partial response with combination with chemotherapy; as combination therapy with primary chemotherapy to achieve remission.
2. Chronic lymphocytic leukemia—in combination with fludarabine and cyclophosphamide (FC), for CD20-positive CLL.
3. Refractory rheumatoid arthritis—in combination with methotrexate it is indicated in adult patients with moderate-to severe rheumatoid arthritis who have an inadequate response to one or more TNF antagonist therapies.
4. Refractory Wegener's granulomatosis and microscopic polyangiitis.

Off-label Uses

Refractory or relapsed cases of the following:

1. Pemphigus vulgaris and foliaceus
2. Epidermolysis bullosa acquisita
3. Bullous pemphigoid
4. Mucous membrane pemphigoid
5. Paraneoplastic pemphigus
6. Dermatomyositis
7. Cutaneous lupus erythematosus
8. Acute and chronic GVHD
9. Vasculitis (Wegener's granulomatosis, microscopic polyangiitis, cryoglobulinemic vasculitis , Churg–Strauss syndrome and Henoch–Schonlein purpura.
10. Hodgkin's lymphoma

Dosage

Preparation: Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate, for intravenous administration. It is currently supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials.

There is currently no consensus on the optimal dosage and schedule of rituximab. The various treatment protocols followed include:

1. Lymphoma protocol: Most commonly followed protocol. Rituximab is administered at a dose of 375 mg/m^2 body surface area weekly for four weeks.
2. Rheumatoid arthritis protocol: Two doses of rituximab 1g are administered at an interval of 15 days.
3. A low dose rituximab regimen consisting of two 500 mg infusions separated by 2 weeks has shown to be effective in pemphigus.
4. Combination therapy: Rituximab has been used in combination with other agents.
5. Long-term rituximab treatment with regular infusions every 4 or 12 weeks following an induction cycle of infusions every week.

Premedication and Rituximab Administration

Premedication is done with hydrocortisone 100 mg intravenous (IV), pheneramine maleate 22.75 mg IV and paracetamol 500 mg orally, 30 minutes prior to infusion.

First infusion is administered at a rate of 50 mg/h IV, escalated every 30 min by 50 mg/h to a maximum infusion rate of 400 mg/h, total infusion time: 5–6 h. Subsequent infusions are initiated at 100 mg/h, with a 30-min escalation of 50 mg/h to a maximum infusion rate of 400 mg/h.

For combined chemotherapy or maintenance regimens: After the first infusion, subsequent doses may be infused over a total of 90 minutes (20% of the dose in the first 30 minutes and remaining 80% over 60 minutes)

A few cases of primary cutaneous B-cell lymphoma have been treated successfully with intralesional rituximab, 1–3 mL of 10 mg/mL solution, variable number of injections administered.

Rituximab has also been administered by intrapleural, intraperitoneal, intrathecal and intraventricular routes.

Drug Interaction

- There is no effect on the pharmacokinetics of rituximab or the other chemotherapeutic agents (cyclophosphamide, fludarabine, methotrexate) on coadministration.
- Antihypertensive medications may enhance the hypotensive effect of rituximab. They should withhold antihypertensive medications 12 hours prior to and during rituximab infusion

- Vaccinations with live virus vaccines is not recommended Vaccinations should be completed 4 weeks prior to initiation of treatment with rituximab or should be withheld for at least 6 months after the last dose. Non-live vaccines may be given during rituximab treatment, however, patients may experience reduced response rates.

Side Effects

Common

- Rituximab is generally well tolerated, though most patients experience mild-to-moderate infusion-related reactions (14–77%) with their first treatment. The most common symptoms include fever (48%), chills (32%), weakness (18%), nausea (17%), headache (13%), pruritus (12%) and rash (11%). The symptoms are usually reversible by temporarily discontinuing the infusion and providing symptomatic relief. Infusion-related side effects tend to diminish or disappear with subsequent infusions
- Lymphopenia, neutropenia
- Infection.

Rare

They may be severe and potentially fatal. These include the following:

- Severe infusion-related reactions
- Tumor lysis syndrome
- Mucocutaneous reactions, such as Stevens–Johnson syndrome (SJS), anaphylaxis
- Serious pulmonary events
- Cardiac arrhythmias
- Renal failure
- Hematological abnormalities
- Bowel obstruction/perforation
- Significant infections, such as bacterial sepsis or reactivation of hepatitis B with fulminant hepatitis.
- Progressive multifocal leukoencephalopathy (PML).

Contraindications

1. Known hypersensitivity to murine proteins and rituximab
2. Relative—history of bronchospasm, hypotension and angioedema.

Monitoring

Prerituximab evaluation should include:

- Complete hemogram, liver and renal function tests

- Chest X ray, Mantoux test, high-resolution CT chest (when indicated)
- Screening for viral infection including- HBsAg, anti-HCV antibody, HIV
- ECG
- Urine R/M
- Few authors also recommend pre-treatment assessment of baseline immunoglobulin (Ig) levels, as reduced baseline level of IgG is a risk factor for severe infections with rituximab.
- Complete blood counts every 2 weeeks has to be obtained during the treatment, and followed by every 1–3 months.

Special Groups

Pregnancy

Rituximab is a pregnancy risk category C drug. It should be avoided during pregnancy unless the potential benefit justifies the risk to the fetus. IgG immunoglobulins are known to pass the placental barrier. Premature births and B-cell depletion have been reported in infants exposed to rituximab *in utero,* but no long-term adverse effects are reported. Hematologic abnormalities following birth have been transient and rapidly recover with no resulting impairment in growth and development. Effective contraception is recommended during and for 12 months following treatment.

Lactation

As human IgG is excreted in breast milk, lactating mothers should discontinue nursing until circulating blood levels are no longer detectable.

Liver Failure

No significant contraindication.

Kidney Failure

No significant contraindication. Standard dose can be administered before or after peritoneal or hemodialysis.

Children

Rituximab has been successfully and safely administered in the pediatric age group.

Geriatric

Patients over 65 years of age are at greater risk of adverse cardiac events and serious pulmonary infections.

Carcinogenicity

No information available.

FURTHER READING

1. Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med. 2006;355:1772-9.
2. Carr DR, Heffernan MP. Innovative uses of rituximab in dermatology. Dermatol Clin. 2010;28:547-57.
3. Cianchini G, Corona R, Frezzolini A, Ruffelli M, Didona B, Puddu P. Treatment of severe pemphigus with rituximab: report of 12 cases and a review of the literature. Arch Dermatol. 2007;143:1033-8.
4. Genentech. RITUXAN® product monograph. South San Francisco, California; March 2012.
5. Graves JE, Nunley K, Heffernan MP. Off-label uses of biologics in dermatology: rituximab, omalizumab, infliximab, etanercept, adalimumab, efalizumab, and alefacept. J Am Acad Dermatol. 2007;56:e55-79.
6. Heinzerling L, Dummer R, Kempf W, et al. Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous b-cell lymphoma. Arch Dermatol. 2000;136:374-8.
7. Kanwar AJ, Tsuruta D, Vinay K, Koga H, Ishii N, Dainichi T, et al. Efficacy and safety of rituximab treatment in Indian pemphigus patients. J Eur Acad Dermatol Venereol. 2011.
8. Kasperkiewicz M, Shimanovich I, Meier M, Schumacher N, Westermann L, Kramer J, et al. Treatment of severe pemphigus with a combination of immunoadsorption, rituximab, pulsed dexamethasone and azathioprine/mycophenolate mofetil: a pilot study of 23 patients. Br J Dermatol. 2012;166:154-60.
9. Regazzi MB, Iacona I, Avanzini MA, et al. Pharmacokinetic behaviour of rituximab. Ther Drug Monit. 2005;27:785-92.
10. US Food and Drug Administration. Drugs: rituximab infusion. 22 October 2012. Available at: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm324890.htm?source=govdelivery.

OMALIZUMAB[5]

Classification

Biologic, monoclonal antibody, anti-IgE.

Category

Humanized monoclonal antibody.

Mechanism of Action

1. Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils.

2. This prevents activation of these inflammatory cells.
3. Omalizumab also promotes Fc€RI downregulation on basophils.
4. It lowers free IgE levels, so less IgE is available for binding to inflammatory cells.

Absorption and Distribution

After subcutaneous administration, omalizumab is absorbed with an average absolute bioavailability of 62%. Following a single subcutaneous dose in adult and adolescent patients, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 7–8 days.

Metabolism

The serum elimination half-life of omalizumab is 24 days on an average. Clearance of omalizumab involved IgG-clearance processes as well as clearance via specific binding and complex formation with IgE. Liver elimination of IgG is by its degradation in the liver reticuloendotherlial system.

Uses and Dosage

FDA-approved for the treatment of adults and adolescents (ages ≥12 years) with asthma.

Disorder (FDA approved/ Unapproved)	*Dose/Duration*
Chronic idiopathic urticaria (FDA approved)	Subcutaneous injection – 150 mg or 300 mg, repeated every 2–4 weeks – total duration of 12 weeks *No dose adjustment based on Serum IgE or body weight is required

Urticaria

As per the 2013 update of the EAACI/GA2LEN/EDF/WAO Guideline for the management of urticaria, omalizumab has a strong recommendation/high level of evidence as **third line** therapy in the management of urticaria.

Omalizumab should be used as add-on to second line therapy, which is the fourfold updosing of modern second generation antihistamines. In patients who do not respond to this measure, add on therapy with other drugs, such as omalizumab is to be considered.

Omalizumab is to be administered as a subcutaneous injection, in a dosage of 150–300 mg, every 4 weeks. Unlike the usage of omalizumab in asthma, dose adjustment based on Serum IgE and body weight is unnecessary for successful treatment in urticaria (Uysal, Eller, Mortz and Bindsley-

Jensen, 2014). The appropriate duration of omalizumab therapy for CIU has not been evaluated, though most studies report duration of 12 weeks of therapy. Periodic reassessment of the need for continued medication is recommended.

Off-label Uses

1. **Atopic dermatitis:** There are some reports in literature about efficacy of omalizumab in atopic dermatitis, as the disease is associated with raised IgE levels. While two case series demonstrated good efficacy with omalizumab, one case series did not report any improvement with Omalizumab in three cases of severe AD.
2. **Systemic mastocytosis**: Omalizumab has been reported to be useful in cases of systemic mastocytosis showing unprovoked anaphylaxis and not responding to other treatments
3. **Bullous urticaria:** One study reports dramatic improvement with omalizumab in a case of bullous Urticaria.

Drug Interaction

No formal drug interaction studies have been performed with Omalizumab and no reports about possible interactions exist.

Special Considerations

1. Omalizumab should only be administered by a physician or health care professional, who is trained in the recognition and treatment of anaphylaxis, and should only be administered in a setting where the appropriate medications and equipment are available to respond to an episode of anaphylaxis.
2. There have been reports of symptoms of systemic eosinophilia, along with clinical features of vasculitis, occurring more often in patients who are on omalizumab and associated with a reduction in oral corticosteroid dosage.
3. Some patients have experienced a constellation of signs and symptoms including arthritis/arthralgia, rash, fever and lymphadenopathy with an onset 1–5 days after the first or subsequent injections of Omalizumab. Therapy should be discontinued if such symptoms occur.
4. Monitoring is advised in patients at high risk for helminthic infections while on omalizumab therapy.

Side Effects

1. **Injection site reactions:** More incidence in omalizumab treated patients as compared to controls. The types of

injection site reactions included: swelling, erythema, pain, bruising, itching, bleeding and urticaria. However, none of the events resulted in study discontinuation or treatment interruption (12%).

2. **Omalizumab-associated anaphylaxis:** In Postmarketing spontaneous reports, the frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2% of patients.
3. **Malignancy:** Malignant neoplasms were observed in 0.5% of omalizumab treated patients, as compared to 0.2% in controls, in studies conducted on asthma patients. Some of the observed malignancies included breast, non-melanoma skin cancer, prostate, melanoma, and parotid. The majority of patients were observed for less than 1 year. The impact of longer exposure to the drug or use in patients at higher risk for malignancy (e.g. elderly, current smokers) is not known.
4. **Others:** Nausea, nasopharyngitis, sinusitis, URTIs, viral upper respiratory infections, arthralgia, headache, cough, etc. has been reported.

Monitoring

In view of rare reports of thrombocytopenia, monitoring of platelet counts at baseline and during therapy may be advisable. However, there are no such recommendations made at present. All reports of thrombocytopenia have been transient and reversible, with no reported incidence of any bleeding episodes.

Special Groups

Pregnancy

Pregnancy Category B

Lactation

Exercise caution while administering omalizumab to a nursing woman. Adequate safety data are not available.

Children

Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients ≥12 years old, the risk-benefit assessment does not support the use of Xolair in patients <12 years of age. Therefore, the use of Xolair in this patient population is not recommended.

Patient need to be monitored for 3 hours after injection for anaphylactic reactions in a hospital where ICU facilities are available.

FURTHER READING

1. Genentech, Inc. Xolair (omalizumab) for subcutaneous use: Full prescribing information. Line 128, Page 6. Date of Revision, March 21, 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103976s5211lbl.pdf . [Last accessed: 01.07.14]
2. Uysal P, Eller E, Mortz CG, Bindsley-Jensen C. An algorithm for treating chronic urticaria with omalizumab: Dose interval should be individualized. J Allergy Clin Immunol. 2014; 133 (3):914-15.

8

CHAPTER

Immunosuppressive Drugs

Rajiv Sekhri[1], Vinoo Sekhri[1], Kabir Sardana

INTRODUCTION

This class of drugs has two major subdivisions, though they frequently overlap. The first class of drugs are the immunosuppressant drugs, which are used to prevent the rejection of transplanted organs and tissues, e.g. heart, heart–lung, kidney, bone marrow. In dermatology, they are used to treat a variety of diseases that have an autoimmune component to their pathogenesis, systemic lupus erythematosus (SLE), psoriasis, scleroderma, vasculitis, etc.

The second class of drugs are used to treat cancer inhibit cell proliferation (Table 8.1). They are therefore toxic to both tumor cells and proliferating normal cells, especially in the bone marrow, gastrointestinal epithelium and hair follicles. Here, it is important to specify that broadly, drugs are only effective during part of the cell cycle (phase-specific drugs), while others (cycle-specific drugs) are cytotoxic throughout the cell cycle. This second group of agents are called cell cycle–nonspecific (CCNS) drugs and can sterilize tumor cells whether they are cycling or resting in the G0 compartment. CCNS drugs can kill both G0 and cycling cells (although cycling cells are more sensitive) (Figs 8.1 and 8.2). Importantly cyclophosphamide is a CCNS drug and thus is more toxic as compared to azathioprine, thus in mild to moderate cases of pemphigus, which is the prototype skin disorder for these drugs, azathioprine should be the preferred drug. In fact this is one of the reasons, why International guidelines, recommend this drug over cyclophosphamide.

The Adaptive Immune System

To understand the action of various drugs, it is important to understand the mechanism involved in the adaptive immunity (Fig. 8.3). The adaptive immune system is mobilized when the the innate response are incapable of coping with an infection. The adaptive immune system has a number of characteristics that contribute to its success in eliminating pathogens.

Table 8.1: Classification of cytotoxic drugs*

Cell cycle–specific (CCS) agents	*Cell cycle–nonspecific (CCNS) agents*
Antimetabolites (S phase) Gemcitabine 6-Mercaptopurine (6-MP) *Methotrexate (MTX)* *Azathioprine* *Mycophenolate Mofetil*	***Alkylating agents*** Cyclophosphamide Busulfan
Epipodophyllotoxin (topoisomerase II inhibitor) (G1–S phase) Etoposide *Leflunomide*	***Anthracyclines*** Doxorubicin Daunorubicin
Taxanes (M phase) Paclitaxel	***Antitumor antibiotics*** Bleomycin Dactinomycin Mitomycin
Vinca alkaloids (M phase) Vinblastine	***Camptothecins (topo-isomerase I inhibitors)***
Antitumor antibiotics (G2–M phase) Bleomycin	***Platinum analogs*** Carboplatin Cisplatin
	Steroid hormones and antagonists *Glucocorticoids* *Estrogens* *Anti-estrogens* *Androgens*

* Drugs exerting their action on cells traversing the cell cycle are called cell cycle–specific (CCS) drugs, the cell cycle–nonspecific (CCNS) drugs can sterilize tumor cells whether they are cycling or resting in the G0 compartment. CCNS drugs can kill both G0 and cycling cells (although cycling cells are more sensitive)

1. The induction of specific adaptive immunity requires the participation of professional antigen-presenting cells (APCs), which include dendritic cells (DCs), macrophages, and B lymphocytes. These cells ingest the antigen, generate peptides, which with **class I or class II MHC proteins** "present" to the cell surface T-cell receptor (TCR). **CD8 T cells** recognize **class I-MHC** peptide complexes while **CD4 T cells** recognize **class II-MHC peptide** complexes. At least two signals are necessary for the activation of T cells. The *first signal* is due to the engagement of the TCR with peptide-bound MHC molecules. The *second signal* involves ligation of costimulatory molecules (CD 80,CD 86, B7-1, B7-2 on the APC to their respective ligands. Activation of T cells is regulated via a negative feedback loop involving another molecule known as T-lymphocyte-associated antigen 4 (CTLA-4).
2. The CD T cell is further differentiated into three cells (Th1, Th2 and Th17) based on the cytokines they secrete after activation. The **Th1** subset characteristically produces IFN-γ, IL-2, and IL-12 and induces **cell-mediated immunity**. The

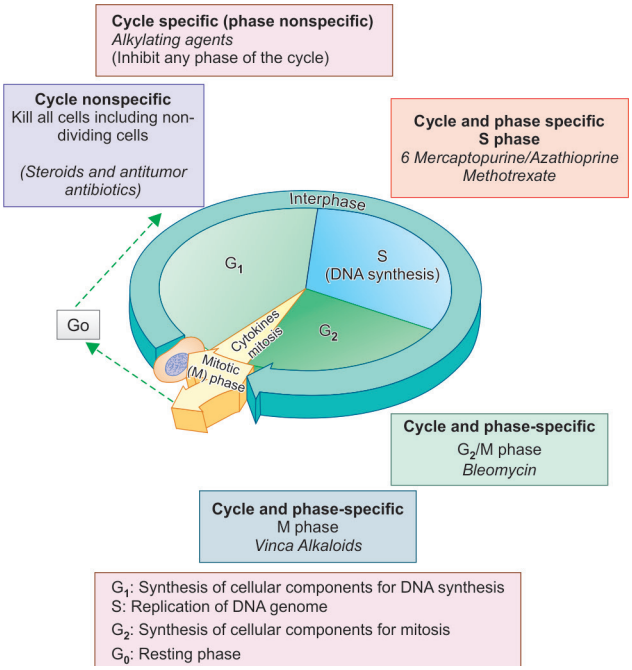


Fig. 8.1: Action of cytotoxic agents depending on cell cycle and phase

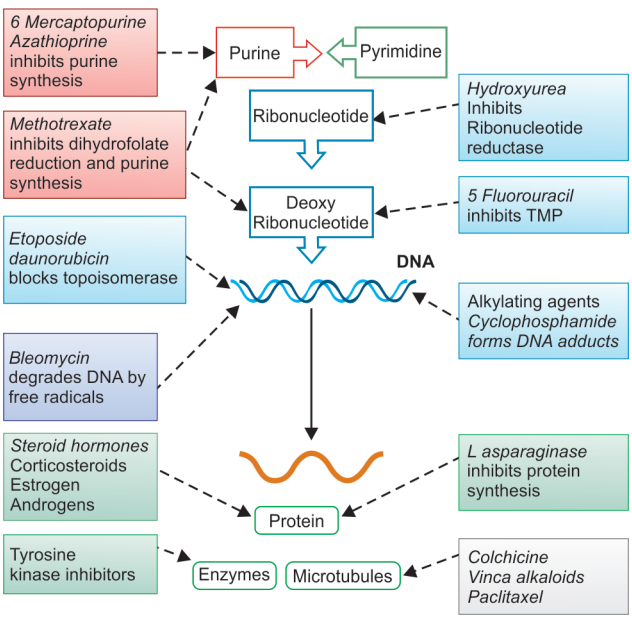


Fig. 8.2: Site of action of cytotoxic drugs

Th2 subset produces IL-4, IL-5, IL-6, and IL-10, which induce B-cell proliferation and differentiation into antibody-secreting plasma cells. **IL-10** produced by TH2 cells *inhibits* cytokine production by TH1 cells while **IFN-γ** produced by TH1 cells *inhibits* the proliferation of Th2 cells.

Extracellular bacteria and **autoimmune** stimuli typically cause the elaboration of **Th2** cytokines, culminating in the production of neutralizing or opsonic antibodies. In contrast, **intracellular** organisms (e.g. mycobacteria), virus and tumor cells elicit the production of **Th1** cytokines, which lead to the activation of effectors cells such as macrophages.

Th1 cells control macrophage (MAC)-initiated responses that are responsible for the release of inflammatory cytokines (tumor necrosis factor-α, TNF-α and IL-1). Th1 responses predominate in a number of diseases, including RA, where TNF-α and IL-1 have a major role in the pathogenesis of the disease.

Recently, Th17 cells were classified as distinct from the previously established Th1/Th2 cells essential in the pathogenesis of autoimmune disease, although the

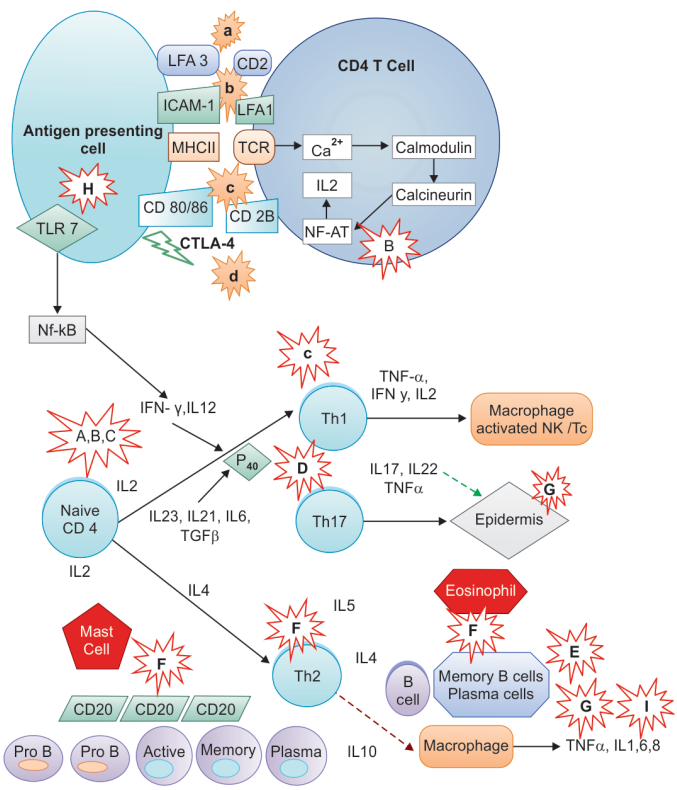


Fig. 8.3: A diagrammatic representation of the interplay of the various cells and cytokines in the adaptive immune response and the site of action of the major classes of immunoregulatory, cytotoxic and DMARD drugs used in dermatology; A = Corticosteroids (Inhibit IL2); B = Cyclosporine and Tacrolimus; C = Azathioprine, Methotrexate, MMF; D = Anti-P 40 ustekinumab; E = Cyclophosphamide; F = Rituximab; G = Thalidomide, TNF mab, Steroids; H = Imiquimod; I = DMARD (methotrexate, hydroxychloroquine, sulfasalazine, penicillamine, aurothiomalate); a. Alefacept; b. Efalizumab; c. Abatacept; d. Ipilimumab

mechanism and influence of the Th17 cell lines continue to be elucidated. They produce distinct cytokines (primarily IL-17, -21, and -22) and are governed by IL-23. **Th17 cells** depend on the IL-12 and -23 cytokine axis. While IL-12 stimulates Th1 cells IL-23 stimulates TH17 cells. IL-12 and -23 have been associated with the pathogenesis of psoriasis, due in part to their relationship to the differentiation of naïve T-cells into Th1 and Th17 cells, respectively growing evidence implicates IL-12 and -23 and Th17 cells (which produce IL-17 and -22) in the pathogenesis of psoriasis and other autoimmune inflammatory conditions.

The common p40 subunit of IL-12 and -23 is (1) over-expressed in psoriatic plaques, and (2) over-expressed in circulating mononuclear cells of multiple sclerosis patients; and agents that modulate these cytokines have shown excellent potential as novel therapeutics. IL-22 is primarily a downstream mediator of IL-23-induced inflammation and a major cause of epidermal hyperproliferation and resultant acanthosis (by mediating abnormal differentiation of keratinocytes). Both IL-12 and -23 are structurally similar (heterodimers) as they share a common p40 subunit that is covalently linked to either a p35 subunit (IL-12) or a p19 subunit (IL-23). The p40 subunit of both interleukins binds the transmembrane IL-12 receptor β1 (IL-12Rβ1) on the surface of T cells and NK cells.

3. B lymphocytes undergo selection in the bone marrow, during which self-reactive B lymphocytes are clonally deleted while B-cell clones specific for foreign antigens are retained and expanded. Upon an encounter with antigen, a mature B cell binds the antigen, internalizes and processes it, and presents its peptide bound to class II MHC to CD4 helper cells, which in turn secrete IL-4 and IL-5. These interleukins stimulate B-cell proliferation and differentiation into memory B cells and antibody-secreting plasma cells.

   B cells arise from stem cells in the bone marrow, where they acquire an antibody receptor bearing a unique variable region. A number of maturation and activation steps take place as the B cells migrate from the marrow compartment, through blood, and to perifollicular germinal centers and memory compartments in lymphoid tissue, before returning to the marrow as mature plasma cells. Because CD20 is **not** internalized and is highly expressed on a range of B lineage cells, including pre-B cells, immature B cells, activated cells, and memory cells, but is not found on stem, dendritic, or plasma cells

(Fig. 8.3), it is an ideal target for B cell depletion by monoclonal antibodies, like rituximab.

4. A less well-defined T-cell subset (Th3) has been described that produces transforming growth factor- (TGF-), whose numerous functions include down-regulation of proliferation and differentiation of T lymphocytes.
5. CD8 T lymphocytes recognize endogenously processed peptides presented by virus-infected cells or tumor cells. These peptides are loaded onto MHC class I molecules in the endoplasmic reticulum.. In some instances, exogenous antigens, upon ingestion by APCs, can be presented on class I MHC molecules to CD8 T cells. This phenomenon is referred to as "cross-presentation" and is thought to be useful in generating effective immune responses against infected host cells that are incapable of priming T lymphocytes. Upon activation, CD8 T cells induce target cell death via lytic granule enzymes ("granzymes"), perforin, and the Fas-Fas ligand (Fas-FasL) apoptosis pathways.

TARGETS OF IMMUNOPHARMACOLOGICAL DRUGS

Cytokines

Because of their multiple functions in the inflammatory process, cytokines offer useful targets for therapeutic intervention. Suppression of immune and inflammatory reactions can be achieved by inhibition of cytokines in several ways:

(1) The inhibition of cytokine *synthesis*, (2) the *decrease* of cytokines in free active form, (3) the *blocking* of the interaction with their receptor, or (4) the inhibition of cytokine-dependent *signaling*.

For each mechanism, at least one clinically relevant example exists (Table 8.2). By far the most predominant target cell for immunosuppressants is the T helper lymphocyte.

1. **Cytostatic drugs** such as *azathioprine* decrease the number of (T) lymphocytes and thereby also of cytokine-producing cells. Monoclonal antibodies directed against T cell epitopes in part also work by this mechanism; antibodies against CD3 or the IL-2-receptor mainly prevent activation or proliferation, respectively. They are effective in preventing transplant rejection and also in the treatment of autoimmune diseases (an example being lupus erythematosus). Without being cytotoxic, by interfering with T cell receptor signaling, modern immunosuppressants, including *cyclosporine or tacrolimus*, very selectively block the synthesis of T

Table 8.2: Overview of drugs that block or modify cytokine

Mode of action	*Example drugs*
1. Inhibition of synthesis	
a. Reduction of the number of cytokine producing cells	
Cytostatic immunosuppressants	Azathioprine, leflunomide
Monoclonal antibodies to cells	Muromonab CD3
b. Regulation of cell activity	
Regulatory cytokines	(interleukin-4, 10)
calcineurin inhibitors	Cyclosporine, tacrolimus
Regulation of cytokine gene expression	Prednisolone
2. Decrease in concentration of active (free) form	
Monoclonal antibodies against cytokines	
anti-TNF antiboides	Infliximab, adalimumab
anti IL-1 antiboides	Canakinumab
anti IL-12/IL-23 antiboides	Ustekinumab
Soluble cytokine receptors	
soluble TNF receptor constructs	Etanercept
soluble IL-1 receptor constructs	Rilonacept
3. Receptor blockade	
Monoclonal antibodies against cytokine receptors	
antibodies against the IL-2 receptor	Basiliximab
antibodies against the IL-6 receptor	Tocilizumab
Cytokine antagonist	Anakinra
4. Inhibition of cytokine-dependent signalining	
Protein kinase inhibitors	Sirolimus

lymphocyte cytokines, predominantly of their growth factor IL-2. In a similar way, *glucocorticoids* (e.g. prednisone) are immunosuppressive by interfering with the gene expression of this cytokine and others synthesized by T lymphocytes. They affect multiple proinflammatory mechanisms, their efficacy largely relies on the capacity to block gene expression of most proinflammatory cytokines, including IL-1 to IL-8, TNF or IFN-γ.

2. *Antibodies* can block the action of *secreted cytokines*. A chimeric (mouse/human) antibody directed to TNF-α (*infliximab*) represented the first example of a specific cytokine-blocking antibody, proving efficacious in rheumatoid arthritis or inflammatory bowel disease. Infliximab has been followed up to now by three further antibodies, including completely human antibodies (generated by phage display technology) with similar properties (*adalimumab, golimumab*) and a construct of the Fab' fragment of a humanized antibody coupled to polyethylene glycol (*certolizumab pegol*). The major side effect of the therapy with anti-TNF anti-bodies is an

increased risk of infections (as might be expected!), including recurrence of tuberculosis and occasionally septic shock. Very recently, a human monoclonal antibody against IL-1 (*canakinumab)* has been approved for the treatment of cryopyrin-associated periodic syndromes (CAPS). Several other anti-cytokine antibodies, including antibodies against IL-1, IL-6, IL-8, IL-12, IL-15, IL-17, IL-18 or IL-23 are being evaluated in clinical trials for the treatment of several autoimmune or chronic inflammatory diseases.

3. In addition to antibodies, blocking of *free active cytokines* can also be achieved in a quite different way. Illustrating the principle of self-limitation, the extracellular domains of many cytokine receptors are released during immune or inflammatory reactions. As these "soluble receptors" contain the full cytokine binding site, they bind the free cytokine and thereby dampen its biological effect. A soluble TNF-receptor construct (*etanercept*) – in which "soluble" TNF receptors were fused to the constant parts of human IgG1 to increase affinity and half-life *in vivo*— has been approved for rheumatoid arthritis, inflammatory bowel disease and psoriasis with similar effectiveness and side effects as infliximab. A similar construct of the extracellular portions of the IL-1 receptor and its accessory protein (rilonacept) was approved for the treatment of CAPS (Table 8.3). As a unique example, a naturally occurring antagonist of IL-1, IL-1ra, has been cloned and approved (*Anakinra*) for rheumatoid arthritis.
4. *Receptors* can be blocked by specific antibodies. *Basiliximab* is directed against the IL-2 receptor and effective as an immunosuppressant in transplanted organ rejection episodes. Table 8.3 summarizes indications for inhibitors of cytokines. Preventing the binding of IL-6, a humanized monoclonal antibody against the IL-6-receptor (tocilizumab) was recently approved for the treatment of rheumatoid arthritis.
5. In the last decade, the signal transduction pathways of many cytokine receptors have been investigated extensively. A core finding was that several phosphorylation cascades exist in which key protein kinases offer targets for pharmacological interventions. Although quite a number of selective protein kinase inhibitors have been found, only very few of them so far have been approved for the prevention of transplant rejection such as *sirolimus or everolimus*. Both drugs, by blocking mammalian target of rapamycin (mTOR, a synonym for sirolimus), prevent IL-2-driven proliferation of activated T lymphocytes.

Table 8.3: A list of drugs that inhibit cytokines

Target cytokine	*Indication*
IL-1*	Autoimmune and chronic inflammatory disease
IL-2	Organ transplantation, autoimmune diseases
IL-4, IL-13	Allergic (type 1) dieases, especially allergic asthma
IL-5	Allergic asthma (?)
IL-6	Chronic inflammatory disease, hyperimmunoglobulinemias
IL-8 (and other chemokines)	Chronic inflammatory disease, autoimmune diseases
IL-12, IL-18	Chronic inflammatory disease
IL-23	Chronic inflammatory disease
TNF-α, β	Septic shock, chronic inflammatory and autoimmune diseases
IFN-γ	Autoimmune diseases

Abbreviations: IFN, inteferon; IL, interleukin; TNF, tumor necrosis factor
*Cytokines in bold font represent those for which inhibitors have been approved

6. The intracellular signaling by cytokine receptors is by the binding of cytokines to their receptors which leads to the activation of cytoplasmic tyrosine kinases. Janus kinases (JAKs), a recently described family of four related cytoplasmic protein tyrosine kinases, further transfer cytokine signaling. There are four JAKs: JAK1, JAK2, JAK3, and TYK2, which transduct signals from cytokine receptors to effector mechanisms. On binding of the cytokine, JAKs bind to the receptor and mediate tyrosine kinase activity and phosphorylation. **Tofacitinib** is one such drug that inhibits the JAK pathway and this and other drugs have been found to be useful in psoriasis and alopecia areata.

Lymphocytes

Most of the drugs used in dermatology work on the lymphocytes notably T cells and the interaction between the APC and T cells (Fig. 8.4). The intricate interaction are beyond the scope of this book, but three levels of interaction are seen. The **signal 1** is signal transduction from the TCR/CD3 complex, **signal 2** is the costimulatory signaling via the interaction between CD28 and B7 (CD80, CD86). **Signal 3** is the downstream pathway where the cytokines act via mTOR and the JAK/STAT pathway.

JAKs play a major role in the so-called signal 3 pathway of T cell activation, similar to but distinct from mTOR-mediated intracellular signaling (calcineurin/CYP representing signal 1, and costimulation representing signal 2). This

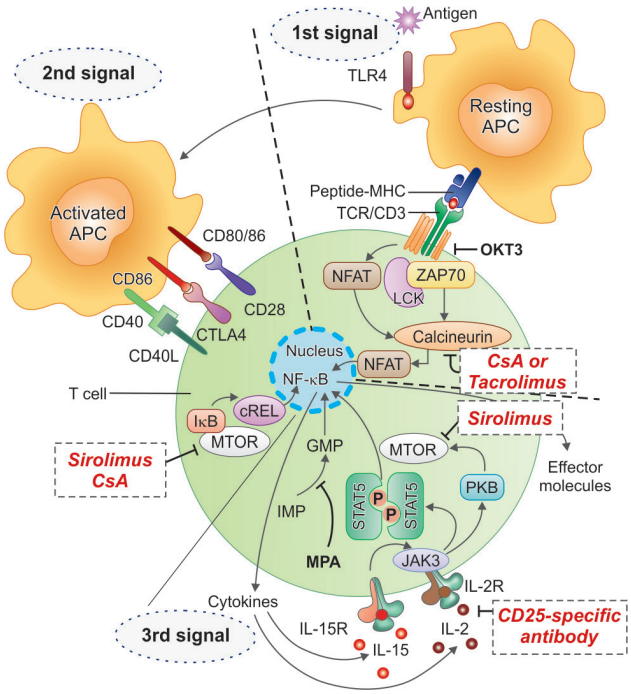


Fig. 8.4: A depiction of lymphocyte activation and site of action of selected drugs (CsA = corticosteroids)

signal 3 pathway involves cytokines like IL-2, IL-4, IL-9, IL-15 and IL-21. There are four JAKs in mammalian cells (JAK1–3 and tyrosine kinase 2), of which JAK3 is restricted to hematopoietic cells and mediates cytokine signaling only via receptors that contain a γ chain. Inhibition of JAK3 could be associated with immunosuppression without the adverse side effects observed on inhibition of the signal 1 pathway.

As seen in Fig. 8.5 JAK inhibitors that are used in psoriasis and alopecia areata work by inhibiting this pathway.

A list of drugs that inhibit various aspects of lymphocytes is Table 8.4.

MODE OF ACTION OF IMMUNOPHARMACOLOGICAL DRUGS

An overview of common drugs used in dermatology and their site of action is discussed below. It is important to understand that the use of drugs in various dermatological disorders, needs an understanding of the main cytokines involved and the kind of lymphocytes, Th1 or Th2 involved in the disease process.

1. **Steroids:** Glucocorticoids are thought to interfere with the cell cycle of activated lymphoid cells. Glucocorticoids are quite cytotoxic to certain subsets of T cells, but their immunologic effects are probably due to their ability to modify cellular functions rather than to direct cytotoxicity.

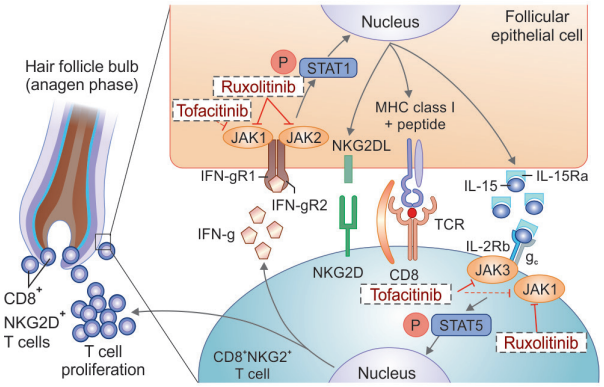


Fig. 8.5: Mode of action JAK inhibitors in alopecia areata depiction of the immunological pathway with in the hair bulb

Table 8.4: Lymphocyte-targeting pharmaceuticals

Target Drugs	*MOA*
Cell proliferation, antimetabolites	
Cyclophosphamide (CY)	Pan cytopenic block
Azathioprine (AZA)	Purine synthesis inhibitor; prodrug of 6-mercaptopurine 6-thioinosinic acid
Mycophenolic mofetil	Inhibitor of IMPDH
Leflunomide	Inhibitor of DHODH
Teriflunomide	Active metabolite of leflunomide
Methotrexate	Folate antagonist, inhibits dehydropholate reductase
Cell surface molecules, lymphocyte depleting antibodies	
Alemtuzumab	Humanized anti-CD52 mAb
Ofatumumab (HuMax-CD20)	Human anti-CD20 mAb
Rituximab	Chimeric anti-CD20 mAb
Denileukin diftitox	Fusion protein between IL-2 and diphtheria toxin
Cell trafficking and adhesion	
Alefacept	Fc fusion protein of extracellular portion of LFA-3: blocks CD2
T cell receptor signaling	
Cyclosporine	Inhibitor of calcineurin
Voclosporin	Inhibitor of calcineurin
Tacrolimus	
Costimulatory blockade	
Abatacept (CTLA4-Ig)	Fc fusion protein of extracellular domain of CTLA-4, blocks CD28-CD80/86
Belatacept (LEA29Y)	Fc fusion protein of extracellular domain of CTLA-4, blocks CD28-CD80/86

Contd...

Contd...

B-lymphocyte signaling	
Belimumab	Human anti-B lymphocyte stimulator (BLyS) mAb; blocks binding of BLys to its receptor(s)
Atacicept (TACI-Ig)	Fusion protein containing the extracellular ligand-binding portion of the transmembrane activator and CAML interactor (TACI): binds BLys (CD257) and a proliferation inducing ligand (APRIL, CD256)
Cytokines/cytokine signaling	
Sirolimus	mTOR inhibitor
Ustekinumab (CNTO1275)	Human anti-IL-12/IL-23 mAb
Infliximab	Chimeric anti-TNF-α mAb
Golimumab	Human anti-TNF-α mAb
Certolizumab	Humanized anti-TNF-α mAb
Anakinra	IL-ra

Abbreviations: IMPDH, Inosine monophosphate dehydrogenase; DHODH, dihydroorotate dehydrogenase

Although *cellular immunity* is more affected than humoral immunity, the primary antibody response can be diminished, and with continued use, previously established antibody responses are also decreased.

a. T-cell activation is inhibited by decreased **IL-2** production (Figs 8.3 and 8.4). Once the T cell activation is blocked there is no secretion of IL-4 and 5 to stimulate mast cells and eosinophils. Although the sub-populations of helper, suppressor, and cytotoxic T lymphocytes are all inhibited, *helper* cells are more affected than suppressor cells.
b. Inhibition of **B-cell** function requires very high doses of GCS. Pulse therapy is a way of delivering high-dose GCS as a means of decreasing antibody production by B lymphocytes. This is the logic of using pulse steroids for SLE (lupus nephritis), which was the original indication, of pulse therapy and pemphigus. Importantly, as high dose steroids are enough to suppress B cell, there is little pharmacological logic in adding cyclophosphamide, which is a cell cycle non- specific drug, and can add to the side-effect.
c. Decreases the release of **IL-1, IL-6, TNF**α.
d. Decrease neutrophilic adhesion, eosinophilic activation and monocyte-macrophage interaction.

2. **Cyclosporine:** Cyclosporine is a peptide antibiotic that appears to act at an early stage in the antigen receptor-induced differentiation of T cells and blocks their activation. (Fig 8.3B). The cytokine **IL-2** is crucial to lymphocyte proliferation (Th1, Th2), and cyclosporine, the most widely used immunosuppressant, acts by inhibiting the transcription and release of IL-2.

Cyclosporine binds to cyclophilin, a member of a class of intracellular proteins called immunophilins. Cyclosporine and cyclophilin form a complex that inhibits the cytoplasmic phosphatase, calcineurin, which is necessary for the activation of a T-cell-specific transcription factor. This transcription factor, NF-AT, is involved in the synthesis of interleukins (e.g. IL-2) by activated T cells. *In vitro* studies have indicated that cyclosporine inhibits the gene transcription of IL-2, IL-3, IFN-γ and other factors produced by antigen-stimulated T cells, but it does **not** block the effect of such factors on *primed T cells* nor does it block *interaction* with antigen.

3. **Tacrolimus:** While cyclosporine binds to cyclophilin, tacrolimus binds to the immunophilin FK-binding protein (FKBP). The complex inhibit calcineurin, which is necessary for the activation of the T-cell-specific transcription factor NF-AT. On a weight basis, tacrolimus is 10–100 times more potent than cyclosporine in inhibiting immune responses and is largely used in transplant cases.
4. **Methotrexate:** *Low-dose* methotrexate, used commonly in dermatology has both immunosuppressive and anti-inflammatory properties, resulting in inhibition of proliferation of CD3 and CD4 lymphocytes, monocytes/macrophages and neutrophils.
   a. At low concentrations, methotrexate induces *apoptosis* of activated T cells from human peripheral blood *in vitro*.
   b. It also modulates cytokine secretion from T helper lymphocytes by **increasing** *IL-4 and Il-10* and **decreasing** *IFN-γ and IL-2.* Thus, it reduces the **Th1** response. In general, low-dose methotrexate alters the cytokine balance by inhibiting the production of *pro-inflammatory cytokines* (TNF, IL-6) and enhancing *anti-inflammatory* cytokines (IL-1ra).
   c. Intracellular methotrexate-polyglutamates inhibit the function of 5-amino-imidazole-4-carboxamide ribosyl-5-phosphate formyltransferase (AICAR-formyl-transferase). The resulting high concentrations of AICAR lead to enhanced release of adenosine into the blood, activating A2a, A2b and A3 extracellular receptors on monocytes/macrophages. In this way, adenosine seems to promote the transcription of MRNA for an IL-1 receptor antagonist and increases the secretion of the potent *anti-inflammatory cytokine IL-10*. Moreover, adenosine inhibits the production of TNF-α, IL-6 and IL-8 and the expression of E-selectin on the cell surface.

5. **Thalidomide:** Thalidomide inhibits angiogenesis and has anti-inflammatory and immunomodulatory effects. It inhibits tumor necrosis factor-alpha (TNF-α),(Fig. 8.3, G) reduces phagocytosis by neutrophils, increases production of IL-10, alters adhesion molecule expression, and enhances cell-mediated immunity via interactions with T cells.
6. **Azathioprine:** Azathioprine and mercaptopurine appear to produce immunosuppression by interfering with purine nucleic acid metabolism at steps that are required for the wave of lymphoid cell proliferation that *follows* antigenic stimulation. The purine analogs are thus cytotoxic agents that destroy stimulated lymphoid cells. This drug and its cytotoxic action inhibits clonal proliferation in the *induction* phase of the immune response. The main side-effect of azathioprine is bone marrow suppression.
   Although continued messenger RNA synthesis is necessary for sustained antibody synthesis by plasma cells, these analogs appear to have *less* effect on this process than on nucleic acid synthesis in proliferating cells. Nevertheless, cellular immunity as well as primary and secondary serum antibody responses can be blocked by these cytotoxic agents.
7. **Mycophenolate Mofetil:** In vitro, it inhibits T- and B-lymphocyte responses, including mitogen and mixed lymphocyte responses, probably by inhibition of de novo synthesis of purines. Mycophenolate mofetil is hydrolyzed to mycophenolic acid, the active immunosuppressive moiety; it is synthesized and administered as MMF to enhance bioavailability.
8. **Leflunomide:** This drugs works by inhibition of IMPDH and this affects not only T cells but also B cells. Hence, leflunomide has been shown to be a potent drug affecting T-dependent and T-independent Ab synthesis. There are reports that leflunomide affects B cells even more potently than T lymphocytes. There are also claims that the drug might be effective in chronic rejection, as demonstrated by the in vitro inhibition of rat smooth muscle cell proliferation, and its efficacy in vivo in rodent vessel transplantation, a model mimicking vascular pathology in chronic rejection of solid organ allografts. Apart from its immunosuppressive activity, the anti-inflammatory action of the drug (inhibition of the production of inflammatory cytokines) might be relevant for this indication.
9. **Cyclophosphamide:** It destroys proliferating lymphoid cells but also appears to alkylate some resting cells. It has been observed that very large doses (e.g. >120 mg/kg

intravenously over several days) may induce an apparent specific tolerance to a new antigen if the drug is administered simultaneously with, or shortly after, the antigen presents.

a. At the cellular level, the drug is able to trigger *apoptosis* and to induce a pronounced *cytotoxic* effect on mature lymphocytes with relative sparing of the respective precursor cells.
b. The generation of *reactive oxygen-free* radicals may be considered another mechanism of action, leading to cell death by damaging DNA and inducing lipid peroxidation.
c. Acrolein—a cyclophosphamide metabolite—seems to be able to inhibit *cell proliferation,* to induce *cell death* by apoptosis and to modulate expression of genes and transcription factors, because it reduces the activation of nuclear factor κB (NF-κB) and activator protein 1 (AP-1). These effects could be increased by the depletion of cellular glutathione, which acts as a detoxifying molecule.

10. **Hydroxychloroquine:** Hydroxychloroquine is an antimalarial agent with immunosuppressant properties. It is thought to suppress intracellular antigen processing and loading of peptides onto **MHC class II** molecules.

    The weakly basic character of the anti-malarial drugs indicates that they should accumulate in acidic organelles in cells, particularly lysosomes, where they may *raise* the pH. This may affect the function of the acidic organelles, particularly *lysosomal* enzymes. One such enzyme is acidic sphingomyelinase, which is located within the lipid membrane of lysosomes and is an important mediator in the signal transduction pathway between the TNF receptor on the cell surface and activation of transcription factor NF-κB in the nucleus. Raising the pH of lysosomes inhibits acidic sphingomyelinase activity, consequently *inhibiting* NF-κB activity and proinflammatory gene expression. Antimalarials have also been reported to inhibit the activity of many other enzymes, including phospholipase A2 and the production of IL-1.
11. **Anti-TNF-Alpha MABS:** Adalimumab, etanercept, and infliximab are antibodies that bind TNF-α, a proinflammatory cytokine. Blocking TNF-α from binding to TNF receptors on inflammatory cell surfaces results in suppression of downstream inflammatory cytokines such as IL-1 and IL-6 and adhesion molecules involved in leukocyte activation and migration. An increased risk of lymphoma is common to each of these agents.

12. **Sulfasalazine:** Sulfasalazine consists of mesalazine (aminosalicylate) and a sulfonamide, sulfapyridine. This drug was synthesized in the late 1930s and originally developed and used on the basis of a belief of an infectious cause of RA. The mode of action of sulfasalazine is unclear, although it has been reported to inhibit AICAR transformylase and, therefore, may act in a similar fashion to methotrexate through the accumulation of adenosine. Oddly, it is not known whether sulfasalazine or its metabolites are therapeutically active. The apparent antirheumatic activity of sulfapyridine indicates that it may be the active metabolite. On the other hand, both sulfasalazine and olsalazine appear active in the treatment of ankylosing spondylitis.

BIBLIOGRAPHY

1. Fitzgerald KA, O'Neill LAJ, Gearing A, Callard RE. The Cytokine Facts Book, 2nd edn. Academic Press, San Diego, 2001.
2. Nijkamp FP, Parnham MJ, (Eds). Principles of Immunopharmacology: 3rd revised and extended edition, DOI 10.1007/978-3-0346-0136-8_6, © Springer Basel AG 2011.
3. Saenz SA, Taylor BC, Artis D. Wellcome to the neighborhood: epithelial cell-derived cytokines license innate and adaptive immune responses at mucosal sites. Immunol Rev. 2008;226: 172-90.
4. Tarner IH, Müller-Ladner U, Gay S. Emerging targets of biological therapies for rheumatoid arthritis. Nat Clin Pract Rheumatol. 2007;3:336-45.
5. Thomson AW, Lotze MT (Eds). The Cytokine Handbook, 4th edition. Academic Press, London. 2003.
6. Urschel S, Altamirano-Diaz LA, West LJ. Immunosuppression armamentarium in 2010: mechanistic and clinical considerations. Pediatr Clin N Am. 2010;57:433-57.

MYCOPHENOLATE MOFETIL[1]

Mycophenolate mofetil (MMF) is an important tool in the arsenal of physicians because of its role as an Immunosuppressant/Immunomodulatory agent that is used in the treatment of various inflammatory dermatoses and in transplant medicine.

MMF is an ester prodrug (2-morpholino-ethyl ester of mycophenolic acid), which is rapidly hydrolyzed by plasma esterases, following oral intake, to the active moiety mycophenolic acid (MPA)(Corvis AK, et al.).

Mechanism of Action

1. MPA, the active metabolite, has a cytostatic effect on lymphocytes. It prevents the proliferation of immune cells

by arresting the synthesis of DNA and RNA in T- and B-cells by inhibiting inosine monophosphate dehydrogenase (IMPDH)(Whirl-Carrillo M et al.; Laliberte et al.). MPA arrests the T-cell cycle at the G0/G1 phase (Laliberte et al.). Two cellular mechanisms exist for purine nucleotide generation: the de novo pathway and the salvage pathway. Lymphocytes are unique in their complete dependence on the former. MPA non-competitively binds to and inhibits inosine monophosphate dehydrogenase (IMPDH), the key enzyme in the de novo pathway. In addition, MMF has a much higher affinity for the isoform of IMPDH that is expressed in activated lymphocytes. Thus by selectively inhibiting the de novo pathway within activated lymphocytes, MMF is able to target those lymphocytes most responsible for disease while having a minimal effect on other organ systems and cell types. The actions of mycophenolic acid are selective and do not principally involve IL-2. MMF inhibits antibody production by activated B-cell lymphocytes. Unlike cyclosporine and tacrolimus, they affect both T- and B-lymphocytes. Unlike azathioprine, MMF is not incorporated into nucleic acids.

2. MMF reduces the recruitment and egress of inflammatory cells into areas of inflammation by altering the expression and processing of cell surface adhesion molecules, specifically reducing expression of VCAM-1, E-selectin, and P-selectin.
3. A secondary effect of the reduced nucleotide pool is a reduced affinity of adhesion molecules which likely contributes to the immunosuppressive activity of

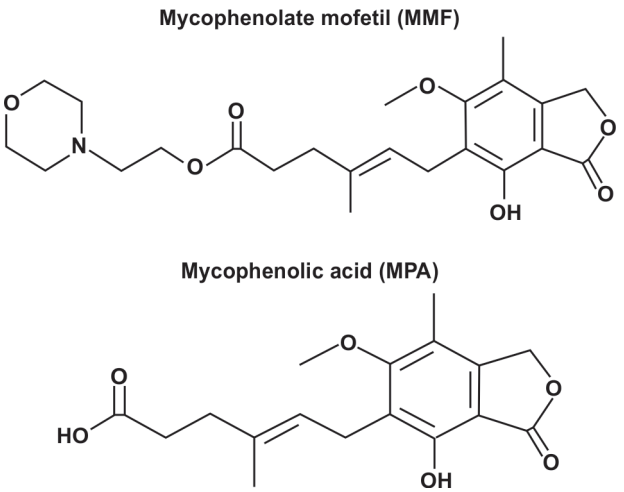


Fig. 8.6: Structure of MMF and its active moiety

mycophenolic acid. MPA impedes the recruitment of leukocytes into sites of inflammation by reducing lymphocyte and monocyte adhesion to endothelial cells. MMF achieves this by blocking glycosylation of lymphocyte and monocyte glycoproteins necessary for adhesion to the endothelial cells (Allison AC et al.).

Absorption and Distribution

MMF is completely and rapidly absorbed after oral and intravenous administration. This is followed by de-esterification, which is not significantly affected by hepatic or renal impairment (Orvis AK et al.).

Peak concentration of MPA is reached within 60 to 90 minutes of oral administration. Oral bioavailability in healthy individuals is reported to be 94% as compared to intravenous administration (Bowalgaha K et al.).

Ninety-seven percent of MPA circulates bound to plasma albumin.

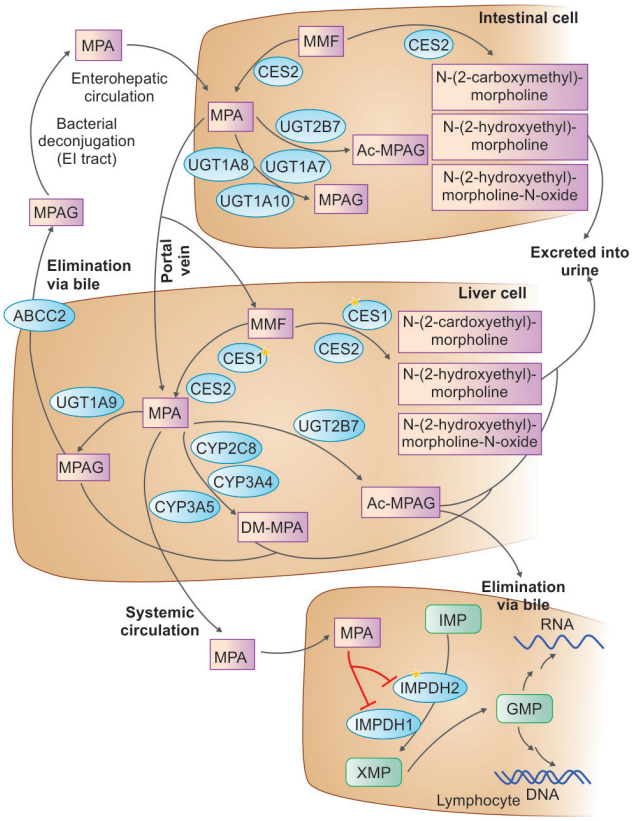


Fig. 8.7: Mode of action of MMF. Schematic representation of mycophenolic acid metabolism
Source: Reproduced with permission from PharmGKB and Stanford University

Metabolism and Distribution

MPA is primarily metabolized by glucuronyl transferase in the liver (Orvis AK et al., Kushari Bowalgaha et al.). Conjugation of the phenol group of MPA forms the inactive but stable compound 7-hydroxy-β-glucuronide referred to as MPAG or mycophenolic acid glucuronide. The other two minor and clinically inactive metabolites are 7-O-glucoside and acyl glucuronide.

This is the principal clearance pathway of MPA. Although the human liver, kidney and jejunum have the capacity to convert MPA to MPAG, liver is the major site of MPAG formation and therefore the organ primarily responsible for the systemic clearance of MPA. MPAG is excreted in bile (Kushari Bowalgaha et al., Bullingham RES et al.). MPAG also binds plasma albumin (82%).

The kidney and the small intestine contribute in a small way and the latter only to first pass metabolism. Renal clearance of unaltered MPA is negligible as the drug is almost exclusively excreted as MPAG (Kushari Bowalgaha et al.).

Circulating MPAG can be converted into active MPA through enterohepatic circulation.

In case the hepatic metabolism is impaired, whether the kidney takes over as the principal site for the clearance of MPA is debatable in the absence of supportive laboratory data.

Less than 1% of the administered dose of MMF is excreted as the active drug MPA (Bullingham et al.). The majority (87%) of the administered dose is excreted as MPAG in the urine and six percent in faeces. Therefore, it is not surprising that there are increased levels of MMF metabolites, both active and inactive, in patients with renal insufficiency (Srinivas et al.). These patients would therefore require a lower dose and/or close monitoring.

Uses/Indications

Dose

Cytotoxic T-cell mediated diseases 25–35 mg/kg.
Antibody-mediated diseases 35–55 mg/kg.
Initial Dose: The starting dose typically depends on the disease being treated and is 1000 to 2000 mg daily in divided doses. Dose range is from 1000 to 3000 mg daily.
Starting Dose: 500 mg for—7 days, then increase to BD and then 500 mg every 2–4 weeks to 1.5 g BD is reached.

MMF is commonly used in synergistic and safe combination with CsA and glucocorticoids. MMF is commonly used with systemic corticosteroids as adjuvant therapy. The full therapeutic effect of MMF, namely on antibody-mediated diseases, should not be expected until **2 or 3 months** after therapy initiation. The therapeutic and toxic profiles of MMF

have led this drug to be the substitute of azathioprine. MMF is slower acting than cyclosporine and corticosteroids. Most patients show improvement between four and eight weeks of starting therapy. The mean onset of initial improvement is 3.9 weeks. However, the drug should be discontinued if no improvement is seen by 8 weeks and complete control by 14 weeks. It is, however, a good alternative treatment to cyclosporine because it can be used safely for longer periods.

Uses

The uses of MMF (Table 8.5) lie in its appeal as a steroid-sparing agent and in its relative lack of toxicity. It is being increasingly used to treat rheumatoid arthritis. Its usage in dermatology is primarily off label (Hiller M et al., Zimmerman et al.) e.g. atopic dermatitis especially severe pediatric atopic dermatitis, second line treatment in patients with chronic urticaria (autoimmune or idiopathic) who are resistant to treatment with histamines and systemic glucocorticoids, and vesiculobullous diseases. MMF may serve as a possible alternative to CsA, especially in those patients with psoriasis, who have or are predisposed to renal dysfunction (Haufs MG et al., Grundmann-Kallmann et a.,). Because the use of MMF for a number of dermatologic diseases is off-label, there are no published dosing recommendations. However, in review

Table 8.5: Indications of MMF

Bullous	Cicatricial pemphigoid Epidermolysis bullosa acquisita Linear IgA bullous disease Pemphigus vulgaris
Vasculitis	Churg–Strauss syndrome Leukocytoclastic vasculitis (including Henoch–Schonlein purpura) Hypocomplementemic urticarial vasculitis Microscopic polyangitis Nodular vasculitis Polyarteritis nodosa Wegener's granulomatosis
Connective tissue disorders	Dermatomyositis Scleroderma Severe cutaneous lupus erythematosus
Dermatitis	Atopic dermatitis Chronic actinic dermatitis Dyshidrotic eczema Psoriasis
Others	Chronic urticaria Cutaneous Crohn's disease Lichen planopilaris Lichen planus Necrobiosis lipoidica Pyoderma gangrenosum Recurrent erythema multiforme Sarcoidosis

the published literature on the use MMF for dermatologic disease, effective dermatologic doses are similar to those recommended in transplant patients (Orvis AK).

a. Pemphigus/BP

Although MMF has been promoted as an effective corticosteroid-sparing agent in the treatment of pemphigus, the RCT do not always prove its superiority over other adjuvants.

A randomized, placebo-controlled non-blinded study compared MMF (2 g daily) plus prednisone, MMF (3 g daily) plus prednisone, and placebo plus prednisone in 75 patients with pemphigus vulgaris, did not demonstrate a significant difference in response rate at 52 weeks among the three groups. The patients on MMF (both doses), however, did show a more rapid and sustained response and received a lower cumulative prednisone dose (Beissert S, 2010).

A multicenter, non-blinded randomized clinical trial of 40 patients with pemphigus vulgaris and pemphigus foliaceus compared methylprednisolone plus azathioprine (2 mg/kg daily) and methylprednisolone plus MMF (2 g daily). Each group demonstrated similar efficacy, with more rapid onset of complete remission with azathioprine/methylprednisolone in 72% of patients at a mean of 74 days compared to 95% at a mean of 91 days in the MMF/methylprednisolone arm. Both had similar corticosteroid sparing effects and adverse events, with no significant difference between the rate of infections, nausea, vomiting, and elevated liver function tests (LFT) (Beissert S, 2006).

A comparison of azathioprine (2 mg/kg daily) plus methylprednisolone versus MMF (2 g daily) plus methylprednisolone again did not demonstrate any marked difference between the two drugs (Beissert S, 2007).

Drug Interaction

General mechanisms for drug interaction:
Two main mechanisms are recognized for drug interaction:

i. Interference with enterohepatic cycling and
ii. Competition with MPAG and other drugs for renal tubular excretion.

No significant interaction is seen with cyclosporine, co-trimoxazole, acyclovir, ganciclovir or combined oral contraceptive (Bullingham RES, et al.).

Special Considerations

MMF is pregnancy category-D drug. Two forms of effective contraception must be used before, during and at least

6 weeks after discontinuing therapy. Nursing mothers are advised to either stop nursing or halt medication. MMF metabolites have been found in the milk of rats given MMF, although human data are not yet available. (Manufacturer's recommendations).

Availability

MMF is available in 250 mg capsules, 500 mg tablets, 200 mg/mL oral suspension, and 500 mg vials for intravenous injection (Orvis AK et al.).

Side Effects

Common Side Effects

GI side effects (Bull C et al.): Nausea, vomiting, diarrhea, abdominal cramps; these are mild and lessen with continued treatment.

Leukopenia, nephrotoxicity and hypertension are seen occasionally. At times laboratory abnormalities are seen in the form of elevated hepatic transaminases and hyperbilirubinemia.

Uncommon Side Effects

Cutaneous infections (Orvis AK et al., Bull C et al.) in the form of herpes zoster or herpes simplex virus infections; herpes retinitis, cutaneous or systemic *Staphylococcus aureus* and fungal infections may be seen. Rarely red cell aplasia may be seen (Engelen W et al.).

MMF is teratogenic in animal studies (Tendron A et al.). However, reports in humans are few and the interpretation is made complex as these patients were on multiple drugs.

Monitoring

Baseline complete blood cell count, differential count and platelet count, kidney function tests, liver function tests and chest X-ray is desirable (Wolverton SE et al.).

While on treatment, CBC with differential continued weekly for the first month, biweekly for the second and third month, and then monthly through the first year of treatment.

BIBLIOGRAPHY

1. Allison AC, Eugui EM. Purine metabolism and immunosuppressive effects of mycophenolate mofetil (MMF). Clin Transplant. 1996;10(1 Pt 2):77-84.
2. Beissert S, Mimouni D, Kanwar AJ, et al. Treating pemphigus vulgaris with prednisone and mycophenolate mofetil: a multicenter, randomized, placebo-controlled trial. J Invest Dermatol. 2010;130:2041-8.

3. Beissert S, Werfel T, Frieling U, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. Arch Dermatol. 2007;143:1536-42.
4. Beissert S, Werfel T, Frieling U, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. Arch Dermatol. 2006;142:1447-54.
5. Buell C, Koo J. Long-term safety of mycophenolate mofetil and cyclosporine: a review. J Drugs Dermatol. 2008;7:741-8.
6. Bullingham RES, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. Clin Pharmacokinet. 1998;34(6):429-55.
7. Engelen W, Verpooten G, Van der Planken M, Helbert MF, Bosmans JL, De Broe ME. Four cases of red blood cell aplasia in association with the use of mycophenolate mofetil in renal transplant patients. Clin Nephrol. 2003;60:119-24.
8. Grundmann-Kollmann M, Mooser G, Schraeder P, et al. Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. J Am Acad Dermatol. 2000;42(5Pt1):835-7.
9. Haufs MG, Beissert S, Grabbe S, Schutte B, Luger TA. Psoriasis vulgaris treated successfully with mycophenolate mofetil. Br J Dermatol. 1998;138:179-81.
10. Heller M, Shin HT, Orlow SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. Br J Dermatol. 2007;157:127-32.
11. Kushari Bowalgaha, John O. Miners. The glucuronidation of mycophenolic acid by human liver, kidney and jejunum microsomes. British Journal of Clinical Pharmacology. 52, 605-9.
12. Laliberte J, Yee A, Xiong Y, Mitchell BS. Effects of guanine nucleotide depletion on cell cycle progression in human T lymphocytes. Blood. 1998;91:2896-904.
13. Orvis AK, Wesson SK, Breza TS, Church AA, Mitchell CL, Watkins SW. Mycophenolate mofetil in dermatology. J Am Acad Dermatol. 2009;60:183-99.
14. Srinivas TR, Herwig-Ulf MK, Kaplan B. Pharmacokinetic principles of immunosuppressive drugs. Am J Transplant. 2005;5:207-17.
15. Tendron A, Gouyon JB, Decramer S. In utero exposure to immunosuppressive drugs: experimental and clinical studies. Pediatr Nephrol. 2002;17:121-30.
16. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, Altman RB and Klein TE. Pharmacogenomics Knowledge for Personalized Medicine. Clinical Pharmacology & Therapeutics. 2012;92(4):414-7.
17. Wolverton SE. Comprehensive dermatologic drug therapy. Philadelphia: WB Saunders; 2001.pp.193-5.
18. Zimmerman et al. The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: Experience in 19 patients. J Am Acad Dermatol. 2012;66:767-70.

METHOTREXATE

It would be difficult to overstate the importance of methotrexate (MTX) in the contemporary management of

rheumatic disease, in particular, rheumatoid arthritis (RA) and psoriasis. The off label uses of the drug especially in dermatology make it one of the most important cytotoxic drugs in dermatology.

Classification

Antimetabolite, cell cycle specific (S phase).

Mechanism of Action (Box 8.1)

Because MTX is a folate analogue, it enters cells via a reduced folate carrier. Leucovorin competes with MTX for uptake using the same reduced folate carrier; however, folic acid enters cells via another group of transmembrane receptors called folate receptors (Ranganathan P, et al.) (Fig. 8.8).

MTX efflux occurs via members of the adenosine triphosphate–binding cassette (ABC) family of transporters, especifically ABCC1-4 and ABCG2. Genetic polymorphisms may affect MTX transporter proteins (influx and efflux) and can result in a variable MTX response and toxicity profile. This can explain the multidrug resistance proteins that have

Box 8.1: Mode of action of methotrexate

Anti-inflammatory effects	Endothelial cell Counterregulation of neutrophils and dendritic cells Cytokine modulation of monocytes and macrophages Suppresses interleukin (IL)-12, tumor necrosis factor (TNF)- α, IL-6, IL-8, macrophage inflammatory protein–1 α, leukotriene B4 Increases Anti-inflammatory mediators
Collagen	Inhibition of the synthesis of collagenase
Immunological Response	Shift from a T helper type 1 to a T helper type 2 response MTX increases anti-inflammatory T helper type 2 cytokine (IL-4 and IL-10) gene expression and decreases proinflammatory T helper type 1 cytokine (IL-2 and interferon- γ)
Cardiovascular effects	Negative inotropic and chronotropic effect Inhibition of vascular smooth muscle cell proliferation Presynaptic inhibition of sympathetic neurotransmitter release, Inhibition of thrombocyte aggregation.
Prostaglandins	(Inhibits) leukotriene B4, Thromboxane B2, activity and prostaglandin E2, inhibitory effect on neutrophil chemotaxis
Miscellaneous	(Inhibits) metalloproteinase-1 (MMP-1) and stromely-sin, upregulate expression of tissue inhibitor of metal-loproteinase-1 (TIMP-1)

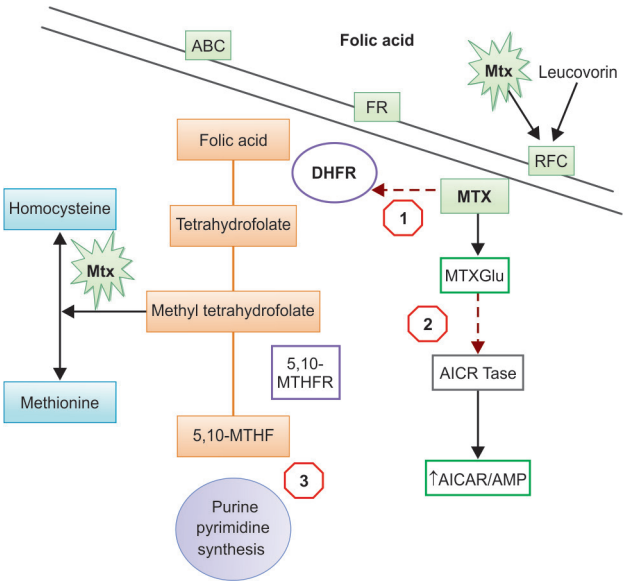


Fig. 8.8: After folic acid has entered the cell, it is sequentially transformed to di- and tetra-hydrofolate through the enzyme dihydrofolate reductase. Tetrahydrofolate is connected to 5,10-methylenetetrahydrofolate (5,10-MTHF) through the enzyme 5,10-MTHFR, which plays an important role in the homocysteine–methionine metabolism, purine synthesis and the production of deoxythymidylate.
On the other hand, after methotrexate has entered the cell, it inhibits *dihydrofolate reductase* (1) thus interfering with purine and pyrimide synthesis. In its polyglutamated form, it also inhibits the enzyme *amino-imidazole-carboxamide-ribonucleotide transformylase* (2), leading to accumulation of adenylate and adenosine, which further exerts anti-inflammatory effects by binding to adenosine receptors (3)
Abbreviations: AICAR, Aminoimidazole-carboxamideribonucleotide; CO, Cobalamine; dTMP, Thymidine monophosphate kinase; MS, Methionine synthase; MTC, Methyl cobalamine; MTHFR, Methylene tetrahydrofolate reductase; MTX, Methotrexate; TS, Thymidyl synthase; RFc, Reduced Folate carrier

been identified that transport MTX, folic acid, and leucovorin out of cells, leading to MTX resistance (Chen Z et al.).

1. Methotrexate binds intracellularly to *dihydrofolate reductase (DHFR)*, preventing the reduction of folic acid metabolites (dihydrofolate to tetrahydrofolate) and inhibiting the *thymidylate synthesis*. Methotrexate polyglutamates further inhibit thymidylate synthase aminoimidazole-carboxamide ribonucleotide (AICAR) transformylase. This inhibits purine synthesis.
2. Methylation of homocysteine to methionine is inhibited, affecting the synthesis of polyamines such as spermidine and spermine. Methotrexate may directly inhibit epidermal cell proliferation by these mechanisms, although lymphoid and macrophage cell lines have been shown to be much more susceptible to the growth inhibitory and cytotoxic effects of methotrexate than epidermal cell lines.

3. Inhibition of *AICAR transformylase* leads to increase in intracellular AICAR, with increase in adenosine and has an anti-inflammatory action. This includes inhibition of polymorphonuclear chemotaxis and adherence and inhibition of secretion of TNF alpha, IL-6, and IL-8 by monocyte/macrophages.
4. Ultimately, adenosine leads to the resolution of inflammation by downregulating macrophage activation and promoting a shift from a T helper type 1 to a T helper type 2 response.

Absorption and Distribution

Orally administered MTX is absorbed via the gastrointestinal tract and passes through the liver via the portal vein, whereas *parenterally* administered MTX passes through the liver via the hepatic artery. The parenteral route should have diminished potential for hepatotoxicity, and this effect has been seen in a retrospective study, in which there were more elevations in transaminases when oral MTX was administered to the same patients versus when given parenterally (Wegrzyn J et al.). Absorption is *not* reduced by concomitant *food* intake except for milk, which may be inhibitory, but absorption may be reduced in the setting of intestinal pathology, such as inflammatory bowel disease.

MTX can be administered *orally or parenterally* (subcutaneous or intramuscular), and absorption is rapid, peaking at 1 to 2 hours (oral administration) and 0.1 to 1 hour (parenteral administration). The absorption rates of low-dose oral and parenteral MTX (<15 mg/week) are roughly equivalent, but when the oral dose *exceeds* **15 mg/week,** absorption diminishes by 30%. Polyglutamate derivatives are formed intracellularly and are the principal bioactive metabolites that are long lasting. Hepatic oxidation forms 7-hydroxy-methotrexate, a minor metabolite. Serum half-life is 6 to 7 hours for the methotrexate, but much longer for the polyglutamate derivatives (10–27 hours)
Onset of Action: moderately rapid (2–4 weeks).

Metabolism

It has a *triphasic* metabolism. The first phase occurs rapidly (0.75 hour), the second phase (2–4 hours) is due to renal excretion while the third phase represents the terminal half-life and varies between 10 and 27 hours. Approximately 50% of MTX is bound to plasma proteins, and the active portion of the drug is the free fraction (unbound) in the plasma. Excretion is by the kidney, with 80% of a dose eliminated unchanged within the first 12 hours. Enterohepatic recirculation occurs to a minor degree.

Uses (Box 8.2)

FDA Approved

Psoriasis

The anti-psoriatic effects of methotrexate were first recognized in the late 1950s and 1960s, and by the late 1980s, more than one-half of dermatologists reported using methotrexate to treat severe psoriasis. A reasonable expectation of oral methotrexate efficacy is that approximately **40%** will achieve *PASI 75*. The advent of pharmacogenomics and identification of gene polymorphisms conferring a better response to methotrexate may facilitate patient screening and increase the percentage achieving optimal control, once such testing becomes more readily available (Hebert HL).

Response: 75–80% of patients respond within **1–4** weeks. Maximum effect by **2–3** months ideal dose for response is **15–20** mg/weekly.

MTX therapy can also improve psoriatic arthritis and is FDA approved for use in conjunction with TNF-α antagonists. There are two methods of giving Mtx.

Box 8.2: Uses of methotrexate in dermatology

FDA Approved	Psoriasis Sezary syndrome	15–20 mg/week 10–25 mg/ week
Off label		
Papulosquamous	Pityriasis rubra pilaris PLEVA Reiters	Not very effective 2.5–5 mg /week 20–30 mg/week
Bullous	Pemphigus vulgaris Bullous pemphigoid Cicataricial pemphigoid EB acquisita	2.5–30 mg/week 15–25 mg/week Not very effective Note very effective
Vasculitis	Leukocytoclastic vasculitis Cutaneous polyarteritis nodosa Behcets disease Pyoderma gangrenosum	15 mg/week 2.5–15 mg/week 15 mg/week
Connective Tissue Disorders	Dermatomyositis SLE /Subacute LE Scleroderma/Morphea	30–35 mg/week 10–30 mg/week 15–20 mg/week
Dermatitis	Atopic dermatitis	7.5–12 mg/week
Others	Sarcoidosis Keloids Lymphomatoid papulosis MF CIU	5–15 mg/week Not very effective 25 mg/week 25 mg/week 10–15 mg/week

1. **Weinstein and Frost Regimen:** Divided weekly oral dosage schedule.
   Based upon cell-cycle kinetic studies, this schedule was proposed by Weinstein and Frost. MTX is given in three doses at 12-h intervals once weekly. A total weekly dose of 15·mg had been recommended with adjustments up to 22.5 mg to increase efficacy, and lowering dosages according to toxicity. Most clinicians initiate dose at recommend 7.5 mg weekly. The complete blood cell count is checked for an idiosyncratic reaction before the next dose is given.
   Initial dose: 7.5 mg/week
   Dose escalation: This dose is continued *weekly* for one month. The dose is increased by **2.5 mg** per week each month after complete blood cell (CBC) counts and other tests are performed as indicated. The total dose needed usually does not exceed 30 mg weekly. 25 mg or less is sufficient for most, but doses up to 37.5 mg may be needed by a few patients. Beyond **15 mg,** there is a rationale for administering the injection *subcutaneously*.
   Dose reduction: After stability of residual psoriasis (or clearing) is attained, an attempt to taper the dose in *monthly 2.5 mg* decrements should be made. Increasing the interval between doses of MTX from 7 to 10 or 14 days serves the same purpose.
   Relapse: The psoriasis may be expected to relapse within weeks to months, depending on the type and severity of the disease. But there is no "rebound flare-up" of psoriasis as some believe, and there is no "resistance" to MTX when it is reinstated.
2. **Weekly oral single dosage:** Once a week, a single dose of MTX is administered orally. A total weekly dose of 25·mg has been recommended but some centers regard a dosage of 37.5 mg per week as safe. Dosages should be adjusted according to safety and efficacy.
3. **Intermittent weekly parenteral dosage schedule:** Once a week, a single dose of MTX is injected parenterally (IM or IV). In general, the intramuscular route is preferred. A starting dose of 15 mg MTX is common. The maximum dosage varies between different centers, but up to 50 mg weekly is regarded as safe.
   There is a range of methotrexate dosing regimens for psoriasis. The methotrexate start-dose in randomized controlled trials varied from **5 to 25 mg/week**, most commonly being either 7.5 mg or 15 mg. Guidelines vary from 5 to 15 mg/week. Methotrexate was administered as a *single dose or in a Weinstein schedule* in 15 and 11

treatment-groups, respectively; both recommended equally in guidelines. A fixed dose ($n = 18$), predefined dose ($n = 3$), or dose adjusted on clinical improvement ($n = 8$) was used, the last also being recommended in guidelines. Ten treatment groups used folic acid; in 2 it was allowed, in 14 not mentioned, and in 3 no folic acid was used. Most guidelines recommend the use of folic acid. Thus, though there are wide variation, though the efficacy rates do not markedly differ in the various regimens (***Menting SP***).

Off Label Use

For *dermatomyositis* and *neutrophilic* dermatoses MTX must be used in maximum weekly doses ranging from **25–35 mg** while for others doses from **10–25 mg** weekly will be adequate for a satisfactory clinical response. Monitoring techniques for these patients differs from the adult psoriasis guidelines only by *not* recommending repeated liver biopsies when liver-derived enzymes remain normal.

1. **Atopic dermatitis:** 7.5–12 mg PO weekly.
2. **Behçet's disease:** 2.5–15 mg PO weekly.
3. **Bullous pemphigoid:** 2.5–30 mg PO weekly.
   Doses between 7.5 and 12.5 mg weekly are sufficient in most with topical clobetasol. Kjellman found that MTX, even without prednisone was found to help with a high rate of remission after 2 years of stopping therapy.
4. **Chronic urticaria:** The required dose to achieve a steroid-sparing effect is 10-15 mg weekly. This may be useful as a treatment for steroid-dependent chronic urticaria.
5. **LE: 10–30 mg PO weekly:** MTX has been reported to be effective in the treatment of cutaneous lupus erythematosus, both subacute and chronic. Wenzel, et al. used IV MTX in 43 patients with 'recalcitrant' cutaneous lupus erythematosus with favorable results. Probably subcutaneous administration is equally effective (Huber A).
6. **Lymphomatoid papulosis:** The dose given is 25 mg or less given at 1 to 4 week intervals for up to several years.
7. **Inflammatory myopathies:** The dose required is higher than that required for psoriasis or RA is (30–35 mg weekly). The average dose required is 25 mg weekly. Pulmonary involvement may also respond to MTX therapy. Overall 75% of cases respond to methotrexate.
8. **Pityriasis rubra pilaris:** PRP does *not* respond as well to Mtx than psoriasis. The doses necessary to control PRP are 1.5–2 times higher than those necessary for control of psoriasis. Some authors believe that a *daily* low-dose regimen rather than a weekly basis has a better response.

9. **Pityriasis lichenoides et varioliformis acuta:** This responds to low doses of MTX (as little as 2.5–5 mg weekly).
10. **Reiter's disease:** 20–30 mg PO weekly.
11. **Sarcoidosis (Vucinic V):** Prospective trials have shown that MTX is efficacious in treatment of corticosteroid-resistant multisystem sarcoidosis.
12. **Scleroderma**

    Morphea: 15–20 mg PO weekly.

    Kreuter, et al. have published studies where MTX in combination with corticosteroids, has been found to be useful in patients of widespread morphea and extragenital lichen sclerosus.
13. **Systemic sclerosis:** MTX has been used in systemic sclerosis. One randomized controlled trial looked at MTX use in early systemic sclerosis and showed a trend for benefit in skin scores and pulmonary diffusion capacity and a significant benefit for physician global assessment (Pope J et al.). A second randomized controlled trial in established systemic sclerosis showed significant benefit in improving skin scores and total creatinine clearance (van den Hoogen F).
14. **SLE (Carneiro J et al.; Sato et al.):** MTX has been shown to be efficacious in controlling cutaneous and articular manifestations of systemic lupus erythematosus (SLE), particularly in disease *resistant* to antimalarials or requiring high doses of systemic steroids. Concomitant folic acid should be administered to abrogate the elevated levels of homocysteine that may be a side effect of MTX therapy, and is considered a risk factor for cardiovascular disease in SLE. The role of MTX in treating more severe SLE involvement, including renal, hematologic, or central nervous system disease, has not yet been established. Extreme caution should be employed in renal disease.
15. **Vasculitis**

    Leukocytoclastic vasculitis: 15 mg IM weekly.

    MTX in conjunction with corticosteroids has shown efficacy in treating early and non–life-threatening Wegener's granulomatosis, including upper airway disease and mild renal disease. It is also used in corticosteroid-resistant Takayasu's arteritis and relapsing polychondritis.
16. **Cardiovascular inflammation reduction:** One of the most interesting and important aspects about mtx is that it is known to inhibit TNFα which is one of the cytokines

that mediate the process of atherosclerosis. Both observational and mechanistic studies suggest that low-dose methotrexate has clinically relevant *antiathero-thrombotic* effects.

An ongoing trial, the Cardiovascular Inflammation Reduction Trial (CIRT) (ClinicalTrials.govNCT01594333) will randomly allocate 7,000 patients with prior myocardial infarction (MI) and either type 2 diabetes or the metabolic syndrome to low-dose methotrexate (target dose 15–20 mg/week) or placebo over an average follow-up period of 3 to 5 years. Low-dose methotrexate is a commonly used anti-inflammatory regimen for the treatment of rheumatoid arthritis and lacks significant effects on lipid levels, blood pressure, or platelet function. If low-dose methotrexate reduces cardiovascular events, CIRT would provide a novel therapeutic approach for the secondary prevention of heart attack, stroke, and cardiovascular death. The take home message is that in dermatology, the rapid onslaught of biologicals, with their short-term side effect profile, should not detract dermatologists from prescribing Mtx which still remains the most cost-effective therapy for psoriasis, with probably added benefits! (Everett BM).

Dosage

Methotrexate is given orally but can be administered subcutaneously or intramuscularly, if there is gastrointestinal intolerance. Typical oncologic doses of methotrexate (100 to 250 mg/m^2/week) are cytotoxic; however, lower doses (7.5 to 25.0 mg/week) are immunomodulatory. In dermatology, methotrexate doses are typically less than 30 mg/week, and are often less than 17.5 mg/week. Cumulative dose must be tracked and recorded, as this impacts monitoring during continued use.

MTX is available as 2.5-mg, 5-mg, 10-mg, and 15-mg tablets, and as a solution of 25 mg/mL, for subcutaneous or intramuscular injection. For those with economic limitations, methotrexate liquid (25 mg/mL) may be more affordable for peroral use.

Dose

a. **Initial:** Methotrexate is commonly given either as a single weekly dose or in three divided doses over 36 hours. Usual dosages are from 5 to 10 mg/m^2 per week (7.5 to 25 mg/week). Ideally a test dose of 5–10 mg is given, and a CBC and liver function tests are taken 6–7 days later.

b. **Increase in dose:** The dosage of MTX can be titrated, and after giving it at 5–10 mg/week it can be raised every 4 to

8 weeks to 25 mg/week, to achieve the desired clinical response. Though the two methods of administration are equally effective and have similar toxicity, the simplicity of a single weekly dose, makes it the most logical dosing scheme.

Parental methotrexate has been found to have a better efficacy (Hamilton RA) and a higher bioavailablity (Hoekstra M, 2004). In case a dose >30 mg a week is given, it can be split in a 12 hourly dose (Hoekstra M, 2006). Thus, a trial of parenteral MTX is generally recommended if patients have active disease despite oral doses of approximately 20 mg/week.

The use of either folic acid (1 to 5 mg/day) or folinic acid (leucovorin, 2.5 to 5 mg, 24 hours after the methotrexate) has been advocated to reduce hematotoxicity and hyperhomocysteinemia and is indicated in patients who develop macrocytosis The decrease in hyperhomocysteinemia may be important to help decrease the cardiovascular risk in patients.

c. **Tapering:** The dose is gradually escalated (2.5–5 mg/week) to a level that provides reasonable benefit without noticeable toxicity. When maximal benefit is reached, the MTX may be tapered by 2.5 mg/week to determine the lowest possible dosage that maintains disease control. The goal is to allow mild or low-grade psoriasis activity and to avoid an unacceptably high dose. It is important to discuss this expectation with the patient to prevent confusion regarding the endpoint.

   Patients receiving intramuscular or intravenous MTX are able to tolerate higher doses because of more rapid renal clearance. For patients treated with intramuscular MTX, it may be more convenient to taper by increasing the *interval* between doses to 2 weeks or more.

d. **Folic acid:** Folate and folinic acid supplementation

   Daily supplementation with 1 to 5 mg of folate reduces nausea, vomiting, stomatitis and oral ulceration, elevated transaminases, and mild myelosuppression without compromising the efficacy of methotrexate. But *liver fibrosis, pneumonitis, and moderate to severe myelosuppression* are *not* mitigated by folate supplementation. Elevated homocysteine levels, common with methotrexate use and an independent risk factor for coronary artery disease, is decreased with folate supplementation. One drawback to folate supplementation is the potential masking of vitamin B_{12} deficiency.

   Recent literature have focused on the dose of folidoced. The first study examined the concomitant use of folic/folinic acid opined that though it is useful, low-dose folic

or folinic acid (a starting dose of ≤7 mg weekly) is enough as the high dose is no longer recommended or used. (Shea B) A second study (Dhir V), found that even with the high doses of MTX used in current practice, there was no additional benefit (or harm) of a higher dose of folic acid (30 mg/week) over a usual dose (10 mg/week). Thus, *7–10 mg per* **week** should be enough to mitigate the side effects of methotrexate.

Drug Interaction

Drugs that Cause Hepatic Damage

Drugs that are known hepatotoxins, such as SSZ, leflunomide, azathioprine, acitretin, leflunomide, alcohol may potentiate liver toxicity when used in combination.

Drugs that cause Renal Damage

Organic acids, such as sulfonamides, salicylates, NSAIDs, penicillin G, piperacillin, and probenecid, competitively inhibit tubular secretion, which delays MTX clearance. MTX also undergoes distal tubular reabsorption, which may be enhanced by the addition of HCQ and blocked by the addition of folic acid. Drugs that affect renal function should be used with caution because of the renal clearance of MTX and the increased risk of MTX.

Increase Levels of Methotrexate

Cyclooxygenase-2 inhibitors, non-steroidal anti-inflammatory drugs, sulfonamides, salicylates, probenecid, penicillins, trimethoprim, dipyridamole, chloramphenicol, phenothiazines, phenytoin and tetracycline.

NSAIDs may increase MTX levels by displacing MTX from plasma proteins and limiting tubular secretion. Despite lack of a significant pharmacokinetic or clinical interaction between low-dose MTX and a variety of NSAIDs, (Skeith KJ) vigilance for MTX toxicity should increase whenever NSAID dosages are changed in patients on stable weekly doses of MTX. Low doses of aspirin used for cardiovascular prophylaxis is not likely to be of any great concern and can be continued.

Increased Risk of Blood Dyscrasias

Lamotrigine.

Increased Hematologic Toxicity

Trimethoprim, sulfonamides, leflunomide, dapsone.

Trimethoprim-sulfamethoxazole should be avoided or used with extreme caution because of possible hematologic

toxicity with MTX. This is because of (a) an additive antifolate effect from trimethoprim, (b) decreased MTX clearance owing to inhibition of tubular secretion by sulfamethoxazole, and (3) altered MTX plasma protein binding.

Special Considerations

Although not prospectively studied in RA patients receiving long-term MTX treatment, the parenteral route should have diminished potential for hepatotoxicity, and this effect has been seen in a retrospective study, in which there were more elevations in transaminases when oral MTX was administered to the same patients versus when given parenterally (Wegrzyn J et al.).

Advice to Patient

- Use two forms of birth control including hormonal and barrier methods. It is suggested that conception should be avoided for *3 months* in males and one ovulatory cycle in females.
- Avoid alcohol.
- Avoid aspirin-containing products and all NSAIDs when taking this drug.
- Receive vaccinations (particularly live attenuated viruses) only with permission from treating physician. It is important to consider vaccination status in any patient who is going to use MTX. RA patients have an increased incidence of death from pneumonia, and MTX may reduce the immune response to pneumococcal antigen. Any patient in whom MTX is going to be used should first receive the pneumococcal vaccination. Any patient already on MTX should not receive live virus vaccinations because they are at increased risk for vaccine-induced infections.
- Use good mouth care to prevent infections of the oral cavity.
- Maintain adequate fluid intake.

Side Effects

Gastrointestinal

Nausea and vomiting are the most frequent adverse effects and are dose-related. Diarrhea and stomatitis may also occur. Folic acid administration, dose-splitting, and parenteral administration may control symptoms. Even though there are reports that suggested that folate supplementation led to reduced efficacy in psoriasis (Salim A, Chladek J) patients

and a leading textbook (Callen JP) suggests not giving folic acid we continue to suggest its use as there are instances of patients mistakenly taking methotrexate daily, which can have fatal consequences without folic acid supplementation.

Hematologic

Cytopenia occurs in 10 to 20% of patients on long-term methotrexate for psoriasis and manifest as either leukopenia, thrombocytopenia, or pancytopenia.

The weekly dose is safer as the cells most susceptible to the higher drug levels attained with daily dosing are those that have the most rapid division which are the hematologic precursor cells. Thus, the commonest cause of marked hematological toxicity is in patients who inadvertently take MTX on a daily basis.

Other *risk factors* include renal insufficiency, increased mean corpuscular volume, older age, concomitant use of trimethoprim-sulfamethoxazole or nonsteroidal anti-inflammatory drugs (NSAIDs), albumin <3 g/dL and major illness.

Hepatic

Hepatotoxicity is a major concern, with a 7% overall risk of severe fibrosis/cirrhosis in psoriatics but an apparent lower incidence in patients with rheumatoid arthritis.

Risk factors include age, total dose, obesity, *heavy* alcohol intake, diabetes, and daily dosage. Reports of severe fibrosis continue to be published and fibrosis may occur in spite of serial normal liver function tests.

Studies have shown that the clinical course of the cirrhosis induced by MTX is often *non-aggressive*. Remarkably a majority of patients in a study continued MTX therapy without a deterioration in their liver histopathology (Zachariae H, 1980). As in psoriasis a *rotational therapy* is followed by most clinicians a patient with abnormal liver biopsy may with time experience a *reversal* of this pathology while off MTX therapy (Newman M). In theory, at least they may be reinstituted with MTX therapy. Aithal and colleagues recently reported their analysis of 121 liver biopsies with psoriasis and concluded that advanced hepatic fibrosis is very *infrequent*, and further that routine use of serial liver biopsies had little impact on the care of these patients. Thus, the guidelines for liver biopsy have been relaxed as given below (Boxes 8.3 and 8.4).

It has been suggested that serial biopsies may *not* be required in the absence of abnormal liver function tests if the initial biopsy is normal, or if the weekly dose is 15 mg or less. Thus, it appears that the risk of liver damage is low for patients whose cumulative dosage is <1.5 g.

Box 8.3: Indications of Pretreatment liver biopsy

Family history of liver disease
History of exposure to known hepatotoxins, including alcohol or intravenous drugs.
Patients with diabetes or obesity.
Abnormal baseline liver function tests or serologic tests for hepatitis
A general rule estimation to calculate the time required to achieve 1.5 g which is the cut off for liver biopsy can be determined by dividing the number '12' by the number of 2.5 mg capsules of MTX taken weekly (4 × 2.5 mg capsules weekly (10 mg), interval between liver biopsies is 12/4 = 3 years)

Box 8.4: Rationale against pretreatment liver biopsy in patient on MTX

Not all patients respond to MTX
Some patients cannot tolerate the drug even at low doses
Long-term MTX may not be required after an impressive early response
MTX <1.5 g risk of damage is low
At a dose of 4.5 g without risk factors, there is a low incidence of side effects
Alcohol intake without Risk factors risk of liver damage is 3% (>100 g/ week)
Liver cirrhosis is non-aggressive
On stopping MTX the liver changes are reversible

There are many situations in which *pretreatment liver biopsy* may *not* be necessary as not all patients may respond to or tolerate methotrexate (Box 8.4). Moreover some have such impressive results that do not require the drug again. Although MTX cumulative doses at or above 4.0 g have been traditionally considered risky for liver fibrosis and cirrhosis, if careful patient selection to avoid important risk factors (renal insufficiency, diabetes mellitus, obesity, and excessive alcohol intake) is done this risk can be lowered even at high doses (Boffa MJ, Van Dooren-Greebe RJ, Malatjalian D). Even the oft-believed fact that alcohol intake and MTX is associated with an increased risk of hepatotoxicity (Price S) has been modified by the suggestion that that in the *absence* of other risk factors, (diabetes, obesity, hepatitis C, psoriasis, and lack of folic acid supplementation), the risk of severe liver disease is roughly 3% if alcohol intake is **>100 g** per week (approximately 10 glasses of wine or spirits).

1. Thus in patients *without* any risk factors for hepatic toxicity who reach a cumulative dose of 3.5 to 4.0 g of oral MTX in the presence of *normal* liver chemistry test results, three options are suggested: a) performing a liver biopsy, b) continuing to monitor without a liver biopsy, or c) switching to an alternative therapy if possible (Kalb RE). Probably a switch to an alternative therapy is a feasible option than inflicting a liver biopsy on the patient.

2. In patients *with* one or more risk factors for hepatic toxicity, more stringent monitoring is necessary if another systemic agent is contraindicated. This entails a liver biopsy soon after onset of therapy, preferably *after* **2 to 6 months** to avoid unnecessary biopsies in those who do not tolerate the drug or show a lack of response, with repeated biopsies after every 1.0 to 1.5 g of oral MTX. Continuation or discontinuation of MTX is based on liver biopsy findings and the recommendations proposed by Roenigk, et al. can be followed in this regard (as below):
   - Patients with grade I or II changes may continue to receive MTX therapy.
   - Patients with grade IIIA changes may continue to receive MTX therapy, but should have another liver biopsy after approximately 6 months of continuous therapy.
   - Patients with grades IIIB and IV should not be given further MTX except in exceptional circumstances,

   There are *no* dosage guidelines for liver biopsy after *subcutaneously* administered MTX (Kalb et al.).

Noninvasive tests: Based on various non-invasive tests, Zachariae (2000) made a strong plea to consider using tests such as ultrasound, dynamic radionuclide scans, and the PIIINP assay to at least *reduce* (not eliminate) the number of liver biopsies required for patients on MTX therapy.

Hepatic ultrasound, is hampered by the inability to discriminate fat from fibrosis. Radionuclide scans and the aminopyrine breath test are inadequate to screen for hepatotoxicity due to MTX. The monitoring of serum levels of the aminoterminal peptide fragment of type III procollagen may also prevent the need for a liver biopsy in patients on long-term MTX therapy but this test is available in Europe but not in USA or India. The key limitation of PIIINP assessments is the lack of *site specificity* as to which organ is undergoing fibrosis; thus, this test is not reliable in patients with significant psoriatic arthritis.

Oncogenic Potential

Methotrexate has been shown to be a significant independent risk factor (relative risk of 2.1) for patients to develop squamous cell carcinoma in severe psoriatics. Two patients with mixed-cellularity Hodgkin's disease have been reported in association with methotrexate use for psoriasis. Recently, an Epstein-Barr virus-associated lymphoproliferative disorder has been documented in a psoriatic on methotrexate. Contrary to cyclophosphamide and azathioprine, methotrexate has generally not been associated with an overall increased risk of lymphoma.

Reproductive Toxicity

Methotrexate is a known abortifacient and teratogen but its effects are much less than the alkylating agents. MTX does not seem to affect female fertility adversely, but can cause reversible sterility in men. A recent study revealed no congenital malformations or increase in spontaneous abortions in 42 pregnancies involving 40 men treated with MTX 7.5–30 mg/week at the time of conception (Beghin D).

In spite of the above facts a delay of at least **12 weeks** between drug discontinuation and conception in women is advised. Conception should be avoided during therapy and 3 months afterward by couples in which the male is on the drug.

Opportunistic Infections

Opportunistic infections are reported in patients on low-dose methotrexate, and are seen more commonly in patients with rheumatoid arthritis than in patients treated with azathioprine, cyclophosphamide, or cyclosporine. Live vaccines should not be administered to patients on methotrexate.

Pulmonary Side Effects

Five clinical pulmonary syndromes have been associated with MTX treatment: acute interstitial pneumonitis (hypersensitivity pneumonitis), interstitial fibrosis, noncardiogenic pulmonary edema (seen in high-dose treatment for malignancy with rare reports in RA), pleuritis and pleural effusions, and pulmonary nodules.

Time lapse from initiation of therapy and cumulative dose before the onset of pulmonary toxicity varies from 1 to 480 weeks and 7.5 to 3600 mg of MTX (Canon G). MTX-induced pulmonary disease is rare and difficult to quantify, but factors that seem to predispose to MTX lung toxicity include age, blue-collar occupation, smoking (in women), diabetes, pleuropulmonary rheumatoid disease, and skin rashes from MTX.

Routine screening chest X-ray studies and pulmonary function testing are not useful in the detection or prevention of pulmonary toxicity. Luckily, this toxicity is rarely reported in psoriasis patients (Phillips TJ).

Miscellaneous

Methotrexate flu: Patients taking MTX may describe flu-like symptoms shortly after taking their weekly dose. Nausea, low-grade fevers, myalgias, and chills are the most common signs of so-called methotrexate flu. These side effects usually

respond to supplementing with folic acid, decreasing the dose, switching from oral to parenteral administration, or changing the time of the dose (so that the patient takes MTX right before going to bed).

Cutaneous

Anaphylactoid reactions have been reported after low-dose methotrexate and can occur during initial exposure. Alopecia, hyperpigmentation, UV burn recall, and toxic epidermal necrolysis have also been reported. Other rare reactions include acral erythema, a papular eruption, vasculitis and painful erosion of psoriatic plaques. The last side effect has recently been re-emphasized as a cutaneous sign of methotrexate toxicity and usually occurs with an alteration in methotrexate dosage and concomitant use of NSAIDs.

Skeletal

Low-dose methotrexate may contribute to the development of stress fractures of long bone.

CNS

CNS toxicities including headaches, dizziness, fatigue, and mood alterations may occur.

CVS

It has been suggested that increased levels of homocysteine complicate long-term, low-dose MTX therapy and can be lowered by concomitant use of folic acid. Higher levels of homocysteine in the serum have been associated with increased potential for cardiovascular disease in general.

Monitoring

A set of guidelines published by the American College of Rheumatology (ACR) provides excellent recommendations for starting and monitoring MTX therapy (Box 8.5).

What to Monitor?

Toxicities that require monitoring include *myelosuppression, hepatotoxicity,* and *pulmonary toxicity*.

Baseline Evaluation

Blood Tests

Baseline evaluation should include a complete blood count with platelets, chest radiograph within the past year, hepatitis B and C serology in high-risk patients, aspartate

Box 8.5: Monitoring for methotrexate

Baseline	Follow up	Interval/Duration
CBC platelet count	Yes	Ideally 7 days after the first dose Then 2 weekly for first 4 weeks and then 3–4 monthly
LFT	Yes	Weekly for first one month; then 3-4 monthly Test after dose escalations
KFT	Yes	6 monthly
Hepatitis B /C HIV CXR		
Liver biopsy (Kalb et al.)*		
	Without any risk factors 3.5 to 4.0 g *With risk factors* Delayed baseline at 2 to 6 months after starting therapy Every 1.0 to 1.5 g	

*In non-psoriatic patients it can be avoided except in cases sarcoidosis; in case of risk factors alternative drug may be used

aminotransferase (AST) or alanine aminotransferase (ALT), albumin, and creatinine.

If the white blood cell count (WBC) is <3500/mm^3, the platelet count is <100 000/mm^3, or there is an increase over **twice** the upper normal value for liver transaminase levels, discontinue or reduce the dosage of MTX. If the laboratory abnormality has resolved the drug may be restarted at a lower dose after a 2–3-week rest.

Liver Biopsy

Liver biopsy before initiating MTX is not routinely recommended. In the rare patient whom the clinician wants to treat with MTX *despite* abnormalities in screening laboratory or other significant risk factors, liver biopsy may be required before starting MTX. In addition, biopsy is recommended only in patients who continue to have enzyme abnormalities and for whom continuation of MTX therapy is contemplated. Monitoring for toxicity should be done every 4 to 8 weeks.

It is reasonable to suggest that a possible 'middle ground' might exist, as follows. If a given patient has had two consecutive liver biopsies (grade II changes at most) at traditional intervals, it seems very reasonable to alternate a non-invasive test of liver structure and/or fibrosis (liver scan, PIIINP—where available—or ultrasound) with a liver biopsy. The net effect of alternating these tests is that after two normal liver biopsies (grade II changes only), the occasional patient on very long-term MTX therapy would have a liver

biopsy every 3.0 g of MTX, and undergo a non-invasive test for hepatotoxicity half-way between liver biopsies.

Clinical Evaluation

Systems review and physical examination should include monitoring for symptoms or signs of myelosuppression (fever, infection, bruising, and bleeding), pulmonary toxicity (shortness of breath, cough, rales), gastrointestinal intolerance (nausea, vomiting, diarrhea), and lymphadenopathy.

Methotrexate Toxicity

The most likely clinical scenarios that may result in overdosage requiring intervention are as follows:

1. A noncompliant patient increases his or her own dose deliberately to improve efficacy or rate of response. The patient may complain of burning or ulceration of psoriasis lesions.
2. A patient develops acute renal failure or an unrelated acute illness with dehydration without reducing the dose of MTX. This is usually revealed by routine laboratory monitoring or leukopenia.
3. The patient is given another drug that increases the serum level of MTX or prolongs the excretion of MTX, thereby increasing the toxicity of MTX. Trimethoprim-sulfamethoxazole is frequently the "other drug."

Management: Leucovorin calcium (citrovorum factor, folinic acid) can bypass the metabolic block produced by MTX and supply the active form of folic acid that cells require. Leucovorin should be readily available must be given as promptly as possible, preferably **within 4 hours** of the last dose of MTX. As the time interval between MTX and leucovorin administration increases, the effectiveness of leucovorin as an antidote diminishes so that, by 24 hours, it is doubtful that leucovorin will have any effect except in patients with severely depressed creatinine clearance.

In general, if an overdose with MTX is suspected, the clinician should give an intramuscular injection of leucovorin *equal to* the **last dose of MTX** or **25 mg**, whichever is greater (Box 8.6). Then blood is sampled to assess hematologic and kidney function parameters and MTX level. In patients with renal impairment, the leucovorin dosing is repeated every 6 hours until the MTX level is 0.1 micromolar or less. Neither hemodialysis nor peritoneal dialysis improve MTX elimination. The patient with dehydration should be rehydrated with normal saline and observed. In patients

Box 8.6: Rescue dose (within 24 hours of methotrexate treatment)

Doses should be given within 24 hours of last dose of methotrexate. Most effective if given within 1 hour of overdose
PO or IV 10 mg/m ^{2}q6h until serum methotrexate is 10 $^{-8}$M
A rough method of administration is giving *methotrexate-equivalent doses* ***up to*** 75 mg q6 h for 4 doses. A delay of >36 h lessens the chance of rescue

with massive overdosage, admission to a hospital is justified for leucovorin rescue. Alkalinization of the urine prevents precipitation of MTX in the renal tubules. G-CSF infusion should be considered if severe neutropenia develops.

Special Groups

Pregnancy

Category X.

Lactation

Contraindicated.

Liver Failure

- Moderate decrease in dosage may be required.
- Bilirubin 3.1–5.0 mg/dL or AST >180 units:75% of standard dose
- Bilirubin >5 mg/dL: contraindicated. Avoid if evidence of severe hepatic dysfunction.

Kidney Failure

Relatively contraindicated, significant dose reduction necessary

When creatinine clearance is 61 to 80 mL/min, dose is reduced by 25%; 51 to 60 mL/min, dose is reduced by 30%; 10 to 50 mL/min, dose is reduced by 50 to 80%; and less than 10 mL/min, use of MTX should be avoided.

Children

Dadlani and Orlow, reviewed its use in children and suggest that it may be safely used for psoriasis, atopic dermatitis, pemphigus, lupus erythematosus, dermatomyositis, and localized scleroderma. They also suggest that monitoring follow the guidelines developed by pediatric rheumatologists.

Dose MTX at a dose of 10 mg/m ^{2} was superior to 5 mg/m ^{2} or placebo in juvenile idiopathic arthritis. In psoriasis, a dose of **0.3-0.4 mg/kg** can be administered *weekly*.

Elderly

Patients older than 65 years represent a special subset of patients receiving pharmacotherapy. This is as pharmacokinetic profiles change in the elderly, including drug distribution owing to decreases in end-organ blood flow and lean body mass, decreased hepatic drug metabolism, and decreased renal drug excretion.

Elderly patients are more likely to have multiple comorbidities, polypharmacy, noncompliance, increased risk for dosage errors, and limited access to medication for financial reasons. In practice, recommended doses should be reduced when initiating therapy and adjusted for renal function based on creatinine clearance. The serum creatinine may be a *misleading* measure of renal function in older patients because of an overall reduction in lean muscle mass.

Dosing recommendations are that initial doses should be around 5 to 7.5 mg/week and should not exceed 20 mg/week.

BIBLIOGRAPHY

1. American Academy of Dermatology Work Group, Menter A, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. J Am Acad Dermatol. 2011;65:137-74.
2. Callen JP, Kalp-Shorten CL. Methotrexate. Comprehensive Dermatologic Drug therapy. Ed SE Wolverton. 3rd Edn. Elseiver. 2013.
3. Dutz JP, Ho VC. Immunosuppressive agents in dermatology. An update. Dermatol Clin. 1998;16(2):235-51.
4. Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine, and Combination Therapies AMY C. CANNELLA • JAMES R. O'DELLKelly Textbook of Rheumatology 9th Edn.
5. Zachariae H. Methotrexate. Textbook of Psoriasis Edited by PCM van de Kerkhof. 2nd edn. 2003. Blackwell Science.

JOURNALS

1. Aithal GP, Haugk B, Das S, et al. Monitoring methotrexate-induced hepatic fibrosis in patients with psoriasis: are serial liver biopsies justified? Aliment Pharmacol Ther. 2004;19:391-99.
2. Beghin D, Courtnot M-P, Vauzelle C, Elefant E. Paternal exposure to methotrexate and pregnancy outcomes. J Rheumatol. 2011; 38:628-32.
3. Boffa MJ, Chalmers RJ, Haboubi HY, et al. Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. Br J Dermatol. 1995;133:774-8.
4. Cannon G. Methotrexate pulmonary toxicity. Rheum Dis Clin N Am. 1997;23:917-37.
5. Carneiro J, Sato E. Double blind, randomized, placebo-controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol. 1999;26:1275-9.
6. Chen Z, Lee K, Walther S, et al. Analysis of methotrexate and folate transport by multidrug resistance protein 4 (ABC4): MRP4 is a component of the methothrexate efflux system. Cancer Res. 2002;62:3144-50.

7. Chladek J, Simkova M, Vaneckova J, et al. The effect of folic acid supplementation on the pharmacokinetics and pharmacodynamics of oral methotrexate during remission-induction period of treatment for moderate-to-severe plaque psoriasis. *Eur J Clin Pharmacol*. 2008;64(4):347-55.
8. Clearfield M, Libby P, Hasan AA, Glynn RJ, Ridker PM. Rationale and design of the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis. Am Heart J. 2013;166(2):199-207.e15
9. Dadlani C, Orlow SJ. Treatment of children and adolescents with methotrexate, cyclosporine and etanercept: Review of the dermatologic and rheumatologic literature. J Am Acad Dermatol. 2005;52:316-40.
10. Everett BM, Pradhan AD, Solomon DH, et al. Comparison of two different folic acid doses with methotrexate – a randomized controlled trial (FOLVARI Study). Arthritis Res Ther. 2015;17:156.
11. Hamilton RA, Kremer JM. Why intramuscular methotrexate may be more efficacious than oral dosing in patients with rheumatoid arthritis. Br J Rheumatol. 1997;36(1):86-90.
12. He´bert HL, Ali FR, Bowes J, et al. Genetic susceptibility to psoriasis and psoriatic arthritis: implications for therapy. Br J Dermatol. 2012;166(3):474-82.
13. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol. 2004;31(4):645-8.
14. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Splitting high-dose oral methotrexate improves bioavailability: a pharmacokinetic study in patients with rheumatoid arthritis. J Rheumatol. 2006;33(3):481-5. Epub 2006 Jan 15.
15. Huber A, Tüting T, Bauer R, et al. Methotrexate treatment in cutaneous lupus erythematosus: subcutaneous application is as effective as intravenous administration. Br J Dermatol. 2006; 155(4):861-2.
16. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol. 2009;60:824-37.
17. Kjellman P, Eriksson H, B*erg P. A retro*spective analysis of patients with bullous pemphigoid treated with methotrexate. Arch Dermatol. 2008;144:612-6.
18. Kreuter A, Gambichler T, Breuckmann F, et al. Pulsed high-dose corticosteroids combined with low-dose methotrexate in severe localized scleroderma. Arch Dermatol. 2005;141(7):847-52.
19. Kreuter A, *Tigges C, Gai*fullina R, et al. Pulsed high-dose corticosteroids combined with low-dose methotrexate treatment in patients with refractory generalized extragenital lichen sclerosus. Arch Dermatol. 2009;145(11):1303-8.
20. Malatjalian D, Ross J, Colwell S, et al. Methotrexate hepatotoxicity in psoriatic patients submitted to long-term therapy. Can J Gastroenterol. 1996;10:369-75.
21. Menting SP, Dekker PM, Limpens J, Hooft L, Spuls PI. Methotrexate Dosing regimen for plaque-type psoriasis: A systematic review of the use of test-dose, start-dose, dosing scheme, dose adjustments, maximum dose and folic acid supplementation. Acta Derm Venereol. 2015 Feb 27. doi: 10.2340/00015555-2081.

22. Newman M, Auerbach R, Feiner H, et al. The role of liver biopsies in psoriatic patients receiving long-term methotrexate: improvement of liver abnormalities after cessation of treatment. Arch Dermatol. 1989;125:1218-24.
23. Perez A, Woods A, Grattan CE. Methotrexate: a useful steroid-sparing agent in Phillips TJ, Jones DH, Baker H. Pulmonary complications following methotrexate therapy. J Am Acad Dermatol. 1987;16:373-5.
24. Pope J, Bellamy N, Seibold J, et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum. 2001;44:1351-8.
25. Price S, James C, Deighton C. Methotrexate use and alcohol. Clin Exp Rheumatol. 2010;28(Suppl 61):S114-S6.
26. Ranganathan P, McLeod H. Methotrexate pharmacogenetics. The first step toward individualized therapy in rheumatoid arthritis. Arthritis Rheum. 2006;54:1366-77.
27. Roenigk HH, Auerbach R, Maibach HI, et al. Methotrexate in psoriasis: revised guidelines. J Am Acad Dermatol. 1998;38:478-85.
28. Salim A, Tan E, Ilchyshyn A, Berth-Jones J. Folic acid supplementation during treatment of psoriasis with methotrexate: a randomized, double-blind, placebo-controlled trial. Br J Dermatol. 2006;154(6):1169-74.
29. Sato E. Methotrexate therapy in systemic lupus erythematosus. Lupus. 2001;10:162-4.
30. Shea B, Swinden MV, Ghogomu ET, Ortiz Z, Katchamart W, Rader T, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. J Rheumatol. 2014;41(6):1049-60.
31. Skeith KJ, Russell AS, Jamali F, Coates J, Friedman H. Lack of significant interaction between low dose methotrexate and ibuprofen or flurbiprofen in patients with arthritis. J Rheumatol. 1990;17(8):1008-10.
32. van den Hoogen F, Boerbooms A, Swaak A, et al. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: A 24 week randomized double-blind trial, followed by a 24 week observational trial. Br J Rheumatol. 1996;35:364-72.
33. Van Dooren-Greebe RJ, Kuijpers AL, Mulder J, et al. Methotrexate revisited: effects of long-term treatment in psoriasis. Br J Dermatol. 1994;130:204-10.
34. Vucinic V. What is the future of methotrexate in sarcoidosis? A study and review. Curr Opin Pulm Med. 2002;8:470-6.
35. Wegrzyn J, Adeleine P, Miossec P. Better efficacy of methotrexate administered by intramuscular injections versus oral route in patients with rheumatoid arthritis. Ann Rheum Dis. 2004;63:1232-4.
36. Wells GA, Tugwell P. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. J Rheumatol. 2014;41(6):1049-60.
37. Wenzel J, Brähler S, Bauer R, et al. Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. Br J Dermatol. 2005; 153(1):157-62.
38. Wilke W. Methotrexate use in miscellaneous inflammatory diseases. Rheum Dis Clin N Am. 1997;23:855-82.

39. Zachariae H, Sogaard H. Methotrexate-induced liver cirrhosis. A follow-up. Dermatologica. 1987;175:178-82.
40. Zachariae H. Liver biopsies and methotrexate: a time for reconsideration. J Am Acad Dermatol. 2000;42:531-4.

AZATHIOPRINE

Chemical Class

It is a synthetic purine analogue which is structurally composed of an imidazole ring attached to 6 -mercaptopurine, and acts as a prodrug as it is quickly converted to 6-mercaptopurine (MP) by a nonenzymatic nucleophilic attack by sulfhydryl compounds present in erythrocytes and body tissues.

Mechanism of Action

The drug is metabolized via 3 competing pathways: thiopurine methyltransferase (TPMT) which catalyzes S-methylation to 6-methyl mercaptopurine, an inactive compound. Xanthine oxidase which catalyzes oxidation to the inactive 6-thiouric acid. Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) that catalyzes the conversion of 6-MP to the active 6-thioguanine metabolites (Fig. 8.9).

The enzyme HGPRT metabolizes 6-mercaptopurine into 6-thioinosine 5-monophosphate (6-TIMP). This product is processed by TPMT to active methylated metabolites or

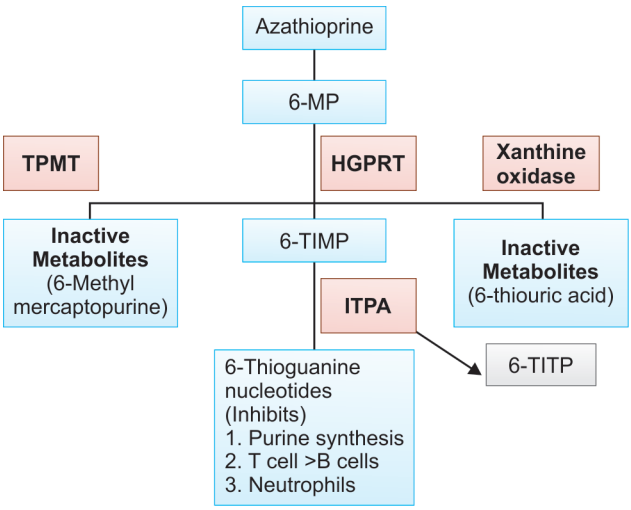


Fig. 8.9: Azathioprine is converted to mercaptopurine (6-MP) by glutathione-S-transferase by non-enzymatic mechanisms. Hypoxanthine-guanine phosphoribosyltransferase (HGPRT) metabolizes 6-MP to active, cytotoxic thiopurine nucleotides. Xanthine oxidase and thiopurine methyltransferase metabolize, 6-MP to the inactive metabolites 6-methylthiouric acid and 6-methylmercaptopurine

Abbreviations: TPMT, thiopurine methyltransferase; 6-TIMP, 6-thioinosine 5-monophosphate; 6-TITP, 6-thioinosine triphosphate; ITPA, inosine triphosphate pyrophosphohydrolase

is phosphorylated to 6-thioinosine triphosphate (6-TITP). 6-TITP is converted to 6-TIMP by inosine triphosphate pyrophosphohydrolase (ITPA). A lack of ITPA, often seen in Asian populations, (Uchiyama K, et al.) leads to an increase in the level of toxic 6-TITP and induces corresponding side effects, such as leukopenia, gastrointestinal disturbances, or elevated liver function test results.

Azathioprine has three major actions, (a) cell cycle specific antimetabolite, (b) inhibition of neutrophil trafficking, (c) inhibition of cellular cytotoxicity.

The 6-MP metabolite inhibits DNA and RNA synthesis by inhibiting the *de novo* purine synthesis. T-lymphocytes are sensitive to inhibition of *de novo* purine synthesis because these cells lack efficient salvage pathways to maintain adequate intracellular stores. The incorporation of thioguanine nucleotides into the nucleic acids of cells is thought to mediate the cytotoxicity of azathioprine, whereas inhibition of purine synthesis may be more important in decreasing cellular proliferation. Leukopenia is unnecessary for immunosuppression.

Azathioprine and mercaptopurine also decrease the circulating lymphocyte count, suppress lymphocyte proliferation, inhibit antibody production, inhibit monocyte production, suppress natural killer cell activity, and inhibit cell-mediated *and* humoral immunity. It also effects the natural killer cell function, T-cell signaling, T-cell cytolytic activity, prostaglandin production, and neutrophil activity.

Pharmacokinetics

Azathioprine is rapidly absorbed after oral administration. The drug has a plasma half-life of only 3 hours owing to its conversion to 6-MP.

Onset of action: The onset of immunomodulatory effects is relatively **slow (8–12 weeks)**, presumably because the active thioguanine metabolites slowly accumulate intracellularly.

Absorption and Distribution

The bioavailability of azathioprine, varies. In healthy volunteers, bioavailability ranged from 27 to 83% with an average of 47%.

Maximal concentrations of mercaptopurine occurs 1 to 3 hours after administration of azathioprine, and the half-life of mercaptopurine is 1 to 2 hours.

Route of elimination: At conventional doses, approximately 1% of mercaptopurine is excreted unchanged in the urine.

Usage Guidelines

Azathioprine is contraindicated in patients with known hypersensitivity to the drug. Dosage adjustment, as guided

by serial blood counts, may be required in hepatic or renal insufficiency. The drug should not be used during pregnancy unless the benefits outweigh the risks. Both the parent drug and its metabolites can cross the placenta and act as potential teratogens. The *magnitude* of the teratogenic risk has been evaluated as *minimal to small*.

In contrast to the other cytotoxic agents, there is no evidence that azathioprine produces gonadotoxicity or infertility.

Dosage

Azathioprine is supplied for oral use as scored 50 mg tablets. **Initial dose**: Azathioprine is often started at a dose of **1 mg/kg daily,** and if this is tolerated, the dose is increased to **2 to 2.5 mg/kg** after 2 to 4 weeks. If TPMT levels can be done a dose of 1–3 mg/kg/day is given in patients with normal TPMT activity but in the 10% of the population with subnormal TPMT activity the dose should be limited to 0.5–1 mg/kg/day. But in Indians and Asian (see below) the TPMT activity is *normal* in a *majority* of cases.

Increase/Maintenance: After 6 to 8 weeks, the dose may be increased by 0.5 mg/kg at 4 week intervals according to white blood cell counts and clinical response, and generally should not exceed 3 mg/kg per day. If there is no beneficial response in 12 to 16 weeks, treatment using azathioprine should be discontinued.

Decrease: The dose is reduced by 0.5 mg/kg monthly till the drug is stopped.

Clinical Use in Dermatology

In the United States, azathioprines use in dermatology is strictly off-label (Schram ME). Although in most European countries, the use of azathioprine is licensed for the treatment of pemphigus vulgaris and dermatomyositis and SLE (http://www.eudrapharm.eu), it is extensively used off-label in India.

As the drug affects T- and B-cell function and antigen-presenting cell function and numbers and leads to depression of T-cell-mediated function and antibody production it is of use in immunobullous dermatoses such as pemphigus vulgaris and bullous pemphigoid.

Immunobullous Disorders

The role of adjuvant drugs with steroids in most bullous disorders is based on data which has been substantiated by reviews on the topic.

Azathioprine has been studied in pemphigus both as a conventional regimen and as the "**Lever mini therapy**". The

Box 8.7: Uses of azathioprine in dermatology

FDA approved	Transplantation cases Severe RA	
Off label uses		
Photodermatitis	Chronic actinic dermatitis Persistent light reactors PMLE	
Bullous disorders	Pemphigus vulgaris Bullous pemphigoid Cicatricial pemphigoid	1–3 mg/kg/d (75–150 mg) 2-2.5 mg/kg/d 1.5-2 mg/kg/d
Vasculitis	LCV Wegener's granulomatosis PAN	1–2 mg/kg/d
Neutrophilic disorders	Behcets PG	1–2 mg/kg/d
Connective tissue disorders	SLE DLE DM	1–2 mg/kg/d
Dermatitis	Atopic dermatitis Contact dermatitis (ABCD) Lichen planus Psoriasis Photodermatitis	1–2 mg/kg/day 100 mg/day 100 mg/day Not very effective 1–2 mg/kg/d
Others	Sarcoidosis EM PRP Vitiligo	1–2 mg/kg/d Not well defined Not well defined 0.6–0.75 mg/kg/day

latter regimen uses an *alternate-day* 40-mg oral prednisone with *azathioprine* 100 mg daily and has been found to be effective in pemphigus (Chams-Davatchi C, Chaidemenos GCh). Though the drug is slow acting, its safety profile as compared to cyclophosphamide makes it the preferred corticosteroid-sparing agent pemphigus vulgaris and bullous pemphigoid worldwide (Yancey KB, Mimouni D).

Meyer V et al. in their review opined that the reports show a tendency in favor of azathioprine concerning corticosteroid-sparing effects and no significant differences regarding disease control, thus azathioprine is a preferred first-line therapy in mild to moderate cases of pemphigus. Mycophenolate mofetil seems to be a valid second-line choice. In severe and rapidly progressing cases, dexamethasone/cyclophosphamide pulse therapy can be considered.

Photodermatoses

Azathioprine is probably the preferred immunosuppressant for photo dermatoses, including chronic actinic dermatitis and polymorphous light eruption. Though CAD is a valid indication its use in polymorphous light eruption and

persistent light reactors, should be restricted only in severe cases.

ABCD (Air Borne Contact Dermatitis)

It has been used as a successful and safe long-term agent with oral steroids in a dose of 50–100 mg which highlights its safety profile on long-term usage and in Indian patients (Verma KK).

AD

Azathioprine can be used for the treatment of atopic dermatitis if registered treatment options fail or are contraindicated.

Vasculitis

In systemic vasculitis, azathioprine is *not* as effective as cyclophosphamide. But in idiopathic LCV refractory to corticosteroids, azathioprine therapy is effective and is the preferred immunosuppressant.

DM/SLE

It has been documented to treat cutaneous features of lupus, including DLE (palmoplantar), subacute LE and SLE.

Azathioprine is used to treat some patients with lupus nephritis, and although it is more effective than corticosteroids alone, it is not as effective as intravenous pulse cyclophosphamide. It is better used as a *maintenance* therapy, after low-dose cyclophosphamide induction.

For refractory myositis and lung involvement, the combination of azathioprine, methotrexate, and corticosteroids has been effective.

Lichen Planus

It has been used for both oral and erosive lichen planus. But the drug should be reserved for cases where conventional treatment options are contraindicated or have failed (Lear JT).

Vitiligo

The use of the drug in vitiligo, like other immunosuppressant's is *not* based on robust evidence. A low-dose azathioprine (at the maximal dosage of 50 mg/day) in association with PUVA has been proposed to be effective in vitiligo. A study performed on 60 patients randomized to receive either azathioprine (0.6–0.75 mg/kg/day) in association with PUVA or PUVA-therapy alone, had demonstrated a potential synergic effect of the two approaches, but true positive

results have been demonstrated only in a minority of the subjects, with the limitation of lack of validated, standardized measures for vitiligo assessment [Radmanesh M].

Special Considerations

Patient Instructions

This medication may be taken with food to reduce stomach upset.

Missed doses. Take a missed dose as soon as possible. If you take the drug once daily and it is time for the next dose, take it at the regular time. Do not double the dose.

Patients who have previously received alkylating agents such as cyclophosphamide, chlorambucil, and melphalan may be at increased risk for carcinogenesis from azathioprine.

Use two forms of birth control including hormonal and barrier methods.

Male patients should use condoms if engaging in sexual intercourse while using this medication.

Receive vaccinations (particularly live attenuated viruses) only with permission from treating physician.

Drug Interactions

- Avoid allopurinol (inhibits the metabolism of azathioprine by xanthine oxidase).
- Methotrexate increases the plasma levels of 6-MP metabolite.
- Sulfasalazine (inhibits TPMT).
- Angiotensin-converting enzyme inhibitors (ACE-I) have been shown to potentiate anemia.
- Both azathioprine and trimethoprim-sulfamethoxazole are antimetabolites that have a synergistic effect in inhibiting bone marrow proliferation.
- Azathioprine may decrease the effect of warfarin.
- Azathioprine may decrease levels of cyclosporine.

Side Effects

Azathioprine is generally well-tolerated (Takatsu N).

Common

Gastrointestinal

Nausea and vomiting are the most frequent side effects. Liver test abnormalities occur in 34%, but are seldom serious. Serious liver toxicity, severe cholestasis, hepatic veno-

occlusive disease, and nodular regenerative hyperplasia and pancreatitis are rare.

Hematologic

Myelosuppression manifest as leukopenia, thrombocytopenia, or pancytopenia is the most significant adverse effect of azathioprine. Reversible myelosuppression is common, is dose related, and varies substantially among individuals, Severe myelosuppression is *uncommon* and is consequent to low or absent TPMT activity.

A recent review opined that the most common side effect of azathioprine is leukopenia (white blood cells <3000/μL), with 18 (15.8%) affected patients. Only 2 patients (1.8%) had severe leukopenia (<1000/μL), followed by a decrease in the dose of azathioprine. Although the mild forms of leukopenia occurred after an average treatment period of 13.7 months (mean; range 1–47 months), the severe forms of leukopenia occurred in less than 1 month.

a. TPMT level: Decreased TPMT activity leads to a decreased ability to detoxify mercaptopurine and results in increased formation of cytotoxic thioguanine metabolites and clinical toxicity (see Fig. 8.9).

TPMT activity is affected by genetic polymorphism, and several point mutations are associated with impaired enzyme activity. TPMT activity in white Americans and African-Americans is polymorphic with a trimodal distribution. Thus, the most frequent TPMT gene polymorphisms can be found in Africans and white patients, whereas Asians have a low prevalence of TPMT gene polymorphisms.

Approximately 90% of subjects show high activity, 10% show intermediate activity, and *0.3%* (the subjects homozygous for the poorly functional polymorphisms) show very low activity (McLeod HL). A study from India (Murugesan R, et al.) showed that 89–94% of individuals possessed high activity, 6-11% intermediate activity and approximately 0.3% low activity. Patients with *intermediate* or *deficient* TPMT activity exposed to thiopurine drugs show severe hematopoietic toxicity.

The 1 in 300 subjects with low or absent TPMT activity are at the great risk of severe azathioprine-induced myelosuppression, which has a delayed but sudden onset, most commonly ***4 to 10 weeks*** after azathioprine has been started (Leipold G). But it is important to understand that in more than 50% of all cases of leukopenia in patients receiving azathioprine have a *normal* TPMT genotype and phenotype (Duley JA). Subjects with intermediate TPMT activity may have more frequent adverse effects, including early nausea and other gastrointestinal effects (Stolk JN).

b. ITPA polymorphism: Because of the high correlation between the side effects of azathioprine therapy and the prevalence of ITPA polymorphism genes in Japanese, it is suggested that in Japanese patients, instead of determination of TPMT gene polymorphisms or activity, a screen for ITPA gene mutations or activity should be introduced (Uchiyama K). A similar study is relevant in Indian patients as we may be having a similar polymorphism.

Rare

Opportunistic Infections

Infection is less common with azathioprine than with alkylating agents; however, infections with a range of bacterial and nonbacterial pathogens, including herpes zoster and cytomegalovirus, may occur.

Oncogenic Potential

Azathioprine has been associated with an increased incidence of malignancy in renal transplant patients. Malignancies include lymphomas, Kaposi's sarcoma, renal carcinomas, carcinomas of the cervix and vulva, and skin cancers. Data regarding the risk of malignancy in patients treated with azathioprine for rheumatologic disease are conflicting. Some studies found an increased risk, particularly of lymphoproliferative malignancies, whereas others did not (Kandiel A). A 24-year retrospective study of 358 SLE patients found no difference in malignancy rates between patients who had received azathioprine and patients who had not received the drug (Takada et al). There are 3 cases of aggressive SCC on the face in cases of eczema, atopic dermatitis and CAD in fair skinned individuals.

Hypersensitivity Reactions

Time of onset is from 3 hours to 42 days after onset of medication use with a mean of 14 days. Manifestations may include hypotension; shock; a maculopapular, urticarial, or vasculitic eruption; fever; acute hepatotoxicity; pancreatitis; rhabdomyolysis; acute renal failure; and pneumonitis.

Monitoring

Measurements of plasma concentrations of azathioprine or mercaptopurine are *not* useful predictors of efficacy or toxicity. Therapeutic monitoring using the red blood cell concentration of 6-thioguanine nucleotides has been attempted, but although there is a relationship between concentrations and efficacy and toxicity, the relationship does not seem to be clinically useful.

Box 8.8: Monitoring protocol for azathioprine

Baseline	*Follow-up*	
		Interval /Duration
CBC platelet count	Yes	Biweekly for the first 15 weeks; then monthly (Stop if WBC <3500/mm^3, Hb < 10 g/dL, Platelet <1 Lakh/mm^3)
LFT	Yes	Biweekly For the first month then 3–4 monthly Test after dose escalations
KFT	Yes	6 monthly
Pregnancy test		
TPMT*		
	< 6.3 U/mL 6.3–15 U/mL 15.1–26.4 U/mL	*No treatment* with azathioprine 1 mg/kg daily 2–2.5 mg/kg *maximum* azathioprine daily dose

*TPMT levels may not always predict toxicity thus in cases where testing is not possible a low dose (1 mg/kg/d) for the first 15 weeks with weekly monitoring is a cost-effective way of circumventing the side effects (see text)

TPMT Levels: Critical Analysis

Determination of pretreatment red-blood cell TPMT activity has been advocated to detect the **1 in 300** patient at risk for early-onset neutropenia. If the drug is used without pretreatment measurement of TPMT activity, it is now recommended that patients be ***counseled*** about the associated risks and the inadequacy of blood count monitoring as a method of preventing early toxicity.

The *clinical utility* and *cost-effectiveness* of genotyping for TPMT and modifying the dose of azathioprine accordingly (from the standard dose of 2.5 mg/kg to 1 mg/kg in heterozygotes and to 0.25 mg/kg in homozygotes) has been studied using a decision analysis model. Although this modeling predicts a modest cost savings and a marked reduction in morbidity (Mara, et al.), a small prospective controlled study in 29 patients found the there was ***no correlation*** between the TPMT activity and the development of AZA-induced adverse events. (Sayani FA). A similar finding was noted from a study from Japan (Takatsu N, et al.). This finding is at least partly because the ability to predict azathioprine toxicity from TPMT activity is limited (Schedel J).

Thus in the absence of TPMT testing, *a low* initial dose and careful *monitoring* of the white blood cell count in patients starting azathioprine is required. Some authors suggest weekly monitoring during the first ***15 weeks*** of azathioprine treatment. This is as the toxicity due to TPMT deficiency occurs between 4–10 weeks and is sudden in onset thus regular monitoring should continue till this time.

When patients are on a stable dose of azathioprine, blood counts are monitored monthly, and liver function tests are monitored every 3 to 4 months.

Special Groups

Pregnancy: D

Azathioprine and mercaptopurine cross the placenta, but drug and metabolite concentrations are lower in the fetal circulation, suggesting placental metabolism. Studies in renal allograft recipients who received azathioprine during pregnancy generally have not found an increased frequency of birth defects. Several studies indicate that thiopurine therapy in IBD during pregnancy is safe. Thus, azathioprine/mercaptopurine should not be withdrawn in strictly indicated cases of pregnant IBD patients. However, breastfeeding is contraindicated during azathioprine/mercaptopurine therapy.

Children

Lactation

CI.

Renal

Kidney disease: creatinine clearance 10–50 mL/min: reduce dose by 25%; creatinine clearance <10 mL/min: reduce dose by 50%.

Hepatic

None.

FURTHER READING

1. Dutz JP, Ho VC. Immunosuppressive agents in dermatology. An update. Dermatol Clin. 1998;16(2):235-51.
2. Schram ME, Borgonjen RJ, Bik CM, van der Schroeff JG, van Everdingen JJ, Spuls PI. Off-Label Working and Project Group of Dutch Society of Dermatology and Venereology. Off-label use of azathioprine in dermatology: a systematic review. Arch Dermatol. 2011;147(4):474-88.

3. Stein CM, Taylor HG. Immunoregulatory Drugs in KELLEY'S Textbook of Rheumatology. 8th edn. Elseiver. 2009.

JOURNALS

1. Chaidemenos GCh, Mourellou O, Koussidou T, Tsatsou F. An alternate-day corticosteroid regimen for pemphigus vulgaris. A 13-year prospective study. J Eur Acad Dermatol Venereol. 2007;21(10):1386-91. PubMed PMID: 17958846.
2. Chams-Davatchi C, Mortazavizadeh A, Daneshpazhooh M, Davatchi F, Balighi K, Esmaili N, et al. Randomized double blind trial of prednisolone and azathioprine, vs. prednisolone and placebo, in the treatment of pemphigus vulgaris. J Eur Acad Dermatol Venereol. 2012, Oct 15. doi: 10.1111/j.1468-3083.2012.04717.x.
3. Duley JA, Florin TH. Thiopurine therapies: Problems, complexities, and progress with monitoring thioguanine nucleotides. Ther Drug Monit. 2005;27:647-54.
4. Kandiel A, Fraser AG, Korelitz BI, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. Gut. 2005;54:1121-5.
5. Lear JT, English JS. Erosive and generalized lichen planus responsive to azathioprine. Clin Exp Dermatol. 1996;21:56-7.
6. Leipold G, Schutz E, Haas JP, et al. Azathioprine-induced severe pancytopenia due to a homozygous two-point mutation of the thiopurine methyltransferase gene in a patient with juvenile HLA-B27-associated spondylarthritis. Arthritis Rheum. 1997;40:1896-8.
7. Marra CA, Esdaile JM, Anis AH. Practical pharmacogenetics. The cost effectiveness of screening for thiopurine s-methyltransferase polymorphisms in patients with rheumatological conditions treated with azathioprine. J Rheumatol. 2002;29:2507-12.
8. McLeod HL, Lin JS, Scott EP, et al. Thiopurine methyltransferase activity in American white subjects and black subjects. Clin Pharmacol Therap. 1994;55:15-20.
9. Meyer V, Beissert S. Azathioprine in the treatment of autoimmune blistering diseases. Immunol Allergy Clin North Am. 2012;32(2):295-307.
10. Mimouni D, Nousari CH, Cummins DL, et al. Differences and similarities among expert opinions on the diagnosis and treatment of pemphigus vulgaris. J Am Acad Dermatol. 2003; 49:1059-62.
11. Murugesan R, Vahab SA, Patra S, Rao R, Rao J, Rai P, et al. Thiopurine S-methyltransferase alleles, TPMT(*)2, (*)3B and (*)3C, andgenotype frequencies in an Indian population. Exp Ther Med. 2010;1(1):121-7. Epub 2010 Jan 1.
12. Sayani FA, Prosser C, Bailey RJ, Jacobs P, Fedorak RN. Thiopurine methyltransferase enzyme activity determination before treatment of inflammatory bowel disease with azathioprine: effect on cost and adverse events. Can J Gastroenterol. 2005;19(3):147-51.
13. Schedel J, Godde A, Schutz E, et al. Impact of thiopurine methyltransferase activity and 6-thioguanine nucleotide concentrations in patients with chronic inflammatory diseases. Ann N Y Acad Sci. 2006;1069:477-91.

14. Stolk JN, Boerbooms AM, de Abreu RA, et al. Reduced thiopurine methyltransferase activity and development of side effects of azathioprine treatment in patients with rheumatoid arthritis. Arthritis Rheum. 1998;41:1858-66.
15. Takada K, Arefayene M, Desta Z, et al. Cytochrome P450 pharmacogenetics as a predictor of toxicity and clinical response to pulse cyclophosphamide in lupus nephritis. Arthritis Rheum. 2004;50:2202-10.
16. Takatsu N, Matsui T, Murakami Y, Ishihara H, Hisabe T, Nagahama T, et al. Adverse reactions to azathioprine cannot be predicted by thiopurine S-methyltransferase genotype in Japanese patients with inflammatory bowel disease. J Gastroenterol Hepatol. 2009;24(7):1258-64.
17. Teml A, Schaeffeler E, Herrlinger KR, Klotz U, Schwab M. Thiopurine treatment in inflammatory bowel disease: clinical pharmacology and implication of pharmacogenetically guided dosing. Clin Pharmacokinet. 2007;46(3):187-208.
18. Uchiyama K, Nakamura M, Kubota T, et al. Thiopurine S-methyltransferase and inosine triphosphate pyrophosphohydrolase genes in Japanese patients with inflammatory bowel disease in whom adverse drug reactions were induced by azathioprine/ 6-mercaptopurine treatment. J Gastroenterol. 2009;44(3):197-203.
19. Verma KK, Manchanda Y, Pasricha JS. Azathioprine as a corticosteroid sparing agent for the treatment of dermatitis caused by the weed Parthenium. Acta Derm Venereol. 2000;80(1):31-2.
20. Yancey KB, Egan CA. Pemphigoid: clinical, histologic, immunopathologic, and therapeutic considerations. JAMA. 2000;284:350-6.

CYCLOSPORINE

- Imusporin (Cipla) 25/50/100 mg.
- Sandimmun Neoral (Novartis) 50 mg/100 mg and solution 50 mg/5 mL and 100 mg/mL (Microemulsion).

Chemical Class

Cyclosporine is a lipophilic cyclic undecapeptide isolated from the fungus *Tolypocladium inflatum*. It has been used for the treatment of severe psoriasis since the early 1980s and has more recently found application in other inflammatory dermatoses.

Mechanism of Action

Cyclosporine acts primarily on T cells.

1. The drug forms a complex with cyclophilin intracellularly which then binds to and inhibits calcineurin.
2. This prevents the activation of nuclear factors involved in the transcription of genes encoding several cytokines

including IL-2 and interferon-gamma. IL-2, is a cytokine that is necessary for full activation of the T-cell pathway, interferon-gamma, and granulocyte-macrophage colony-stimulating factor (GM-CSF).

3. Consequently, cyclosporine depletes lymphocytes and macrophages in the epidermis and dermis and inhibits the activation of T cells (CD4/CD8), natural killer cells, and antigen-presenting cells.
4. Cyclosporine also inhibits keratinocyte hyperproliferation, inhibits the release of histamine from mast cells, and downregulates the expression of cellular adhesion molecules on dermal capillary endothelium.

Pharmacokinetics/Absorption and Distribution

Cyclosporine is insoluble in water. In a traditional formulation, given orally as a soft gelatin capsule, the absorption is erratic, with a bioavailability of approximately 30% with high interpatient and intrapatient variability.

Peak blood levels occur after 2 to 4 hours, with an average serum half-life of 18 hours. Tissue concentrations are highest in adipose tissue and 80% is bound to lipoproteins. There is poor CNS penetration. The drug is metabolized by the cytochrome P450 3A system with bile excretion and enterohepatic recirculation. Metabolites are inactive and only 6% of the drug is excreted in the urine in the form of metabolites.

A new microemulsion formulation is now the standard formulation in Canada and Europe. It is absorbed more rapidly, with a peak serum concentration 1 hour earlier than the original formulation, and an increase in bioavailability resulting in higher maximum concentrations and lower intrapatient and interpatient variability. This is associated with an increase in clinical efficacy and in a comparable safety profile. A decreased tolerability with a 1:1 dose conversion has been noted with an increase in reported gastrointestinal adverse effects. However, a 1:1 dose conversion is still recommended when converting patients from the original formulation to the microemulsion formulation.

The specific brand of cyclosporine should be specified at each visit because of differences in bioavailability between the original and microemulsion formulations of cyclosporine.

Usage Guidelines

Cyclosporine was first used to prevent rejection in solid organ transplant recipients. It was approved by the US Food and Drug Administration for the treatment of psoriasis in 1997.

Cyclosporine is available in capsule form (in 25- or 100-mg capsules) or as a bioequivalent solution (100 mg/5 mL). The

oral solution should be drawn up with the syringe provided and mixed with orange or milk juice.
Adults 2.5–5.0 mg/kg/day
Children 5–7 mg/kg/day.

Dosage

Initial dose: The recommended starting dose is 2.5 mg/kg per day.
Escalation and maximum dose: If improvement is not noted within 2 to 4 weeks, the cyclosporine dose can be increased in increments of 0.5 to 1.0 mg/kg per day to a maximum of 5 mg/kg per day. The US FDA recommends a maximum dosage of 4 mg/kg/day.
Tapering of dosage: With psoriatic patients going into remission, defined as a reduction in the psoriasis area and severity index of greater than 75 percent, the CsA dose should be down-titrated at 4-week intervals.

A higher serum concentration of cyclosporine results when the drug is administered *before* rather than after meals. *Ideal body weight* rather than actual body weight should be used to calculate the required dose. In the *clinical setting*, however, it is generally the lowest effective dose to achieve disease control that guides the maintenance dose.
(Estimate ideal body weight in (kg): Males—IBW = 50 kg + 2.3 kg for each inch over 5 feet. **Females—**IBW = 45.5 kg + 2.3 kg for each inch over 5 feet).

Clinical use in Dermatology

Cyclosporine is typically used as a "rescue" or "induction" therapy for periods of up to 6 months because of its rapid onset of action and considerable efficacy. In a small subset of patients, particularly the pediatric population, it is still used as a maintenance therapy for periods of up to 1 year. In India, due to the cost of the drug in most cases a "rescue mode" of therapy is better practiced. Though a list of conditions is detailed below (Table 8.6) we will focus on the commonly used indications.

1. **Psoriasis:** Current consensus guidelines recommend a starting dose of 2.5 mg/kg/day, unless a rapid improvement is considered necessary, when a dose of up to 5 mg/kg/day may be used. Failing an adequate response with low dose cyclosporine after 4 weeks of treatment, the dose can be increased gradually by 0.5 to 1.0 mg/kg/day at 2- to 4-week intervals, to a maximum of 5 mg/kg/day. If an adequate response has not been achieved after 3 months of treatment at a dose of 5 mg/kg/day, cyclosporine should be withdrawn. Once a good response is obtained, the dose can be reduced in steps of 0.5 to 1.0 mg/kg/day at two

Table 8.6: Indications and dosages

Approved (FDA/UK)	*Unapproved*	*Regimen/Results*	*Dose/Duration*
Psoriasis		Intermittent short-term therapy	2.5–5 mg/kg/day for 12–16 weeks, This course is repeated when relapse occurs
		Rescue therapy	5 mg/kg/day for 12–16 weeks for flaring of disease
		Long-term therapy	≤5 mg/kg/day for up to 1 year; then reducing dose to the lowest effective dose
		Rotational therapy	3–4 mg/kg/day, max 5 mg/kg/day with MTX 15 mg/week
Atopic dermatitis (Approved Europe and the UK)		Excellent response 2 weeks (50% response) and by 6 weeks (80% response)	2.5–3 mg/kg/day, max 5 mg/kg/day -12–16 weeks

Contd...

Contd...

	Pyoderma gangrenosum	Excellent response (Combination with pulse therapy)	5 mg/kg/day >6 months
	Pompholyx	Results are *comparable* to high potent steroid creams About 77% of patients continued to have a 54% improvement at 1 year after stopping therapy	2.5–3 mg/kg/day for 6 weeks, up to 16 weeks
	Chronic urticaria	Used in cases refractory to steroids or as a steroid sparing agent (**33%** relapse at 3–6 months though the relapse is less severe)	4 mg/kg/day -12–16 weeks
	Behcet disease	Very good results Used for refractory eye disease, topical steroid resistant mucocutaneous disease, and arthritis	5 mg/kg/day for 6 months
	Pityriasis rubra pilaris	Mixed results Used in erythrodermic classic adult and erythrodermic juvenile PRP	3–5 mg/kg/day, maintenance Dose 2 mg/kg/day >8 months
	Dermatomyositis	Very good results Used only in cases refractory to Mtx/Aza with steroids	1–1.8 mg/kg/day, 200 mg/day

Contd...

Contd...

	Pemphigus vulgaris	Better options are available	1–3 mg/kg/day
	Photodermatoses Chronic actinic dermatitis PMLE	Good results	4–4.5 mg/kg/day 3–4 mg/kg/day for one week before exposure
	Lichen planopilaris	CsA may be effective in the initial phases before severe follicular damage occurs	3–5 mg/kg/day for 3–5 months
	Lichen planus	Pruritus improves in 2 weeks, with clearing of the lesions in 6 weeks	5 mg/kg/day
	Prurigo nodularis	Good	3.5–4 mg/kg/day for 6–9 months
	Severe alopecia areata	Variable results (33–86% of patients have 70% hair regrowth, 76% maintain the hair regrowth at 12 months follow-up)	5 mg/kg/day for 2–12 months

Table 8.7: Drug interaction with cyclosporine

Drugs that inhibit the cytochrome P450 system, leading to a higher concentration of cyclosporine	Calcium channel blockers (diltiazem, nicardipine, verapamil) Antifungals (fluconazole, itraconazole ketoconazole and voriconazole) Macrolide antibiotics (erythromycin, clarithromycin, and josamycin) Doxycycline Gentamicin and tobramycin Ticarcillin Ciprofloxacin Oral contraceptives and androgen steroids Allopurinol Bromocriptine Amiodarone Ranitidine and cimetidine Metoclopramide Methylprednisolone Protease inhibitors Statins (especially atorvastatin and simvastatin) Danazol Thiazide diuretics Furosemide Warfarin Grapefruit juice
Drugs that stimulate the cytochrome P450 system, leading to a lower cyclosporine level	Anticonvulsants (carbamazepine, phenobarbitone, phenytoin, and valproate) Rifampicin Rifabutin Isoniazid Octreotide Orlistat Terbinafine Sulfinpyrazone Probucol Troglitazone Ticlopidine Metamizole Selective serotonin reuptake inhibitors (sertraline) Nafcillin St John's Wort (*hypericum perforatum*)
Drugs thaI impair renal function during cyclosporine treatment	Nonsteroidal antiinflammatory drugs Aminoglycosides (gentamycin and tobramycin) Vancomycin Ciprofloxacin Trimethoprim with sulfamethoxazole Clotrimazole and ketoconazole Fibrates Amphotericin B Acyclovir Melphalan Methotrexate Colchicine Cimetidine and ranitidine

Contd...

Contd...

Drugs which affects metabolism causing increased levels	Digoxin Statins (simvastatin. lovastatin. atorvastatin, and pravastatin) Prednisolone Diclofenac Methotrexate Colchicine Drugs for erectile dysfunction (sildenafil tadalafil, and vardenafil) Benzodiazepines
Treatments where cyclosporine increases carcinogenicity	High cumulative dows of ultraviolet light irradiation Radiotherapy

weekly intervals to the lowest possible dose that maintains control of disease.

Current guidelines limit the continuous use of cyclosporine in the United States to 1 year, with those in the United Kingdom and Europe recommend a limit of 2 years.

2. **Atopic dermatitis:** Cyclosporine is the only immunosuppressant approved in Europe and the United Kingdom for the *short-term* treatment of severe atopic dermatitis that cannot be controlled with topical therapy. While cyclosporine does not have formal FDA approval for this use, it has been recommended by the AAD Guidelines of Care Committee as being effective for the treatment of atopic dermatitis refractory to conventional treatment with no statement as to the recommended dosage.

   In the treatment of atopic dermatitis with cyclosporine, a regimen commencing at 5 mg/kg/day for 2 weeks with a gradual tapering as dictated by the clinical response over the next 3 months is recommended to a dose of 1.5 mg/kg/day where possible has been suggested.
3. **Urticaria:** Cyclosporine may be used to treat chronic urticaria as an alternative to corticosteroids, either as a steroid-sparing agent or in chronic urticaria that is refractory to corticosteroid therapy. Furthermore, low-dose cyclosporine treatment (2.5 mg/kg/day) for 4 weeks lowered the serum levels of cytokines IL-2R, IL-5, and tumor necrosis factor-alfa, which are increased in patients with chronic idiopathic urticaria. Approximately, 75% of patients with chronic urticaria treated with low-dose cyclosporine will have full remission or significant improvement.

   It is suggested that the most effective treatment is cyclosporine 3 mg/kg/day (given as two doses) for 6 weeks, followed by 3 weeks at 2 mg/kg/day, then 3 weeks at 1 mg/kg/day before discontinuing.

4. **Lichen planus:** Oral cyclosporine is one of the treatments for disseminated lichen planus or lichen planus resistant to systemic corticosteroids and retinoids. On average, pruritus improves in 2 weeks, with clearing of the lesions in 6 weeks.

High doses up to 6 mg/kg/day have been used in studies to treat lichen planus, with resolution of cutaneous lesions within 1 to 8 weeks and sustained remission for up to 10 months. A maximum dose of 5 mg/kg/d is now recommended. Mucosal forms tend to be more resistant to treatment, requiring higher doses (not exceeding 5 mg/kg/d) for adequate control. A sensible approach is to use the drug as a "bridge therapy" with oral steroids in rotation.

Special Considerations

Contraindication

Cyclosporine is contraindicated in uncontrolled hypertension, renal disease, serious infections, and in those with a previous history of malignancy, excluding basal cell carcinoma.

Cyclosporine should be avoided in those with a high cumulative dose of previous psoralen and ultraviolet A light phototherapy.

Patient Instructions

Take this medication on a regular schedule relative to the time of day and meals.

The oral solution may taste better if mixed with another liquid like milk, chocolate milk, or orange juice. Neoral may be mixed with orange juice or apple juice. Using a glass container, mix the cyclosporine solution with the milk or juice, stir well, and drink immediately to ensure that the entire cyclosporine dose is swallowed. Do not refrigerate the oral solution. Use the oral solution within 2 months after opening. Grapefruit juice can interact with cyclosporine.

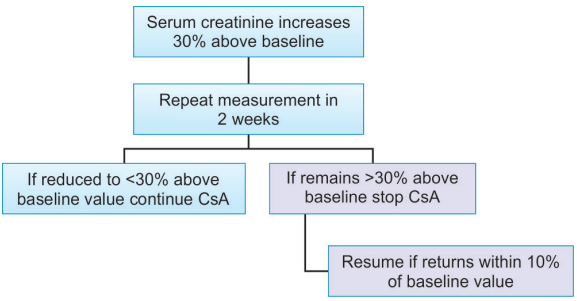


Fig. 8.10: Monitoring of serum creatinine in patients on cyclosporine

Drug Interactions

Cyclosporine is metabolized by the cytochrome P450 system and interacts with drugs that inhibit or stimulate this system. Nephrotoxic drugs should be avoided. A full drug history should be taken at every patient visit.

Side Effects

A maximum dose of 5 mg/kg should be used for up to 1 year only. Acute renal deterioration is typically reversible on withdrawal of cyclosporine treatment, while chronic impairment may be irreversible (Fig. 8.10). If serum creatinine increases 30% over the patient's baseline value on two consecutive readings 2 weeks apart, the dose should be reduced. When hypertension develops, the dose should be reduced by 25 to 50% or antihypertensive therapy introduced; calcium channel blockers of the dihydropyridine class are the antihypertensives of choice.

1. Nausea, vomiting, anorexia, and diarrhea commonly occur with the use of CsA.
2. **Headache** is a common complaint, especially in patients with a history of migraine. It tends to resolve spontaneously as therapy continues. CsA-induced seizures appear to be associated with hypomagnesemia and concomitant use of high doses of systemic corticosteroids. Thus, serum magnesium levels should be always monitored and kept above the lower normal range in CsA-treated patients. Cortical blindness, lethargy, confusion, seizures, hemiplegia, tremors, and paresthesias have also been described in patients receiving CsA.
3. **Renal dysfunction** is reported though there is no documented case of a psoriasis patient on the drug developing any significant kidney damage. About 25% of patients develops clinical and laboratory evidence of altered renal function, including hypertension. Two types of CsA-induced nephrotoxicity are described. The first type usually starts within 2 to 3 weeks after drug initiation, and it is usually associated with high CsA blood levels. There is an insidious decrease in glomerular filtration rate along with hypertension, and tubular dysfunction in association with a complete recovery of renal function upon dose-lowering or discontinuing therapy. The second type is likely a result of cumulative sub-clinical chronic renal toxicity. This may occur in the absence of any detectable elevation of creatinine or blood pressure. Histologic changes include interstitial fibrosis, tubular atrophy, and some degree of vasculopathy.

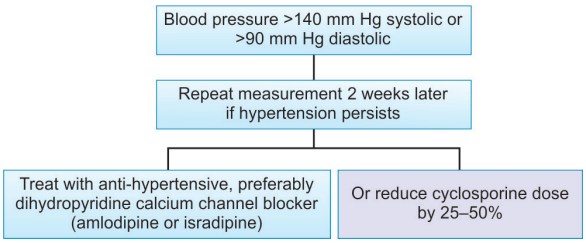


Fig. 8.11: Monitoring of BP in patients on cyclosprine

Although renal function can improve somewhat after discontinuation of the drug, this type of toxicity is generally irreversible.

Calcium channel antagonists exert beneficial effects on CsA-induced hypertension and nephrotoxicity, presumably through the inhibition of endothelin-1. Other drugs, including angiotensin converting inhibitors (enalapril, lisinopril, etc.) and angiotensin receptor blockers (losartan, valsartan, etc.), are also effective mainly when used in combination with other antihypertensive drugs. Diuretics and nephrotoxic drugs should be used with caution in CsA-treated patients.

4. Elevations of **liver enzymes** greater than 100 percent over baseline should be managed by reduction of the CsA dose by 25 percent weekly, until enzyme levels normalize.
5. **Hypertension:** Mild and develops in 27% of cases of psoriasis, is mild and reversible (Fig. 8.11).
6. **Hyperlipidemia:** This is commonly seen. Apart from dietary modifications, statins can be initiated. But simvastatin, atorvastatin interact with cyclosporine thus fluvastatin, rosuvastatin and pravastatin should be given as they are not substrates of CYP3A4.
7. **Electrolyte imbalance:** Hyperklemia, hyperuricemia and hypomagnesemia.
8. CsA-treated transplant recipients have a relative risk for all skin cancers of 6.8 versus 2.2 to 5.5 in patients receiving other immunosuppressive therapies. CsA-treated dermatologic patients also have a higher risk of skin cancers, including squamous cell carcinomas, basal cell carcinomas, human papilloma virus–associated anogenital carcinoma, and Kaposi sarcoma. The high incidence of squamous cell carcinoma in psoriatic patients treated with CsA could be biased by previous exposures to psoralen and ultraviolet A light or ultraviolet B.
9. **Musculoskeletal:** Myalgia, lethargy, arthralgia.

10. **Osteoporosis** seems to result from the CsA's action on osteoblasts and osteoclasts, and by altering lymphokine release. CsA can induce hyperuricemia in up to 15 percent of patients, and it is also an indicator of early CsA-induced nephrotoxicity. Myopathy has been reported in transplant patients receiving high doses of CsA, and thus, caution should be used with the concomitant use of statins.
11. **Skin:** Hypertrichosis occurs in virtually all patients on long-term CsA therapy. It is not limited to androgen-dependent, hair-bearing areas, and shows no tendency to spontaneous remission. Gingival hypertrophy is reported in up to 70 percent of CsA-treated patients; it is more common in children, individuals with poor oral hygiene and concomitant use of calcium channel drugs. Improvement of this gingival complication with topical or systemic azithromycin and metronidazole can be seen. An acneiform eruption, indistinguishable from that seen in steroid-induced acne, is frequently reported. A disseminated comedonal or cystic acneiform eruption can also occur. These side effects can appear at any time during CsA therapy, although they are more commonly described at the time of initiation of CsA therapy. Keratosis pilaris, sebaceous hyperplasia, warts, and epidermal inclusion cysts occur in up to one-third of CsA-treated patients.

Monitoring

1. Take a history: Previous infections: TB, hepatitis B/C; history of hypertension, kidney disease, liver disease, or malignancy; full medication history, which should be repeated at every subsequent visit.
2. Physical examination: Actinic damage/cutaneous malignancies; herpes simplex; viral warts.

Baseline	*Follow-up*	*Interval*
CBC with differential WBC count and platelets	Yes	Every month, then every 2–3 months
Renal function tests: BUN, S. creatinine, creatinine clearance Baseline (mean of 2 separate fasting measurements; if discrepancy of >10%, repeat again)	Yes	Every 2 weeks for 3 months, then every month (decrease dose if creatinine increase is >30% over baseline; if persistent over 2 evaluations, discontinue)
Urinalysis	Yes	Monthly

Contd...

Contd...

Blood pressure	Yes	every 2 weeks for 3 months, then every month (If BP >105 diastolic on one occasion, or >95 diastolic decrease dose or add nifedipine, avoid diuretics)
Liver function tests potassium, uric acid, magnesium	Yes	Monthly
S. cholesterol, triglycerides	Yes	Every 2–3 months

Special Groups

Pregnancy

Cyclosporine crosses the placental blood barrier and is a category C drug in pregnancy. Pregnancy registries show no increase in the risk of teratogenicity, although there were trends towards low-birth weight and prematurity.

Children

Children have comparable bioavailability of orally ingested CsA, but have a higher renal drug clearance rate (11.8 mL/min per kg vs 5.7 mL/min per kg in adults), and a correspondingly shorter blood level half-life (7.3 hours vs 10.7 hours in adults). Children may therefore require somewhat higher dosages and more frequent administration to achieve comparable trough levels to adults.

Children are less susceptible to cyclosporine-induced nephropathy than adults. Cyclosporine has been used in transplant recipients as young as 1 year of age with no serious adverse effects. The safety and efficacy of both intermittent and continuous cyclosporine therapy in children for the treatment of atopic dermatitis for up to a year at doses of up to 5 mg/kg/day has also been shown.

Lactation

Cyclosporine is excreted in breast milk.

Elderly

Same as adult dosage. Age-related loss of renal function and comorbid conditions can predispose geriatric patients to cyclosporine-induced nephrotoxicity or hypertension.

FURTHER READING

1. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. J Am Acad Dermatol. 2010;63(6):925-46.

2. Dehesa L, Abuchar A, Nuno-Gonzalez A, Vitiello M, Kerdel FA. The use of cyclosporine in dermatology. J Drugs Dermatol. 2012;11(8):979-87.
3. Dutz JP, Ho VC. Immunosuppressive agents in dermatology. An update. Dermatol Clin. 1998;16(2):235-51.
4. Stein CM , Taylor HG. Immunoregulatory Drugs in KELLEY'S Textbook of Rheumatology. 8th edn. Elseiver. 2009.

CYCLOPHOSPHAMIDE

Classification

Cyclophosphamide is a cell cycle *non-specific inhibitor* and due to the strong association with of bladder toxicity, myelotoxicity, gonadotoxicity, and malignancy, its use should be reserved for serious and potentially life-threatening disorders in which the benefit outweighs the risks. This drug was developed to be a less reactive drug, more selectively cytotoxic to neoplastic cells. But the theory that tumor cells would selectively activate cyclophosphamide, resulting in selective cytotoxicity to neoplastic cells, proved incorrect and is now believed to be a pan-cytotoxic drug.

There are advantages of IV cyclophosphamide over oral cyclophosphamide but *only* when given *alone*. If the two are combined, which may be justified in oncology, the cumulative immunosuppression is detrimental to the patients immunity. This coupled with studies confirming malignancy in cases of pemphigus followed-up for 15 years is a strong reason to in avoid the uniform application of combination of oral and

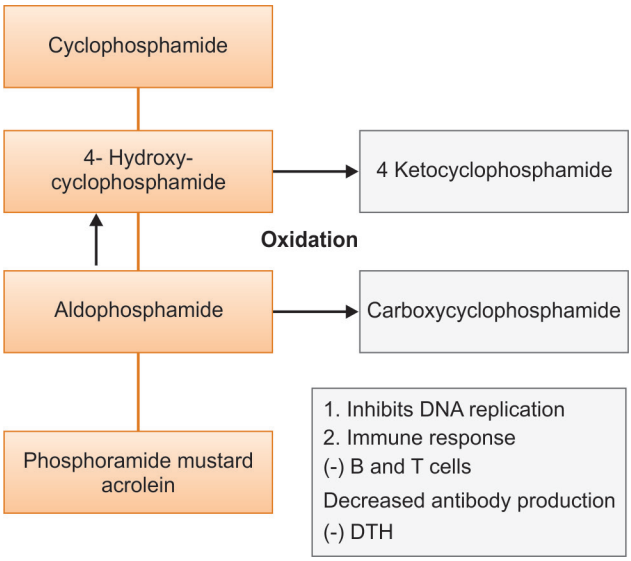


Fig. 8.12: Mode of action of cyclophosphamide

IV cyclophosphamide (DCP pulse therapy) in all cases of pemphigus. This will be discussed in the text.

Mechanism of Action

The active moiety of the drug is phosphoramide mustard. The primary mechanism of action is through the alkylation of DNA by active metabolites. This causes cross-linking of DNA, breaks in DNA, decreased DNA synthesis, and apoptosis. The cytotoxicity of alkylating agents correlates with the amount of DNA cross-linking, but the relationship between cytotoxicity and immunoregulatory effects is unclear.

It action is not *S-phase specific* and it can affect noncycling cells. This accounts for its side effect profile. Cyclophosphamide results in alterations of most humoral and cellular immune responses. There is a differential cytotoxicity to various lymphoid cell populations, with selective suppression of B cells. Hence, this drug has its greatest effect in suppressing *humoral immunity* though it can suppress cellular immune responses. The effects of cyclophosphamide include decreased numbers of T lymphocytes and B lymphocytes, decreased lymphocyte proliferation, decreased antibody production, and suppression of delayed hypersensitivity (Makinodan T, Fauci AS).

Cyclophosphamide has a more variable response on cell-mediated immunity, and low dose cyclophosphamide has been shown to potentiate immune responses in experimental systems. Immunostimulation has recently been related to increased IL-12 gene expression. The conventional doses though inhibit the DTH response to *new* antigens with relative preservation of *established* delayed hypersensitivity. (Makinodan T, Fauci AS).

Absorption and Distribution

It is well absorbed after oral administration, with peak plasma levels within 3 hours. The plasma half-life is 5 to 6 hours, with 12 to 14% of the drug being plasma bound.

Metabolism and Elimination

Cyclophosphamide, itself inactive, is rapidly metabolized, largely by the liver, to active and inactive metabolites. The formation of the active 4-hydroxycyclophosphamide is mediated by several cytochrome P-450 (CYP) enzymes. The formation of 4-hydroxycyclophosphamide, which is cytotoxic, but not at physiologic pH, allows entry of the drug into cells and subsequent formation of the active phosphoramide mustard.

Cyclophosphamide is eliminated predominantly in the urine, mostly as inactive metabolites. Ten to twenty percent

is eliminated as unaltered cyclophosphamide, however, and some active metabolites, such as phosphoramide mustard and acrolein, are present in urine.

Uses (Approved/Unapproved) (Box 8.9)

Box 8.9: Uses of cyclophosphamide

FDA Approved	Mycosis fungoides Cancers: Lymphoma, leukemia, multiple myeloma, neuroblastoma, ovarian and breast cancer, retinoblastoma	
Off label		
Bullous	Bullous pemphigoid Cicatricial pemphigoid Pemphigus	Not the preferred Drug Not the preferred drug Mild/Moderate case: 1–2 mg/kg/day Severe case, Pulse therapy
Vasculitis	Churg–Strauss syndrome Leukocytoclastic vasculitis (including Henoch–Schonlein purpura) Microscopic polyangitis Polyarteritis nodosa Wegener's granulomatosis	1–2 mg/kg/d 1–2 mg/kg/d 1–2 mg/kg/d 1–2 mg/kg/d 1–2 mg/kg/d
Connective tissue disorders	Dermatomyositis Scleroderma Severe cutaneous lupus erythematosus	1–2 mg/kg/d (Not the preferred drug) Not preferred drug Pulse therapy, 0.5 to 1.0 g/m^2 (SLE)
Neutrophilic dermatoses	Behçet disease Erythema elevatum diutinum Pyoderma gangrenosum	1–2 mg/kg/d
Others	Cytophagic histiocytic panniculitis/subcutaneous panniculitic T-cell lymphoma Ichthyosis linearis circumflexa Langerhans' cell histiocytosis Lichen myxedematosus/ scleromyxedema Multicentric reticulohistiocytosis Severe eczematous dermatitis Stevens–Johnson, Xanthoma disseminatum	

Cyclophosphamide remains the drug of choice for most patients with systemic necrotizing vasculitis or Goodpasture's syndrome, for many patients with organ-threatening SLE, and for some patients with autoimmune disease–associated interstitial lung disease and inflammatory eye disease.

In dermatology, the drug is used as an immunosuppressive and 'steroid-sparing' agent, particularly for the treatment

of autoimmune bullous disorders and vasculitis. Cyclophosphamide may be a lifesaving drug, but it also can induce life-threatening adverse effects. Meticulous monitoring and good clinical judgment are required to use it effectively. It is the prevalent trend now to transition to a pulsed or intermittent dosing or use alternative agents for maintenance therapy to minimize long-term side effects.

At any cost cyclophosphamide should probably ***not*** be a first-line therapy for men or women who wish to *conceive* following treatment.

Pemphigus

This has been traditionally been the major use of the drug in some parts of the world (Mimouni D). It is the view of experts that though combination therapy using dexamethasone is effective in limiting disease activity and can lower the dose of doses of systemic glucocorticosteroids, safer alternative exist, like azathioprine and mycophenolate mofetil. Interestingly the consensus of two studies amongst experts favored azathioprine over cyclophosphamide, only 16% of experts reported using cyclophosphamide, compared to 44% who reported the use of azathioprine and 20% who reported use of mycophenolate mofetil (Mimouni D).

An Asian group reported azathioprine use in 82.8% of the responders (Samadi Z). This is possibly because though slow acting azathioprine is immeasurably safer and has equal efficacy as compared to cyclophosphamide. A recent review (Atzmony L) has examined the various adjuvants and opined that, adjuvants have a role in pemphigus treatment, at least in reducing the risk of relapse, but *not* in achieving *remission*. Another study (Esmaili N) from Iran also found no significant difference between the various adjuvants (azathioprine, MMF, cyclophosphamide). Thus, the choice of adjuvant should be based on the safety profile, where azathioprine seems to be the clear choice, worldwide, though in India cyclophosphamide is used.

Vasculitis

In vasculitis, including Churg–Strauss syndrome, leukocytoclastic vasculitis (including Henoch–Schonlein purpura), microscopic polyangiitis, polyarteritis nodosa, Wegener's granulomatosis, and many other forms of necrotizing vasculitis cyclophosphamide is the drug of choice. This is true in *Wegener's granulomatosis* where more than 90% of patients treated with this drug will attain some clinical improvement, with about 75% patients manifesting a complete remission.

Box 8.10: NIH protocol of administering cyclophosphamide and steroids in lupus nephritis*

Regimen 1 (Oral cyclophosphamide with steroids)
Prednisolone 1 mg/kg/day for 4 week decreasing, if possible, to achieve a prednisone dose of approximately 60 mg alternate days at 3 months
Cyclophosphamide
a. **Initial dose:** 2 mg/kg/day by mouth; very ill patients receive 3–5 mg/kg/day for 2–3 days, then 2 mg/kg/day; decrease dosage 25–50% for renal impairment
b. **Subsequent dose:** Increase daily dose in 25 mg increments at 1–2 week intervals if disease active; adjust dosage to avoid leukopenia (WBC <**3000**/mm^3) and granulocytopenia
c. **Tapering:** Taper cyclophosphamide after **1 year** of remission; alternatively, after remission is induced, consider alternative maintenance therapy, such as methotrexate or azathioprine

Regimen 2 (IV cyclophosphamide with steroids)
Prednisolone 0.5–1 mg/kg/day for 4 week decreasing the every-other-day dose each week, if possible, by 5 mg to achieve a prednisone dose of 0.25 mg/kg on alternate days
Cyclophosphamide
a. **Initial dose:** 0.5–0.75 g/m^2 infused IV in saline over 30–60 minutes; decrease dosage by approximately 30% if glomerular filtration rate is less than one third of normal. Mesna every 3 hourly 4 doses orally or IV (each dose 20% of cyclophosphamide dose)
b. **Subsequent dose:** If WBC nadir 10–14 days after the previous dose is >4000/mm^3, increase the dose 25% to a maximum of 1 g/m^2; adjust dosage to avoid WBC nadir/mm^3; if WBC nadir <1500/mm^3, decrease dosage by at least 25%
c. **Tapering:** Monthly cyclophosphamide for 6 months, then a maintenance dose every 3 months; continue maintenance cyclophosphamide for 1 year after remission, or consider ***alternative*** maintenance therapy, such as mycophenolate or azathioprine

*We are detailing the **National Institutes of Health Protocol** for administration and monitoring of pulse cyclophosphamide therapy. As the DCP regimen was largely based on the regimen for lupus nephritis, it is pertinent to point out that in case the parenteral regimen is chosen for pemphigus the NIH regimen can be a viable and eminently practical option

Dosage/Modifications

Dosage and Monitoring

a. **Oral:** Cyclophosphamide is supplied for oral use as 25 and 50 mg tablets. The recommended oral dosage is 1 to 3 mg/kg per day (50 to 200 mg/day). This should be taken in the morning followed by adequate hydration throughout the day (3 L of fluid/day).
b. **Parenteral:** In long-term studies in patients with systemic lupus erythematosus (SLE), monthly intravenous cyclophosphamide regimens preserve renal function better than oral cyclophosphamide or azathioprine-based regimens (Steinberg AD). In monthly intravenous pulse therapy, 0.5 to 1.0 g/m^2 (http://www.halls.md/body-surface-area/bsa.htm) is infused over 1 hour followed by vigorous intravenous hydration, and optional mesna

usually at 160% of the cyclophosphamide dose separated into 4 doses at 0, 3, 6, and 9 hours.

The DCP therapy regimen follows this regimen, though with a arbitrary dose. Further pulses should be adjusted to obtain a white blood cell count nadir of 2 to 3000/mm^3 10 to 14 days later.

In India, the DCP regimen employs a fixed arbitrary dose of cyclophosphamide (500 mg) with IV dexamethasone 100 mg for three days. The merits and demerits of this regimen in view of the safety and efficacy of other drugs including azathioprine in pemphigus followed by most guidelines in the world (Kasperkiewicz M, Martin LK, Ruocco E) and the reports of TCC appearing in pemphigus cases (Cummins DL) on long-term follow-up should temper its use in only the severe cases of pemphigus vulgaris. Two studies from India (Sethy PK, Sharma VK) have shown that using monthly cyclophosphamide with prednisolone is as good as DCP regimen with probably less long-term side effects. The issue of carcinoma in patients with long-term use of cyclophosphamide is important as, pemphigus patients after successful therapy, tend to have a normal life span and carcinomas may take upto 15–20 years to develop after *being-off* therapy.

Two dose regimens are given (Box 8.10) which have been validated by NIH. These are relevant as these can be used in pemphigus if cyclophosphamide is chosen as a therapy option. The DCP regimen was largely based on the regimen for lupus nephritis and the regimens given in Box 8.10 have faced scientific scrutiny and thus seem to be on a more firm ground for clinical applicability even in dermatology.

Drug Interaction

Increased levels of cyclophosphamide: Allopurinol, chlorpromazine, ciprofloxacin, H2 blocker, fluconazole.

Decreased levels of cyclophosphamide: Dexamethasone, prednislone, nevirapine, odansentron, phenobarbital, phenytoin rifampin.

Increased levels of: Succinylcholine.

Increased cardiac toxicity: Doxorubicin.

Increased effect of: Warfarin.

Increased risk of immunosuppression: Alefacept.

Increased risk of bone marrow suppression: Rituximab, zidovudine.

Decreased levels of: Digoxin.

Decreased effects: Vaccines.

Special Considerations

1. Several mechanisms of *cellular resistance* to alkylating agents have been proposed, including increased

intracellular concentrations of glutathione and other thiols, increased activity of enzymes such as aldehyde dehydrogenase that produce inactive metabolites of cyclophosphamide, and increased DNA repair mechanisms.
2. Adjust the dose of cyclophosphamide to avoid a significant degree of leukopenia (see below).
3. To decrease the risk of infection by concomitant high-dose corticosteroids, the dose of corticosteroids should be reduced after a clinical response has been obtained, and alternate-day glucocorticoids can be considered in the maintenance phase.
4. Oral cyclophosphamide is best administered as a single dose in the morning with the patient drinking plenty of fluids and emptying the bladder frequently to dilute the urinary concentration of acrolein and to minimize the time the bladder is exposed to it.
5. Prophylaxis against *Pneumocystis jiroveci* pneumonia is often prescribed, particularly during the induction phase when doses of cyclophosphamide and corticosteroids are higher.
6. In case remission is achieved, the drug should be stopped and changed to methotrexate or azathioprine.
7. Smokers have a higher risk of developing bladder carcinomas, thus, ideally they should not be given cyclophosphamide.

Contraindications

Hypersensitivity to drug or class, severe bone marrow suppression, use with other alkylating agents or immunosuppressants, use of live viral vaccines, pregnancy.

Box 8.11: Cumulative dosage and reproductive side effects*

6–10 g: Azoospermia and amenorrhea
18 g = the azoospermia is generally reversible*
2.8–100 g: Hemorrhagic cystitis
25–80 g: Malignancy
Amenorrhea: 5.2 g for patients over 40 years of age, 9.3 g for patients aged 30–39, and 20.4 g for patients aged 20–29. Menses returned in 50% of patients under 40 years of age

* Buchanan JD, Fairley KF, Barrie JU. Return of spermatogenesis after stopping cyclophosphamide therapy. Lancet. 1975;2:156–7.

Box 8.12: Cumulative dose of cyclophosphamide in DCP therapy

Phase 1 DCP therapy till remission
Phase II (nine DCPs/DPs in exactly 28-day cycles along with 50 mg cyclophosphamide per day) × 9 months
Phase III (only 50 mg cyclophosphamide per day) × 9 months

Cumulative dose
One month of DCP pulse = (500 mg pulse + 100 mg daily × 30 days = 35000 mg; 3.5 g)
Phase 1 (Average 10 months) = 35 g
Phase II 9 months = (9 × 3.5 gm) = 31.5 g
Phase III 9 months = (9 × 1500 mg) = 13.5 g
Total dose = **80 g**

Side Effects

A summary of the dose dependent side effects are detailed below (Box 8.11) as also the cumulative dose achieved by the DCP regimen (Box 8.12), which gives an estimate of the possible side-effects.

1. **Hematologic:** Reversible myelosuppression, consisting primarily of leukopenia, is the most common adverse reaction and can be dose-limiting. Platelet counts generally are *not* affected with pulse doses of less than 50 mg/kg, but with long-term oral use, a mild decrease in platelet count is common.

   After intravenous administration, the nadir occurs at **8 to 12 days** and recovery takes 18 to 25 days. A similar lag is noted with oral therapy. During the leukopenia, the patient is at increased risk of infection by pathogenic and opportunistic organisms.

   WBC nadir: 3000 cells/mm^3 after a dose of 1 g/m^2 (approximately 25 mg/kg) and 1500 cells/mm^3 after a dose of 1.5 g/m^2. With long-term use, there is increased sensitivity to the myelosuppressive effects of cyclophosphamide, and doses usually need to be ***decreased*** over time. Thrombocytopenia and anemia occur less frequently (Grochow LB, et al.).
2. **Gastrointestinal:** Anorexia, nausea, and vomiting occur commonly with intravenous administration, are dose related, and have been associated with the phosphoramide mustard metabolite. Recently, oral ondansetron and dexamethasone have been shown to control nausea resistant to standard antiemetics in patients treated with intravenous cyclophosphamide for lupus nephritis [ondansetron 4–8 mg orally every 4 hour for 3–4 dose of dexamethasone 10 mg orally].
3. **Urological:** Urologic adverse effects are one of the major toxicities of this drug and can include dysuria, urgency, hematuria, bladder fibrosis, necrosis. Pulse intravenous cyclophosphamide regimens *if* used in conjunction with mesna in dermatological/rheumatological doses, in contrast to high-dose oncology regimens, do not generally result in bladder toxicity.

   Bladder toxicity, a particular problem with long-term oral cyclophosphamide, is largely due to acrolein, a metabolite of cyclophosphamide. The short half-life of mesna renders it suboptimal for the prevention of bladder toxicity in patients at greatest risk—patients receiving daily oral cyclophosphamide—but oral mesna administered three times a day with daily oral cyclophosphamide decreased the incidence of bladder toxicity to 12% and may also decrease the risk of bladder cancer (Reinhold-Keller E).

a. **Hemorrhagic cystitis:** Hemorrhagic cystitis can develop at significantly lower dosages and with shorter durations of therapy in patients treated intravenously rather than orally. At the dose commonly used in dermatology, the average risk is 5 to 10%. *Nonglomerular hematuria*, which may range from minor, microscopic blood loss to severe, macroscopic bleeding, is the *most common* manifestation of cyclophosphamide-induced cystitis. Nonglomerular hematuria occurred at some time in 50% of 145 patients treated with oral cyclophosphamide and was related to the duration of therapy, cumulative cyclophosphamide dose and smoking and was chronic and recurrent in 38% even after discontinuation of the drug. Acrolein is the metabolite believed to be responsible for urotoxicity. Dehydration is an undisputed risk factor. High fluid intake and concurrent administration of mesna (sodium 2-mercaptoethane sulfonate) reduce the risk of this complication during intravenous administration.

b. The absolute risk of bladder cancer is difficult to quantify specially in pemphigus cases as a long-term follow-up is difficult to ensure. In a large study, the risk of bladder cancer was increased 31-fold with **5%** cases who had developed **bladder cancer** (Radis et al). This developed 7 months to 15 years after initiating therapy and was preceded by nonglomerular hematuria in all patients. This is relevant as in cases on DCP/oral cyclophosphamide therapy are *not* usually followed-up for a long time *off therapy*. Six of the seven patients had a cumulative dose of more than ***100 g*** of cyclophosphamide and a duration of therapy of more than 2.7 years (Radis et al). This is again relevant as in case of DCP some patients whose initial phase exceeds one year will exceed this dose. Smokers are at increased risk of hemorrhagic cystitis and bladder cancer.

   In dermatological literature (Ho VC) a cumulative dose of >***25 g*** or *hematuria* is a risk factor for malignancy. Importantly Cummins, et al. have noted cases of TCC after long-term follow-up in pemphigus cases.

4. **Oncogenic potential:** Cyclophosphamide increases the risk of other malignancies two-fold to fourfold (Stein CM). The absolute risk is difficult to quantify, however, because few patients have been studied long-term. In the largest study, 119 patients with RA who had been treated with oral cyclophosphamide were followed for 20 years. There were 50 cancers in 37 patients in the cyclophosphamide group compared with 26 cancers in 25 of 119 control RA patients (Baltus JA). Bladder, skin, myeloproliferative, and

oropharyngeal malignancies occurred more commonly in the cyclophosphamide group. The risk of bladder and other malignancies increased with the cumulative dose of cyclophosphamide, and ***53%*** of patients who received more than ***80 g*** of cyclophosphamide developed malignancy. This dose is reached by most patients on DCP therapy and if patient are followed-up, it is not unreasonable to except malignancy in a proportion of these patients.

5. **Reproductive toxicity:** Alkylating agents are probably the most potent agents in producing this effect, considering their mutagenic properties. Spermatogenesis and fertility may return after several years. Amenorrhea, associated with disappearance of mature and primordial ovarian follicles, is seen in women treated with alkylating agents. The risk of sustained amenorrhea after cyclophosphamide therapy has ranged from 11 to 59%. The frequency of this effect increases with the age of the woman and is more likely to be irreversible in older women.

   The risk of ovarian failure may be lower with intravenous pulse cyclophosphamide regimens than with oral regimens, but the difference is not substantial. Note that in DCP, both IV and oral cyclophosphamide is given. Regardless of the route of cyclophosphamide administration, the risk of ovarian failure increases with the age of the patient and the cumulative dose of cyclophosphamide (Mok CC). Patients younger than **25 years** old receiving 6 pulses of intravenous cyclophosphamide had a very low frequency of ovarian failure (none of four patients), whereas patients older than ***31 years*** receiving ***15 to 24 pulses*** all had ovarian failure (four of four patients) (Boumpas DT, et al.). In the DCP regimen these pulses are exceeded by phase II and thus the regimen should be strictly avoided in female patients who have not completed their family or are unmarried.

   In dermatological literature a dose of ***>6–10 g*** (Ho VC) has been linked to a*zoospermia and amenorrhea.* Administered as single agents, alkylating drugs produce permanent damage to the seminiferous epithelium. Cyclophosphamide administered in total doses of **9 g** results in universal azoospermia. In total doses up to **18 g,** the azoospermia is generally reversible (Buchanan JD).

   In men undergoing chemotherapy with regimens that include an alkylating agent, the frequency of azoospermia has ranged from 50 to 90% (Nicholson HS), Less information is available in autoimmune disease, but azoospermia or severe oligospermia was found in 11 of 17 men receiving cyclophosphamide for Behçet's syndrome (Fukutani K).

Box 8.13: Monitoring

Baseline	*Follow-up*
	Interval/Duration
CBC platelet count	1–2 weekly (Decrease dose if WBC <4000/mm^3 or platelet <1,00,000/mm^3) × 1 month Then 3–4 monthly
LFT	1–2 weekly × 1 month Then 3–4 monthly (if dose is stable)
KFT	Monthly Till 3–6 months Then 4 monthly
Part of urinalysis	Weekly for first 3 months, then monthly
i. In case of nonglomerular hematuria or >50 g dose (Cytology/cystoscopy)	3–6 months
Bladder **ii. (Lifelong evaluation for TCC/ Carcinoma*)** (Cytology/cystoscopy/USG/CT Urography/Bladder Check ™)	**Once a year even after stopping therapy**

*(As the latency for developing carcinoma can be as long as 15 years)

Options to preserve fertility

a. If the clinical situation allows, sperm or ova can be banked before starting treatment.
b. Suppression of luteinizing hormone and follicle-stimulating hormone can be achieved by a high dose of estrogen or using a gonadotropin-releasing hormone analogue (leuprolide acetate) (Somers EC).
c. In males, testosterone (100 mg intramuscularly every 15 days) can be administered (Masala A).

6. **Opportunistic Infections:** Infection with a range of common and opportunistic pathogens is a frequent complication and can be the cause of death. The *route* of administration does not matter and is equally common in patients receiving oral or intravenous cyclophosphamide. It is associated with a white blood cell nadir at some point in treatment of less than 3000/mm^3. The concomitant steroid dose is also important and doses should be kept low (20–30 mg).
   Oral cyclophosphamide regimens generally pose a *greater* risk of infection than intravenous pulse regimens. Serious infections occurred in 41% and 70% of patients with Wegener's granulomatosis treated with pulse intravenous and daily oral cyclophosphamide. These rates of infection are higher than rates reported in long-term. National Institutes of Health protocols, in which 48% of 158 patients experienced 140 infections requiring hospitalization.

Despite differences in clinical experience, infections are a common and potentially serious complication of all cyclophosphamide-based regimens.
In DCP, there is a concomitant use of oral and intravenous therapy which can lead to a *high* rate of infections.

7. **Pulmonary:** Cyclophosphamide-induced pulmonary toxicity occurs in less than 1% of patients. Early-onset pneumonitis,1 to 6 months after exposure to cyclophosphamide may respond to withdrawal of the drug and treatment with corticosteroids. A more insidious, irreversible, late-onset pneumonitis and fibrosis with radiographic findings of diffuse reticular or reticulonodular infiltrates may occur after treatment with oral cyclophosphamide for 1 to 13 years.
8. **Miscellaneous:** Anagen effluvium, mucositis, and hyperpigmentation have been reported. When used in higher dosages, cardiomyopathy, pneumonitis, pulmonary fibrosis, hepatotoxicity, and syndrome of inappropriate antidiuretic hormone (SIADH) have been reported.

Monitoring (Box 8.13)

1. CBC with differential WBC count and platelets:
   Decrease dose if WBC (white blood cell count <3000/mm^3 for daily oral therapy or a nadir of <2000/mm^3 for pulse intravenous therapy), platelets <1 × 10^5/mm^3
2. Renal function tests: BUN, Creatinine :
   a. **Urinalysis:** Every 3 to 6 months even *after* the drug is *discontinued*.
   b. Urine cytology should be done every 6 to 12 months or when >50 g total dose is achieved.
   c. Routine cystoscopy is considered every 1 to 2 years for all patients with a history of microscopic hematuria. In case of Hemorrhagic cystitis, there is increased risk of developing bladder cancer, and thus *lifelong* surveillance is required with urinalysis, urine cytology, and, if indicated, cystoscopy. Another alternative though less effective option is USG of the bladder on a yearly basis. Recently a urine spot test (BTA) has been approved to diagnose TCC.
3. **Liver function tests:** Monthly.
4. Chest X-ray every 6 months.

Special Groups

Liver Failure

The half-life of cyclophosphamide is increased to 12 hours in patients with liver failure compared with 8 hours in controls. Toxicity is not increased, however, suggesting that exposure to cytotoxic metabolites is not increased, and dose modification in liver disease is generally not required.

Kidney Failure

Renal impairment. Some studies have shown little alteration in drug disposition with no increase in toxicity in patients with impaired renal function. Small amounts of unchanged cyclophosphamide and its active metabolites are excreted by the kidneys, however, and some accumulation of these would be expected. In patients with autoimmune disease and a creatinine clearance of 25 to 50 mL/min and 10 to 25 mL/min, exposure to cyclophosphamide increased approximately 40% and 70%. In clinical practice, initial cyclophosphamide doses are decreased by approximately 30% in patients with moderate-to-severe renal impairment. Subsequent doses are titrated according to clinical response and effects on the leukocyte (white blood cell) count.

FURTHER READING

1. Dutz JP, Ho VC. Immunosuppressive agents in dermatology. An update. Dermatol Clin. 1998;16(2):235-51.
2. Ho VC, Zloty DM. Immunosuppressive agents in dermatology. Dermatol Clin. 1993;11(1):73-85.
3. Stein CM , Taylor HG. Immunoregulatory Drugs in KELLEY'S Textbook of Rheumatology. 8th edn. Elseiver. 2009.

JOURNALS

1. Atzmony L, Hodak E, Leshem YA, Rosenbaum O, Gdalevich M, Anhalt GJ, et al. The role of adjuvant therapy in pemphigus: A systematic review and meta-analysis. J Am Acad Dermatol. 2015 Jun 15. pii: S0190-9622(15)01609-6.
2. Baltus JA, Boersma JW, Hartman AP, et al. The occurrence of malignancies in patients with rheumatoid arthritis treated with cyclophosphamide: A controlled retrospective follow-up. Ann Rheum Dis. 1983;42:368-73.
3. Boumpas DT, Austin HA, Vaughan EM, et al. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. Ann Intern Med. 1993;119:366-9.
4. Buchanan JD, Fairley KF, Barrie JU. Return of spermatogenesis after stopping cyclophosphamide therapy. Lancet. 1975;2:156-7.
5. Cummins DL, Mimouni D, Anhalt GJ, Nousari CH. Oral cyclophosphamide for treatment of pemphigus vulgaris and foliaceus. J Am Acad Dermatol. 2003;49(2):276-80.
6. Esmaili N, Chams-Davatchi C, Valikhani M, Daneshpazhooh M, Toosi S, Karimi A, et al. Assessment of the therapeutic benefit of oral prednisolone and common adjuvant therapy in stage II of randomized controlled trial study for management of pemphigus vulgaris. Arch Iran Med. 2014;17(9):626-8.
7. Fauci AS, Wolff SM, Johnson JS. Effect of cyclophosphamide upon the immune response in Wegener's granulomatosis. N Engl J Med. 1971;285:1493-6.
8. Fukutani K, Ishida H, Shinohara M, et al. Suppression of spermatogenesis in patients with Behcet's disease treated with cyclophosphamide and colchicine. Fertil Steril. 1981;36:76-80.

9. Grochow LB, Colvin M. Clinical pharmacokinetics of cyclophosphamide. Clin Pharmacokinet. 1979;4:380-94.
10. Kasperkiewicz M, Schmidt E, Zillikens D. Current therapy of the pemphigus group. Clin Dermatol. 2012;30(1):84-94.
11. Makinodan T, Santos GW, Quinn RP. Immunosuppressive drugs. Pharmacol Rev. 1970;22:189-247.
12. Martin LK, Werth V, Villanueva E, Segall J, Murrell DF. Interventions for pemphigus vulgaris and pemphigus foliaceus. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006263.
13. Masala A, Faedda R, Alagna S, et al. Use of testosterone to prevent cyclophosphamide-induced azoospermia. Ann Intern Med. 1997;126:292-5.
14. Mimouni D, Nousari CH, Cummins DL, et al. Differences and similarities among expert opinions on the diagnosis and treatment of pemphigus vulgaris. *J Am Acad Dermatol.* 2003; 49:1059-62.
15. Mok CC, Lau CS, Wong RW. Risk factors for ovarian failure in patients with systemic lupus erythematosus receiving cyclophosphamide therapy. Arthritis Rheum. 1998;41:831-7.
16. Nicholson HS, Byrne J: Fertility and pregnancy after treatment for cancer during childhood or adolescence. Cancer. 1993;71(10 Suppl): 3392-9.
17. Radis CD, Kahl LE, Baker GL, et al. Effects of cyclophosphamide on the development of malignancy and on long-term survival of patients with rheumatoid arthritis: A 20-year follow-up study. Arthritis Rheum. 1995;38:1120-7.
18. Reinhold-Keller E, Beuge N, Latza U, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: Long-term outcome in 155 patients [erratum appears in Arthritis Rheum. 2000;43(10):2379]. Arthritis Rheum. 2000;43:1021-32.
19. Ruocco E, Wolf R, Ruocco V, Brunetti G, Romano F, Lo Schiavo A. Pemphigus: Associations and management guidelines: Facts and controversies. Clin Dermatol. 2013;31(4):382-90.
20. Samadi Z, Gorouhi F, Davari P, Firooz A. Think globally, act locally: expert opinions from Asia on the diagnosis and treatment of pemphigus vulgaris. Indian J Med Sci. 2007;61(3):144-51.
21. Sethy PK, Khandpur S, Sharma VK. Randomized open comparative trial of dexamethasone-cyclophosphamide pulse and daily oral cyclophosphamide versus cyclophosphamide pulse and daily oral prednisolone in pemphigus vulgaris. Indian J Dermatol Venereol Leprol. 2009;75(5):476-82.
22. Sharma VK, Khandpur S. Evaluation of cyclophosphamide pulse therapy as an adjuvant to oral corticosteroid in the management of pemphigus vulgaris. Clin Exp Dermatol. 2013;38(6):659-64.
23. Somers EC, Marder W, Christman GM, et al. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Arthritis Rheum. 2005;52:2761-7.
24. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. Arthritis Rheum. 1991;34:945-50.

9

CHAPTER

Corticosteroids

Kabir Sardana

INTRODUCTION

Glucocorticoids are arguably the most widely used and misused drug in dermatology. Thus this chapter will be comprehensive and focus on almost all the aspects of this class of drugs. It is important to align with gobal practices and thus one aim will be to analyze the various CS classes with respect to the side effect profile and one goal is to restrict the use of long-acting steroids, both in the oral and IV form as the side effects of these drugs can cause more harm than good. Some practices that are ingrained in certain centers, specially the use of dexamethasone pulses could possibly be reviewed in view of the markedly safer drug profile of methyl prednisolone.

History

The first CS to be isolated, in 1935, was the naturally occurring glucocorticoid hormone, cortisone.

It was synthesized in 1944 and subsequently became available for clinical use. In 1948, cortisone (then called compound E) was administered by the American physician Philip S Hench to a 29-year-old woman with active rheumatoid arthritis (RA) of longer than 4 years' duration with dramatic improvement. Her joints were so painful she could "hardly get out of bed." Hench published this case improvement in 1949 and won the 1950 Nobel Prize in Physiology or Medicine for his research.

In dermatology, the credit for the use of CS goes to Sulzberger and associates who in 1951 described the use of cortisone and ACTH in a variety of inflammatory dermatoses. To curtail the side effects of the drug, in 1961, Reichling and Kligman suggested alternate-day CS use. It is now a useful intervention to use adjuvant drugs like azathioprine and cyclophosphamide, to achieve a 'steroid-sparing' effect. The use of high-dose pulse intravenous (IV) methylprednisolone therapy has been used in certain select disorders, which is in striking contrast to the use of dexamethasone in India, a drug

that has potentially more side effects. But with the advent of novel drugs, with more specific action (Rituximab) the era of the use of high pulse therapy, is probably going to wane, in disorder like pemphigus.

Classification

The precursor molecule of all steroid hormones is cholesterol, which is also a building block for vitamin D and cell membranes and organelles. Steroid hormones can be classified on the basis of their main function into sex hormones (male and female), mineralocorticoids, and glucocorticoids. Sex hormones are synthesized mainly in the gonads, but also in the adrenal cortex. Although, separation of corticoids into the classes mineralocorticoids and glucocorticoids is not absolute it is more precise to use the term glucocorticoid.

No qualitative differences have been noted between the glucocorticoid effect of endogenous cortisol and that of exogenously applied synthetic glucocorticoids because these effects are, except for higher doses, predominantly genomic (see below).However, quantitative differences have been identified. The potency and other biologic characteristics of glucocorticoids depend on structural differences in the steroid configuration. The introduction of a double bond between the 1 and 2 positions of cortisol yields prednisolone, which has about **four times** more glucocorticoid activity than cortisol (Table 9.1). Addition of a six-methyl group to prednisolone yields methylprednisolone, which is about **five times** more potent than cortisol. All the aforementioned glucocorticoids also have a mineralocorticoid effect. The synthetic glucocorticoids triamcinolone and dexamethasone have negligible mineralocorticoid activity, however. There is an *inverse correlation* between the duration of action and the relative MC effect of the various CS.

Another aspect that determines the action is the form of the CS. Thus there are two forms, the free form (as alcohol) or chemically bound (as ester or salt). In their free form, glucocorticoids are virtually insoluble in water, so they can be used in tablets but not in parenteral preparations. Esters, such as (di)acetate and (hex)acetonide, are lipid soluble but have limited water solubility and are suitable for oral use and intramuscular, intralesional, and intra-articular injection. Salts, such as sodium phosphate and sodium succinate, are generally more water soluble and thus are also suitable for intravenous use.

Table 9.1: Overview of systemic steroids

	Equivalent dose (mg)	*Glucocorticoid potency*	*Mineralocorticoid potency*	*Protein Binding*	*Plasma Half-life (hours)*	*Biological half-life (hours)*
Short Acting						
Cortisone	25	0.8	0.8		0.5	8–12
Hydrocortisone (cortisol)	20	1	1	++++	1.5–2	8–12
Deflazacort (1,6,12,24 mg)	6–9	5	0.5	++	1.1–1.9 h	<12 h
Intermediate Acting						
Prednisolone (2.5, 5,10,20,50 mg)	5	4	0.6	+++	2.1–3.5	12–36
Methylprednisolone (2, 4, 8, 16 mg)	4	5	0.5	-	>3.5	12–36
Triamcinolone (4, 8 mg)	4	5	0	++	2 ≥ 5	12–36
Long Acting						
Dexamethasone (0.5,1,2 mg)	0.75	20–30	0	++	3–4.5	36–54
Betamethasone (0.5,1,2 mg)	0.6	20–30	0	++	3–5	36–54

Mechanism of Action

A. Genomic and Nongenomic Effects

Glucocorticoids at any therapeutically relevant dosage exhibit pharmacologic effects via classic genomic mechanisms. The lipophilic glucocorticoid after crossing the cell membrane, attaches to the cytosolic glucocorticoid receptor and heat shock protein, and binds to glucocorticoid-responsive elements on genomic DNA (Fig. 9.1). This process takes time (30 min). In case of pulse therapy, glucocorticoids act within minutes by *nongenomic* mechanisms; this occurs via specific receptor-mediated activity or via nonspecific membrane-associated physicochemical activity. The response to high-dose pulse methylprednisolone therapy may be biphasic, consisting of an early, rapid, nongenomic effect and a delayed and more sustained classic genomic effect (Lipworth BJ). Clinically, genomic and nongenomic effects cannot be separated, however.

Transactivation: The activated glucocorticoid receptor–glucocorticoid complex is translocated into the nucleus, where it binds (as a dimer) to specific sites in the DNA (glucocorticoid-responsive elements), regulating the transcription of a large variety of target genes (Fig. 9.1).

The binding of transcriptional factors to DNA is ***inhibited*** by glucocorticoids, resulting in depressed expression of these genes and inhibition of their amplifying role in inflammation. Activated glucocorticoid receptors also may inhibit protein synthesis by decreasing the stability of mRNA through the induction of ribonucleases.

Transrepression: Suppression of genes also may be mediated by mechanisms involving interaction of the glucocorticoid

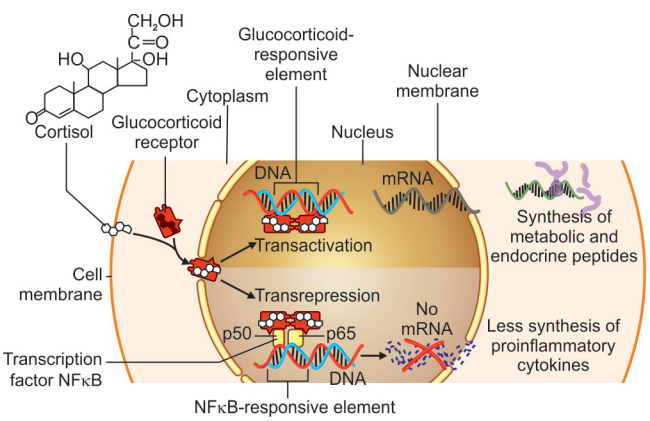


Fig. 9.1: Activation of transcription (transactivation) by binding of glucocorticoid receptor-glucocorticoid dimers to glucocorticoid-responsive elements of DNA up-regulates synthesis of regulatory proteins, thought to be responsible for metabolic effects and also some anti-inflammatory/immunosuppressive effects of steroids

receptor–glucocorticoid complex (as a monomer) with transcriptional factors, such as activator protein-1 and nuclear factor κB. Scheinman et al found that NFκB is biologically inactive as long as it is bound to IκB (inhibitor κB). NFκB is activated when any of a wide variety of biologic stimuli degrade IκB, thus freeing the NFκB to be an biologically active transcription factor. Free NFκB translocates to the nucleus, where it induces transcription of numerous cytokines (Fig. 9.2). There is tremendous overlap with the inflammatory response genes induced by AP-1 and NFκB (Foletta VC).

CS *reduces* the effects of NFκB by, increasing IκB formation, leading to subsequent NFκB binding by this inhibitory protein. Also the CS–GCR complex can directly bind to NFκB, thus inhibiting this transcription factor. The CS inhibition of AP-1 activation and DNA binding serves to further augment the biologic effects of NFκB inhibition by CS.

There is a prevalent hypothesis that *side effects* of glucocorticoids, such as diabetes mellitus, osteoporosis, skin atrophy, growth retardation, and cushingoid appearance, may be based predominantly on *transactivation* of genes after binding of glucocorticoid receptor–glucocorticoid to DNA, whereas the *anti-inflammatory* effects may be due mostly to the binding of a single glucocorticoid receptor-glucocorticoid complex to transcription factors or co-activators, resulting in gene repression (*transrepression*). Understanding of these molecular mechanisms may lead to development of novel glucocorticoids, such as selective glucocorticoid receptor agonists, with a more favorable balance of transactivation and transrepression and, clinically, to a more favorable balance of metabolic and endocrine side effects and therapeutic effects (Rhen T et al.).

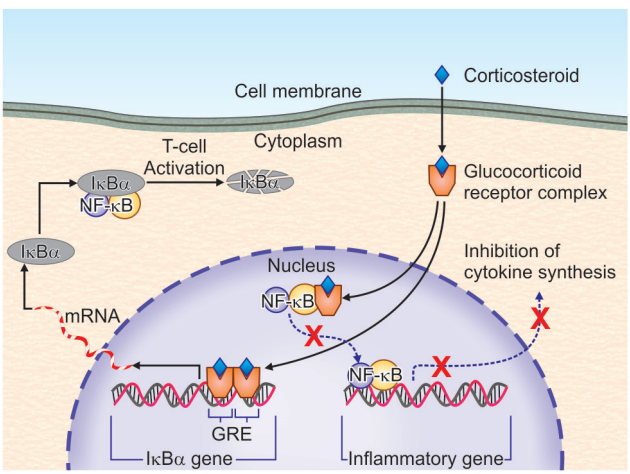


Fig. 9.2: Transrepression action of CS via IkB-α which leads to downregulation of NFkB

B. Immune System

Glucocorticoids reduce activation, proliferation, differentiation, and survival of a variety of inflammatory cells, (Table 9.2**)** including macrophages and T lymphocytes, and promote apoptosis, especially in immature and activated T cells. B lymphocytes and neutrophils are less sensitive to glucocorticoids, and their survival may be increased by glucocorticoid treatment.

1. Administration of glucocorticoids leads to an *increase* in the *total leukocyte* count caused by an increase in circulating *neutrophil* granulocytes in the blood, although the numbers of other leukocyte subsets in blood such as eosinophil and basophil granulocytes, monocytes/macrophages (decreased myelopoiesis and bone marrow release), and T cells (redistribution effect) are decreased. The redistribution of lymphocytes, which is maximal 4 to 6 hours after administration of a single high dose of prednisolone and returns to normal within 24 hours, and has ***no*** clinical consequences.

Table 9.2: Effects of glucocorticoids on immune cells and cytokines

Lymphocytes	Apoptosis of autoreactive T cells B cells: With higher CS doses significant B-cell effect, reduced immunoglobulin production T cells: (CD4 > CD8 effect);↓ IL-2 production (Th1 cells) ↓ natural killer (NK) cell activity, ↓ antibody-dependent cellular cytotoxicity mediated by K-cells
PMN	↓ PMN marginization, ↓ chemotaxis, increased blood count, unaltered function
Macrophages and monocytes	Decreased blood count, decreased trafficking, decreased phagocytosis and bactericidal effects, inhibited antigen presentation, decreased cytokine (↓ IL-1 and IFN-γ) and eicosanoid release
Eosinophils, basophils	Decreased blood count, increased apoptosis
Mast cells	Inhibit degranulation, with resultant ↓ release histamine, kinins, other mediators
Fibroblasts	↓ production of collagen, ground substance, fibronectin and collagenase
Langerhans cells	↓ characteristic surface markers, impaired antigen processing and presentation
Cytokines	↓ Th1 cytokines: IL-1β, IL-2, IL-3, IL-6, TNF, interferon-γ , IL-17 (indicative of Th17 helper cells), and granulocytemacrophage colony-stimulating factor Th2 cytokines: Unaffected or increased such as IL-4, IL-10, and IL-13 . At *high* doses they are *suppressed*
Inflammatory enzymes	↓ production of various prostaglandins, leukotrienes, 12-HETE ,15-HETE inflammatory mediators, COX 2 inhibiton

2. The major effect of CS is via the cytokines and is largely on the **Th1** cytokines at normal doses. At *high* doses it tends to suppress the Th2 response.

3 An important part of the inflammatory cascade is arachidonic acid metabolism, which leads to the production of prostaglandins and leukotrienes, most of which are strongly proinflammatory. Through the induction of lipocortin (an inhibitor of phospholipase A 2), glucocorticoids inhibit the formation of arachidonic acid metabolites. Glucocorticoids also have been shown to inhibit the production of COX-2 and phospholipase A 2 induced by cytokines in monocytes/macrophages, fibroblasts, and endothelial cells. In addition, glucocorticoids are potent inhibitors of the production of metalloproteinases in vitro and in vivo, especially collagenase and stromelysin, which are the main effectors of cartilage degradation induced by IL-1 and TNF.

4. Adhesion Molecules and Permeability Factors:

Pharmacologic doses of glucocorticoids dramatically inhibit exudation of plasma and migration of leukocytes into inflammatory sites. This is by modulation of the adhesion molecules, through inhibition of proinflammatory cytokines and by direct inhibitory effects on the expression of adhesion molecules, such as intercellular adhesion molecule-1 and E-selectin. Chemotactic cytokines attracting immune cells to the inflammatory site, such as IL-8 and macrophage chemoattractant proteins, also are inhibited by glucocorticoids. Nitric oxide production in inflammatory sites is increased by proinflammatory cytokines, resulting in increased blood flow, exudation, and probably amplification of the inflammatory response is also inhibited by glucocorticoids.

C. Hypothalamic–Pituitary–Adrenal Axis

There are three main endogenous controls for cortisol secretion (Fig. 9.3). The *first* control is the negative feedback effect that plasma cortisol has on inhibiting the secretion of CRH and ACTH by the hypothalamus and pituitary. The *second* control is the pulsatile secretion of ACTH based on a circadian rhythm. ACTH pulses begin to increase in amplitude 3 to 5 hours after the onset of sleep, reaching a maximum around the time of waking. Subsequently, these levels decline throughout the day, reaching a nadir 1 or 2 hours after beginning sleep. In persons who work at night, the diurnal pattern resets itself depending on sleep habits. The *third* control comes from neural effects on the hypothalamic-pituitary-adrenal (HPA) axis as a result of various emotional or physical stresses. These neural stimuli, which include

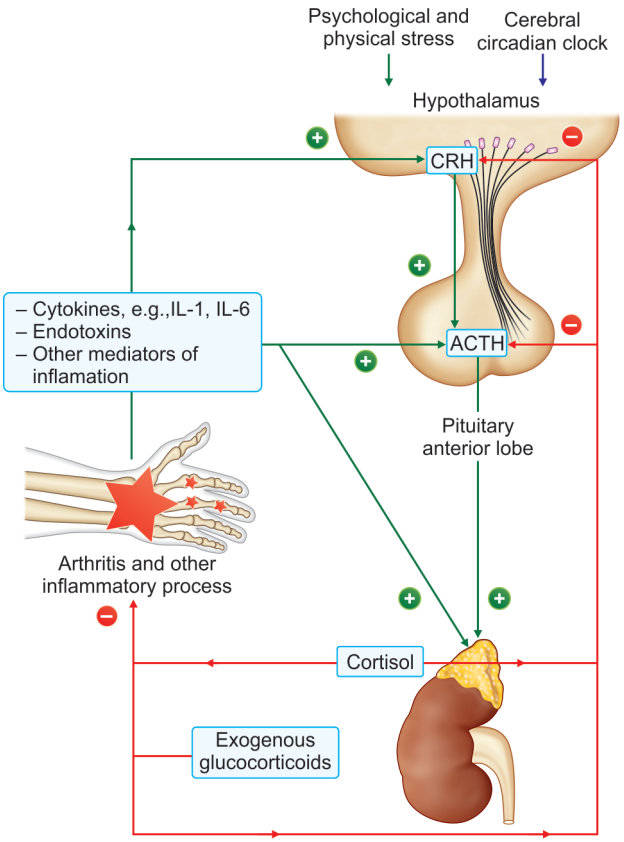


Fig. 9.3: Hypothalmine, pituitary–adrenal axis and its control mechanism

catecholamine production from the brain stem, CRH from sites other than the hypothalamus, and vasopressin, all contribute to regulation of HPA axis function.

Proinflammatory cytokines, activate corticotropin-releasing hormone (CRH) at the hypothalamic level. This activation stimulates the secretion of adrenocorticotropic hormone (ACTH). Chronic suppression of the hypothalamic-pituitary-adrenal axis by glucocorticoids leads by negative feedback loops on CRH and ACTH to failure in pituitary ACTH release, and thus to partial functional adrenal atrophy with loss of cortisol secretory capability in the fasciculata-reticularis zone. This inner cortical zone is the site of cortisol and adrenal androgen synthesis and is dependent on ACTH for structure and function. The outer cortical (glomerulosa) zone is involved in mineralocorticoid (aldosterone) biosynthesis and is functionally independent of ACTH. It stays functionally intact.

The hypothalamus is not only the site most susceptible to drug-induced suppression, but is also the quickest to recover after cessation of therapy. This relatively prompt recovery

occurs in most clinical scenarios within **14–30 days** after cessation of CS therapy. The **adrenal gland** is more **resistant** to suppression and, likewise, is **slower** to recover once CS therapy is stopped. Overall, the hypothalamus is the most important part of the axis in terms of stress responsiveness.

The time required to achieve suppression depends on the *dosage* and the *serum half-life* of the glucocorticoid used, and the *individual* differences in glucocorticoid sensitivity and rates of glucocorticoid metabolism. Prediction with certainty of chronic suppression of the hypothalamic-pituitary-adrenal axis and adrenal insufficiency is impossible.

Secondary adrenal insufficiency generally has a less dramatic presentation than primary adrenal insufficiency because aldosterone levels, which are controlled predominantly by the renin-angiotensin system, are preserved; mineralocorticoid therapy is not necessary.

The duration of the anti-inflammatory effect of one dose of a glucocorticoid approximates the duration of hypothalamic-pituitary-adrenal suppression (Cooper et al.). Thus a wide variation exists between the various steroids (Table 9.3), though with chronic therapy, it is accepted that a duration of more than **3 weeks** leads to adrenal suppression, for variable lengths of time (Table 9.3). Patients who have received glucocorticoids for less than 3 weeks or have been treated with alternate-day prednisolone therapy do *not* have zero risk of suppression of the hypothalamic-pituitary adrenal axis, depending on the dose, but the risk is low (Ackerman GL, Schlaghecke R).

Cortisol levels generally range from 5 to 30 mg/dL, with levels up to 60 mg/dL with physical stressors. With prolonged therapy, cortisol levels **<10 μg/dL** suggest impaired basal HPA axis function. Thus before stopping chronic therapy a test of the basal cortisol level is advisable to prevent adrenal crisis (see below).

Absorption and Distribution

Most orally administered glucocorticoids, whether in free form or as an ester or salt, are absorbed readily, probably within about 30 minutes.

1. Plasma-protein Binding

The affinity of the different glucocorticoids for various plasma proteins varies (see Table 9.1). Of cortisol in plasma, 90% to 95% is bound to plasma proteins, primarily transcortin (also called corticosteroid-binding globulin) and, to a lesser degree, albumin. Protein-bound cortisol is ***not*** biologically active, but the remaining 5–10% of free cortisol is. Prednisolone, in contrast to methylprednisolone, dexamethasone, and triamcinolone, has high affinity for transcortin and competes

Table 9.3: Overview of HPA axis suppression with corticosteroids use

Basal secretion	Cortisol : 5.7 to 10 mg/m^2/d = 15–25 mg cortisol = 4–6 mg prednisolone
Suppression (days)	**a. Single Dose** 1. 50 mg of prednisolone/40 mg of methylprednisolone= 1.25–1.5 days 2. 40–80 mg of methylprednisolone= 4 to 8 days 3. 40 mg of triamcinolone/5 mg of dexamethasone = 2.25 and 2.75 days 4. Intramuscular administration 40 to 80 mg triamcinolone acetonide=2–4 weeks **b. Chronic Therapy** 1. 7.5 mg of prednisolone or equivalent or more for at least 3 weeks more risk. 2. Glucocorticoids < 3 weeks or alternate-day prednisolone therapy less risk. 3. 25 mg of prednisolone or equivalent daily—5–30 days causes suppresson in 45% of cases. **c. Other Factors** 1. Doses significantly exceeding physiologic levels for at least 3–4 wks 2. Divided-dose regimens 3. Single-dose therapy given in the evening 4. Longer-acting CS preparations
Recovery	Short course of therapy= 14–30 days after cessation Chronic Therapy: 6–9 months after cessation
Tests	8 AM Cortisol test value >10 µg/dL indicates a normal adrenal response

with cortisol for this binding protein. The other synthetic glucocorticoids with little or no affinity for transcortin are two-thirds (weakly) bound to albumin, and about one-third circulate as free glucocorticoid. Thus as only unbound glucocorticoids are pharmacologically active, patients with low levels of plasma protein, such as albumin (e.g. because of liver diseases or chronic active inflammatory diseases), are more susceptible to both effects and side effects of glucocorticoids.

CBG is decreased by hypothyroidism, liver disease, renal disease, and obesity, all of which may result in increased amount of the endogenous and synthetic CS free fraction. CBG is *increased* by estrogen therapy, pregnancy, and hyperthyroidism, all of which may reduce the free fraction of endogenous and synthetic CS. High-dose therapy and prolonged CS treatment typically increases the free fraction of the drug. Thus of the intermediate-acting steroids **methylprednisolone** which has negligible protein binding is least affected by the variables and is a good choice for *short* duration therapy.

2. Half-life

Glucocorticoids have biologic half-lives 2 to 36 times longer than their plasma half-lives (see Table 9.1). Maximal effects of glucocorticoids lag behind peak serum concentrations, this

is as transcortin binds these compounds more strongly than does albumin. The plasma elimination of glucocorticoids bound to transcortin is slower than that of glucocorticoids that do not bind (see Table 9.1).

Synthetic glucocorticoids have ***lower*** affinity for transcortin but ***higher*** affinity for the cytosolic glucocorticoid receptor than does cortisol. The affinity of prednisolone and triamcinolone for the glucocorticoid receptor is approximately ***two*** times higher, and for dexamethasone it is ***seven*** times higher.

A much more important measure of duration of activity is the duration of ACTH suppression after the administration of a single dose of a given CS. This duration of activity correlates well with glucocorticoid and anti-inflammatory effects.

3. Rate of Metabolism

Pharmacologically active glucocorticoids are metabolized primarily in the liver into inactive metabolites and are excreted by the kidneys. An inverse correlation has been noted between prednisolone clearance and age, which means that a given dose may have a greater effect in older individuals. In patients with cirrhosis of the liver, clearance of unbound steroid is about two-thirds of normal—a difference that should be taken into account with dosing.

Pulse Therapy

The pharmacologic effects of a single pulse dose last for about **2 days**. Whether these effects differ quantitatively or qualitatively from the effects of smaller, split doses of GCs is unclear. Doubling the dose of GC increases the time of action by one half-life. When a 10 mg dose of methylprednisolone, with a half-life of 3 hours and a duration of action of 10 hours, is doubled seven times to 1280 mg, the action has been prolonged by 21 hours to 31 hours. Thus a huge *increase* in dose is associated with only a *modest increase* in duration of action. This example assumes that the pharmacokinetics is linear and not dose dependent, which is unknown.

The effect of GCs on neutrophil and lymphocyte number is short lived with peak effects at 4–6 hours after the pulse, with a return to baseline within **24 hours**. GC suppression of the hypothalamic-pituitary-adrenal axis is short-lived after a pulse, with recovery after **2–3 days.**

As prednisolone at a dose of 200–300 mg results in nearly complete occupation of all the GC receptors in an adult because 7.5 mg and 15 mg of prednisolone results in 42% and 63% binding of receptors. It is possible that higher doses, such as those seen with GC pulse therapy, may result in additional therapeutic benefit because of the **nongenomic** effects.

Uses

Corticosteroids form the basis of therapy of numerous disorders (Table 9.4), though in most cases adjuvants are needed, which is proof both of the lack of its curative potential and its potential side effects. It is important to understand that in some indications, like vitiligo and alopecia areata, there is little evidence for their use and the relapses after stopping therapy are a deterrent to their use. Pulse therapy is only approved for lupus nephritis, where methylprednisolone is used worldwide.

Table 9.4: Indications of GCS in dermatology

	Disorder (FDA approved)	*Unapproved*
Connective tissue diseases	Dermatomyositis Juvenile idiopathic arthritis Lupus erythematosus (systemic) Reactive arthritis Rheumatic fever Rheumatoid arthritis	Mixed connective tissue disease Polymyalgia rheumatic Sjögren's syndrome, Primary systemic sclerosis
Bullous	Bullous pemphigoid Erythema multiforme minor Pemphigus vulgaris Stevens–Jöhnson syndrome/TEN	Cicatricial pemphigoid Epidermolysis bullosa acquisita Herpes gestationis Linear IgA bullous dermatosis
Dermatitis		Atopic dermatitis Contact dermatitis Exfoliative erythroderma
Neutrophilic dermatoses		Behçet's disease/ aphthous ulcers Pyoderma gangrenosum Sweet's syndrome
Autoimmune dermatoses		Alopecia areata Lichen planus Psoriasis Vitiligo
Vasculitis		Cutaneous Systemic
Other dermatoses		Sarcoidosis Sunburn Urticaria Androgen-excess (acne/ hirsutism) Postherpetic-neuralgia
Pulse therapy		
	Lupus nephritis (with cyclophosphamide)	Pyoderma gangrenosum Pemphigus vulgaris Bullous pemphigoid Sweet's syndrome Urticarial vasculitis Alopecia areata

In dermatological disorders, like pemphigus, good quality evidence does not show a superiority over conventional interventions. In fact in pemphigus, the high cure rates have been with regimens where oral steroids have been added for variable periods of time and include mild to moderate case of pemphigus, where pulse therapy is not needed. It is a global opinion that pulse forms should be used only for severe forms of disease as the only advantage they have is with regard to the B cell suppression which is more rapid than with oral forms of therapy. A list of indications and summary of dose regimens is given in Tables 9.4 and 9.5 as an easy reckoner.

Acne

Patients with severe inflammatory acne vulgaris, acne fulminans, and pyoderma faciale should be given oral prednisolone (0.5–1.0 mg/kg daily) for 4–6 weeks; then the dose should be tapered. In acne fulminans and pyoderma faciale it is preferable to use steroids for 3–4 weeks ***before*** administering isotretinoin. Similar, oral doses are also indicated for patients whose acne flares up remarkably while on isotretinoin [Cunliffe WJ].

In practise, the clinician *anticipates* a flare and steroid are initiated as acne worsening is observed between the *third* and the *sixth week* and may be very severe and even trigger genuine manifestations of acne fulminans. This has been termed "**pseudo" acne fulminans**, since systemic features are minimal or almost absent, and no pyrexia occurs. *P. acnes* destruction is thought to result in mediator release, inducing neutrophil chemotaxis, which may be responsible for flares detected during isotretinoin therapy. Patients who develop severe flares may be exhibiting an exaggerated tissue response [Jansen T]. It has also been suggested that isotretinoin induces increased fragility of the pilosebaceous duct, which leads to a massive contact with *P. acnes* antigens.

A long-term study showed that the simultaneous use of isotretinoin and corticosteroids in very inflammatory and severe acne from the start of therapy avoided the early exacerbation phenomenon that an antigen–antibody reaction may trigger.

The therapy scheme applied includes three steps:

1. Firstly weight-dependent doses (e.g. 80 kg) of an initial isotretinoin dose of 20 mg/day for a week, with slow dose increases until the desirable dose of 1 mg/kg/day was reached by the **sixth week** (150 mg/kg).
2. Methylprednisolone initiated at a starting dose of 40 mg *alternate* day (***32 mg*** in India) for **6 weeks.**

Table 9.5: A summary of use of systemic CS in various dermatoses

Indication	*Adjuvant drugs*	*Dose* (Prednisolone/equivalent)*				*Pulse*	*IL/IM*
		Low	*Medium*	*High*	*Very High*		
Aphthous stomatitis	Colchicine Thalidomide Dapsone Pentoxifylline			1 mg/kg (40–60 mg) × 14 d			
Alopecia areata	AZA				Yes	Methylprednisolone (8 mg/kg/d) >30% involvement	
Acne (NCCAH)		0.125–0.375 mg (Dexa) or Prednisolone 5–7.5 mg HS					
Acne conglobata fuminans			0.5–1 mg/kg/d X 4–6 weeks (Isotretinoin 0.25–1 mg/kg/d)				Yes
Acute dermatitis (for 3 wks)				1 mg/kg (40–60 mg) over 2–3 weeks			

Contd...

Contd...

Pemphigus (Long course)	AZA CYCLO MMF (Rituximab)			1–2 mg/kg/d (120–140) Aim to taper off to 40 mg in 4–6 weeks		Yes in severe cases	
Bullous pemphigoid (3–6 m)	AZA Dapsone Tetracycline			1mg/kg/d Aim to taper in 2 months		No	
Cicatricial pemphigoid	MMF AZA CYCLO Dapsone			1–1.5 mg/kg			
SJS/TEN	Supportive Cyclosporine IV IgG					2–2.5 mg/kg Methylprednisolone	
Erythema multiforme minor (2-3 week)	Antiviral		1 mg/kg				
Lichen planus	Cyclosporine Dapsone AZA			40–60 mg tapered over 4–6 weeks			Yes

Contd...

Contd...

SLE (only severe disease) Subacute cutaneous LE Lupus panniculitis Bullous LE Systemic LE/Acute LE	Antimalarials Dapsone Retinoids Thalidomide	20 mg prednisone alternate day to a maximum of 60 mg daily (For severe skin disease)				Yes in severe cases	
DM (slow taper over 3-6 m)	AZA MTx Antimalarials			1–1.5 mg/ kg daily.			
Vasculitis (only for severe cases)	Colchicine Dapsone Indomethacin			1 mg/kg daily Taper to 20 mg alternate day			
Pyoderma gangrenosum	Dapsone Azathioprine		40–60 mg , taper to low-dose alternate-day therapy			methylprednisolone	

*(**Low dose** ≤7.5 mg prednisolone or equivalent per day; **Medium dose** >7.5 mg, but ≤30 mg prednisolone or equivalent per day; **High dose** >30 mg, but ≤100 mg prednisolone or equivalent per day; **Very high dose** >100 mg prednisolone or equivalent per day; **Pulse therapy** ≥250 mg prednisolone or equivalent per day for 1 day or a few days)
Abbreviations: AzA, Azathioprine; MTx, methotrexate; CYCLO, cyclophosphamide; MMF, mycophenolate mofetil

3. At 6 weeks progressively decreasing to discontinue the corticosteroid by the **tenth week**, and to then continue with isotretinoin as sole therapy.

With the simultaneous administration of isotretinoin and corticosteroids for the severe types of inflammatory acne (nodules, abscesses, cysts), this serious manifestation may be prevented. Consequently, this combination therapy prevents the development of "pseudo" acne fulminans as a complication derived from the use of isotretinoin (Kaminsky A).

Alopecia Areata

Systemic corticosteroids have been used for decades in patients with extensive AA. Several regimens have been used with varying success. The only randomized placebo-controlled study on oral prednisolone was published in 2005 (Kar BR). Forty-three patients with extensive AA were randomized to receive prednisolone 200 mg weekly or placebo. The treatment period was 3 months followed by 3 months of observation time. Significant hair regrowth was noted in 35% of patients in the treatment group compared with none in the placebo group. The relapse rate was 25% during the observation period. Significant hair regrowth was noted in 28 of 34 patients (82%) with extensive AA treated with prednisolone 300 mg once monthly for 3–6 months (Ait Ourhroui M). Poor response was associated with presence of other autoimmune abnormality, nail involvement, and universalis form. Only 15% of the patients had side effects in that report.

Other systemic corticosteroids regimens include prednisolone 40 mg daily tapered over 6 weeks, dexamethasone 5 mg on 2 consecutive days weekly, intravenous methylprednisolone 250 mg twice daily on 3 consecutive days monthly, dexamethasone 0.5 mg daily for 6 months, intramuscular triamcinolone acetonide 40 mg monthly, and prednisolone 80 mg daily on three consecutive days every 3 months.

The reported relapse rate is 14–100% (Alsantali A). The addition of 2% topical minoxidil 3 times daily may alleviate poststeroid relapse (Olsen EA). Thus systemic steroids used in AA is not a favored option because of the side effect profile and high relapse rate.

Acute Febrile Neutrophilic Dermatosis (Sweet's syndrome)

A short course of systemic glucocorticoids remains the treatment of choice for Sweet's syndrome. In addition, a positive response to corticosteroid therapy is a minor criterion for the diagnosis. The recommended dose of prednisolone is 0.5–1.5 mg/kg/d tapered over 4–6 weeks. Both the systemic symptoms and the cutaneous lesions will resolve

within a week of therapy, although relapses occasionally do occur. Identification of the underlying cause and its potential eradication are important in the prevention of relapse.

Atopic Dermatitis

In general, the use of systemic glucocorticoids to treat atopic dermatitis in both children and adults is ***not*** recommended. Although effective at achieving rapid control of the signs and symptoms, atopic dermatitis is by definition a chronic, relapsing disease and steroid-sparing alternatives should be sought by the dermatologist.

There is a small subset of patients with exceptionally severe disease who may benefit from short courses of oral or intramuscular glucocorticoids in order to treat recalcitrant lesions or acute exacerbations, but it is a good practice to treat the bacterial superinfection, which in my experience is the trigger in most cases.

Behçet's Disease

Because topical steroids can sometimes be effective at resolving the mucocutaneous ulcers of Behcet's disease, systemic GCS are reserved for the most severe cases with a short to intermediate duration of treatment. Intravenous pulse therapy with methylprednisolone 1 g on three alternate days or prednisolone 1 mg/kg per day tapered over several weeks are recommended doses. For the long-term treatment of Behcet's disease, steroid-sparing options such as colchicine and thalidomide are preferable.

Hemangiomas

For the life-threatening or functionally disruptive infantile hemangioma, high-dose systemic corticosteroids are an important treatment in preventing complications, such as airway blockage, ulceration with secondary infection, and visual obstruction. The recommended dose is 2–3 mgkg/day for at least 8 weeks followed by a slow taper. The average response rate to a mean dose of 2.9 mg/kg/day was 84% and the average rebound rate upon withdrawal of therapy was 36%. A lesser response was noted in doses <2 mg/kg/day. With an approval for propanolol there is little justification in giving steroids except in Kasabach–Meritt syndrome

Herpes Zoster and Postherpetic Neuralgia

There is considerable controversy over the use of systemic corticosteroids for both the acute neuralgia of herpes zoster and the prevention of postherpetic neuralgia. The optimal dose of prednisolone is 40–60 mg daily for 1–3

weeks with or without a rapid taper. There are certain indications for the use of CS including, (i) patients with facial involvement, (ii) patients with severe acute pain during the cutaneous eruption, and (iii) patients over 55–60 years of age, where using combined antiviral and CS therapy, initially in the disease course is useful.

It must be pointed out that the initial data of the use of CS was with acyclovir and the newer antivirals have a higher bioavailability and here such a steroid use may not be warranted.

Kerion

Kerion is an acute inflammatory hypersensitivity reaction that can accompany dermatophyte infection of the scalp. Scarring alopecia can occur as a consequence of kerion, and systemic GCS are believed to prevent this complication. This is to be given ideally in combination with oral antifungals.

Lichen Planus

Systemic GCS in the form of 40–60 mg of prednisone daily tapered over 4–6 weeks is effective is clearing widespread lichen planus. However, relapses are common when GCS are withdrawn, and an alternative therapy with steroid-sparing agents may be necessary to provide the patient with lasting remission.

Pemphigus

Though this a common indications, there is a shift from the high dose regimens to the use of adjuvants.

Adjunctive therapy generally employed include (i) azathioprine, (ii) cyclophosphamide, (iii) cyclosporine, (iv) methotrexate, (v) mycophenolate mofetil, or (vi) plasmapheresis. Rituximab has changed the therapy, with its superlative results.

Pulse methylprednisolone may be used to attain rapid disease control in severe cases of pemphigus vulgaris though in India the pulse dexamethasone and cyclophosphamide is used for such cases. The dose used initially is high (2 mg/kg daily in divided doses) and can be reduced gradually after new lesions stop appearing (see below). Disease control is usually attained by 4–6 weeks. Once a dose of 40 mg is reached tapering can be initiated (see in Fig 9.3). The ideal adjuvant ranges from azathioprine (mild-to-moderate case) to cyclophosphamide (severe cases).

Pulse therapy: The most extensive evaluation of pulse IV CS therapy has been for pemphigus vulgaris and a research paper by Roujeau et al, examined six different studies regarding pulse IV-CS for pemphigus vulgaris, found that this

modality had comparable results to traditional therapy with 1–2 mg/kg daily prednisolone starting dose, with or without adjunctive immunosuppressive therapy. In India, we give pulse cyclophosphamide and dexamethasone, with oral steroids in severe cases with oral cyclophosphamide. There has never been any scientific logic of giving cyclophosphamide *both* as oral and IV except in lupus nephritis (which has been discussed in the chapter on cylophosphamide), but the DCP therapy combines multiple modes of therapy and thus it is difficult to judge the superiority of dexamethasone in this regimen. Methylprednislone due to its favorable profile is a better agent.

Bullous Pemphigoid

In patients with bullous pemphigoid, moderate doses of CS up to 1 mg/kg daily are used for a period of 3–6 months or less, with a goal to achieve ideally a physiologic dose range within 1–2 months. In adults azathioprine and in children dapsone is the preferred adjuvant.

Cicatricial Pemphigoid (Mucous Membrane Pemphigoid)

Cicatricial pemphigoid is less responsive to steroids and the main therapy lies in the judicious use of systemic immunosuppressives, like mycophenolate mofetil (moderate disease), though other agents used include azathioprine, cyclophosphamide, cyclosporine, and methotrexate. For ocular disease cyclophosphamide in combination with systemic CS is the choice. Steroids are used in a dose of 1–1.5 mg/kg daily of prednisolone.

Sarcoidosis

Both pulmonary and certain types of cutaneous sarcoidosis are treated with systemic GCS as a first-line therapy, in a dose of 40 mg of prednisolone daily until regression of the infiltrated lesions is observed, which generally occurs within 2–3 months of therapy, at which point it can be tapered. Long-term, low-dose therapy is often indicated, especially for pulmonary disease, and a corticosteroid-sparing alternative agent such as methotrexate or hydroxychloroquine is often used to minimize the dose of prednisolone.

Stevens–Jöhnson Syndrome and Toxic Epidermal Necrolysis

The trend is to move away from steroids, to cyclosporine, immunoglobulin or conservative therapy (Kirchhof MG, Bansal S). If the patient presents in the first 48 hours there is a role of high dose steroids. Thus if the patient

presents late (>2 days) routine care in burn unit care is a better option. This is as there is a a high fatality rate, particularly from sepsis, in CS-treated patients, than in patients managed in a burn unit without CS therapy.

Thus, systemic CS can be used (Tripathi A), **early** in the disease course (before significant sloughing of skin), followed by rapid tapering of CS, but after widespread sloughing occurs (>10% of total surface area), the risk of infection clearly outweighs the potential CS benefits. Thus in a ideal scenario steroid can be used in a dose of 2–2.5 mg/kg daily of IV methylprednisolone in divided doses, with relatively rapid tapering to more moderate doses when new blister formation ceases.

Lupus Erythematosus

Because of the efficacy of topical and intralesional steroids for localized disease and the efficacy of steroid-sparing agents for widespread disease, systemic GCS plays a limited role in the treatment of discoid lupus erythematosus without systemic involvement.

The indications include, cutaneous vasculitis, bullous lupus erythematosus, as well as wide spread disfiguring discoid lupus erythematosus. Subacute cutaneous LE and lupus panniculitis are two subtypes of cutaneous LE that may respond to systemic GCS. In SLE, systemic GCS is a first-line agent useful in controlling internal organ involvement.

When psychosis develops in patients with SLE on GCS, it may be difficult to determine if the psychosis is the result of the underlying disease or due to the steroid. If GCS doses are reduced, steroid psychosis should improve, whereas mental status should worsen or remain the same in case of lupus encephalopathy.

Dermatomyositis

Long-term therapy is often required to control the myositis with the addition of an immunosuppressive agent either initially or later in the course as the patient is weaned off the GCS.

Corticosteroid-sparing agents should be used early in this disorder after initial control is obtained, as GCS may actually increase the tendency for muscle atrophy. The initial dose is prednisolone is 1 mg/kg per day for weeks to months with a slow taper (3–6 months). During the weaning process, the patient is monitored closely for rebound of myositis with clinical examination and muscle enzyme levels. Ordinarily, an immunosuppressive agent is required and options include methotrexate, azathioprine, and intravenous immunoglobulin.

Steroid myopathy can be confused with worsening of myositis. The former is seen with dexamethasone and

Table 9.6: A comparison of steroid myopathy and myositis

Steroid myopathy	*Myositis*
Normal CK	Elevated CK
Normal EMG	Abnormal EMG
Muscle biopsy shows atrophy	Muscle biopsy shows myositis
Improves with decreased steroid dose	Worsens with decreased storoid dose
Weakness without myalgias	Weakness plus myalgias
Likely with high doses	Unlikely with high doses
Urine creatine elevated but decreases with decreased dose	Urine creatine elevated but increases with decreased dose

triamcinolone but it can occur with long-term prednisolone therapy. The **(Table 9.6)** above summarizes methods of distinguishing steroid myopathy from myositis.

Vasculitis

Although nonsystemic cutaneous vasculitis usually resolves spontaneously with identification and eradication of a trigger, the treatment of chronic cutaneous vasculitis may necessitate systemic GCS in order to achieve remission.

The *indications* of CS include gastrointestinal, renal, and joint involvement and selected cases of chronic cutaneous leukocytoclastic vasculitis with ulcers, infarction, or persistent painful lesions (1 mg/kg daily of prednisolone). Rapid tapering to alternate-day dosing of prednisolone 20 mg (or less) is successful in maintaining the improvement achieved by daily doses.

Adjuvants used include dapsone, colchicine and indomethacin. High doses of systemic corticosteroids, along with cyclophosphamide, methotrexate, or azathioprine, is the first-line therapy for severe, multisystem vasculitis in which skin lesions are only one component of the disease.

Vitiligo

Oral Minipulse Steroid: The oral minipulse steroid (OMP) therapy with either betamethasone or dexamethasone can arrest the progression of the spreading disease, but this modality has been grossly overused and misused. It is of little clinical use in stable vitiligo and does not lead to repigmentation of the lesions. Even the original trials in India have never claimed to achieve complete pigmentation.(Pasricha JS).

Moreover, the results from other centers in India and abroad do not share the excellent repigmentation reported by the original study. Also, the dose of 5 mg every day for two consecutive days per week is not necessary in all cases. In a land-mark study, (Rath et al. 2008) used OMP with

phototherapy in a four-arm study and it was found that oral minipulse of steroids had only an adjunctive value and was **not** effective by itself.

Dose: It can vary from 2.5 to 7.5 mg. With the dose of 5 mg/d, it is tapered off in 6 months while with 2.5 mg/d, the treatment can be stopped abruptly. In western literature, a different regimen is followed where low-dose oral corticosteroids (0.3 mg/kg/d) is given for a 4-month course.

Pyoderma Gangrenosum

A short-term course of high doses of prednisolone (1–1.5 mg/kg/day) is a highly effective treatment for healing the acute lesions of pyoderma gangrenosum. Intravenous pulse therapy with methylprednisolone has also been advocated. A corticosteroid-sparing alternative agent or low doses of systemic GCS, however, will often be necessary for maintaining remission as the disease frequently recurs. Thus, dapsone and azathioprine are often co-prescribed.

Acute/Subacute Eczema

Severe acute contact dermatitis requires a 2–3-week burst of systemic CS therapy. If given for a shorter time (10–14 days) a rebound can occur.

Dose

The use of CS should be proceded by a checklist (Box 9.1), but a few basic tenets are enshrined below, which will be discussed before focusing on the dosage regimens.

1. For most dermatological indications, ***short- and intermediate-*** acting steroids are preferable. For serious conditions (pemphigus) a slow taper (longer intervals) is advised.
2. For duration <3 weeks, the limit for HPA axis suppression, tapering is not required.

Box 9.1: Contraindications to oral steroid therapy

Absolute	Ocular herpes simplex\Untreated tuberculosis
Relative	Acute or chronic infections Pregnancy Diabetes mellitus Hypertension Peptic ulcer Osteoporosis Psychotic tendencies Renal insufficiency CHF (excluding that secondary to active rheumatic carditis) Diverticulitis Recent intestinal anastomoses

Box 9.2: Dose regimens for steroids

Low dose	≤7.5 mg prednisolone or equivalent per day
Medium dose	>7.5 mg, but ≤30 mg prednisolone or equivalent per day
High dose	>30 mg, but ≤100 mg prednisolone or equivalent per day
Very high dose	>100 mg prednisolone or equivalent par day
Pulse therapy	≥250 mg prednisolone or equivalent per day for 1 day or a few days

3. The dosage range from low to high and are based on pathophysiologic and pharmacokinetic data (Box 9.2).
4. There are two regimens of administering prednisolone, *daily* and *alternate* day regimens. The later is useful in case of long-term usage and is usually employed with intermediate-acting steroids.

   Alternate-day therapy uses a single dose administered every other morning, which is usually equivalent to, or higher than, twice the usual or preestablished daily dose. The rationale for this regimen is that the body, including the hypothalamic–pituitary–adrenal axis, is exposed to exogenous glucocorticoid only on alternate days. This rationale makes sense ***only*** for usage of glucocorticoid that suppresses the hypothalamic-pituitary-adrenal axis activity for less than 36 hours after a single dose (Table 9.1). ***Another*** prerequisite is that the patient should have a responsive hypothalamic–pituitary–adrenal axis that is not chronically suppressed by previous glucocorticoid regimens. The alternate-day schedule does ***not*** work in patients on **long-term** *medium- or high-dose* glucocorticoids suppressing hypothalamic-pituitary-adrenal axis activity for longer than 36 hours (Table 9.1). Though in dermatology this regimen is actively promoted, in rheumatology, it is rarely used, except in juvenile idiopathic arthritis, where alternate-day glucocorticoid usage results in less inhibition of body growth than is associated with daily usage.
5. The ideal steroid is one with minimal protein binding, short acting and minimal MC action. As seen in Table 9.1 *deflazacort, methylprednisolone* satisfy these conditions. Due to costs, prednisolone is generally the systemic CS of choice for most dermatoses as they have been standardized for most conditions treated. Also for alternate day therapy, a intermediate-acting drug is useful thus prednisolone and methyl prednislone are ideal drugs for most indications.

   Deflazacort (Eberhardt R) an oxazoline derivative of prednisolone introduced in 1969, was initially thought to be as effective as prednisolone while inducing fewer adverse events, but there is the issue of the real equivalence

ratio compared with prednisolone (Saviola G) thus this drug has not represented a major breakthrough. The one advantage though is the short duration of action which makes it safer for acute dose regimens.

6. **Oral Mini Pulse therapy:** OMP refers to giving a higher than the usual daily dose of corticosteroid on two consecutive days, a week and leaving the remaining five days treatment-free. A long-acting corticosteroid is preferred so that the effect lasts for about 3 days at a time. Hence, it is preferred to give a long-acting corticosteroid on two consecutive days in a week rather than once in three days to give the hypothalamic–pituitary–adrenal axis (HPA) time to revert back to normal before the next dose. The standard regimen is to give oral betamethasone 5 mg (5 tablets of the 1 mg betamethasone tablets) after breakfast on Saturday and Sunday (or any other two consecutive days) every week. But the ideal drug to administer is dexamethasone which has been used in doses of 5 mg or 10 mg, as betamethasone has no non-genomic effect.
7. **Injectable Glucocorticoids**
   They are classified according the duration of the suppression of the inflammatory reaction.
   - Short acting (hours to days)
     - Dexamethasone sodium phosphate
     - Methylprednisolone
   - Intermediate acting (1–2 weeks)
     - Betamethasone acetate
     - Betamethasone sodium phosphate
     - Dexamethasone acetate
     - Triamcinolone diacetate
   - Long acting (3 to 4 weeks)
     - Triamcinolone acetonide
     - Triamcinolone hexacetonide.

Most commonly, triamcinolone acetonide is used and the concentration depends on the site of injection and the nature of the lesion (Box 9.3). Lower concentrations (2–3 mg/mL) is used on the face to prevent atrophy of the skin, whereas keloids may require concentrations of 40 mg/mL. It is best to limit the total monthly dose of Triamcinolone acetonide to 20 mg to assure that the hypothalamic-pituitary-adrenal axis is not suppressed. There are serious drawbacks to intramuscular administration because of erratic absorption and lack of daily control of the dose. Because, Triamcinolone acetonide is longer, acting than prednisolone, there are more potential side effects, including increased hypothalamic-pituitary-adrenal (HPA) suppression and myopathy.

For IV dosing (Box 9.4), methylprednisolone is used in a dose of 500 mg to 1 g daily because of its high potency and low

Box 9.3: Overview of IM (intramuscular) steroids

Salient features	Constant levels without diurnal variance Absorption is highly variable from patient to patient HPA-axis suppression: 3–4 weeks after a single dose Interval: Shorter interval leads to higher suppression of HPA axis MOA: Marked suppression of B lymphocytes with pulse CS therapy than with standard doses of oral CS probably due to CS-induced apoptosis
Choice of steroid	Acute dosage: Short- to intermediate-acting products (methyl prednislone/hydrocortisone) Chronic dosage: Triamcinolone acetonide (3–4 injections per year)
Side effects	Acute: Cardiac arrest (acute electrolyte shifts), atrial fibrillation, anaphylaxis

Box 9.4: Overview of pulse steroids

Salient features	High dose short duration (Pulses are usually given daily for 3–5 days) First use for pyoderma gangrenosum by Johnson and Lazarus in 1982 It decreases antibody production by B lymphocytes, with maximal effect occurring 2 to 4 weeks
Choice of steroid	1. **Methylprednisolone** (roughly 10–15 mg/kg daily; 500–1000 mg) is given IV over at least 60 minutes. This dose is repeated on a daily basis for 5 consecutive days (Preferred as it is short acting, has less side effects, less protein binding) 2. **Dexamethasone:** 2 to 5 mg/kg (50–200 mg) Always give a slow infusion over 3 hours
Side effects	**Minor:** Acute psychosis, depression, metallic taste, reversible memory impairment, facial flushing, hiccups, arthralgias, and hyperglycemia
	Severe: Cardiac arrhythmias, hypotension or hypertension, electrolyte abnormalities, aseptic necrosis, sepsis, seizures, gastrointestinal bleeding or perforation, anaphylaxis, pulmonary edema and congestive heart failure, and sudden death

sodium-retaining activity. Serious side effects associated with intravenous administration include anaphylactic reactions, seizures, arrhythmias, and sudden death. Other adverse reactions include hypotension, hypertension, hyperglycemia, electrolyte shifts, and acute psychosis. Slower administration over 2–3 hours has minimized many of the serious side effects. It is important to monitor serum electrolytes before and after pulse therapy, particularly when patients are on concomitant diuretic therapy. Recent studies suggest that doses that are less than the traditional high-dose (1 g methylprednisolone

daily for 3 days) IV pulse therapy may be equally efficacious and safer.

Dosage Regimens (Fig. 9.4)

Acute dosage options : This is reserved for acute disorders including eczema and occasionally acne fulminans. The ideal drug is an intermediate-duration CS such as prednisolone. The ideal regimen involves a single morning dose, which approximates the body's own diurnal variation of cortisol production. Divided doses, given twice daily, are reserved for acute therapy for severe, potentially life-threatening illnesses such as pemphigus vulgaris and will cause more HPA axis suppression. Physiologic (replacement) CS therapy is 5–7.5 mg daily of prednisolone or its equivalent. Three main goals of tapering for relatively short-term therapy include:

1. To be off therapy by 2–3 weeks
2. To reach physiologic CS doses (5–7.5 mg) by 3–4 weeks
3 In the unlikely event of a prolonged therapy it is better to adopt alternate-day therapy and add steroid-sparing' agents

Chronic dose**:** When the duration of therapy is > **4 weeks**, the issue of tapering arises. In fact there are two important problems that crop up, one is the method of tapering and the kind of steroid sparing agent to be initiated. The concept of tapering is based on a control of disease, the definition of which varies, followed by tapering that is rapid initially, but slower as the physiological dose is achieved.

Glucocorticoid Withdrawal Regimens

Because of potential side effects, glucocorticoids usually are tapered off as soon as the disease being treated is under control. Tapering must be done carefully to avoid recurrent activity of the disease and, infrequently, cortisol deficiency resulting from chronic hypothalamic-pituitary-adrenal axis suppression. Gradual tapering permits recovery of adrenal function. There is ***no*** best scheme based on controlled, comparative studies for tapering glucocorticoids. Tapering depends on the individual disease, the disease activity, doses and duration of therapy, and clinical response, which also depends on each individual's glucocorticoid sensitivity. Only generic guidelines can be offered (Fig. 9.4).

A rough guideline for tapering intermediate- to chronic-duration CS therapy (more than 1 month) would be to reduce the dose by 20–30% every 1–2 weeks for mild disease and more gradual tapering at intervals of 3–4 weeks or more for severe disease. The prednisolone dose should be increased to the last effective dose level if a significant disease flare occurs during the tapering process.

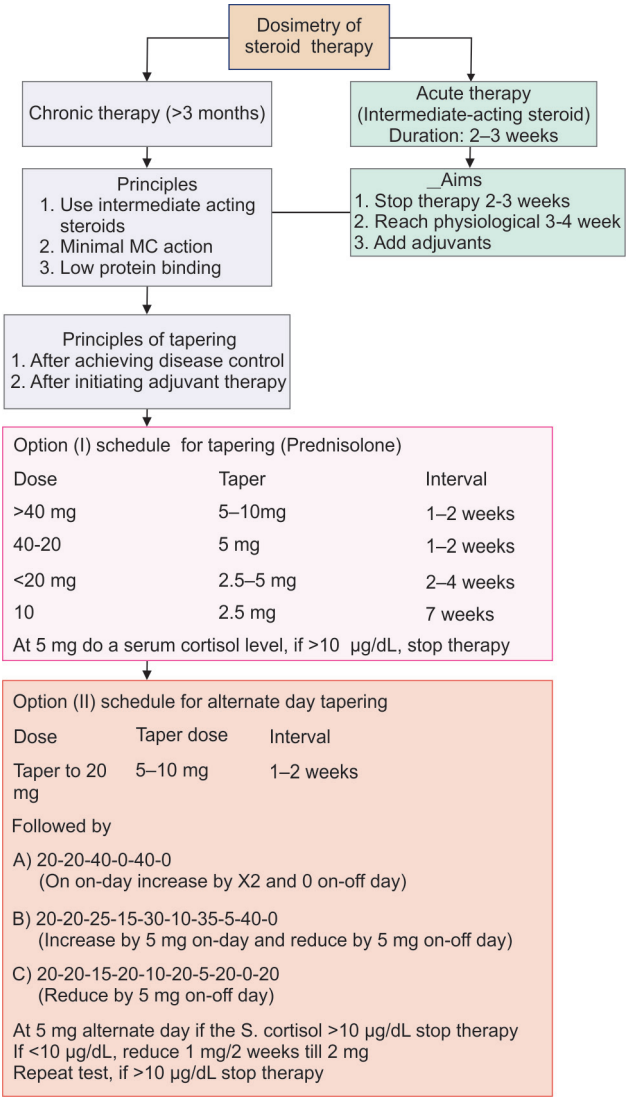


Fig. 9.4: Steroid dosimetry and tapering schedule

When the daily dose exceeds physiologic levels for more **than 1 month**, clinicians should always consider attempting alternate-day therapy, specially if *intermediate duration* CS are given. Nearing the end of long-term high-dose CS therapy, basal HPA function can be determined through a morning cortisol level. A cortisol value >10 µg/dL ensures adequate basal HPA function, although stress doses of CS may still be appropriate as previously discussed.

The conceptual basis for alternate-day therapy is that the anti-inflammatory benefits of CS therapy persist longer than the duration of HPA-axis suppression when intermediate-duration CS therapy, such as prednisolone, is used. Thus during the 'off day,' cell-mediated immunity,

white blood cells subset levels, and potassium excretion all are essentially normalized. The risk of *cataracts, osteoporosis, and possibly osteonecrosis* are *not* reduced by alternate-day CS therapy. The HPA axis recovery advantages of alternate-day therapy **no** longer exist once the dose reaches physiologic levels (**10–15 mg** of prednisolone on alternate days).

Tapering Schedule

1. The daily dose is first gradually tapered to **40 or 50 mg** of prednisolone.
2. Either the dose can be kept constant on 1 day and reduced on the alternate day by 5 mg decrements down to 5 mg/day, or, the steroid dose can be increased on 1 day and reduced by a similar amount on the alternate day.
3. After dose is tapered to **5 mg** on *alternate* days, the 8 A.M. plasma cortisol level is measured 4 weeks ***after*** the 5-mg dose has been reached. If the plasma cortisol level is less than 10 μg/dL, the alternate-day prednisolone dose should be decreased by 1 mg every 1–2 weeks to a maintenance dose of 2 mg/day. Then the 8 A.M. plasma cortisol level should be rechecked every 2 months until it is greater than 10 μg/dL, at which point maintenance GCs can be terminated.
4. *Recovery* of the HPA axis can take longer than **9 months**. The HPA axis is rapidly suppressed after the onset of GC therapy. However, if therapy is limited to 1 to 3 weeks, the recovery of the HPA axis is rapid. Longer daily GC therapy is associated with suppression of the HPA axis for up to 1 year after therapy is terminated.
5. During any stressful situations, it is necessary to give high doses of GCs, generally 25–70 mg/day of prednisolone or 100–300 mg/day of cortisol in divided doses. Thus, 25 mg of hydrocortisone equivalents for minor surgeries, 50–75 mg for moderate surgeries, and 100–150 mg for major surgery for 2–3 days, is advisable to patients who have been given long durations of steroids.

Drug Interaction

1. Drugs that increase effects/toxicity of corticosteroids
   Broad-spectrum antibiotics (macrolides), azole antifungal agents, anticholinergics, oral contraceptives, cyclosporine, loop diuretics, thiazide diuretics, NSAIDs, tricyclic antidepressants.
2. Drugs that decrease effects/toxicity of corticosteroids:
   Anticonvulsants, barbiturates, cholestyramine, ketoconazole, phenytoin, rifampin (CYP 3A4 inducer).

3. Corticosteroids increase effects/toxicity of following drugs: Diuretic–potassium depleting effect, immunosuppressants, digitalis glycosides, neuromuscular blocking drugs.
4. Corticosteroids decrease effects of vaccines, toxoids, isoniazid, insulin.

Special Considerations

Glucocorticoid Sensitivity and Resistance

A small proportion of patients do not react favorably to glucocorticoids or even fail to respond to high doses. The same is true for the susceptibility to adverse effects of glucocorticoids. Hereditary glucocorticoid resistance is rare and increased susceptibility to glucocorticoids have been related to specific polymorphisms of the glucocorticoid receptor gene(Barnes PJ). The glucocorticoid receptor exists as α and β isoforms, but only the α isoform binds glucocorticoids. The β isoform functions as an endogenous inhibitor of glucocorticoids and is expressed in several tissues. Glucocorticoid resistance has been associated with enhanced expression of this β receptor, but this is unlikely to be an important mechanism for glucocorticoid resistance because in most cells, apart from neutrophilic granulocytes, expression of the β receptor is much less than that of the α receptor. The protein lipocortin-1 (or annexin-1) inhibits eicosanoid synthesis. Glucocorticoids are thought to stimulate lipocortin-1.

Although glucocorticoids exert most of their immunosuppressive actions through inhibition of cytokine production, high concentrations of cytokines, especially IL-2, antagonize the suppressive effects of glucocorticoids in a dose-dependent manner (Saviola G). A high local concentrations of cytokines may result in localized glucocorticoid resistance that cannot be overridden by exogenous glucocorticoids. Other possible mechanisms of glucocorticoid resistance include activation of mitogen-activated protein kinase pathways by certain cytokines, excessive activation of the transcription factor activator protein-1, reduced histone deacetylase-2 expression, and increased P-glycoprotein–mediated drug efflux (Barnes PJ). Also, drugs may play a role in glucocorticoid sensitivity and resistance. Sulfasalazine increases the sensitivity of immune cells for glucocorticoids and thus might be a future option for preventing or treating glucocorticoid resistance (Oerlemans R). Mifepristone is an antiprogesterone drug and glucocorticoid receptor antagonist; chlorpromazine inhibits glucocorticoid receptor mediated gene transcription.

Side Effects

Given the diversity of their mechanisms and sites of action, it is not surprising that glucocorticoids can cause a wide array of adverse effects (Table 9.7). Most of these adverse effects cannot be avoided. However, the risk of most complications is dosage and time dependent; minimizing the quantity of glucocorticoid minimizes the risk of complications. Dose-related patterns of adverse effects of glucocorticoids have been described. Low-dose glucocorticoid therapy is safer than is commonly thought, and medium- to long-term glucocorticoid therapy is associated with limited toxicity compared with use of placebo, but sensitivity for adverse effects differs among individuals.

It is a clinical observation that some patients develop adverse effects after small doses of glucocorticoids, whereas other patients receive high doses without serious adverse effects. Apparent individual susceptibility to adverse effects does not seem to always parallel individual susceptibility to beneficial effects. Osteoporosis, diabetes, and cardiovascular disease are ranked among the most worrisome adverse effects of glucocorticoids. However, the frequency and the severity of glucocorticoid-related adverse effects have seldom been studied systematically. A problem for nonrandomized studies looking at glucocorticoid-related adverse effects is bias by indication: patients with severe disease tend to take glucocorticoids more frequently than those with less severe disease, and the disease as well as the glucocorticoids can cause unfavorable signs and symptoms ; on the other hand, glucocorticoids decrease disease activity and therewith influence the frequency and severity of disease-associated signs and symptoms. Though we will be discussing the major side effects in detail a summary of their management is given in Table 9.8.

1. Cutaneous Side Effects

There are numerous side effects that involve the skin and include skin infections, fungal flares, acne and Cushing's syndrome. Steroids are known to cause acne which is usually monomorphic and are composed of papules. The reason probably is a alteration in the growth potential of Pityrosporum ovale and increased androgenicity.

2. Skeletal Adverse Effects

a. Osteoporosis

Osteoporosis is a well-known adverse effect of glucocorticoids that can be prevented to a large degree. This affect is **not** decreased with alternate day therapy. CS therapy has been

Table 9.7: Common complication with systemic steroids

Dermatologic	**Acne** Alteration of fat distribution (Cushingoid) (usually after **2 to 3 months**) Urticaria Facial erythema Atrophy Striae Lanugo hair Alopecia (Telogen effluvium) Actinic purpura Inhibition of wound healing (Non-healing wounds, ulcers, striae, atrophy, telangiectasias)
Central nervous system and behavioral	Pseudotumor cerebri, **Psychiatric disorders** (*>40–80 mg* : Psychosis) Epidural lipomatosis Peripheral neuropathy
Musculoskeletal	Osteoporosis with spontaneous fractures, **Osteonecrosis** (*>30 mg/d, 2-3 months*), Aseptic necrosis of femur **Myopathy** (*>30 mg/d*)
Ocular	Glaucoma **Cataracts** (*15 mg – 1 yr;5 mg-2 yr*) Refraction changes (from CS-induced hyperglycemia)
Gastrointestinal	Fatty infiltration of the liver Nausea, vomiting Intestinal perforation Pancreatitis **Peptic ulceration** (*>1 g* cumulative in combination with nonsteroidal anti-inflammatory drugs)
Cardiovascular and fluid retention	Hypertension (CS with high MC effect, duration> 1 yr, pulse CS) CHF (↑ sodium retention, resultant fluid overload in predisposed individuals) Sodium and fluid retention Hypokalemic alkalosis Atherosclerosis
Suppression of host defenses	Immunosuppression, Anergy effects on phagocyte kinetics and function, Increased incidence of infections, **Recurrent tuberculosis** (*>15 mg*)
Endocrinologic	**Suppression of hypothalamic-pituitary-adrenal axis** (*therapy > 4 weeks*), Growth failure (less with alternate day therapy), Secondary amenorrhea Diabetes mellitus, Changes in lipid metabolism Enhanced appetite and weight gain
Metabolic	Hyperglycemia (high CS dose) Nonketotic hyperosmolar states, Hyperlipidemia (high CS dose), Drug interactions, Fibroblast inhibition Subcutaneous atrophy (striae, purpura)

Contd...

Contd...

Mortality	Adrenal crisis Bowel perforation Perforated PUD Pancreatitis Severe hyperglycemia Opportunistic infections/malignancy

Pulse therapy: Electrolyte shifts ,Cardiac dysrhythmias,Seizures

Table 9.8: Prevention of side effects with chronic (>3 months) glucocorticoid use

Symtoms	*Management*
Hypertension	Blood pressure (baseline; repeat with each visit)
Weight gain	Weight (baseline; repeat with each visit)
Re-activation of infection	Purified protein derivative, anergy panel at baseline (can be done up to 12 days after starting prednisolone) Hepatitis screen Consider Pneumocystis carinii pneumonia prophylaxis (Bactrim 1 DS three times a week)
Metabolic abnormalities	Electrolytes, lipids, glucose [Baseline; repeat early after starting therapy; repeat annually; more frequent monitoring with known risk factors (e.g. diabetes, hyperlipidemias)]
Osteoporosis	Bone density (baseline; repeat annually) Instruct about diet, exercise, other measures Calcium and vitamin D supplementation Start bisphosphonate for men, post-menopausal women Evaluate post-menopausal women for hormone replacement therapy Serum testosterone after treatment started in men; if low (<300 ng/mL), check prostate specific antigen, prostate examination before starting testosterone replacement.
Eyes	**Cataracts:** Slit-lamp examination (every 6–12 months) **Glaucoma:** Intraocular pressure examination (at 1 month and every 6 months)
Peptic ulceration	In patients with two or more risk factors, consider prophylaxis with H_2-antagonist or proton-pump inhibitor
Suppression of hypothalamic-pituitary-adrenal axis	Single, early morning doses, preferably every other day. Check **8 AM serum cortisol** before tapering prednisolone < 3 mg/day. If <10 μg/dL, repeat every 1–2 months and maintain low prednisolone dose until baseline cortisol level is adequate

'attributed' to induce 47% of all hip fractures and 72% of all vertebral fractures.

Concomitant risk factors for GCS-induced osteoporosis include preexisting or family history of osteoporosis, menopause, sedentary lifestyle, immobilization, low calcium diet, high sodium diet, high caffeine intake, tobacco or alcohol use, hyperthyroidism, hyperparathyroidism, renal

failure, and rheumatoid arthritis. Long-term anticonvulsant therapy, long-term heparin therapy, or excessive vitamin A ingestion may contribute to these effects.

***Cause*:** ↑ osteoclast activity, ↓ osteoblast activity, ↓ GI absorption of calcium, ↑ renal excretion of calcium leading to resultant secondary hyperparathyroidism and bone resorption.

GCS therapy also induces decreased gonadal function in both sexes, which can contribute to osteoporosis. Molecular mechanisms that may be involved include inhibition of prostaglandin E_2, which normally stimulates collagen synthesis; down-regulation of c-fos oncogene; up-regulation of P53 tumor-suppressor gene; and reduction in insulin-like growth factor I, which normally stimulates bone growth. GCSs down-regulate type I collagen gene expression by transcriptional and post-transcriptional mechanisms and up-regulate collagenase 3 expression by post-transcriptional mechanisms. Collagenase 3 from osteoclasts and chondrocytes breaks down type I and II collagen, the major components of bone and cartilage matrix. Matrix proteins are decreased, and proteases for matrix destruction are increased.

Clinical Features

Osteoporosis occurs in 40% of individuals treated with systemic GCs; it is especially prominent in children, adolescents, and post-menopausal women.

1. Approximately 30% of patients have evidence of vertebral fractures after 5–10 years of GC treatment, but this proportion is higher in post-menopausal women.
2. Bone loss occurs most rapidly in the first *6 months* of GC use, but continues at a slower rate after that, with loss of 3–10% of bone per year in many patients.
3. In women receiving moderate long-term daily prednisolone (30 mg/d), a 20–50% reduction of bone mineral content of the lumbar spine can occur without proper preventive measures. Low doses (prednisolone, 10 mg/d), may lead to a reduction of 10–20% of the bone mineral density.
4. Low doses of prednisolone (2.5–5 mg/d) adversely affect bone and increases vertebral and hip fractures. *Trabecular bone* is primarily affected, leading to painful vertebral fractures.
5. Patients with the greatest percentage of bone loss are *young men* because they have the greatest pretreatment bone mass. Postmenopausal women are most at risk for fractures; however, because this population has a lower bone mass at initiation of therapy.

6. GCS-induced bone loss affects trabecular bone and the cortical rim of vertebrae **(axial skeleton)** more so than cortical bone (long bones). This situation is due to the much higher metabolic turnover rate of trabecular bone. The proximal femur has trabecular bone and can show bone loss with GCS therapy. With prolonged therapy, cortical bone also shows demineralization and increased fragility.

Diagnosis

1. CXR: Plain x-ray skeletal surveys are not sensitive enough to detect osteoporosis until 20% to 60% of bone mass is lost. But they are useful for detecting vertebral compression fractures.

2. DEXA: The best measurement of osteoporosis is quantification of bone mineral density. Different techniques have been used to study bone mineral density, including single X-ray absorptiometry, quantitative CT scan, simple photon absorptiometry, and others, but the preference is for dual-energy X-ray absorptiometry (DEXA) because of its sensitivity, reproducibility, and low radiation exposure.

In patients on long-term GCS therapy, bone density studies should be done every 12 months, ideally with a baseline study at initiation of therapy. The serial studies should be performed on the same site (lumbar spine or hip) because there is variability in density between bones. If only one area is to be studied, the *lumbar area* should be targeted in patients *younger* than 60 years old and the *femoral neck* targeted in *older* patients because vertebral osteophytes may cause vertebral studies to be unreliable. Calibration differs among different densitometry machines so that repeat examinations preferably should be performed on the same machine by the same operator.

In densitometry reports, T scores are used to reflect the patient's bone density compared with means of the same sex and race. A T score of -1 connotes 1 standard deviation below the mean. Normal bone density includes T scores up to 1 standard deviation below the mean. Osteopenia is defined as a T score between -1 and -2.5; a T score less than -2.5 (bone density >2.5 standard deviations below the mean) defines osteoporosis.

Management

Calcium and vitamin D together, but not calcium alone, preserve bone mass in patients receiving long-term treatment (>3 m) with GCs at an average of *15 mg/day*.

Patients taking GCs should be given elemental calcium, **1500 mg/day,** and vitamin D, **400 units** twice daily. Activated forms (alfacalcidiol,1g/day, or calcitriol, 0.5–1.0 g/day) can be given, but more frequent monitoring is required for

hypercalciuria and hypercalcemia. Patients with a history of renal stones should not receive supplemental calcium and vitamin D.

For patients with a DEXA T score less than -1 and premenopausal women who become amenorrheic because of GCs benefit from hormone replacement therapy (HRT). Such therapy helps to prevent the effects of GCs on bone. For post-menopausal women; HRT is effective for preventing osteoporosis. The Women's health initiative, a large randomized controlled primary prevention trial, demonstrated that combined estrogen plus progestin significantly reduced fractures at the hip, vertebrae, and other sites compared to placebo. Post-menopausal women can be treated with oral conjugated estrogen (Premarin), 0.625 mg/day. Women with a uterus should also receive medroxyprogesterone (Provera), 2.5 mg/day, which prevents the increased endometrial carcinoma that occurs in women receiving estrogen alone.

Men with low serum testosterone levels who are receiving GCs should have testosterone supplementation. Based on recommendations published by the American Association of Clinical Endocrinologists and the American College of Endocrinology, men with serum testosterone levels below the physiologic range (less than 300 ng/mL) should receive replacement therapy. Testosterone replacement therapy can be considered if a patient has a normal prostate specific antigen test, and benign findings on prostate examination. Replacement is administered either by the intramuscular route (testosterone enanthate or cypionate, 200 mg intramuscularly every 2 weeks or 100 mg every week to avoid cycling) or by testosterone patches (4 or 6 mg applied daily). Serum testosterone should be checked after replacement to assure adequate treatment.

The increased osteolysis caused by steroids has led to the use of a number of agents that inhibit bone resorption, such as the bisphosphonates and calcitonin. As bone formation proceeds at a much slower pace than resorption, anti-resorptive drugs produce a period of time up to 2 years where formation is greater than resorption. Several intravenous and oral bisphosphonates are now available and have revolutionized the approach to prevention and treatment of steroid-induced osteoporosis. Oral bisphosphonates include alendronate, 70 mg/week or 5 mg/day (10 mg/day for post-menopausal women not on HRT); risedronate, 30 mg/week or 5 mg/day; etidronate, 400 mg/day for 2 weeks every 13 weeks; and Ibandronate, 150 mg/month. **An approach is given in Fig 9.5 and an overview is given in Table 9.9.**

b. Osteonecrosis

This complication is usually seen with long-term prednisolone (or comparable doses of other systemic CS) for at least

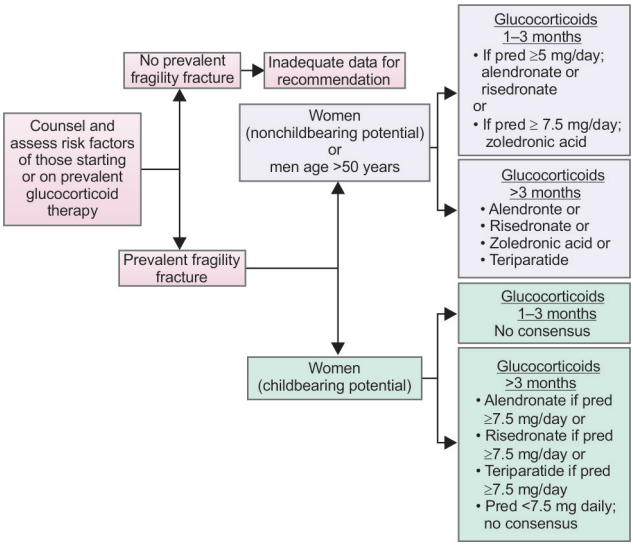


Fig. 9.5: Approach to premenopausal women and men above the age of 50 years initiating or receiving glucocorticoid therapy

Abbreviation: Pred, prednisolone

Source: American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

2–3 months for life-threatening conditions. It is described mostly in children and patients with SLE. The most common site is the *proximal femur,* although the humeral head or distal femur occasionally may be affected. In contrast to osteoporosis, osteonecrosis affects *active* patients most frequently and *men* more commonly than women.

Other populations at increased risk are patients with systemic lupus erythematosus, alcoholics and others with fatty infiltration of the liver, renal transplant patients, and patients with lipid abnormalities. Osteonecrosis occurs in most patients after at least 6–12 months of GCS therapy.

Cause: Vascular mechanisms seem to be involved. Ischemia possibly may be caused by microscopic fat emboli or impingement of the sinusoidal vascular bed by increased intraosseous pressure caused by fat accumulation. This fat can originate from fatty deposits in the liver, whereas others believe that the fat is bone derived and redirected from the bone sinusoids to the arterial tree from a pressure gradient. The end result of the osteonecrosis is loss of subchondral support with collapse of the joint and subsequent osteoarthrosis.

Clinical Features

An early symptom is diffuse pain, which becomes persistent and increases with activity. The usual initial presentation is localized pain during activity. Eventually the pain also occurs at rest and generally requires analgesics for relief. Most frequently, hip or knee joints are involved; ankle

Table 9.9: Prevention of osteoporosis on steroids (GIOP guidelines)

Prevention	Patients starting GC therapy at a dose equivalent to prednisolone ≥5 mg/day for 3 month or longer should: ■ Modify risk factors for osteoporosis (stop smoking, decrease excessive alcohol consumption) ■ Start regular weight-bearing physical exercise Initiate intake of calcium (total 1500 mg/day) and vitamin D (400–800 IU/day) ■ Consider BMD testing to predict risk of fracture and bone loss ■ Initiate bisphosphonate therapy (alendronate 5 mg/day or 35 mg/wk, or risedronate 5 mg/d or 35 mg/wk)
Treatment	Patients on long-term GC therapy should be tested for osteoporosis using BMD measurement. **A. If the T-score is –1 to –3:** 1. Risk factor modification including reducing risk of falls 2. Regular weight-bearing physical exercises 3. Calcium and vitamin D supplementation 4. Replacement of gonadal steroids, if deficient **Women** Bisphosphonate therapy (alendronate 10 mg/day or 70 mg/wk, or risedronate 5 mg/d or 35 mg/wk) If bisphosphonates are contraindicated or not tolerated, consider calcitonin as second-line agent (200 IU daily), intravenous bisphosphonate (pamidronate or zolendronate), or parathyroid hormone Repeat BMD measurement annually or biannually **Men** Alendronate 70 mg weekly or risedronate 35 mg weekly (if GI side effects, use IV pamidronate or zolendronate, or intranasal calcitonin) Consider testosterone 250 mg IM monthly, if testosterone low and no contraindications **B. If DEXA T score is –3 or below, or if osteoporotic fracture:** Consider teriparatide 20 μg sq daily, stopping any bisphosphonate therapy

and shoulder joints are involved less frequently. For early assessment, magnetic resonance imaging is the most sensitive investigative tool. This is as t*wenty percent* of patients with AVN have *normal* X-rays. Plain radiographs are adequate only for follow-up.

Management

Treatment in the early stage includes prompt referral, immobilization and decreased weight bearing. Surgical decompression, joint replacement, or both follow this if needed. No preventive measures are known; awareness is the most important factor in early detection.

c. Growth Impairment in Children

This is rarely an issue for most dermatologic indications. Even with CS use in transplantation settings and for serious systemic autoimmune conditions in children, catch-up growth is possible when CS are reduced to physiologic levels or below.

Some patients may have permanent loss of height, particularly if GCSs are given during the *two* major growth *spurts* of childhood—before age 2 and at puberty. With GCSs given just before puberty, epiphyseal closure may prevent the usual compensatory growth spurt.

Cause: Due to ↓ growth hormone and IGF-1 production; net result delayed skeletal maturation. This risk is less with alternate day dose therapy. GCSs interfere with nitrogen and mineral retention necessary for growth, inhibit bone formation directly and indirectly, inhibit chondrocyte mitoses, and inhibit collagen synthesis. Other aspects of regulation are GCS inhibition of the pulsatile release of growth hormone and reduction of growth hormone receptor expression.

Diagnosis and Treatment

Monitoring for growth suppression requires accurate measurements at least **3 months** apart. Because childhood growth can occur sporadically and because therapy for the underlying disease is important, decisions concerning growth inhibition and dosing should require at least **6 months** of growth data, unless marked suppression seems to have occurred. Growth hormone therapy for treatment of GCS growth inhibition shows promise. This therapy may help not only to restore linear growth, but also it may reverse or prevent some.

3. Myopathy

Weakness in *proximal* muscles, especially of the l*ower* extremities, occurring within weeks to months after initiation of treatment with glucocorticoids, or after an increase in the dosage, may indicate steroid myopathy. It is often suspected but is infrequently found; it occurs almost exclusively in patients treated with high dosages (**>30 mg/day** prednisolone or equivalent). It can also occur with pulse doses of steroids

Cause: ↓ glucose and amino acid uptake by muscles, leading to muscle atrophy/wasting.

Clinical: Diagnosis is clinical and can be confirmed by a muscle biopsy specimen that reveals atrophy of type II fibers and lack of inflammation; no elevation of serum muscle enzymes is noted. A ratio of greater than 1:4 of urinary

creatine to urinary creatine plus creatinine is advocated by some investigators to substantiate the diagnosis.

Treatment: Consists of withdrawal of the glucocorticoid; if this is possible, a prompt decrease in symptoms may ensue. A rare syndrome of rapid onset, acute myopathy, occurring within days after the start of high-dose glucocorticoids or pulse therapy, has been described; muscle biopsy specimens show atrophy and necrosis of muscle fibers.

4. Gastrointestinal Adverse Effects

Peptic Ulcer Disease

Data from the literature on upper gastrointestinal safety of oral glucocorticoids are inconclusive. The fact that glucocorticoids inhibit the production of COX-2 without hampering the production of COX-1 supports studies that found no increased risk. When glucocorticoids are used in combination with NSAIDs, the relative risk of peptic ulcer disease and associated complications is about 4.

Cause: ↓ mucus production, ↑ acid production; CS not a direct gastric irritant.

Treatment: Therefore in cases of co-medication with NSAIDs, consider co-treatment with a proton pump inhibitor, or prescribe a COX-1- sparing NSAID. In patients treated with glucocorticoids without concomitant use of NSAIDs, no indication for gastrointestinal protective agents exists, unless other risk factors for peptic complications are present.

Bowel Perforation

This rare side effect is not dependent on dose or duration of CS. CS may mask signs and symptoms of perforation. Thus, it is better to avoid CS after a recent bowel anastomosis.

Other Gastrointestinal Adverse Effects

Other side effects include, pancreatitis, asymptomatic and symptomatic colonization of the upper gastrointestinal tract with *Candida albicans*.

5. Immunologic Adverse Effects

At high doses, glucocorticoids diminish neutrophil phagocytosis and bacterial killing in vitro, whereas in vivo, normal bactericidal and phagocytic activities are found. Monocytes are more susceptible; during treatment with medium to high doses of glucocorticoids, bactericidal and fungicidal activity in vivo and in vitro is reduced. These factors may influence the risk of infection.

From epidemiologic studies, treatment with a daily dose of less than **10 mg** of prednisolone or equivalent seems to lead to no or only slightly increased risk of infection; however, if doses of **20–40 mg** daily are used, the risk of infection is increased (relative risk of 1.3 to 3.6) (Stuck AE). This risk increases with increased dose and duration of treatment (Wolfe F et al.).

Non-human immunodeficiency virus (HIV)-associated *Pneumocystis carinii* infections occur most commonly in patients on daily systemic GCS therapy. A dose greater than **15 mg** daily of prednisolone for over 2 months should ideally be started on prophylaxis of *Pneumocystis pneumonia* in patients on long-term GCS therapy. Trimethoprim-sulfamethoxasole, dapsone, or aerosolized pentamidine can be used for prophylaxis.

A tuberculosis history should be taken, and a baseline radiograph is suggested by some physicians but it is mandatory in TB endemic countries. The relative risk (RR) of *tuberculosis* is higher at dose **>15 mg/d.** Concomitant isoniazid has been advocated in patients with a positive tuberculin skin test having induration of greater than 10 mm.

Normal antibody responses to immunizations occur in patients receiving less than approximately 20 mg/d of prednisolone. Any live virus vaccine should not be given to children receiving GCS therapy. Although GCS therapy may increase significant complications associated with naturally acquired varicella, there is evidence that children on alternate-day therapy have fewer complications than those treated with daily doses.

6. Cardiovascular Adverse Effects

Mineralocorticoid Effects

Some glucocorticoids have mineralocorticoid actions (see Table 9.1), including reduced renal excretion of sodium and chloride and increased excretion of potassium, calcium, and phosphate. This activity may lead to edema, weight gain, increased blood pressure, and heart failure (caused by reduced excretion of sodium and chloride); cardiac arrhythmia (resulting from increased excretion of potassium); or tetany and electrocardiographic changes (related to hypocalcemia).

Low doses of glucocorticoid **(<10 mg)** and short durations **(<2 weeks)** are not a cause of hypertension, in contrast to higher doses.

Atherosclerosis

Accelerated atherosclerosis and elevated cardiovascular risk have been reported in patients with SLE and in patients with RA.

Cause: Glucocorticoids may enhance cardiovascular risk via their potentially deleterious effects on lipids, glucose tolerance, insulin production and resistance, blood pressure, and obesity.

However, these conditions are not adverse effects of low-dose glucocorticoids. Furthermore, atherosclerosis itself has been recognized as an inflammatory disease of arterial walls, for which glucocorticoids may be beneficial; glucocorticoids have been found to inhibit macrophage accumulation in injured arterial walls in vitro, possibly resulting in attenuation of the local inflammatory response.

Management

Blood pressure, serum lipids, and glucose levels should be measured serially. Abnormalities should be treated with dietary manipulation and medication as necessary. Patients who smoke should be encouraged to stop. Female sex hormones protect against the development of atherosclerosis, and thus hormone replacement therapy for post-menopausal women on GCs makes sense. However, recent data suggest that women with established atherosclerosis actually do worse with hormone replacement therapy, and there was a 58 percent increase in coronary heart disease events in the first year after myocardial infarction in patients treated with an estrogen/progestin combination. If patients develop increased levels of cholesterol or triglycerides while taking GCs, there are now good approaches to treatment, particularly with some of the newer statins, that impact on the development of atherosclerosis and prevent myocardial infarctions.

Patients should be treated or referred for treatment on the basis of guidelines that emphasize the importance of assessing the risk of atherosclerosis. These *guidelines* recommend *treatment* when patients have low-density lipoprotein (LDL) cholesterol levels greater than 160 mg/dL and fewer than two coronary heart disease risk factors (high LDL cholesterol, smoking, hypertension, diabetes, male sex, family history of premature heart disease); LDL cholesterol levels greater than 130 mg/dL with two or more additional risk factors for heart disease; and LDL cholesterol levels greater than 100 mg/dL for patients with established coronary artery disease. High-density lipoprotein cholesterol levels lower than 35 mg/dL independently predict increased coronary mortality rates in men and should be taken into account in therapeutic decisions.

Several trials have demonstrated reduction in both coronary heart disease and total mortality rates with statin therapy. Patients should supplement the diet with folate and B_6 to control any elevations in homocysteine.

Lipodystrophy

Up to 66% of patients on long-term therapy of at least 20 mg of prednisolone daily have lipodystrophy, including moon face, 'buffalo hump', and central obesity. This is associated with increased risk of metabolic syndrome (increased BMI, hypertension, hyperlipidemia, hyperglycemia), with resultant increased cardiovascular disease risk. This abnormality is the most distressing aspect of CS therapy to patients, possibly affecting compliance. Prednisolone doses <10 mg daily will generally allow reversal of the lipodystrophy.

7. Ocular Adverse Effects

Cataract

Glucocorticoids tend to stimulate the formation of *posterior subcapsular* cataract and also increase the the risk of cortical cataract and this effect depends on dose and duration of treatment. Alternate day dosage does **not** reduce this risk. The exact cause is not known though altered lens proteins is implicated.

In patients treated long term with glucocorticoids at a dosage of ≥**15 mg of** prednisolone daily for **1 year**, cataract is observed frequently while in patients receiving long-term therapy with less than 10 mg of prednisolone daily, the percentage of cataract is less (10%), but cataract may develop at dosages greater than **5 mg/day** of prednisolone equivalent for **2 years**. These cataracts are usually bilateral but progress slowly. They may cause glare disturbance but usually cause little visual impairment, except at end stages.

Glaucoma

By increasing intraocular pressure, glucocorticoids may cause or aggravate glaucoma. Patients with a family history of open-angle glaucoma and patients with high myopia are probably prone to develop this adverse effect, especially when receiving high doses of glucocorticoids; check of intraocular pressure is then warranted. If increased, patients need to be treated with medications that reduce intraocular pressure, often for a prolonged period after stopping the glucocorticoid. Topical application of a glucocorticoid in the eye has a more pronounced effect on intraocular pressure compared with systemic glucocorticoid therapy.

8. Endocrine/Metabolic Adverse Effects

Glucose Intolerance and Diabetes Mellitus

Glucocorticoids increase hepatic glucose production and induce insulin resistance by inhibiting insulin-stimulated

glucose uptake and metabolism by peripheral tissues. Glucocorticoids probably also have a direct effect on beta cells of the pancreas, resulting in enhanced insulin secretion during glucocorticoid therapy. It may take only a few weeks before glucocorticoid-induced hyperglycemia occurs with low and medium glucocorticoid doses. The risk increases with higher daily doses of glucocorticoids. Thus **>20 mg prednisolone** or equivalent per day is a risk factor.

It is likely that risk is increased further in patients with other risk factors for diabetes mellitus, such as a family history of the disease, advanced age, obesity, and previous gestational diabetes. Postprandial hyperglycemia and only mildly elevated fasting glucose concentrations are characteristic of glucocorticoid-induced diabetes mellitus. Worsening of glycemic control can be expected in patients with established glucose intolerance or diabetes mellitus. Usually, glucocorticoid-induced diabetes is reversible when the drug is discontinued, unless clear glucose intolerance was pre-existent.

Medical therapy of GCS-induced glucose effects depends on insulin because oral agents often take weeks for onset of effect. Because GCSs induce a relative insulin resistance, patients already on insulin often must increase their dose by 1.5 to 2 times the pre GCS dose.

Fat Redistribution and Body Weight

One of the most notable effects of long-term endogenous or exogenous glucocorticoid excess is the redistribution of body fat. Up to 66% of patients on long-term therapy of at least 20 mg of prednisolone daily have lipodystrophy, including moon face, 'buffalo hump', and central obesity. This is associated with increased risk of metabolic syndrome (increased BMI, hypertension, hyperlipidemia, hyperglycemia), with resultant increased cardiovascular disease risk. This abnormality is the most distressing aspect of CS therapy to patients, possibly affecting compliance. Prednisolone doses <10 mg daily will generally allow reversal of the lipodystrophy.

Cause: Potential mechanisms include increased conversion of cortisone to cortisol in visceral adipocytes, hyperinsulinemia, and changes in expression and activity of adipocyte-derived hormones and cytokines, such as leptin and TNF. Protein loss resulting in muscle atrophy also contributes to the change in body appearance.

Increased appetite influences body weight during glucocorticoid therapy (>1 month of therapy), but patients with active inflammatory disease tend to lose weight, which can be prevented with disease control by drugs, including glucocorticoids.

9. Suppression of the Hypothalamic–Pituitary–Adrenal Axis

This has been discussed in detail previously. It suffices to say that rapid tapering is restricted only for durations less than *3 weeks*. Acute cessation of glucocorticoid therapy without tapering is indicated for corneal ulceration by herpes virus, which can lead rapidly to perforation of the cornea, and glucocorticoid-induced acute psychosis. In these patients, assessment of adrenal responsiveness on a corticotropin test seems prudent. Not all patients with a blunted cortisol response have signs or symptoms of adrenal insufficiency, however.

Clinical Features

Clinical signs and symptoms of *chronic adrenal hypofunctioning* are *nonspecific* and include fatigue and weakness, lethargy, orthostatic hypotension, nausea, loss of appetite, vomiting, diarrhea, arthralgia, and myalgia. In general, stressors are required to produce vascular collapse due to secondary exogenous adrenal insufficiency. The paucity of serious outcomes is largely explained by the preservation of MC function in (drug-induced) secondary exogenous adrenal insufficiency. Alternative non-steroidal mechanisms of stress response also help assure sodium and glucose homeostasis in these settings.

These symptoms partially overlap *glucocorticoid withdrawal symptoms*, such as fatigue, arthralgia, and myalgia. When in doubt, measurements of serum cortisol levels and the corticotropin stimulation test are indicated which are normal. It is postulated that there may be a sudden decrease in CS available at the cellular level. There is evidence to suggest that IL-6 (and to a lesser extent IL-1β and TNF-α) is responsible for much of the symptomatology. The return to higher CS doses, with more gradual subsequent CS tapering, will typically eliminate these symptoms.

Glucocorticoid withdrawal symptoms are sometimes difficult to discriminate from symptoms of the primary disease, such as polymyalgia rheumatica. Because mineralocorticoid secretion remains intact via the renin-angiotensin-aldosterone axis, serious electrolyte disturbances are uncommon.

10. Central Nervous System and Behavioral Effects

Glucocorticoid treatment is associated with a variety of behavioral symptoms. Although most attention has been directed toward specific dramatic disturbances collectively described under the term glucocorticoid psychosis, less florid effects also occur that may cause distress to a patient and warrant medical attention. Up to 30% of patients on

short-term CS therapy develop hypomania and sleep disorders early in the course. Up to 10% of patients on short-term CS therapy develop significant depression, often during CS taper. Psychosis occurs roughly twice as often in CS-treated patients as in controls minor behavioral manifestations may also occur on withdrawal of glucocorticoids.

Steroid Psychosis

Overt psychosis is rare and usually is associated with high-dose glucocorticoids or glucocorticoid pulse therapy, but psychosis may also be a complication of the disease itself, especially SLE. This makes it difficult to distinguish in an individual SLE patient with psychosis whether the condition is a complication of the disease, of the therapy, or of both.

Cause: Possibly due to electrolyte shifts, altered nerve excitability, possibly mild cerebral edema. Isolated psychosis is seen in about 10% of glucocorticoid related cases, and in most patients, affective disorders are present as well.

Clinical: Around 40% of cases of glucocorticoid-induced psychosis manifest as depression, whereas mania, often dominated by irritability, is predominant in 30% of cases. Psychotic symptoms usually start just after initiation of treatment (60% within the first 2 weeks, 90% within the first 6 weeks), and remission after drug dose reduction or withdrawal follows the same pattern. Although the data are largely anecdotal, individuals developing steroid psychosis frequently have had prior evidence of some dissociative symptoms. Occasionally, remission occurs without dose reduction.

Minor Mood Disturbances

Glucocorticoids have been associated with a wide variety of low-grade disturbances, such as depressed or elated mood (euphoria), insomnia, irritability, emotional instability, anxiety, memory failure, and other cognition impairments.

Although the symptoms may not become severe enough for a specific diagnosis, they warrant attention—not only because they cause distress to the patient, but also because they may interfere with evaluation and treatment of the underlying disease. Most physicians recognize the occurrence of such symptoms in many glucocorticoid-treated patients; these symptoms may occur in varying degrees in up to 50% of treated patients within the first week. The exact incidence in rheumatic patients exposed to the usual doses of glucocorticoids is unknown; most series dedicated to mood disturbances studied high doses. It is important to inform patients about these minor mood disturbances before starting glucocorticoid therapy.

11. Menstrual Disturbances

These are seen with IM CS but also with oral prednisolone. About 40% of premenopausal women on at least 20 mg prednisolone daily experience significant menstrual abnormalities.

Monitoring

A basic monitoring protocol is given below:

Baseline	Follow Up*	Interval 1 m	3 m	6 m	9 m	12 m
BP, weight, height†		Y	Y	Y	Y	Y
S. lipids (TG >500 mg/dL: caution)		Y	Y	Y	Y	Y
S. glucose, S. Electrolytes ††		Y	Y	Y	Y	Y
Mantoux test	No					
Chest X-ray	No					
DEXA/MRI				Y		Y
Eye examination				Y		Y
Serum cortisol						Before stopping therapy
ECG††	No					

*in case of long-term steroid use,† children;†† in case of pulse therapy before and after each pulse

Special Groups

Pregnancy

GCS are lipophilic and have a low molecular mass and thus they can pass through the cell membrane easily. The enzyme 11β-HSD in the placenta, catalyzes the conversion of active cortisol, corticosterone, and prednisolone into the inactive 11-dehydro-prohormones (cortisone, 11- dehydrocorticosterone, and prednisolone), and thus protects the fetus from glucocorticoids in the blood of the mother which accounts for the maternal-to-fetal prednisolone blood concentration ratio of about 10 : 1. Dexamethasone has little or no affinity for transport proteins and is poorly metabolized by 11β-HSD thus the dexamethasone blood concentration ratio is about 1 : 1.

If a *pregnant* woman has to be treated with glucocorticoids, *prednisolone*, and *methylprednisolone* would be good choices; if the *unborn child* has to be treated, fluorinated glucocorticoids, such as *betamethasone* or *dexamethasone*, would be indicated (Temprano KK).

As there is a small but increased risk of an oral cleft palate, it is advised to avoid high doses (1 to 2 mg/kg prednisolone equivalent) in the first trimester of pregnancy, whereas low to moderate doses of prednisolone seem to be safe.

Lactation

Prednisolone and prednisone are excreted in small quantities in breast milk. Breastfeeding is generally considered safe for an infant whose mother is taking these drugs. Because curves of milk and serum concentrations for prednisolone are virtually parallel in time, exposure of the infant is minimized if breastfeeding is avoided during the first 4 hours after the intake of prednisolone (Temprano KK).

Children

Growth impairment in children: This is rarely an issue for dermatologic indications. Even with CS use in transplantation settings and for serious systemic autoimmune conditions in children, catch-up growth is possible when CS are reduced to physiologic levels or below.

BIBLIOGRAPHY

1. Ackerman GL, Nolsn CM. Adrenocortical responsiveness after alternate-day corticosteroid therapy. N Engl J Med. 1968;278:405-9.
2. Ait Ourhroui M, Hassam B, Khoudri I. Treatment of alopecia areata with prednisolone in a once-monthly oral pulse. Ann Dermatol Venereol. 2010;137(8-9):514-8.
3. Alsantali A. Alopecia areata: a new treatment plan. Clin Cosmet Investig Dermatol. 2011;4:107-15.
4. Bansal S, Garg VK, Sardana K, Sarkar R. A clinico-therapeutic analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis with an emphasis on the predictive value and accuracy of Score of Toxic Epidermal Necrolysis. Int J Dermatol. 2015;54(1):e18-26.
5. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. Lancet. 2009;373:1905-17.
6. Buttgereit F, Burmester GR, Lipworth BJ. Optimised glucocorticoid therapy: the sharpening of an old spear. Lancet. 2005;365:801-3.
7. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med. 2003;348:727-34.
8. Cunliffe WJ, Stables G. Optimal use of isotretinoin. J Cutan Med Surg. 1996;1:14-25.
9. Eberhardt R, Kruger K, Reiter W, et al. Long-term therapy with the new glucocorticosteroid deflazacort in rheumatoid arthritis: double-blind controlled randomized 12-months study against prednisolone. Arzneimittel forschung. 1994;44:642-7.
10. Foletta VC, Segal DH, Cohen DR. Transcriptional regulation in the immune system: all roads lead to AP-1. J Leukocyte Biol. 1998; 63:139-52.

11. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken). 2010; 62(11):1515-26.
12. Jackson S, Gilchrist H, Nesbitt LT Jr. Update on the dermatologic use of systemic glucocorticosteroids. Dermatol Ther. 2007; 20(4):187-205.
13. Jansen T, Romiti R, Plewig G. Acute severe acne in a female patient (acne fulminans?). Br J Dermatol. 1999;141:945-7.
14. Johannes WG, Johannes J, Bijlsma WJ. Glucocorticoid therapy. Kelley's Textboook of Rheumatology. 9th edn.
15. Kaminsky A. Less common methods to treat acne. Dermatology. 2003;206:68-73.
16. Kar BR, Handa S, Dogra S, et al. Placebo-controlled oral pulse prednisolone therapy in alopecia areata. J Am Acad Dermatol. 2005;52(2): 287-90.
17. Kirchhof MG, Miliszewski MA, Sikora S, Papp A, Dutz JP. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine. J Am Acad Dermatol. 2014; 71(5):941-7.
18. Lipworth BJ. Therapeutic implications of non-genomic glucocorticoid activity. Lancet. 2000;356:87-9.
19. Oerlemans R, Vink J, Dijkmans BA, et al. Sulfasalazine sensitises human monocytic/macrophage cells for glucocorticoids by upregulation of glucocorticoid receptor alpha and glucocorticoid induced apoptosis. Ann Rheum Dis. 2007;66:1289-95.
20. Olsen EA, Carson SC, Turney EA. Systemic steroids with or without 2% topical minoxidil in the treatment of alopecia areata. Arch Dermatol. 1992;128(11):1467-73.
21. Pasricha JS, Khaitan BK. Oral mini-pulse therapy with betamethasone in vitiligo patients having extensive or fast-spreading disease. Int J Dermatol. 1993;32:753-7.
22. Rath N, Kar HK, Sabhnani S. An open labelled, comparative clinical study on efficacy and tolerability of oral minipulse of steroid (OMP) alone, OMP with PUVA and broad/narrow band UVB phototherapy in progressive vitiligo. Indian J Dermatol Venereol Leprol. 2008;74(4):357-60.
23. Rhen T, Cidlowski JA. Anti-inflammatory action of glucocorticoids: new mechanisms for old drugs. N Engl J Med. 2005;353:1711-23.
24. Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken). 2010;62(11):1515-26.
25. Roujeau JC. Pulse glucocorticoid therapy. The 'big shot' revisited. Arch Dermatol. 1996;132:1499-502.
26. Sabir S, Werth VP. Pulse glucocorticoids. Dermatol Clin. 2000; 18(3):437-46.
27. Saviola G, Abdi AL, Shams ES, et al. Compared clinical efficacy and bone metabolic effects of low-dose deflazacort and methyl prednisolone in male inflammatory arthropathies: a 12-month open randomized pilot study. Rheumatology (Oxford). 2007; 46:994-8.
28. Saviola G, Abdi AL, Shams ES, et al. Compared clinical efficacy and bone metabolic effects of low-dose deflazacort and methyl

prednisolone in male inflammatory arthropathies: a 12-month open randomized pilot study, Rheumatology (Oxford). 2007; 46:994-8.
29. Scheinman RI, Cogswell PC, Lofquist AK, et al. Role of transcriptional activation of I kappa B alpha in mediation of immunosuppression by glucocorticoids. Science. 1995;270:283-6.
30. Schlaghecke R, Kornely E, Santen RT, Ridderskamp P. The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. N Engl J Med. 1992;326:226-30.
31. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis. 1989;11:954-63.
32. Temprano KK, Bandlamudi R, Moore TL. Antirheumatic drugs in pregnancy and lactation. Semin Arthritis Rheum. 2005; 35:112-21.
33. Tripathi A, Ditto AM, Grammer LC, et al. Corticosteroid therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. Allergy Asthma Proc. 2000;21:101-5.
34. Williams LC, Nesbitt LT Jr. Update on systemic glucocorticosteroids in dermatology. Dermatol Clin. 2001;19(1):63-77.
35. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisolone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum. 2006;54:628-34.

10

CHAPTER

Nonsteroidal Anti-inflammatory Drugs

Kabir Sardana

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are being covered here as they are possibly the commonest group of drugs written by physicians all over, though in dermatology our focus will be largely on aspirin.

The NSAIDs form a chemically diverse group (Table 10.1), but they all have the ability to inhibit cyclo-oxygenase (COX), and the resulting inhibition of prostaglandin synthesis is largely responsible for their therapeutic effects. Unfortunately, the inhibition of prostaglandin synthesis in the gastric mucosa frequently results in gastrointestinal damage (dyspepsia, nausea and gastritis). More serious adverse effects include gastrointestinal bleeding and perforation. COX exists in the tissue as a constitutive isoform (COX-1) but, at sites of inflammation, cytokines stimulate the induction of a second isoform (COX-2).

Inhibition of **COX-2** is thought to be responsible for the *anti-inflammatory* actions of NSAIDs, while inhibition of **COX-1** is responsible for their *gastrointestinal toxicity*. Most NSAIDs are somewhat selective for **COX-1,** but more recently

Table 10.1: A classification of NSAIDs

Salicylates	Aspirin Diflunisal
Para-aminophenol derivative	Acetaminophen
Acetic acid derivatives	Indomethacin Sulindac Etodolac ▪ Aceclofenac ▪ Ketorolac
Propionic acid derivatives	Ibuprofen Fenoprofen Naproxen
Oxicams	Enolic acid derivatives Piroxicam
Coxibs	COX-2 selective inhibitors Celecoxib Meloxicam

selective COX-2 inhibitors have been introduced. Celecoxib, etoricoxib and lumiracoxib are selective COX-2 inhibitors that have similar efficacy to nonselective COX inhibitors, but the incidence of gastric perforation, obstruction and bleeding is reduced by at least 50%. However, these new drugs do not provide any cardioprotection and are associated with an increased incidence of myocardial infarction.

Mode of Action

Inhibition of Prostaglandin Biosynthesis By NSAIDs

The first enzyme in the prostaglandin synthetic pathway is prostaglandin G/H synthase, also known as COX. This enzyme converts arachidonic acid (AA) to the unstable intermediates PGG2 and PGH2 and leads to the production of thromboxane A2 (TXA2) and a variety of prostaglandins (Fig. 10.1).

Therapeutic doses of aspirin and other NSAIDs reduce prostaglandin biosynthesis by **blocking COX**, and there is a reasonably good correlation between potency of COX inhibitors and anti-inflammatory activity. Aspirin and NSAIDs inhibit the COX enzymes and prostaglandin production; they do not inhibit the lipoxygenase pathways of AA metabolism and hence, do not suppress LT formation. Aspirin covalently modifies COX-1 and COX-2, irreversibly inhibiting COX activity. This is an important distinction from all the NSAIDs because the duration of **aspirin's** effects is related to the **turnover rate of COX** in different target tissues. The duration of effect of **nonaspirin NSAIDs**, which competitively inhibit the active sites of the COX enzymes,

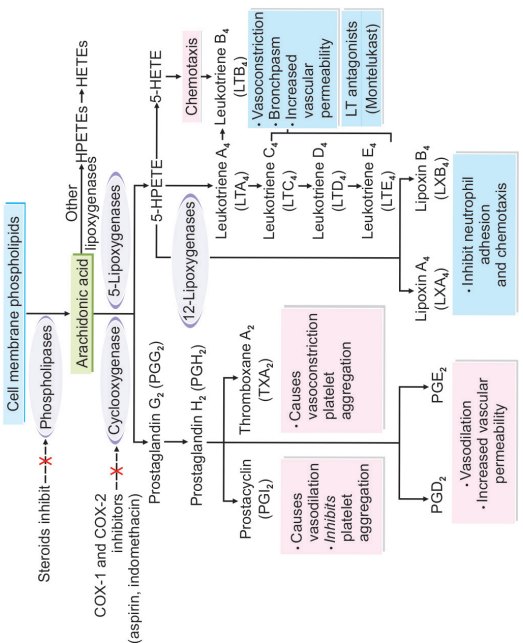


Fig. 10.1: Arachidonic acid metabolism and the site of action of NSAIDs

relates more directly to the **time course** of drug disposition. The importance of enzyme turnover in relief from aspirin action is most notable in platelets, which, being anucleate, have a markedly limited capacity for protein synthesis. Thus, the consequences of inhibition of platelet COX (COX-1) last for the lifetime of the platelet. Inhibition of platelet COX-1–dependent TXA 2 formation, therefore, is cumulative with repeated doses of aspirin (at least as low as 30 mg/day) and takes roughly 8–12 days (the platelet turnover time) to recover once therapy has been stopped.

Aspirin [acetylsalicylic acid (ASA)] is the longest-standing NSAID and is an effective analgesic, with a duration of action of about 4 hours. Aspirin is well absorbed orally. As it is a weak acid (pK a = 3.5), the acid pH of the stomach keeps a large fraction of aspirin nonionized and therefore promotes absorption in the stomach, although much aspirin is absorbed via the large surface area of the upper small intestine. The absorbed aspirin is hydrolysed by esterases in the blood and tissues to salicylate (which is active) and acetic acid. Most salicylate is converted in the liver to water-soluble conjugates that are rapidly excreted by the kidney. Alkalinization of the urine ionizes the salicylate and, because this reduces its tubular reabsorption, excretion is increased.

Aspirin was widely used in the treatment of inflammatory joint disease, but up to 50% of patients could not tolerate the adverse effects (nausea, vomiting, epigastric pain, tinnitus) caused by the high doses of soluble aspirin necessary to achieve an anti-inflammatory effect. For this reason, newer NSAIDs are generally preferred to treat the symptoms of inflammatory joint disease (pain, stiffness and swelling). NSAIDs seem to have similar effectiveness. However, there is considerable patient variation in response and so it is impossible to know which drug will be effective in an individual, although 60% of patients will respond to any drug. Because the propionic acid derivatives (e.g. ibuprofen, naproxen) are associated with fewer serious adverse effects, these are often tried first.

Paracetamol has no significant anti-inflammatory action, but is widely used as a mild analgesic when pain has no inflammatory component. It is well absorbed orally and does not cause gastric irritation. It has the disadvantage that, in overdosage, serious hepatotoxicity is likely to occur

Therapeutic Effects

1. Anti-inflammatory Effects

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used as first-line agents for the symptomatic relief of many different inflammatory conditions. In double-blind, randomized clinical trials of inflammatory arthritis, NSAIDs have been compared with placebo, aspirin and

each other. Clinical trials of NSAID efficacy in rheumatoid arthritis (and osteoarthritis) most often employ a design whereby the current NSAID is discontinued and the patient must have an increase in symptoms or flare to enter the study. Efficacy superior to that of placebo is easily demonstrated for NSAIDs within 1–2 weeks in patients with active RA who are not receiving corticosteroids or other anti-inflammatory medications. Comparisons of adequate doses of traditional NSAIDs or COX-2-selective NSAIDs with one another almost always show **comparable** efficacy.

Despite improvement in pain and stiffness with NSAIDs, these agents do not usually reduce acute phase reactants, nor do they modify radiographic progression. The anti-inflammatory effects of NSAIDs have also been demonstrated in rheumatic fever, juvenile rheumatoid arthritis, ankylosing spondylitis, gout, osteoarthritis and systemic lupus erythematosus (SLE).

2. Analgesic Effects

Virtually all NSAIDs relieve pain when used in doses substantially lower than those required to suppress inflammation. The analgesic action of NSAIDs is due to inhibition of PG production in peripheral tissues and in the central nervous system (CNS).

In the periphery, PGs do not induce pain per se but rather sensitize peripheral nociceptors to the effects of mediators, such as bradykinin or histamine. PGs released during inflammation or other trauma lower the activation threshold of tetrodotoxin resistant sodium channels on sensory neurons. In the CNS, where NSAIDs and acetaminophen exert analgesic effects, PGs also play an important role in neuronal sensitization. COX-2 is constitutively expressed in the dorsal horn of the spinal cord, and its expression is increased during inflammation. Centrally generated PGE 2 activates spinal neurons and also microglia that contribute to neuropathic pain. Both COX-1 and COX-2 play a role in nociception as demonstrated by reductions in experimental pain in mice deficient in either COX-1 or COX-2.

3. Antipyretic Effects

The NSAIDs and acetaminophen effectively suppress fever in humans and experimental animals. Fever results from the production of PG, primarily PGE 2, from vascular endothelial cells via COX-2 and mPGES-1. These PGs generate neuronal signals that activate the thermoregulatory center in the preoptic area of the anterior hypothalamus. PGE 2 synthesis is stimulated by endogenous (e.g., interleukin-1) or exogenous (e.g. lipopolysaccharide) pyrogens. Little evidence suggests that any NSAID has superior efficacy as an antipyretic.

However, in fever associated with viral illnesses, aspirin should be avoided due to the association with hepatocellular failure (Reye's syndrome).

4. Antiplatelet Effects

Aspirin and traditional NSAIDs inhibit platelet COX-1 to variable degrees. *Except* for aspirin, inhibition of platelet aggregation is **reversible** and depends on the concentration of drug in the platelet. Aspirin acetylates platelet COX-1, which cannot be resynthesized. The antiaggregation effect of as little as 80 mg of aspirin can last for up to 4–6 days, until the bone marrow can synthesize new platelets.

On the basis of accumulated data showing its benefits, the FDA has approved ASA for use in the secondary prevention of cardiovascular disease. Major trials have shown that meaningful decreases in nonfatal myocardial infarction (MI), nonfatal stroke, and death can be realized by daily administration of ASA of 75–325 mg. Major vascular events can be reduced by 10–20 events for every 1000 patients treated, at a cost of one to two major GI bleeds. The U.S. Preventative Health Task Force has updated its recommendations to encourage use of low-dose ASA in *men* aged 45–79 and *women* aged 55–79. ASA used for primary prevention of cardiovascular events appears to lower the risk for MI in men and for stroke in women.

5. Cancer Chemoprevention

A large body of epidemiologic and animal studies provides evidence that a high-fat diet can be associated with a risk for cancer. AA, one of the major ingredients of animal fats, and the eicosanoids derived from AA are shown to be important contributors to cancer development. Large-scale epidemiologic studies have long indicated that long-term NSAID use reduces the incidence of a variety of cancers **including colon, intestinal, gastric, breast and bladder**, by 40–50%. Given the ability of the NSAIDs to inhibit COX and PG production, the COX pathway immediately becomes implicated as playing an important role in the pathogenic process. It is well recognized that growth factors, tumor promoters and oncogenes stimulate PG production via the induction of COX-2 and that human tumorigenic tissues exhibit increased COX activity compared with their normal, nontumorigenic counterparts. COX-2 is overexpressed in 80% of colorectal cancer tissues.

ASPIRIN

Mechanism of Action

Acetylsalicylic acid inhibits the platelet activation: Blocking the platelet cyclooxygenase by acetylation, it inhibits

thromboxane A2 synthesis, a physiological activating substance released by the platelets.

Inhibition of TXA2-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesize new cyclooxygenase, which had been acetylated by ASA.

Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7–10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24–48 hours after treatment interruption.

Acetylsalicylic acid extends bleeding time on average by approximately 50–100%, but individual variations can be observed.

Experimental data suggest that ibuprofen may inhibit the effect of low dose ASA on platelet aggregation when they are dosed concomitantly.

Uses (Approved/Unapproved)

FDA approved and off-label uses of aspirin are indicated Table 10.2.

Table 10.2: Indication of aspirin

FDA approved	Secondary prevention of myocardial infarction ■ Prevention of cardiovascular morbidity in patients suffering from stable angina pectoris ■ History of unstable angina pectoris, except during the acute phase ■ Prevention of graft occlusion after coronary artery bypass grafting (CABG) ■ Coronary angioplasty, except during the acute phase ■ Secondary prevention of transient ischemic attacks (TIA) and ischemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out
Off label	Dermatological uses (see below in text)

1. Livedoid Vasculopathy (Atrophie Blanche)

Low-dose aspirin in combination with dipyridamole has been reported to improve atrophie blanche in two studies. The aspirin dose should be no higher than 325 mg daily. Titrating with baby aspirin (81 mg), between 1 and 3 daily, may be tried if one adult aspirin (325 mg) is not successful.

2. Antiphospholipid Antibody Syndrome

Low-dose aspirin therapy, along with other anticoagulant therapy, is generally recommended in patients with recurrent thrombotic events.

3. Erythema Nodosum

Aspirin is considered adjunctive therapy to enhance the resolution of erythema nodosum. In this setting, antiinflammatory doses of aspirin (325 mg, 4–8 daily) would be required.

Dosage

Anti-inflammatory: Aspirin should be used in low doses initially and titrated up to the desired dose, which should not exceed 650 mg, 6 times a day. Aspirin should be taken with food, or a large glass of water. For antiplatelet effects, doses of aspirin in the range of 81–325 mg daily are typically used.

Drug Interaction

Contraindicated Combinations

Methotrexate (used at doses >15 mg/week): The combined drugs, methotrexate and ASA, enhance hematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by ASA. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with aspirin is contraindicated.

Not Recommended Combinations

Uricosuric agents, e.g. Probenecid

Combinations requiring precautions for use or to be taken into account

Anticoagulants e.g. Coumarin, Heparin, Warfarin

Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored.

Anti-platelet agents (e.g clopidogrel and dipyridamole) and selective serotonin reuptake inhibitors (SSRIs; such as sertraline or paroxetine)
Increased risk of gastrointestinal bleeding.

Antidiabetics, e.g. sulphonylureas

Salicylics may increase the hypoglycemic effect of sulphonylureas.

Digoxin and Lithium

Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations.

Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with ASA. Dose adjustment may be necessary.

Diuretics and Antihypertensives

Nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.

Systemic Corticosteroids

The risk of gastrointestinal ulceration and bleeding may be increased when ASA and corticosteroids are co-administered.

Methotrexate (used at doses >15 mg/week)

The combined drugs, methotrexate and ASA, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by ASA. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Other NSAIDs

Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.

Ibuprofen

Experimental data suggest that ibuprofen may inhibit the effect of low dose ASA on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Cyclosporine, Tacrolimus

Concomitant use of NSAIDs and cyclosporine or tacrolimus may increase the nephrotoxic effect of cyclosporine and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and ASA.

Valproate

Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin

Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Alcohol

Concomitant administration of alcohol and ASA increases the risk of gastrointestinal bleeding.

11

CHAPTER

Psoralens (UVA)

Shivani Bansal, Kabir Sardana

PSORALEN

Melanocyl tab (8MOP): 10 mg, Trimop tab (5/25 mg); Melanocyl lotion 1%/ointment 0.75%, Octamop lotion 0.75%.

Classification

Photoactive Agent, Psoralen Compound

Psoralens are naturally occurring linear tricyclic furocoumarins that are found in a large number of plants, but commercially there are several synthetic psoralen compounds. For oral and topical (bath, cream) PUVA, 8-MOP (methoxsalen) is used; it is of plant origin but also available as a synthetic drug.

The synthetic compound, 4,5′,8-trimethylpsoralen (TMP, trioxsalen), is less phototoxic than 8-MOP after oral administration, but more phototoxic when bath-water-delivered. TMP is used primarily in Scandinavia for bath PUVA. In India it is used both for PUVA and PUVA sol.

5-Methoxypsoralen (5-MOP, bergapten) is also therapeutically effective when given orally; it is less erythemogenic and is not associated with gastrointestinal intolerance, and it is used largely in Europe.

Newer psoralens have been synthesized, including the angular furocoumarin 4,6,4′-trimethylangelicin and the monofunctional 7-methylpyridopsoralen, 6 methyl anyllin and 7 methyl pyridopsoralen and 3 carbethoxypsoralen.

Mechanism of Action

After photoactivation, psoralen forms conjugates and covalent bonds with DNA and thus inhibits DNA synthesis and decreases cell proliferation. It has a dual anti-inflammatory and immunosuppressive, action (Table 11.1).

Immunomodulatory Action

At least under *in vitro* conditions, UVB, UVA, and PUVA radiation may have very similar or even identical immunosuppressive consequences. The actual therapeutic

Table 11.1: Mode of action of photochemotherapy

Anti-inflammatory/ immunosuppressive	UVB/UVA-1	Increase IL-10 Decrease IFN-γ Increase alpha-MSH Increase prostaglandin (PG)E 2
Effect on cytokines	UVB/UVA-1 UVB	Increase MMP-1 protease Increased expression of the decoy receptor IL-1RII and Decreased expression of the signaling molecule IL-1RI.
Adhesion molecule expression	UVB/UVA	Decrease ICAM-1
T cells		Anergy in effector Th 1 cells and preferential activation of regulatory TH 2 cells.
Growth factors	PUVA	inhibition of EGF binding
Induction of apoptosis	UVA1/NBUVB/ BBUVB	Induces apoptosis in T-helper cells present

relevance of these effects, however, is determined by the physical properties of the type of UV radiation employed. Ultraviolet B radiation mainly affects epidermal keratinocytes and Langerhans' cells, whereas UVA radiation can penetrate more deeply into the dermis and thereby also affect dermal fibroblasts, dermal dendritic cells, endothelial cells, and skin-infiltrating inflammatory cells such as T lymphocytes, mast cells, and granulocytes (Fig. 11.1).

The 3 main actions include the followings:

1. **Effects on production of soluble mediators:** There is evidence that phototherapeutic modalities suppress the production of proinflammatory cytokines. In addition, beneficial effects observed after UVA-1 phototherapy in scleroderma patients have been attributed to the production of cytokines, which upregulate matrix metalloproteinase expression in human skin.

A keratinocyte-derived cytokine of particular therapeutic relevance is interleukin (IL)-10, which is functionally defined by its capacity to *suppress* the production of interferon (IFN)-γ by T lymphocytes of the T helper-1-like subtype (Fig. 11.1).

UVB and, in particular, UVA-1 radiation, have the capacity to *increase* significantly IL-10 mRNA and protein expression in cultured normal human keratinocytes. Successful phototherapy (UVA-1 or UVA/UVB) of *atopic dermatitis* is associated with downregulation of IFN-γ expression in atopic eczema and this effect may, at least in part, be explained by phototherapy-induced expression of IL-10 and subsequent paracrine suppression of IFN-γ production.

In vitro exposure of human keratinocytes to UVB or UVA-1 radiation increases the synthesis of pro-opio-

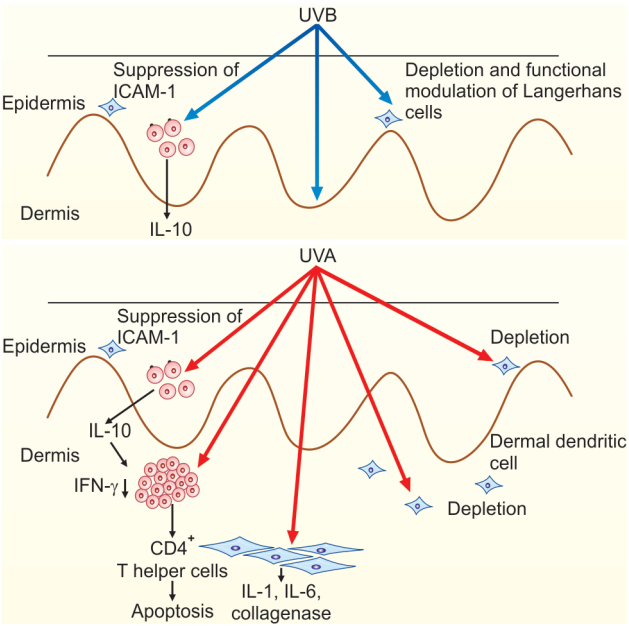


Fig. 11.1: Mode of action of UVB and UVA in the epidermis and dermis

melanocorticotropin-derived peptides including **alpha-MSH.** Alpha-MSH has a variety of anti-inflammatory (e.g. inhibition of IL-1 or tumor necrosis factor (TNF)-α-mediated inflammation) and immunosuppressive effects (e.g. inhibition of cell-mediated immune responses). It has therefore been proposed that UV radiation-induced production of alpha-MSH constitutes a UV-inducible, anti-inflammatory agent.

A third example is that of UVB and UVA radiation-induced production of prostaglandins in epidermal keratinocytes. Prostaglandin (PG)E 2 is a potent immunosuppressant that affects the expression of costimulatory molecules on the surface of antigen-presenting cells and thereby prevents the activation of selected T-cell subsets (especially Th 1 -like cells).

2. **Modulation of the expression of cell-surface-associated molecules.**

3. **The induction of apoptosis in pathogenetically relevant cells:** Both UVA and UVB induce T-cell apoptosis. Successful UVB phototherapy of psoriatic patients induced a reduction in the number of skin-infiltrating T cells, which was followed by a normalization of keratinocyte morphology. *In vitro* UVB irradiation induced T-cell apoptosis, suggesting that the reduction of the inflammatory infiltrate resulted from UVB radiation-induced T-cell apoptosis.This hypothesis has recently been proven by the demonstration of apoptotic T cells in lesional psoriatic skin of patients undergoing UVB phototherapy. Induction of T-cell apoptosis was observed regardless of whether broadband UVB or 311-nm UVB

phototherapy was employed. It should be noted, however, that because of its physical properties, a much greater level of 311-nm UVB radiation penetrates into *human* dermis, and therefore apoptosis occurs in both epidermal and dermal T cells. This difference may at least partially explain the clinical observation that 311-nm UVB phototherapy is superior to broadband UVB phototherapy for the treatment of psoriasis.

From a phototherapeutic point of view, UVA-1 phototherapy is *superior* to UVB or PUVA therapy for skin diseases in which induction of apoptosis in pathogenetically relevant cells is of critical importance (Fig. 11.1). Thus, as a consequence, UVA-1 phototherapy, but not PUVA, was associated with mast cell depletion from skin and longer lasting remission periods in patients with mastocytosis. The unique properties of UVA-1 radiation have also stimulated interest in its therapeutic use for patients with cutaneous T-cell lymphoma.

4. Psoralens also stimulate melanogenesis: This involves the photoconjugation of psoralens to DNA in melanocytes, followed by mitosis and subsequent proliferation of melanocytes, increased formation and melanization of melanosomes, enhanced transfer of melanosomes to keratinocytes, and increased synthesis of tyrosinase via stimulation of cAMP activity.

Pharmacology

1. **Natural 8-MOP** (methoxsalen): For oral and topical (bath, cream) PUVA.
2. **Synthetic compound**, 4,5′,8-trimethylpsoralen (TMP, trioxsalen): This is *less phototoxic* than 8-MOP after oral administration, but more phototoxic when bath-water-delivered. Its use is in children and in PUVAsol.
3. **5-Methoxypsoralen** (5-MOP, bergapten): It is less erythemogenic and is not associated with gastrointestinal intolerance. In Europe (where available), it is now used for routine PUVA.

The action spectrum for 8-MOP-induced delayed erythema has its maximum activity in the 350–360 nm range and the antipsoriatic activity of 8-MOP (plus UVA) appears to parallel its erythema action spectrum.

Absorption and Distribution

Oral

Currently,8-MOP and 5-MOP are available as oral preparations that either contain crystals, micronized crystals, or solubilized psoralens in a gel matrix. The liquid preparation

induces earlier, higher and more reproducible peak plasma levels than the crystalline preparations.

5-MOP is less water-soluble than 8-MOP and liquid preparations of 5-MOP give higher and earlier peak serum levels than do crystalline formulations.

Psoralens are metabolized through the liver and small amounts of the drug (8-MOP) are almost completely metabolized by the liver during the first pass and therefore may be therapeutically inactive. 70% of them are excreted through the kidney in 12 hours.

The serum levels of 8-MOP and 5-MOP have an unpredictable pharmacokinetic behavior due to inter- and intraindividual variations in intestinal absorption, first-pass effect, blood distribution in the body, and metabolism and elimination of the drug. In a particular individual, serum levels of 8-MOP correspond fairly well with skin reactivity, with the peak of skin phototoxicity coinciding with peak serum levels. After 24 hours no significant phototoxicity can be detected

Intake of food before taking psoralens slows absorption and reduces the peak blood levels, specially if the food has high fat intake. Though it is advised to take the drug in fasting conditions this is difficult as the drug can cause nausea. It is generally believed that 8-MOP doses *below 20 mg* are not clinically effective because of this first-pass effect.

Topical

The pharmacokinetics of topical 8-MOP depend on the mode of application. An 8-MOP administered topically as a 0.15% emulsion or solution has been shown to result in plasma levels comparable to those obtained by oral delivery, when large areas of the body are treated. In contrast, due to the much lower concentrations that are used, plasma levels following bath-PUVA treatment of almost the entire body surface are very low. Bath-water-delivered psoralens are readily absorbed into the skin, but are promptly eliminated without cutaneous accumulation.

PUVA Erythema

PUVA erythema does not occur before 24–36 hours, and it peaks at 72–96 hours or even later after exposure and has steeper dose response curve. Erythema is the only available parameter that allows an assessment of the magnitude of the PUVA reaction and thus represents an important factor for determining UVA dose adjustments.

In India skin, erythema is difficult to ascertain. Pigmentation, the second important effect of PUVA, may develop without clinically evident erythema. In normal

skin, PUVA pigmentation peaks about 7 days after exposure and may last from several weeks to months. As with sun-induced tanning, the individual's ability to tan is genetically determined, but the dose-response curve is much steeper. A few PUVA exposures result in a much deeper tan than that produced by multiple exposures to solar radiation.

Usage Guidelines

1. Oral PUVA

Oral: 8-MOP: **0.4 to 0.5** mg/kg (rounded off to the nearest 10 mg) to be given 1–3 (usually 1.5 hrs) hours before exposure; TMP **(0.6–0.8 mg/kg)**; 5-MOP, the usual dosage is 1.2–1.8 mg/kg.

UVA source: Either a PUVA chamber or Sunlight (PUVAsol). In the latter case TMP is preferred.

PUVA chamber: The initial UVA doses are selected either by skin typing or by determining the minimal phototoxicity dose (MPD). The doses range from 0.5 to 5 J/cm^2 if 8-MOP is used and 1–10 J/cm^2 if 5-MOP is used. In India mostly a dose format according to skin type is followed (see appendix) (Table 11. 2).

Erythema readings are performed 72 (not later than 96) hours after irradiation, when the phototoxicity reaction usually peaks. As with the MED, the MPD should be determined on previously non-sun-exposed skin (lower back or buttocks). This will yield lower values than on previously exposed skin and thus contributes to a safer initial dosimetry. Although performing an MPD is more time-consuming than phototyping, it should be done whenever possible, since it allows for far more accurate and higher UVA doses during

Table 11.2: Difference in the PUVA protocols in US and Europe

	US	*Europe*
UVA dosimetry	Predetermined dose according to *skin phototype*	Individualized dose according to *MPD determination*
Frequency of treatment	Two to three times per week	Four times per week
Dose increments	Predetermined	Individualized
Principle of approach	Rigid, cautious	Flexible, aggressive
Goal	To clear without ponderous testing and acute side effects	To clear rapidly before maximum pigmentation develops
Clearing rate	88%	88.8%
Exposures	25	20
Time to clearing	12.7 weeks	5.7 weeks
Cumulative UVA dose	191 J/cm^2 (type I) 296 J/cm^2 (type II)	96 J/cm^2

the initial treatment phase. As with UVB therapy, some experienced therapists do not consider phototesting to be mandatory.

2. *Bath PUVA*

This concept though *not* approved by US FDA is used in Scandivanian countries. It ensures a uniform drug distribution over the skin surface, very low psoralen plasma levels, and a quick elimination of free psoralens from the skin, thereby reducing the period of photosensitivity. Though originally, TMP was used but now but 8-MOP and 5-MOP are being used. Bath PUVA consists of 15–20 minutes of whole body (or hand and foot) immersion in solutions of 0.5–5.0 mg of 8-MOP per liter of bath water. Irradiation has to be performed immediately thereafter, as photosensitivity decreases rather rapidly. TMP is more phototoxic after topical application and thus is used at lower concentrations than 8-MOP.

3. Topical PUVA

Application of 8-MOP (0.1–0.01%) in creams, ointments or lotions, followed by UVA irradiation, is used for localized dermatoses. It has some issues like unpredictable phototoxic erythema reactions, inadvertent application to surrounding uninvolved skin and hyperpigmentation. It is not FDA approved in children.

4. Topical PUVAsol

Topical treatment application of 8-MOP in creams, ointments or lotions followed by UVA irradiation is effective in limited plaque psoriasis and for palmoplantar disease. A lotion containing 0.1–1% 8-MOP is applied and exposed to sunlight either immediately or after one to two hours. Among the psoralens, TMP is most convenient for topical application because of its weak penetrability. The penetrated drug makes photo adducts with DNA molecules even if UVA light is given as soon as the drug is painted resulting in significant inhibition of epidermal DNA synthesis. In India, this is also used for treating vitiligo.

5. P-NBUVB

Although the action spectrum of psoralens falls in the UVA range (320–360 nm), they also increase the sensitivity of skin to NBUVB. It has been seen that 8-MOP augments the UVB erythema response at 6 hours after irradiation and a different mechanism of erythema production for PUVB has been suggested. It is likely that P-NBUVB works by both direct UVB effect and psoralen photochemistry. It has been seen that P-NBUVB acts faster than NBUVB in vitiligo, produces

a greater percentage reduction in VASI scores and requiring a lesser cumulative dose (Bansal S). Further evaluations of psoralen and UVB need to be conducted.

Clinical Use in Dermatology

Clinical uses of photochemotherapy in dermatology are enlisted in Box 11.1.

Box 11.1: Uses of photochemotherapy in dermatology

Disorder (FDA approved/ unapproved)	*Dose/duration*
FDA approved	Psoriasis, vitiligo
Unapproved	Alopecia areata Atopic dermatitis Cutaneous T-cell lymphoma Chronic hand dermatitis Dyshidrotic eczema Graft-versus host disease Granuloma annulare Lichen planus Morphea Palmoplantar pustulosis Parapsoriasis Pigmented purpuric dermatoses Pityriasis lichenoides Polymerphous light eruption Pityriasis rubra pilaris Pruritic dermatoses Seborrheic dermatitis Urticaria pigmentosa

Psoriasis

PUVA therapy is successful in clearing about 90% of patients with plaque-type psoriasis in a course of up to 30 treatments. (Parrish JA et al.). Practitioners of PUVA may note the heartening fact that with 90% of patients clearing or virtually clearing, the vast majority of PUVA-treated patients would consistently *exceed* the current standard of determining efficacy of new therapies for psoriasis.

In *recalcitrant* cases, a combination approach of *acitretin or methotrexate* can be used with PUVA. Broadband (BB-) UVB therapy is much less effective than PUVA therapy in chronic psoriasis, whereas narrowband (311 nm) UVB (NB-UVB) phototherapy is almost *as* effective as PUVA.

a. Oral PUVA

Adults: Dosage depends on weight. 30–50 kg: 20 mg; 51–65 kg: 30 mg; 66–80 kg: 40 mg.

Or

8 MOP (0.6–0.8 mg/kg) or 1.2 mg/kg 5-MOP, 1 h and 2 h before UVA exposure.

In Europe, oral 5-MOP PUVA is an alternative to 8-MOP PUVA. With this drug the lesions clear with a comparable number of exposures, but 5-MOP requires significantly ***higher*** cumulative UVA doses as this has a lower phototoxic potential. But 5-MOP has certain advantages namely absence of nausea and vomiting, and the lower incidence of pruritus and severe phototoxic skin reactions. Twice weekly irradiation is found to be more appropriate than thrice weekly.

Response: About 10–20 treatments over 4–8 weeks.

Maintenance: Maintenance therapy is recommended in the European regimen. It consists of weekly sittings at the last UVA dose for 4 weeks then biweekly for 2 months then finally monthly. The British Photodermatology Group has suggested restricted use of this only if relapses are rapid following clearance. Thus, maintenance treatment is *largely ineffective* in preventing early relapse of psoriasis (Radakovic S et al.) and should be avoided though this may need more studies for a firm recommendation.

PUVA Sol: In this oral 8 MOP is taken 2 hours before UVA exposure.

Dosage Schedule: The recommended dose is 0.6 mg/ kg body wt. (<30 kg: 10 mg; 30–50 kg: 20 mg; 51–65 kg: 30 mg: 66–80 kg: 40 mg).

The sunlight exposure can begin at 5 minutes and increased gradually to a maximum of 30 minutes. Treatment may be continued up to the recommended number of exposures or till complete remission. For solar radiation, the best exposure time is when the sun is at the zenith. The position of the patient should be lying down.

A study by Aggarwal K et al. found that PUVAsol has comparable results with PUVA (75%:93.75%) though the treatment failure was more in the PUVAsol group. In a resource constraint setting, PUVAsol will be twice as cost effective as PUVA. The protocol for use of this drug is given in the Appendix.

b. Topical PUVA

Topical psoralen plus UVA irradiation is effective in clearing psoriasis but has several issues including unpredictable phototoxic erythema and vesiculation. It is a time consuming and laborious process and is useful primarily in palmoplantar psoriasis and in patients with hepatic, renal and gastrointenstinal dysfunction. It is not commonly practiced nowadays. 8-MOP is used as a 0.15% solution painted on the lesions 20 min before exposure.

Bath PUVA: Trisoralen (trimethylpsoralen; TMP) is preferred. Bath-PUVA therapy is especially useful for patients with severe nausea from the oral form. Irradiation with UVA should be performed within 15 minutes after the bath as light sensitivity drops dramatically after one hour.

Though the results of oral PUVA and bath PUVA are similar this only when the European protocol is followed. The greater reported therapeutic efficacy is justified due to a higher penetration of psoralens through the abnormal stratum corneum overlying psoriatic plaques as compared with healthy perilesional skin where phototoxicity is monitored during the therapy. Obviously nausea and vomiting are less frequent than oral PUVA.

Recently 8 MOP has been used in bath PUVA and found to be as effective as PUVA (Berneburg M et al.).

An overview of phototherapy is given below

Phototherapy in psoriasis		
Broadband UVB	Eruptive and seborrheic forms respond favorably	Not as effective as PUVA UVB may be given with topical tars Goeckerman regimen or anthralin applications (Ingram regimen). The combination with topical steroids is discouraged because it may result in reduced remission times
Narowband UVB	It does not work on palms and sole Treatments 3/wk Average of 30 treatments are required	As effective as PUVA but more costly. Shorter remission period than PUVA in Indian skin types though PUVA is better Combined with retinoids (RePUVA), anthralin and calcipotriol

Combination Treatments (Psoriasis)

The main *indications* for combination treatment are skin types IV to VI, erythrodermic psoriasis, generalized pustular psoriasis, thick plaques, and very active inflammatory psoriasis. In addition, BB-UVB plus PUVA therapy is useful in patients showing a relatively slow response to PUVA therapy alone. It is important to note that NB-UVB activates 8-MOP as effectively as UVA radiation, so the use of a combination of NB-UVB plus PUVA would give the patient three different treatments, though a protocol for this has not been standardized.

i. Topical Combination

Topical adjuvant therapies include corticosteroids, anthralin and tar, and, more recently, calcipotriol and tazarotene.

ii. Methotrexate, Cyclosporine Bioengineered Immunomodulators

The combination of PUVA and methotrexate (MTX) during the clearing phase reduces the duration of treatment, number of exposures, and cumulative UVA dose, and is also effective in clearing patients unresponsive to PUVA or UVB alone. The use of MTX is for a *short duration* as PUVA and MTX could act synergistically in the development of skin cancers, though this has not been reported to date. This combination should be restricted to the *clearing phase*. Another protocol is to start with methotrexate therapy for 3weeks, then follow with PUVA + Mtx till clearance and then maintain on PUVA therapy.

In contrast, cyclosporine plus PUVA has been clearly shown to dramatically enhance skin *carcinogenesis*. Presently, there are no studies evaluating the safety and efficacy of the combination of any bioengineered immunomodulators ("biologics") with PUVA.

iii. Retinoids

The combination of PUVA with systemic retinoids (RePUVA) is one of the most ***potent*** therapeutic regimens for psoriasis. The therapeutic efficacy of PUVA therapy is significantly enhanced upon daily combination with oral retinoids (acitretin, isotretinoin) (0.75–1 mg/kg for etretinate and isotretinoin, 0.5–0.75 mg/kg for acitretin) administered for *5–10* days *before* PUVA is started, with the combination continued throughout the clearing phase. RePUVA reportedly can reduce the number of exposures by one-third and the total cumulative UVA dose by more than one-half. RePUVA can also clear "poor PUVA responders".

This combination is useful as (i) it helps in a reduction in the inflammatory infiltrate, (ii) causes an accelerated desquamation of the psoriatic plaques leading to increased penetration of UV light. The added advantage is that retinoids may also reduce the long-term carcinogenic risk of PUVA by reducing the number of exposures and providing chemoprevention against skin cancers. This is proved by a reduced risk of SCC but not a significantly altered incidence of BCC. But there is an increased risk of photosensitivity with sun as effects of UV light are enhanced.

Vitiligo

On PUVA the actual improvement of vitiligo can be first seen as early as after 15–20 irradiations, when perifollicular and marginal repigmentation appears. This is darker than the tanned unaffected skin but the pigmentation may be punctuated with gradual deceleration or complete stagnation and at this point instead of increasing the UVA doses it is better to *change* to a different photosensitizer (from khellin or 8-MOP

to 5-MOP) or to use a drug combination (e.g. 8-MOP plus TMP). It is largely believed that PUVA-induced repigmentation persists in the majority of patients for many years. But after finishing PUVA treatment in 40% patient, recurrence of vitiligo has been reported. An overview is given below.

Factoids on Treatment Response with PUVA in vitiligo

Initial response	30–40 treatments
Perifollicular pigment	25- Facial 50- elsewhere
Ideal response	150 sessions
Time for response	6 m–1 year
Stop therapy if unresponsive	After 4 months
Response rate	40–60%

As TMP is poorly absorbed, has a higher affinity for serum proteins, it consequentially causes less concentration in the skin and is thus less photosensitising. Thus, it is not preferred in PUVA but is a safer option in PUVAsol.

A summary of the various psoralens and their effect in vitiligo is listed in Table 11.3.

Table 11.3: Use of various psoralens in vitiligo

Photosensitizer	*PUVA*		*PUVA sol*		*Children*
	Oral	Topical	Oral	Topical	Oral/topical
8 MOP	Y	Y	Y	Y*	Topical (Y)
TMP	Y	Y	Y		Oral (Y)
5-MOP	Y	Y	Y		Oral (Y)
Khellin	Y	Y	Y	Y	Topical(Y)
Phenylalanine	Y		Y		Oral (Y)

*In India, this is used with sunlight though it is not recommended in the West (Y = Yes)

a. PUVA

Oral 8-MOP and TMP are the photosensitizers commonly used in India. Khellin (KUVA) and Phenylalanine (PAUVA) have been tried but are not used commonly in India. Combination of TMP/8MOP therapy can be considered in patients that demonstrate extreme sensitivity (gastrointestinal side effects, phototoxicity) to higher doses of 8MOP. The recommended dose would be **half** the standard dosage of **each** of the aforementioned medications.

It is crucial that the patient understands that PUVA, like other vitiligo therapies, may require months or even years to achieve a satisfactory result. A optimistic prognoses regarding therapeutic efficacy and length of time to produce adequate repigmentation should be avoided. The patients must also be aware that the treatments stimulate the pigmentation of

normal skin, which will intensify the contrast between normal and vitiliginous skin. The therapeutic effect becomes apparent with the development of follicular dots of pigmentation in areas of vitiligo. A marginal band of repigmentation may be seen simultaneously. Often, these repigmented areas are darker than the surrounding normal skin. With an optimal response, follicular dots start to appear after **20–50** exposures and gradually enlarge to produce even pigmentation of the whole area. However, the therapeutic response may come to a halt without reaching full repigmentation despite continued treatments.

Dose: The oral doses used for vitiligo treatment is usually less as compared to those for psoriasis (0.3–0.6 mg/kg 8-MOP) (0.6–0.8 mg/kg) for 5-MOP and TMP. With the use of 8-MOP and 5-MOP, determination of the MPD is strongly recommended to avoid phototoxic side effects. Oral TMP does not induce a clinical phototoxic reaction because the dosimetry follows a fixed regimen. Irradiations start at 1–2 J/cm^2 with weekly increases by 1 J/cm^2 until a maintenance dose of 10–15 J/cm^2 is reached.

Schedule: At least twice a week, but not more than three times. If there is no response after *4–5 months* or approximately *30–40 treatments*, PUVA should be terminated.

Responsiveness is defined as development of multiple perifollicular macules of repigmentation, or, in the case of small (<2 cm) lesions, contraction in size. If treatment is discontinued, reversal of acquired repigmentation may occur unless the lesion has *completely* repigmented. Completely repigmented areas can be stable for a decade or more without relapse (Ortel B et al.). It is estimated that of the patients treated, **40–60%** respond out of which about **20-25%** respond completely and **30%** of patients do not respond at all *Patient Selection*: Age 10–12 years or older, must be available for 12–24 months of continuous therapy.

Poor response: Lips, distal dorsal hands, fingers and toes, palms, soles and nipples are poor responders.

Good response: Stable disease, segmental vitiligo present for at least a year.

Course of therapy: Perifollicular pigmentation is seen within **25** exposures with **facial** lesions and **50** exposures with involvement elsewhere; if not, treatment should be discontinued.

Sittings: At least **150** exposures.

Adjustment of dosage: Pediatric: Safety and efficacy have not been established in children <12 years.

b. PUVA (Sol)

Because of weaker phototoxicity, oral **TMP** is preferred to 8-MOP for treatment with sunlight as the radiation source.

This is relevant where the patients is unable to afforded or have the time to visit the PUVA centre. Some authors have advocated (Halder RM) the use of 8-MOP if the sunlight exposure is properly titrated.

Dose: The dosage is 0.6–0.8 mg/kg (TMP).

Exposure: The initial sun exposure should be 5 minutes between 10:00 AM and 4:00 PM. Subsequent sun exposure is increased by 5 minutes, until lesional erythema appears. Treatments are given three times weekly.

A landmark study on PUVAsol by Pathak et al. compared 8-methoxypsoralen (8-MOP), 4,5',8-trimethylpsoralen (TMP), and a combination of TMP and 8 MOP and sunlight. Patients in prone and supine positions were exposed to the sun for 45–60 minutes in gradually increasing doses between 11 am and 2 pm thrice weekly and 2 hours after oral ingestion of the drug.

Dose schedule was 0.3 and 0.6 mg 8-MOP/kg; 0.8, 1.8, and 3.6 mg TMP/kg and a combination of **0.3 mg/kg** 8-MOP and **0.6 mg/kg** of TMP. After almost 2 years, the faces of those 45% receiving the combination dose of 8-MOP plus TMP or low-dose 8-MOP (0.3 mg/kg) were fully repigmented, and nearly 60% achieved 75–100% repigmentation of the head and neck. The chest, abdomen, and back were repigmented nearly as well and better than the arms and legs. The patients receiving high-dose schedules of TMP and psoralen achieved better repigmentation response than those on lower dosage but still not as good as patients on 8-MOP or the combination group of 8-MOP plus TMP.

Thus an excellent option in patients who are unable to undergo PUVA in phototherapy units,is the a combination of 0.3 mg/kg 8-MOP and 0.6 mg/kg of TMP which also helps to reduce the gastric side effects of 8-MOP.

c. Bath PUVA

Dilute 1 mL of 8-MOP solution (1 mg/mL standard solution) in 2 L of warm water in a basin or dilute 10 mL of 0.1 mg/mL trioxsalen (trimethylpsoralen in 95% ethyl alcohol) in 2 L of warm water which must be agitated during soaking. The patient soaks the affected area of the body to be treated for 15 minutes, pats the skin dry, and then protects the nonaffected skin from the UV light. The initial dose for bath PUVA for all skin types is 0.5 J/cm^2 of UVA. The frequency is one to two times a week.

d. Topical PUVA

This is used in localized (less than 5% total body surface area) vitiligo or in children in whom one may hesitate to use systemic PUVA.

Topical 8-MOP preparations (0.01% or 0.1% 8-MOP in a cream or ointment base) is applied evenly on the treatment area *30 minutes* prior to irradiation. Exposure times (beginning at ≤0.25–0.5 J/cm^2) is increased weekly in increments of 0.25 J/cm^2 unless marked erythema occurs. Once- to twice-weekly treatments are recommended. *TMP* and 5-MOP are more phototoxic so are *not* preferred. To prepare the conc of 0.01%, alcohol, propylene glycol or Cetaphil can be mixed with topical 8-MOP.

e. Topical PUVA (sol)

Though in India this is usually practiced it must be emphasized that sunlight as a source of UV light is not recommended by the US FDA for phototherapy with topical psoralen. Even if it is to be done ***8-MOP*** is preferred as TMP and 5-MOP are more phototoxic than 8-MOP. A concentration of 0.1% with sunlight as a UVA source is absolutely forbidden because of the significantly increased potential of developing a severe phototoxic reaction.

In special situations, where in-office topical photochemotherapy treatments are inconvenient and costly a modified protocol has been modified to allow for daily sunlight exposure as the UVA light source using a very dilute (**0.001%)** concentration of topical 8 MOP.

Protocol: This protocol is strictly reserved for patients with less than 10% cutaneous surface involvement (Grimes PE).

1. A thin coat of 0.001% ointment is applied to affected areas 30 minutes before exposure to the sun.
2. Vitiliginous sites are then exposed to sunlight for 15–30 minutes between 10:00 AM and 4:00 PM.
3. After two weeks, exposure time may be increased to 45 minutes to one hour, if mild erythema has not occurred.

It is to be noted that in India a different protocol is followed (**see Appendix under PUVAsol for vitiligo**)

f. P-NBUVB

The effect of using psoralen with NB UVB is superior to the effect of using NBUVB alone in the treatment of vitiligo. The combination of 8-methoxypsoralen (MOP) with UVB decreased the minimal erythema dose (MED) by a factor of 3.8. It was suggested that both ranges of UV light produce the same therapeutic effect with psoralens. This might be because UVB lamps produce some UVA and vice versa, or it could be because psoralens work both in the UVA and the UVB range, irrespective of the exact peak. The exact mechanism of action of psoralen ultraviolet B (PUVB) phototherapy is unknown. It seems likely to be through both a direct therapeutic effect of 311nm radiation on melanocytes, as well as through psoralen –mediated photochemical responses (Bansal S et al.).

Children

Children younger than 12 years should not receive oral PUVA treatment, because the spectral properties of the anterior segment of the eye allow UVA penetration. But some authors (Halder MR) have used TMP in children for vitiligo.

Similarly topical 8-MOP application is generally avoided as it can cause phototoxic effects. Bath PUVA is a option (0.0002% 8-MOP) as has topical khellin and oral l-phenylalanine and UVA.

Systemic TMP-sensitization has been successfully used in combination with office treatments and also in combination with sunlight (Halder RM and Nordlund JJ). Recently, NB-UVB has been used in children with promising results and will likely replace most photochemotherapeutic regimens for childhood vitiligo.

Combination

In places where sunlight is available with sufficient intensity throughout the year, solar phototherapy may be combined with topicals, such as corticosteroids. Other agents that have been used include tacrolimus (NbUVB/Excimer light), calcipotriol (sunlight, PUVA, NbUVB), minoxidil (PUVA), pseudocatalase and calcium and recently afamelanotide (NbUVB).

PUVA for Cutaneous T-cell Lymphoma, in Particular Mycosis Fungoides

Three types of phototherapy regimens have been employed to treat CTCL (i) conventional broad-spectrum UVB irradiation, (ii) UVA irradiation in combination with a systemically administered photosensitizing drug, such as 8-methoxypsoralen, and (iii) UVA irradiation in combination with a topically administered photosensitizing drug.

PUVA is indicated for histologically confirmed plaque or tumor stage MF or the erythrodermic form of CTCL. Treatment schedules and dosimetry in the photochemotherapy of MF are essentially the same as for psoriasis, consisting of three phases—clearing, maintenance and follow-up. If a relapse occurs, the patient is again treated with three or four PUVA exposures per week until complete clearing.

Response: The best initial complete response rates were obtained for stages IA (~90%), IB (~76%) and IIA (~78%), as compared to stages IIB and III (~60%). In the first follow-up study of 44 PUVA-treated patients, 56% (5/9) with stage IA disease and 39% (10/26) with stage IB disease remained in remission during a mean follow-up period of 44 months. Patients who experienced relapses had mean disease-free intervals of 20 months for stage IA and 17 months for stage IB. All patients (7/7) with stage IIB disease had multiple recurrences.

PUVA is an excellent treatment option for early stage (IA–IIA) CTCL. High rates of complete clearing can be achieved and a substantial percentage of patients remain free of disease for many years. In advanced stages (IIB–IVB), PUVA is not sufficient as monotherapy, but as adjunctive treatment, it can reduce the tumor burden in the skin and can improve the quality of life for patients. Presently, no therapeutic regimen is known to arrest eventual progression of advanced stages of MF to tumor formation, dissemination and fatal outcome.

PUVA for Atopic Dermatitis

UVA-1 therapy may represent a novel monotherapeutic approach to treating patients with acute, severe exacerbation of atopic dermatitis. This process involves an early initiation phase that is dominated by the expression of Th2 -like cytokines, which is then switched into a second, later phase. The latter is characterized by the predominance of the Th1 -like cytokine (IFN-γ), which is responsible for the development and maintenance of clinically apparent eczema Successful phototherapy of atopic dermatitis with UVA-1 radiation is associated with a marked reduction in the number of skin-infiltrating T cells and subsequent downregulation of IFN-γ expression in lesional atopic skin.

PUVA therapy is of limited use for the treatment of patients with acute atopic dermatitis. 311-nm UVB therapy may represent the phototherapeutic modality of choice to induce long-term improvement in patients with chronic atopic dermatitis.

If PUVA is used the treatment guidelines are essentially the same as for psoriasis. However, as compared to psoriasis, atopic dermatitis is more *difficult* to treat; quite often, a *higher number* of treatments is required. Although atopic eczema may be cleared by PUVA, *recurrence* rates are high and rapid, requiring frequent maintenance exposures. Due to the patient's young age; however, long-term maintenance therapy should be avoided. A combination of PUVA with topical corticosteroids appears to be superior to PUVA alone in maintaining remissions, and in a recent study involving patients with severe atopic dermatitis, PUVA provided better short- and long-term responses than did medium-dose UVA1 (Tzaneva S et al.).

Phototherapy in AD (Meduri NB et al.)		
Acute, severe AD	High-dose UVA-1, PUVA, extracorporeal photopheresis	Ideal is **UVA1** and can supplant the use of steroids
Chronic, moderate	311-nm, UVB, UVA/UVB, low-dose UVA-1, broadband UVB, broadband UVA	It should be used in combination with topical steroids. Ideal is **NB UVB**

PUVA for Lichen Planus

PUVA may often be an effective therapeutic option for extensive LP, but longer treatment periods and higher cumulative doses than for psoriasis appear necessary, and early relapse is possible. The pruritus typically disappears within the first 10 sessions, although at least **30 sessions** are required for the lesions to disappear completely. Maintenance dosage is variable and patient specific.

There are certain issues which are relevant in pigmented skin including (i) marked postinflammatory hyperpigmentation, and (ii) an exacerbation during PUVA treatment. A combined RePUVA regimen (as is used for psoriasis) may accelerate clearing in disseminated and particularly keratotic forms of lichen planus.

NB-UVB appears now to be the phototherapy of choice in lichen planus with PUVA used for resistant cases.

PUVA for Graft-versus-Host Disease

The therapeutic regimen used for the treatment of chronic GVHD is basically the same as for psoriasis. UVA doses should not be increased too aggressively, in order to avoid erythema and possible (re)activation of GVHD. The UVA dosage is increased by no more than 0.5 J/cm^2 every second to fourth exposure and patients are treated three to four times weekly. After clearing of skin lesions, exposures are reduced according to the maintenance schedule outlined for psoriasis.

The lichen-planus-like skin manifestations of progressive onset and quiescent onset limited chronic cutaneous GvHD as well as of late-occurring, acute GvHD after reduction or withdrawal of cyclosporine respond best to photochemotherapies. PUVA bath appears to be the phototreatment of choice for disseminated morphea-like lesions of limited, *de novo* onset chronic GvHD. PUVA bath and UVA 1 are best for more widespread sclerodermoid GvHD.

PUVA for Urticaria Pigmentosa

PUVA causes a temporary involution of cutaneous mastocytosis (Christophers E et al.). The treatment results in loss of Darier's sign, relief of itching, and flattening and sometimes even complete disappearance of cutaneous macules and papules. Surprisingly, even systemic symptoms, such as histamine-induced migraines and flushing fade gradually as treatment is continued. In most patients, the manifestations of the disease recur several months after discontinuation of PUVA. The recurrences respond as well as the original lesions, and complete clearing of signs and symptoms can again be achieved. In children, PUVA is also

often helpful, and appears to be justified in widespread, disabling mastocytosis. To avoid sudden mediator release from mast cells, a PUVA regimen of *gradually increasing* doses, especially during the initial phase, seems advisable, although the therapy should otherwise be undertaken according to the usual guidelines.

PUVA for Photodermatoses

Tolerance to sunlight can be induced in several photodermatoses with PUVA though Narrowband UVB and PUVA are comparably effective in the photoprevention of polymorphic light eruption (PLE).

In *polymorphic light eruption* (PMLE), the most common photodermatosis, PUVA is a very effective preventive treatment (via hardening) (Hönigsmann H et al.). In approximately 70% of patients with this condition, a 3- to 4-week course of PUVA suffices to suppress the disease upon subsequent exposure to sunlight. The initial exposure and dose increments should be performed according to the guidelines outlined for psoriasis.

PUVA induces pigmentation rapidly and intensively at relatively low (suberythemogenic) UVA doses that usually remain well below the threshold doses for eliciting the PMLE. About 10% of the patients develop typical lesions during the initial phase of PUVA. Interruption of treatment or reduction in the UVA dose is rarely required in such cases. Usually, brief symptomatic treatment with topical corticosteroids suffices.

PUVA hardening is indicated in patients with (i) severe PMLE or those, (ii) whose disease cannot be prevented with the use of sunscreens or UVB phototherapy. Treatment is given *three times weekly* over a period of *4 weeks* in the early spring. The PUVA therapy protects only temporarily, and regularly repeated sun exposures are subsequently required to maintain protection. However, a considerable number of patients remain protected for 2–3 months, even after pigmentation has faded.

Mechanism: Induces tolerance to sunlight are not clear. Hyperpigmentation and thickening of the stratum corneum may be important factors for this protective effect. However, other mechanisms may also be involved, since PMLE does occur in darkly pigmented individuals and even patients with skin type I who do not tan profit from hardening. Modulation of cutaneous immune functions is a possible explanation.

There is also some experience with PUVA prophylaxis of other photodermatoses including *solar urticaria*, where it appears to be the most effective preventive treatment available. Successful photochemotherapy has also been reported in occasional patients with *chronic actinic*

dermatitis (Hindson C et al.) and *hydroa vacciniforme* (Jaschke E et al.). Limited experience in patients with *erythropoietic protoporphyria* indicates that, with a very cautious approach and in combination with β-carotene, PUVA may increase light tolerance considerably.

PUVA for Miscellaneous Dermatoses

PUVA has been used for various other disorders including perforating dermatoses, livedo reticularis,*livedoid vasculopathy, granuloma annulare, pririgo nodularis, urticaria, eosinophilic fasciitis.* UVA therapy is effective in a variety of pruritic dermatoses, with a course of 30–40 treatments typically achieving a complete remission.

a. Alopecia Areata

The first treatments using photosensitizers and the sun suggested the beneficial effect of this association in alopecia areata. Later research has documented beneficial effects, with different results depending on the investigators. In 1980, a prognostic criterion was proposed to specify the treatment with PUVA for the different clinical forms. Half the patients respond well to PUVA, but symptoms typically reappear within a few months which begs the question of whether this is an efficient treatment for alopecia areata or it should be reserved only for special cases, such as ophiasis or alopecia in adults. It is not indicated for infant, alopecia totalis, or universal alopecia.

PUVA Turban therapy is one modality used in the treatment of alopecia areata. A cotton towel is soaked with a 0.0001% 8-MOP solution (1 mg/L) at 37 degrees C, wrung gently to remove excess water and wrapped around the patient's head in a turban fashion for 20 min. This is directly followed by UVA radiation. Treatment sessions are three to four times per week. This therapy has been shown to be a well-tolerated and is an efficient therapeutic alternative in the treatment of alopecia areata.

b. Morphea

Though UVA1 is touted as the best modality, consistent results have been observed with UVA also. Dose ranging from a low of 5 and 10J/cm^2 to 20J/cm^2 have been used. A dose of 20J/cm^2 three times per week for 20 sessions leads to softening of skin lesions and reduction in concentration of collagen on skin biopsy. It is the opinion of various authors that UVA seems to produce similar improvement as UVA 1 with and without the addition of oral or bath psoralen (El Mofty et al, Fisher GJ et al.).

c. Seborrheic Dermatitis

It has been seen that this condition generally improving in summer and on sunny holidays thus inspiring the use of artificial UVB and PUVA. Some cases (8%) can have a worsening of facial seborrheic features. Recently NBUVB has been used successfully in this disorder.

d. Scleredema

A case report describes the use of cream PUVA (35 irradiations) which produced marked clinical improvement and softening of the skin (Grundmann-Kollmann M et al.).

e. Pityriasis Rosea

It has been suggested that BB-UVB may be used but given the disorders universally self-limiting benign course, it may not always affect its course.

f. Pityriasis Lichenoides and Lymphomatoid Papulosis

Sunlight phototherapy is the treatment of choice for pityriasis lichenoides. By extension of this fact, BB-UVB should probably be used first because of their relative safety, with PUVA reserved for resistant cases.

Pityriasis lichenoides in both the acute and the chronic forms responds to PUVA therapy, sometimes with long remissions, but more often prolonged maintenance PUVA therapy is required.

g. Prurigo

The effectiveness of PUVA, UVA-UVB, and UVB alone has been compared in the treatment of prurigo, the "itchy red bump disease." Good results have been reported for PUVA treatment of nodular prurigo, with remissions lasting several months.

h. Palmar and Plantar Pustulosis

This is a difficult conditions to treat but responds both to oral PUVA and topical PUVA, with a better response in the palms than in the soles. Secondary effects can be mitigated by employing bath-PUVA rather than oral-PUVA, with no loss of effectiveness.

i. Palmoplantar Dermatoses

NB-UVB seems helpful for most patients with chronic inflammatory disease of the palms, although further studies concerning optimal exposure doses and treatment course

lengths would be useful. The beneficial effect of local as well as systemic PUVA for palmoplantar pustulosis has also been noted by other groups, while LeVine et al. reported the successful use of systemic PUVA in dyshidrotic eczema. Bath PUVA and cream PUVA therapy has also been used (0.0006% 8-MOP).

j. Scleroderma

Bath PUVA has been used with 20 sessions, initially 4/week with a starting dose of 0.2 J/cm^2 which was gradually reduced to twice weekly over 5 weeks and led to complete or almost complete remission of the sclerotic patches after 30 sessions. Oral PUVA has been tried in progressive pansclerotic morphea with joint contractures and therapy resistant cases. One regimen tried is systemic PUVA initiated at a UVA dose of 0.5 J/cm^2 and given four times weekly over 2 months up to a maximum dose of 1.8 J/cm^2, with maintenance therapy at that dose twice weekly for 6 months.

UVA-1 phototherapy has also been tried in localized morphea and disabling pansclerotic morphea. The high dose regimen is effective (130 J/cm^2 vs 20 J/cm^2), and this has also been tried in lichen sclerosus et atrophicus (LSA) and in extragenital LSA. The vast majority of studies utilizing UVA-1 therapy have been performed in Europe. Finally, a recent PubMed database search study has also suggested that UVA-1 phototherapy is an effective treatment option for a whole variety of connective tissue and related disorders.

The modes of action of PUVA and UVA-1 therapy in scleroderma remain to be determined, but both *in vitro* and *in vivo* studies have demonstrated that UV irradiation induces collagenase synthesis, thereby increasing collagen degradation. In addition, both UVA and PUVA induce cytokine release, particularly of tumour necrosis factor-α and interleukin-6, which also induces collagenase and inhibit collagen synthesis, perhaps further contributing to the beneficial effect. Finally, the well-recognized immunosuppressive effect of phototherapy, too, may help.

k. Pruritus

Fjellner and Hägermark demonstrated in 1982 that BB-UVB, UVA and PUVA can all significantly reduce cutaneous responsiveness to the histamine liberator 48/80, although the UVB was effective only after the direct injection of histamine. It is worth noting that dryness and associated itching of the skin may itself result from long-term recurrent exposure to UV radiation, and the regular use of topical emollients in phototherapy-treated patients is therefore advised.

UVB therapy can be beneficial for various forms of pruritus, particularly associated with diabetes and hepatic disorders and some idiopathic types, while a number of controlled studies have demonstrated its efficacy also in uremic pruritus.

Uremic pruritus responds (BB-UVB) but hepatic pruritus does not usually respond. Aquagenic pruritus responds to PUVA and NB-UVB.

Monitoring

A baseline examination is done to rule out any signs skin cancer, premalignant lesions and actinic damage. Lifelong evaluation is required to rule out NMSC (Box 11.2).

Box 11.2: Monitoring of patients on PUVA

Baseline	*Follow-up*	*Interval*
Ocular Slit lamp, fundoscopy, Vision chart	Yes	Yearly
LFT/KFT	Yes	3 monthly
ANA	No	

Special Considerations

1. Patient should be advised to take psoralen with food and milk to decrease nausea.
2. The following foods may increase the toxicity of methoxsalen: carrots, figs, celery, mustard, parsley. These foods should be avoided.
3. Light-sensitive diseases including porphyria cutanea tarda, xeroderma pigmentosa, systemic lupus erythematosus, melanoma, variegate aphakia (absence of the lens of the eye), squamous cell carcinoma of the skin, cataract, invasive squamous cell cancer.
4. Wear UVA-protective glasses for at least 12 hours following treatment.
5. Protect the skin and avoid direct or indirect sunlight for at least 24 hours after oral therapy and 48 hours after topical therapy.
6. Wrap around sunglasses should be worn for 24 hours after UVA treatment.
7. Treatments should be given one to two times weekly and never for 2 days in a row. Genitalia should be protected during treatment session. Patients should be instructed to wear plastic-lens sunglasses known to block UVA before and after exposure on treatment days (UVA passes through glass). On nontreatment days, sun exposure should be restricted for patients on 8-MOP. Following treatment, a sunscreen effective against UVA should be applied to all exposed skin; this will provide partial protection. Those

who sunburn easily may benefit from using a UVB sunscreen all day, even during treatment. Prolonged exposure to sunlight beyond the treatment period should be avoided for 8 hours after the medication has been ingested. Nontender, minimal pink coloration of the patches of vitiligo is acceptable, but if increasing redness develops, discontinue treatment until only faint pinkness remains.

Drug Interactions

Drugs that increase effects/toxicity of methoxsalen: tetracyclines, thiazide diuretics, griseofulvin, coal tars, phenothiazines, halogenated salicylamides, organic dyes (methylene blue).

Adverse Effects

When combined with UVA

- **Common**: Nausea, pruritus, erythema, headache, malaise, leg cramps.
- **Serious**: Squamous cell carcinoma (skin), cataracts if proper eye wear is not used. The latter is an overestimated risk as human eyelid skin blocks UVA.

A long latency period (15 years or longer) and a large number of treatments (>250 J/cm^2 or >200 exposures) are required to induce the melanoma and nonmelanoma skin cancers (Box 11.3).

Box 11.3: Adverse effects of PUVA therapy

Short-term adverse effects of PUVA therapy	*Long-term adverse effects of PUVA therapy*
Due to psoralens—nausea, headache, dizziness, bronchoconstriction, toxic hepatitis, drug fever	Chronic actinic damage – PUVA lentigines, dryness, telangiectasia
Phototoxicity—erythema, pruritus, photoonycholysis, friction blister, Koebner phenomenon	Premature cataract
Others—PMLE, lupus erythematosus, herpes simplex, guttate psoriasis	Increased risk of squamous cell carcinoma

1. Photoaging of the skin occurs in all patients of skin types I through IV who have long-term exposure to the treatment. It is the most significant adverse effect for most patients. The so-called PUVA lentigines, which are usually large, dark, and irregularly shaped, form part of this chronic photoaging spectrum. They are partially reversible on stopping PUVA treatment.

2. Non-melanoma skin cancer and melanoma:
   Non-melanoma skin cancer (NMSC) is markedly increased in patients but is seen mostly in Caucasians. The predominant cancer is SCC, and it is biologically more aggressive than actinically induced SCC. It is seen with > **250** treatments.

The increased incidence of melanoma first appeared 15 years after the first PUVA treatment and is seen in patients who received more than 250 treatments.

Special Groups

Pregnancy: Category C.

Lactation

No data available. Best to avoid.

BIBLIOGRAPHY

1. Aggarwal K, Khandpur S, Khanna N, et al. Comparison of clinical and cost-effectiveness of psoralen + ultraviolet A versus psoralen + sunlight in the treatment of chronic plaque psoriasis in a developing economy. Int J Dermatol. 2013;52(4):478-85.
2. Bansal S, Sahoo B, Gaarg V. Psoralen-narrowband UVB phototherapy in treatment of vitiligo in comparison to narrowband UVB alone. Photodermatol, Photoimmunol Photomed. 2013;29(issue 6):311-7.
3. Berneburg M, Herzinger T, Rampf J, Hoetzenecker W, Guenova E, Meisner C. Efficacy of bath psoralen plus ultraviolet A (PUVA) vs. system PUVA in psoriasis: a prospective, open, randomized, multicentre study. Br J Dermatol. 2013 Sep;169(3):704-8.
4. British Photodermatology Group guidelines for PUVA. Br J Dermatol. 1994;130:246–55.
5. Christophers E, Hönigsmann H, Wolff K, et al. PUVA-treatment of urticaria pigmentosa. Br J Dermatol. 1978;98(6):701-2.
6. El-Mofty M, Mostafa W, El-Darouty M, Bosseila M, Nada H, Yousef R. Different low doses of broad-band UVA in the treatment of morphea and systemic sclerosis. Photodermatol Photoimmunol Photomed. 2004;20(3):148-56.
7. El-Mofty M, Zaher H, Bosseila M, et al. Low-dose broad-band UVA in \morphea using a new method for evaluation. Photodermatol Photoimmunol Photomed.2000;16(2):43-9.
8. Fisher GJ, Kang S. Phototherapy for scleroderma: biologic rationale, results, and promise. Curr Opin Rheumatol. 2002; 14(6):723-6.
9. Grimes PE. Psoralen photochemotherapy for vitiligo. Clin Dermatol. 1997;15(6):921-6.
10. Grundmann-Kollmann M, Ochsendorf F, Zollner TM, Spieth K, Kaufmann R, Podda M. Cream PUVA therapy for scleredema adultorum. Br J Dermatol. 2000;142(5):1058-9.
11. Hindson C, Spiro J, Downey A. PUVA therapy of chronic actinic dermatitis. Br J Dermatol 1985; 113:157-60.

12. Hönigsmann, A. Tanew, WL. Morison. Photo (chemo)therapy for Psoriasis H. Jean Krutmann et al. (Eds.), Dermatological Phototherapy and Photodiagnostic Methods. 2009.pp.79-101.
13. Hönigsmann H, TanewA. Photo(chemo)therapy for Cutaneous T-Cell Lymphoma. Jean Krutmann et al. (Eds.), Dermatological Phototherapy and Photodiagnostic Methods 2009.pp.135-49.
14. Hönigsmann H. Polymorphous light eruption. Photodermatol Photoimmunol Photomed. 2008; 24:155-61.
15. Jaschke E, Hönigsmann H. Hydroa vacciniforme-action spectrum. UV-tolerance following photochemotherapy. Hautarzt 1981; 32:350-3.
16. Jean Krutmann et al. (Eds.): Dermatological Phototherapy and Photodiagnostic Methods.
17. Meduri NB, Vandergriff T, Rasmussen H, Jacobe H. Phototherapy in the management of atopic dermatitis: a systematic review. Photodermatol Photoimmunol Photomed. 2007;23(4):106-12.
18. Melski JW, Tanenbaum L, Fitzpatrick TB, Bleich HL, Parrish JA. Oral methoxsalen photochemotherapy for the treatment of psoriasis: a cooperative clinical trial. J Invest Dermatol. 1977; 68:328-35.
19. Ortel B, Petronic-Rosic V, Calzavara-Pinton P. Phototherapeutic Options for Vitiligo. Jean Krutmann et al. (Eds.), Dermatological Phototherapy and Photodiagnostic Methods 2009.pp.151-183.
20. Parrish JA, Fitzpatrick TB, Tannenbaum L, et al. Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. N Engl J Med. 1974;291:1207-11.
21. Pathak MA, Mosher DB, Fitzpatrick TB. Safety and therapeutic effectiveness of 8-methoxypsoralen, 4,5',8-trimethylpsoralen, and psoralen in vitiligo. Natl Cancer Inst Monogr. 1984;66:165-73.
22. Radakovic S, Seeber A, Hönigsmann H, Tanew A. Failure of short-term psoralen and ultraviolet A light maintenance treatment to prevent early relapse in patients with chronic recurring plaque-type psoriasis. Photodermatol Photoimmunol Photomed. 2009;25(2):90-3.
23. Rebat M. Halder, James J. Nordlund. Chemophototherapy of Pigmentary Disorders. The Pigmentary System: Physiology and Pathophysiology, Second Edition Edited by James J. Nordlund, Raymond E. Boissy, Vincent J. Hearing, Richard A. King, William S. Oetting, Jean-Paul Ortonne Copyright © 2006 Blackwell Publishing Ltd.
24. Schwarz T, Hawk J. Phototherapy and Photochemotherapy: Less Common Indications for Use. Jean Krutmann et al. (Eds.), Dermatological Phototherapy and Photodiagnostic Methods 2009.pp.205-27.
25. Tzaneva S, Kittler H, Holzer G, Reljic D, Weber M, Hönigsmann H. 5-Methoxypsoralen plus ultraviolet (UV) A is superior to medium-dose UVA1 in the treatment of severe atopic dermatitis: a randomized crossover trial. Br J Dermatol. 2010;162(3):655-60.

UPDATE ON TREATMENT OF VITILIGO AND THE ROLE OF PUVA

Though a lot has been written about vitiligo therapy, nothing much of consequence has happened beyond the existing

regimens. Amongst the systemic agents, probably PUVA is the simplest method of intervention which in India can be sufficiently replaced by PUVAsol. Though evidence-based practice may not always be followed, a recent Cochrane review has looked at this and we summarize the gist below, the details of which are alluded to in the text that follows.

Analyzes from **eight** studies reported >**75% repigmentation** these include.

1. Calcipotriol plus PUVA(psoralen with UVA light) > versus PUVA.
2. Hydrocortisone-17-butyrate plus excimer laser > excimer laser alone.
3. Oral minipulse of prednisolone (OMP) plus NB-UVB (narrowband UVB)> OMP alone.
4. Azathioprine with PUVA > PUVA alone.
5. 8-Methoxypsoralen (8-MOP) plus sunlight > psoralen.
6. Clobetasol propionate > PUVAsol (PUVA with sunlight).
7. Split skin grafts with PUVAsol > minipunch grafts with PUVAsol.

New *topical* interventions included topical antioxidant gel containing pseudocatalase, superoxide, glutathione, coenzymeQ10, carotenoids, vitamins A, E, C, and selenium, antioxidant plus mitochondrial stimulating cream (Galarza 2009) and tetrahydrocurcuminoid cream (Asawanonda 2010). In terms of oral interventions, two new studies (Elgoweini 2009; Nistico 2012) examined the use of oral vitamin E.

New *light therapies* consisted of oral psoralen plus narrowband ultraviolet B light (P-NB-UVB) (Bansal 2013), helium-neon laser, broadband ultraviolet A light (BB-UVA) and broadband ultraviolet B light (BB-UVB) (El Mofty 2013b).

New *combination treatments* included topical treatments such as pseudocatalase cream in combination with NB-UVB, pimecrolimus in combination with 308-nm ex-cimer laser, tacrolimus cream in combination with NB-UVB light, topical clobetasol propionate cream in combination with oral zinc sulphate, superoxide dismutase combined with catalase and topical tacalcitol combined with 308-nm xenon chloride excimer laser. In terms of new combination light therapies, Mohaghegh 2012, used needling plus NB-UVB. New surgical interventions included dermabrasion and ablative fractional CO_2 laser.

The most important clinical criterion remains, percentage of repigmentation >75%,though the patient is desirous of a lot more ! It goes without saying that a combination intervention that included some form of light treatment is crucial for success. In the recent review (Whitton ME et al.) only eight studies achieving statistically significant increased chance of repigmentation (75%).

1. Khalid 1995 showed a result in favour of clobetasol propionate versus PUVAsol.
2. Sassi 2008 showed a result in favor of hydrocortisone-17-butyrate plus excimer laser versus excimer laser alone.
3. Parsad 2003 showed a result in favour of Ginkgo biloba versus placebo.
4. Rath 2008 showed a result in favour of oral minipulse of prednisolone (OMP) plusNB-UVB versus OMP alone.
5. Radmanesh 2006 showed a result in favour of azathioprine plus PUVA versus PUVA alone.
6. Pathak 1984 showed results in favour of 8-MOP plus TMP versus psoralen plus sunlight (comparison of psoralen plus sunlight versus 8-MOP plus TMP) and also 8-MOP plus sunlight versus psoralen.
7. Ermis 2001 found that calcipotriol plus PUVA group resulted in a higher likelihood of achieving greater than 75% repigmentation sooner than placebo plus PUVA.
8. Khandpur 2005 showed a result in favour of split skin grafts plus PUVAsol versus mini punch grafts plus PUVAsol.

Of these the largest study remains of Pathak et al. with 596 cases, and it is my favored regimen, specially in patients who cant afford phototherapy, which in India with its abundant sunlight is probably a confounding factor in most therapeutic trials !Though it is believed that NB-UVB show equivalent efficacies to UVA, PUVA or 308-nm EL, in the treatment of vitiligo, the evidence from the cochrane review suggests that combination therapies, particularly those involving some form of light, are superior to monotherapies.

Conclusion

It is important to stress that, at present, there is neither a cure for vitiligo nor an effective method of limiting the spread of the disease. Current treatment practices tend to center on whatever theory is believed to be the most important while newer, more controversial ideas take time to become established. There is moderate evidence for the use of topical corticosteroids, although long-term use is likely to lead to adverse effects. When used as monotherapy, it may be preferable to use ***superpotent preparations*** to give a better chance of therapeutic response, but close monitoring for adverse effects will be necessary. The topical immunomodulator, ***tacrolimus***, seems to be a reasonable alternative to topical corticosteroids, particularly on anatomical **sites** where there may be a higher risk of adverse effects with topical corticosteroids.

Most of the studies that assessed combination interventions employed ***light therapies*** (UVA, PUVA, or

UVB, particularly NB-UVB) and laser light therapies. Some studies have shown that a combination of light therapy (UVA and UVB) used alone or in combination with psoralens, topical corticosteroids,vitamin D analogues, 5-fluorouracil, azathioprine, and oral prednisolone, are useful; though of these, the use of PUVAsol and azathioprine and PUVA are useful clinicaly. There is also limited evidence for the benefit of oral Ginkgo biloba, and split thickness skin grafts plus PUVAsol.

Surgical therapies can be effective for small areas in people with stable disease. Clinicians should bear in mind that suction blister grafts may result in adverse effects, the most significant of which is precipitation of new areas of vitiligo at donor sites, due to the Koebner phenomenon. Autologous transplantation of melanocytes is a promising novel therapy, giving superior cosmetic results compared to more conventional surgical therapies, but access to this treatment may be limited.

Although vitiligo commonly presents before the age of 20 years, only seven of the 96 included studies looked specifically at interventions for vitiligo in children. The remainder of the studies either included adults alone or had no specified age. Treatment in children is limited by compliance, tolerance of treatment and concerns regarding long-term side effects. None of the studies had long-term follow-up beyond two years. These seven studies looked at a range of interventions, including topical treatments, such as tacrolimus and corticosteroids, NB-UVB, PUVA, 308-nm excimer laser and dermabrasion.

Thus, at present depending on the site and extent of involvement the following interventions have the best evidence for therapy.

1. Calcipotriol plus PUVA: Localized vitiligo.
2. Hydrocortisone-17-butyrate plus excimer laser: Localised vitiligo.
3. Oral minipulse of prednisolone (OMP) plus NB-UVB: Widespread vitiligo (<50% BSA).
4. Azathioprine with PUVA: Widespread vitiligo (<50% BSA).
5. 8-Methoxypsoralen (8-MOP) plus sunlight: Widespread vitiligo (<50% BSA).
6. Clobetasol propionate; Localized vitiligo.
7. Split skin grafts with PUVAsol L: Localized vitiligo.

BIBLIOGRAPHY

1. Asawanonda P, Klahan SO. Tetrahydrocurcuminoid cream plus targeted narrowband UVB phototherapy for vitiligo: a preliminary randomized controlled study. Photomedicine and Laser Surgery. 2010;28(5):679-84.

2. Bansal S, Sahoo B, Gaarg V. Psoralen-narrowband UVB phototherapy in treatment of vitiligo in comparison to narrowband UVB alone. Photodermatology, Photoimmunology and Photomedicine 2013;29(issue 6):311-7.
3. Elgoweini M, Nour El Din N. Response of vitiligo to narrowband ultraviolet B and oral antioxidants. J Clin Pharmacol. 2009;49(7): 852-5.
4. El Mofty M, Mostafa W, Youssef R, El-Fangary M, El-Ramly A, Mahgoub D, et al. BB-UVA vs NB-UVB in the treatment of vitiligo: a randomized controlled clinical study (single blinded). Photodermatology, Photoimmunology and Photomedicine 2013;29(5):239-46.
5. Ermis O, Alpsoy E, Cetin L, Yilmaz E. Is the efficacy of psoralen plus ultraviolet A therapy for vitiligo enhanced by concurrent topical calcipotriol? A placebo-controlled double-blind study. Br J Dermatol. 2001;145(3):472-5.
6. Galarza C, Ramos W, Gutierrez EL, Oré R, Chía H, Ávila J,et al. Efficacy and security of topical antioxidant therapy versus placebo in the treatment of vitiligo of recent onset . Dermatología Peruana. 2009;19:198-204.
7. Khalid M, Mujtaba G, Haroon TS. Comparison of 0.05% clobetasol propionate cream and topical PUVAsol in childhood vitiligo. Intern J Dermatol. 1995;34(3):203-5.
8. Khandpur S, Sharma VK, Manchanda Y. Comparison of minipunch grafting versus split-skin grafting in chronic stable vitiligo. Dermatologic Surgery. 2005;31(4):436-41.
9. Parsad D, Pandhi R, Juneja A. Effectiveness of oral Ginkgo biloba in treating limited, slowly spreading vitiligo. Clinical & Experimental Dermatology. 2003;28(3):285-7.
10. Pathak MA, Mosher DB, Fitzpatrick TB. Safety and therapeutic effectiveness of 8-methoxypsoralen, 4,5',8- trimethylpsoralen, and psoralen in vitiligo. National Cancer Institute Monograph 1984;66:165-73.
11. Radmanesh M, Saedi K. The efficacy of combined PUVA and low-dose azathioprine for early and enhanced repigmentation in vitiligo patients. J Dermatol Treatment. 2006;17(3):151-3.
12. Rath N, Kar HK, Sabhnani S. An open labelled, comparative clinical study on efficacy and tolerability of oral minipulse of steroid (OMP) alone, OMP with PUVA and broad/narrow band UVB phototherapy in progressive vitiligo. Indian J Dermatol Venereol Leprol. 2008;74(4):357-60.
13. Sassi F, Cazzaniga S, Tessari G, Chatenoud L, Reseghetti A, Marchesi L, et al. Randomized controlled trial comparing the effectiveness of 308-nm excimer laser alone or in combination with topical hydrocortisone 17-butyrate cream in the treatment of vitiligo of the face and neck. Br J Dermatol. 2008;159(5):1186-91.
14. Whitton ME, Pinart M, Batchelor J, Leonardi-Bee J, González U, Jiyad Z, et al. Interventions for vitiligo. Cochrane Database Syst Rev. 2015 Feb 24;2:CD003263.

APPENDIX (TREATMENT PROTOCOLS)

PSORIASIS

Systemic Psoralen Plus Ultraviolet A (PUVA) Protocol

1. Dosage of 8 MOP is 0.5–0.6 mg/kg.
2. Male patients should wear an athletic supporter/to cover the genital organ.
3. Patients may apply mineral oil on the plaques of psoriasis prior to phototherapy session.
4. Eye protection in the form of UV goggles must be worn by all patients when inside the phototherapy unit.
5. Determine the initial PUVA dose (J/cm^2) according to the patient's skin type as classified by the physician (Table 11.1).

Table 11.1: Dose escalation in PUVA therapy

Skin type	*Initial UVA dose*	*Subsequent increment*
Type I	0.5 J/cm^2	0.5 J/cm^2
Type II	1 J/cm^2	1 J/cm^2
Type III	1.5 J/cm^2	1 J/cm^2
Type IV	2.0 J/cm^2	1 J/cm^2
Type V	2.5 J/cm^2	1 J/cm^2
Type VI	3 J/cm^2	1 J/cm^2

Subsequent Treatments

The frequency of PUVA treatments for the diagnosis of psoriasis is *2 or 3 times a week* unless otherwise ordered by a physician.

On subsequent visits the patient should be asked about redness, light pink color and tenderness of the skin in the previous night. The aim is a light pink color. This is not always seen in Indian skin so look for signs of toxicity (itching, burning) and increase the dose (J/cm^2) if the UVA light by the amount as in the Table 11.1. If the treatment has been withheld due to side effects with a break of 3 days, add the dose to the previous dose delivered to the patient till there are signs of cleaning (decreased erythema, scaling, infiltration). If subsequent treatments occur at intervals longer than 3 days, the following guidelines will be used:

- 4–7 days—keep the dose the same
- 1–2 weeks—decrease dose by 25%
- 2–3 weeks—decrease dose by 50%
- 3–4 weeks—decrease dose by 75%
- More than 4 weeks—start over.

When 95% or more of the original area of psoriasis has cleared, the patient is changed to a maintenance schedule.

Maintenance Therapy for PUVA

Once there has been acceptable improvement in the severity of the psoriasis, patients may be kept on intermittent treatments as a maintenance therapy. There is great variability in selection of the optimal frequency and dose of PUVA needed to keep an acceptable control of psoriasis. These general guidelines may be used:

If psoriasis has cleared (>75%): Once a week treatment for 4 weeks ; then once in two weeks; once in three weeks and then once in a month

Once an acceptable response (75–100% clearance) has been achieved, then maintenance therapy at once every 2–4 weeks can be continued to keep the activity of the psoriasis under control in many patients. Long-term therapy, whether in the form of combination therapy or systemic therapy, would need to be discussed between the patient and physician.

PUVAsol

Dose: 0.6 mg/kg to be taken alternate day with milk

- Sun exposure after about 2 hours after drug intake, twice a week initially between 11 AM and 2 PM
- Exposure is to be started at 5 minutes and increased gradually to a maximum of 30 minutes.

We prefer the following schedule:

1. Monday, Wednesday, Friday; 5 minutes /week gradually increased to a maximum of 30 minutes.
2. After about 30 exposure almost 80% of patients achieve a PASI 75 or sometimes even PASI 100.
3. Maintenance: Not recommended but once a week exposure is usually advised in flare periods.

VITILIGO

Systemic Psoralen Plus Ultraviolet A (Puva) Treatment

Protocol

The dosage of 8 MOP for use in the treatment of vitiligo is 0.5 mg/kg. The initial dose of UVA light for all vitiligo patients is 1.0 J/cm^2.

Instruct the patient to come out of the ultraviolet light box when the lights go out or if they become uncomfortable during the treatment either from burning or stinging of the

skin. Inform the patient that the light-box doors are not locked.

Subsequent Treatments

The frequency of PUVA treatments for the treatment of vitiligo is once or twice a week unless otherwise ordered by a physician.

On subsequent visits, the patient will be asked about *redness, light pink color and tenderness* of the skin the previous night. If the skin is a light pink color, the phototherapist should keep the dose the same as the previously delivered treatment dose. Increase the UVA dose by the amount below until the patient reports that slight erythema is observed at the sites of vitiligo *within 24 hours* after treatment. Symptomatic erythema should be avoided because excess phototoxicity may produce a Köbner reaction.Subsequent treatments – increase by 0.5 J/cm^2

Do not continue to increase the dose if slight erythema at the sites of vitiligo occurs *within* 24 hours after the last treatment. The erythema should *not persist* for 24 hours and should not sting or burn. If there is persistence of erythema or burning for 24 hours or longer, reduce the dose by 25%. Do *not* exceed a dose of 5 J/cm^2 unless ordered by the attending physician.

Psoralen Lotion Plus Ultraviolet A (Paint PUVA)

Protocol

A *lotion* containing ***0.01%*** of 8-methoxypsoralen should be prescribed to the patient for their use. The compounding of this lotion should be done by a pharmacist. The 8-methoxypsoralen may also be prepared in an ointment base using Aquaphor or a vaseline base. The concentration for the ointment-based psoralen preparation is ***0.1***% of 8-methoxypsoralen.

Apply the psoralen lotion to the involved areas with a cotton-tipped applicator. Only apply the psoralen to the sites to be treated.

The duration of the pretreatment with the topical psoralen should be 30 minutes. The delivery of the dose of UVA light should follow the 30-minute pretreatment period. If desired, uninvolved areas adjacent to the treated sites can be wrapped with multiple layers of cloth to provide protection from UVA light.

The initial dose of UVA for paint PUVA is 0.5 J/cm^2 for all skin types.

After the UVA treatment is given, the patient must thoroughly wash the treated areas to remove any medication residue on the surface of the skin. Sunblock (UVA/B) is

provided to the patient to apply as a precautionary measure to avoid additional UV exposure that day.

Instruct the patient to avoid excessive sunlight for the remainder of the day. A burn may not show up until 48 hours after treatment.

Treatments are not usually given on 2 consecutive days. This allows the nurse to observe accurately for erythema.

Each patient should be seen by the attending physician 4 weeks after the first treatment, and then every 6–8 weeks during treatment.

Subsequent Treatments

Increase by 0.5 J/cm^2 every treatment as tolerated up to 2 J/cm^2. Consult the attending physician if burning has occurred. Higher doses of UVA must be ordered by the physician. The frequency of paint PUVA treatments for the diagnosis of vitiligo is 1–2 times a week unless otherwise ordered by a physician.

If the skin is red adjustment in the dose for treatment can be made. If the skin is a light pink color, the dose is the same as the previously delivered treatment dose.

If subsequent treatments occur at intervals longer than 3 days, the following guidelines will be used:

1 week – keep the dose the same; 2 weeks – decrease the dose by 50%; 3–4 weeks weeks – start over again.

Oral TMP (TMP/8 MOP)/PUVAsol

	Light skin	*Medium skin*	*Dark skin*
Initial exposure	15 min	20 min	25 min
Second exposure	20 min	25 min	30 min
Third exposure	25 min	30 min	35 min
Fourth exposure	30 min	35 min	40 min

Subsequent exposure: Gradually increase exposure based on erythema and tenderness of the amelanotic skin.

Topical PUVAsol

1. **Apply 8 MOP** by diluting upto 1:10 with Eau De Cologne (i.e.1 part of **OCTAMOP LOTION 8 MOP** to be mixed with 10 parts of Eau De Cologne) for the first 15 days of treatment.
2. Apply the correct dilution of **8-MOP LOTION**, as advised by doctor, with the brush provided. Rubbing is not necessary. Wash the finger afterwards to avoid photosensitization and possible burns.
3. One hour after application, expose the areas to sunlight/UVA.

4. After sunlight/UVA exposure, wash off **8-MOP LOTION** from the patches, and cover all the treated vitiligo patches to protect from further ultraviolet radiation.
5. **Sunlight Exposure – Time and Method:** The schedule of exposure to be followed very accurately is as follows:
   - *Half a minute* per day for the first week
   - *One minute* per day for the second week
   - *Two minute* per day for the third week.

After every exposure, the patient should cover all the treated vitiligo patches. This protective measure is essential as most of the local reactions are due to inadvertent exposure and additional solar radiation. The proper time for solar exposure is between 11:30 am and 1:30 pm.

What to Expect?

This exposure provokes a slight erythema (irritation blister). The exposure could be increased in duration according to the patient's tolerance. Within a few months, the threshold of erythema (irritation blister) can be reached, in 5–6 minutes. Once the patch becomes red, the duration of exposure should not be increased beyond 15 minutes.

12

CHAPTER

Retinoids

Kabir Sardana, Usha Ranganathan

SYSTEMIC RETINOIDS

Before we address the major drugs under this category, it is relevant to focus first on the metabolism of retinoids and to understand how they modulate their effects in the body (Fig. 12.1).

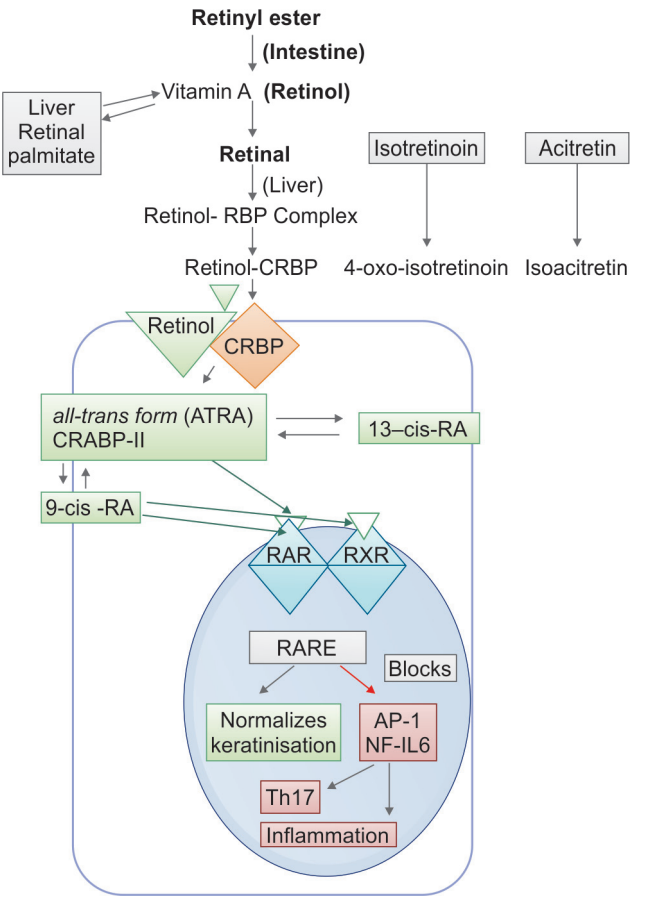


Fig. 12.1: Metabolism and mechanism of action of natural retinoids
Abbreviations: CRABP, cytosolic retinoic acid-binding protein; CRBP, cytosolic retinol binding protein; RAR, retinoic acid receptor; RBP, retinol binding protein; RXR, retinoid X receptor

Metabolism and Mode of Action

The precursors of vitamin A, β-carotene, are carotenoids which are essentially synthesized by plants. One molecule of β-carotene is converted into two molecules of retinal in the intestines before being absorbed. Retinyl ester derived from meat and animal products, is converted in the intestines into retinol which is stored as retinal palmitate in the liver.

The major metabolite of isotretinoin is produced by oxidation, which forms 4-oxo-isotretinoin. Acitretin metabolism differs from isotretinoin metabolism primarily in the initial metabolism, which involves isomerization instead of oxidation. This is converted into isoacitretin.

Most of the retinoids are transported as the all-*trans* form (atRA) with a small fraction transported as 13-*cis* RA. The intracellular carrier is cytosolic retinoic acid-binding protein (CRABP) of which CRABP-II is the predominant form in human epidermis. A*t*RA is the primary active ligand that binds to the three known nuclear RARs. In the nucleus the retinoids bind to two families of retinoid receptors, a retinoic acid receptor (RAR) family and a retinoid X receptor (RXR) which have three isoforms (α, β, and γ). Retinoid receptors belong to the large superfamily of receptors consisting also of glucocorticosteroid, thyroid hormone and vitamin-D_3 receptors, all of which are DNA-binding proteins and function as *trans*-acting transcription modulating factors. The genes regulated by retinoids contain a retinoic acid response element (RARE), which is a DNA sequence to which the RAR–RXR heterodimer binds.

In addition to *direct* upregulation of gene transcription via binding of retinoid–receptor complexes to RAREs, retinoids can have *indirect* effects on gene transcription that result from the downregulation of genes that do not contain RAREs in their promoter region. The retinoid–receptor complex is thought to antagonize transcription factors such as activator protein-1 (AP1) and nuclear factor-interleukin-6 (NF-IL6) (Fig. 12.1) by competing for the same set of required co-activator proteins, thereby leading to decreased expression of AP1 and NF-IL6-responsive genes. The antiproliferative and anti-inflammatory actions of retinoids are believed to be mediated (Fig. 12.1) by this type of indirect negative gene regulation. AP1 and NF-IL6 are key transcription factors in proliferative and inflammatory responses, and "dissociating retinoids" have been synthesized that possess indirect anti-AP1 function but are not capable of direct gene transactivation. Retinoic acid can also inhibit proinflammatory Th17 cells and modulate toll-like receptors (TLRs; especially TLR2).

The clinical effects of systemic retinoids in dermatology are related to their ability to affect pathways involved in

inflammation, cellular differentiation, apoptosis and sebaceous gland activity. In addition to their actions on the skin, retinoids exert broad effects in multiple tissues, a complete description of which is beyond the scope of this Chapter.

Classification

The epidermis is a privileged tissue for the expression of RAR-γ and RXR-α, the major isoforms of their respective families in this tissue, whereas RAR-α is ubiquitous. In the skin, RAR-β is primarily found in the dermis.

Three domains within the retinoic acid molecule govern its biologic activity: An acidic function at one extreme and a lipophilic domain at the other, linked by a group that determines their relative spatial orientation. Synthetic retinoids also require an acidic function pointing away from a lipophilic portion for receptor affinity and transcription. The successive generations of retinoids have resulted from modification of the retinoic acid skeleton with structural rigidification, through addition of aromatic rings in place of the vulnerable double bonds found in retinoic acid. This makes the *third-generation* retinoids more *photostable* when compared to the first- and second- generation molecules; some compounds within this family have displayed significantly reduced irritation potential. Although third-generation retinoids are much more potent than earlier retinoids, unfortunately their therapeutic index shows no significant improvement (Table 12.1).

Table 12.1: Classification of retinoids

	RAR αβγ	*RXR* αβγ	*Comments*
First generation			
Tretinoin (All trans Retinoic acid)	+++	---	RAR-β > γ >> α RXR-β, γ > α (After conversion to 9-cis retinoic acid, binds to RXR receptors)
Alitretinoin	+++	+++	RXR>RAR
Isotretinoin	- - -	- - -	Probably the metabolites interact with receptors
Second generation			
Etretinate			RAR (weak interaction)
Acitretin			
Third generation			
Bexarotene		+++	RXR-α, β, γ
Adapalene	- ++		RAR-β, γ > α Does not bind to CRABP Chemically stable Photostable Less side effects
Tazarotene	- ++		RAR-β, γ > α

Retinoids primarily work by interacting with receptors and this is the basis of their classification.

ISOTRETINOIN

Category

It is a prodrug that is converted intracellularly to metabolites that are agonists for RAR and RXR nuclear receptors.

Mechanism of Action

Isotretinoin has numerous actions (Table 12.2). It affects cell-cycle progression, cellular differentiation, cell survival and apoptosis. It lowers sebum production significantly although the exact mechanism is poorly understood. It also reduces comedogenesis as well as surface and ductal *P. acnes* and has anti-inflammatory properties.

All-trans-RA is thought to be the active metabolite of isotretinoin within cells following enzymic conversion from 13-cis-RA. The antiproliferative effect of retinoids on human sebocytes in vitro was found to be mediated by RAR.

Sebocytes are probably a specific target of 13-cis RA activity because of their ability to selectively isomerize 13-cis RA to

Table 12.2: Mode of action of isotretinoin

Site	*Target steps*	*Mode of action*
Sebocyte	Proliferation(Inhibition)	Intracellular isomerization in tretinoin(RAR mediated)
	Proliferation/Apoptosis	Cell-cycle arrest (Retinoid receptor-independent)
	Lipid synthesis (Reduction)	Inhibition of terminal differentiation (RAR- and RXR-mediated)
	Decreased androgen synthesis	Inhibition of 3 alpha-hydroxysteroid activity of retinol dehydrogenase
Inflammation	Inflammation/Inhibition of the migration of neutrophils NF-kB and activator protein-1 Metalloproteinases	Reduction in pro- MMP-9 and MMP-13 Inhibits MMP-9/13 Inhibit neutrophils Inhibits LTB4
Others	TGFβ-2 and TGFβ-3 (have been shown to reduce cell proliferation and lipogenesis in human) FoxOs, NO, TNF-α	RA induces the rapid and transient expression of TGFβ-2 and TGFβ-3, FoxOs
Immune response	TLR-2 T_{417} cells	Down-regulation

atRA at an intracellular level and to reduce atRA inactivation processes. Nelson (2009) found that isotretinoin leads to a decrease in sebaceous gland size beginning at one week of treatment and continuing through 8 weeks of treatment and perhaps beyond with a subsequent decrease in the expression of genes involved in lipid production. A dose of 0.5–1.0 mg/kg/day dramatically reduces sebum excretion by the order of **90%** within **6 weeks.** Also, isotretinoin increases neutrophil gelatinase-associated lipocalin (NGAL) of levels by 2.4-fold on the skin surface and this increase precedes decreases in sebum and *P. acnes* counts (Lumsden et al). Augmented production of NGAL in the skin by isotretinoin has been correlated with human sebocyte apoptosis within sebaceous glands, which leads to decreased production of sebum. The sebosuppressive effect does not appear to fully explain the long-term remission of acne vulgaris (AV) associated with oral isotretinoin use, as *sebum production* returns to 60–95% of pretreatment levels within **four** months of completion of oral therapy isotretinoin.

Within **one week** of therapy, oral isotretinoin significantly decreased monocyte TLR-2 expression and subsequent pro-inflammatory cytokine response to *P. acnes*. These inhibitory effects last over a period **of six months** after stopping oral isotretinoin. Isotretinoin appears to induce "*immunologic memory*" by potentially normalizing the innate immune response to *P. acnes*. The modulation of **TLR-2** expression may correlate with prolonged remission after discontinuation of therapy.

Absorption and Distribution

After oral administration, isotretinoin is absorbed in 2–4 hours and it is increased by food.

Oral bioavailability is low (25%). It is absorbed better with a meal, therefore it is advisable to take the capsules with food at the same time of day. More than 99% of isotretinoin is protein-bound, mainly to albumin.

It is metabolized in the liver to its major metabolite *4-oxo-isotretinoin*. The terminal elimination half-life of isotretinoin is 10–20 hours, while that of the 4-oxo metabolite may be up to 50 hours. Equal amounts of a dose appear in the feces, mainly as unchanged drug, and in the urine as metabolites.

The physiological levels of retinoids are attained about *2 weeks* after stopping therapy. (Two days for atRA to 10 days for 4-oxo-isotretinoin). The normal levels in human plasma are 0.88 ± 0.32 ng/mL for atRA and 1.63 ± 0.80 ng/mL for 13-cis RA. Therefore, pharmacologically **1 month** of post-therapy contraception provides an adequate safety margin to avoid teratogenicity.

Metabolism

Isotretinoin is believed to be a prodrug and is metabolized into: 4-oxo-13-cis-retinoic acid (4-oxo-isotretinoin), all-trans-RA (tretinoin), all-trans-4-oxo-retinoic acid (4-oxo-tretinoin), 9-cis-retinoic acid and 4-oxo-9-cis-retinoic acid.

Isotretinoin is superior to 9-cis-retinoic acid or all-transretinoic acid with respect to its suppression of sebum production and sebaceous gland activity.

Tretinoin and 4-oxo-tretinoin bind to RAR-γ, which is the receptor that is thought to be important in retinoid treatment of acne.

Differences in the plasma concentrations of these metabolites could therefore explain the differences in the intensity of the therapeutic response and the severity and/or occurrence of side effects in individual patients.

Uses

US-Food and Drug Administration (FDA) approved: AV (severe)/severe recalcitrant nodular acne. Severe, by definition, means 'many' as opposed to few or several.
European guidelines recommend isotretinoin in severe papulopustular/moderate nodular acne and severe nodular/conglobate acne.

We have listed the main indications and doses for ready reference below (Table 12.3).

Other

- Atrophoderma vermiculatum
- Condylomata acuminata
- Darier's disease
- Dissecting cellulitis
- Erosive oral lichen planus
- Extranodal Rosai-Dorfman disease
- Fordyce spots
- Fox-Fordyce disease
- Gram-negative folliculitis
- Granuloma annulare
- Grover's disease
- Hidradenitis suppurativa
- HIV-associated eosinophiic folliculitis
- Keratoacanthoma
- Keratodermas
- Langerhans cell histiocytosis
- Lichen planus
- Lupus, discoid
- Lupus miliaris disseminatus faciei
- Nipple hyperkeratosis

Table 12.3: Summary of dose regimens of isotretinoin for common dermatoses

Disorders	*Dose*
Acne vulgaris (Severe)	I. Start at 0.5 mg/kg /day × 1 month ; Increase to 1 mg/kg/day Cumulative dose 120–150 mg/kg (Wt=70 kg : Total dose 8400 mg, 40 mg × 30 days = 1200 mg, 60 mg × 4 months = 7200 mg. Total duration about 5 months) II. High dose >1.3 mg/kg/d
(Mild/moderate)	0.25–0.4 mg/kg/day. Cumulative dose 60–90 mg/kg
Acne fulminans and rosacea fulminans	Prednisolone 0.5–1.0 mg/kg- 4–6 weeks, reduced over 2 weeks, with Isotretinoin start 0.5 mg/kg body weight/day increased gradually to 1 mg/kg/day
Atrophoderma vermiculatum	Isotretinoin 0.50 mg/kg/day for 6 months
Chemoprevention	Actinic keratosis: 20 mg/day for 3 weeks +topical fluorouracil Cutaneous T-cell lymphoma: Combination therapy includes 1 mg/kg/day of isotretinoin +INFα at mean dose of 5×10^6 IU/m^2/day Leukoplakia: Induction dose of 1–1.5 mg/kg/day for 3 weeks followed by a maintenance dose of 0.5 mg/kg/day (55% responded and 92% remained relapse free at 9 months Nonmelanoma skin cancer in high-risk groups: 5–10 mg/day for 3 years
Condylomata acuminata	0.5–1 mg/kg/day + INFα-2a (3×10^5 U subcutaneously) given 3 times/week
Darier's disease	Isotretinoin 0.2 mg/kg/body weight/day increased to 1 mg/kg/d; Responses noted by 2–4 weeks of therapy

Contd...

Contd...

Dissecting cellulitis	Commonly used in combination therapy at 1mg/kg/day for at least 4 months and then a maintenance dose of 0.75–1 mg/kg/day
Gram-negative folliculitis	Isotretinoin 0.2–0.5 mg/kg/day
Generalized granuloma annulare	Isotretinoin 0.5–1 mg/kg/day; Remission at 6 months-1 year post therapy; near complete clearing appreciated by about 2–6 months
Hidradenitis suppurativa	Average of 44 mg/day for 4–8 months; only 14 of 88 (~16%) patients noted improvements
Lichen planus	Isotretinoin 1 mg/kg/day
Lupus erythematosus	Isotretinoin 1 mg/kg daily × 4 weeks (Hypertrophic LE) Subacute cutaneous lupus erythematosus : 0.5–1mg/kg/day; higher recurrence rates upon discontinuation than with methotrexate
Pityriasis rubra pilaris	Isotretinoin 1 to 1.5 mg/kg/body weight /day. Duration 4–6 months, typical response by 4 months
Psoriasis	0.5 mg/kg/day +narrowband ultraviolet B; reduce the number of phototherapy sessions and accumulative dose
Rosacea	1. Isotretinoin 10 mg/day (0.3 mg/kg/day) 2. Isotretinoin 20 mg/day for 4 months; Dose reduced to 20 mg/week by 8 months 3. Extrafacial Rosacea : 10–20 mg/day. Also used in combination with azithromycin and oral glucocorticoid
Sebaceous hyperplasia	20–40 mg 3–4 times a week with maintenance of 40 mg twice weekly or topical isotretinoin; improvements noted as early as week 1

- Papular mucinosis
- Persistent facial edema of acne
- Pityriasis rubra pilaris
- Rosacea, papulopustular
- Sarcoidosis, cutaneous
- Scleromyxedema
- Sebaceous hyperplasia
- Ulerythema ophryogenes.

ACNE VULGARIS

Standard Dose

European directive: 0.5 mg/kg/day and may be increased to 1.0 mg/kg/day. (Duration 6 months)

US: 1 mg/kg daily with a cumulative dose of 120–150 mg/kg.

However, as some patients develop severe early flaring of AV with multiple deep inflammatory papules and nodules, and others experience a greater intolerability of dose-related side effects, such as xerophthalmia, xerosis, cheilitis and myalgia, there is a consensus that the optimal initial daily dose of oral isotretinoin is 0.5 mg/kg/day; this can be increased to 1 mg/kg/day in 4–8 weeks. The use of lower doses of isotretinoin during the first 3–4 weeks of therapy is recommended to minimize the incidence of side effects in relation to alteration of the expression of pro- or antiangiogenic growth factors such as VEGF/vascular permeability factor.

Duration (4–6 months): The duration of therapy should be adjusted to give at least ***90%*** clearance of acne based upon initial clinical acne grade scoring techniques followed by ***4–8 weeks*** of consolidation. It is believed that the dose and duration affect the benefit and relapse rate, but there is no pharmacokinetic reason to support the concept of accumulation of drug or a cumulative dose effect.

Response: *85%* are clear by 16 weeks,13% require 5/ 6 months, 3% require a longer course. Less than 1% require 12 months therapy *(See Appendix)*.

Flare: Seen in **6%** of cases.

Predictive factors for *acne flare* during isotretinoin treatment include male gender and the presence of macrocomedones, truncal comedones, severe acne with facial nodules, and a high number of facial comedones and this flare lasts for 2–3 weeks. (On JCS and Zeichner J)

a. **Minor flare:** An antibiotic can be used in combination with isotretinoin, such as erythromycin 1 g daily, azithromycin 250 mg or trimethoprim 200–300 mg twice daily.
b. **Severe flare:** Start oral prednisolone (0.5–1.0 mg/kg/day-2–3 weeks. Slowly decreased over 6 weeks). Isotretinoin

should be stopped or reduced to a dosage of 0.25 mg/kg/day. If stopped, the drug can be slowly reintroduced at a dose of 0.25 mg/kg/day and then gradually increased. Alternatively, patients may be pretreated with 1–2 weeks of systemic corticosteroids prior to starting isotretinoin.

In order to avoid initial worsening and adverse events, treatment can begin with a low or very low dose of 0.2–0.3 mg/kg/day for 1 month and then slowly increase to 0.5–0.7 mg/kg/day for the remaining of treatment (accumulative dose of 120–150 mg/kg)

Relapse: The conventional regimen has a variable relapse rate of 22–30%. (Table 12.4) Importantly, the relapse rate depends on the duration of the follow-up, varying from short (38%) to long-term follow-up (41%). As improvement may continue for several months after withdrawal and at least **2 months** should elapse before determining whether further treatment is necessary.

A nested case-control analysis found that 41% of subjects experienced a relapse, with 26% requiring treatment with a second course of oral isotretinoin. (Azaoluay et al.). Relapse was found to be highest in those patients treated with 0.1 mg/kg/day (42%), which was two-fold higher than with 0.5 mg/kg/day (20%) and four-fold higher than with 1 mg/kg/day (10%) (Strauss et al.).

In one report of patients followed over five years post-treatment after their initial course of isotretinoin, 22.7% required a repeated course of oral isotretinoin, with 17% treated with two courses, and 5% treated with three courses. (Stainforth Jm et al.). The relapsed patients were retreated with topical therapy alone (16–21%), topical therapy and oral antibiotics (3.3–27%), or at least one repeat course of oral isotretinoin (16–23%).

Although, the relapse rate has been shown to be higher in patients treated with a lower daily dose, cases of relapse have also been reported in some patients treated with a higher daily dose over the same duration of therapy.

Relapse is seen commonly in females, polycystic ovarian disease, lower cumulative dose, acne on the back, seborrhea and high pretreatment acne count.

Further courses of therapy are usually successful when required. There are no reports of cumulative toxicity from using repeat courses and tachyphylaxis has not been noted.

Low Dose

This therapy is only for patients with mild-to-moderate acne and entails a dose of 0.1–0.4 mg/kg/day with a cumulative dose of 90 mg/kg. (Sardana K). Expert opinion supports the use of isotretinoin for patients with moderate acne who are failing to respond to conventional therapy, for whatever reason.

Though **cumulative dose** is necessary to prevent relapse, this has not been rigorously tested. Thus, there is a risk that patients may become dependent on these small doses, and is *not* deemed appropriate for a female of reproductive potential.

a. **Relapse/persistent acne**
   The regimens below have been used for adult patients and females who come with relapses or have persistent low grade acne.
   i. **Microdose:** 20 mg/d *1-2 d/wk* (adult patients who relapsed).
   ii. **Mini dose:** 20 mg/day (1 day every week).
b. **Moderate grade acne**
   i. **Daily low dose:** 0.25–0.4 mg/kg/day.
   ii. **Intermittent** therapy:
      a. 0.5–0.75 mg/kg/day (1 week/month)
      b. 10 days/month for 6 months.
   iii. **Alternate** day dose
      a. 20 mg every alternate day (approximately 0.15 mg/kg/day to 0.28 mg/kg/day) for 6 months along with topical clindamycin gel.
c. **Mild acne:** 5 mg/daily for 16 weeks.
d. **Mature adults with persistent and late-onset acne:** 0.5 mg/kg/day taken 1 week out of 4 for a period of 6 months.

High Dose

It has been suggested that using higher daily doses of the drug than what is typically prescribed (>1 mg/kg/day) and achieving a higher total cumulative dose of oral isotrefinoin than what is generally recommended (>150 mg/kg) produces a lower risk of acne relapse, although well-controlled comparative studies or data analyses have not been completed. In addition, the use of these higher doses did not reduce the duration of therapy with the goal of achieving a cumulative total dose of 120–150 mg/kg over a shorter duration; instead they achieved cumulative total doses that were substantially higher without shortening of the duration of therapy.

A dose of (≥1.3 mg/kg/day) produced 100% total clearance, with 12.5% requiring an additional course of oral isotretinoin within three years of follow-up. (Blasiak RC1)

Another study(Cyrulnik AA) divided the patients into two groups, those receiving <220 mg/kg (group A, n=38) and those receiving >220 mg/kg (group B, n=78), with the average duration of the initial oral isotretinoin course reported to be 6.3 months. At the 12-month follow-up point, acne relapse was reported in 47.4% in group A and in 26.9% in group B. Two patients (1.72%) required retreatment with oral isotretinoin, both from group B.

Thus, even a **higher dose** does not prevent relapses and it is better to stratify therapy according to the severity of acne, and thus low dose is ideal for mild-to-moderate acne, while the standard dose is advised for severe grades of acne.

How to Decide the Ideal Dose Regimen ?

A simple method to arrive at an appropriate dose is to first, decide on the grade of acne. In mild-to-moderate acne a dose <0.5 mg/kg/d for 6–9 months or a cumulative dose of 90 mg/kg is sufficient in most cases with a relapse rate comparable to conventional dose regimens for severe acne. In the latter a dose of 120–150 mg/kg is ideal though higher doses are also needed in some cases.

It is important to recognize that short-term treatment success, defined as complete clearance of acne at the end of the treatment course, can occur across a broad range of oral isotretinoin daily dosages, with clinical studies including both higher (≥1mg/kg/day) and lower daily doses (0.1–0.5mg/kg/day) in patients with severe nodular inflammatory acne. The issue is of recurrence which is more with lower dosages and thus doses less than 0.5 mg/kg/d should never be given for severe acne, as the initial results are good on short-term therapy, thus the patient invariably stops the therapy early and is thus prone to recurrence. A summary of salient aspects of isotretinoin use in acne is listed in Table 12.4.

Acne Variants

Acne fulminans and rosacea fulminans

Start prednisolone 0.5–1.0 mg/kg for 4–6 weeks which is reduced over 2 weeks, while isotretinoin is initiated at 0.5 mg/kg body weight/day, increased gradually to 1 mg/kg/day.

Acne conglobata and gram-negative folliculitis

Isotretinoin 0.2–0.5 mg/kg/day.

Atrophoderma Vermiculatum

Dose 0.50 mg/kg/day for 6 months, can result in partial remission.

Condylomata Acuminata

A double-blinded placebo-controlled clinical trial was performed wherein a dose of 0.5 mg/kg daily was used for 12 weeks in cervical warts recalcitrant to therapy resulting in complete resolution in 62% of patients.

Table 12.4: Factoids on isotretinoin use for acne

Short-term treatment success	This is **not** dependent on the **daily dose** of isotretinoin (based on mg/kg) with no significant differences in acne clearance between 0.1mg/kg/day, 0.5 mg/kg/day and 1mg/kg/day (over treatment duration of 20 weeks)
Long-term treatment success	This is dependent on achieving a specific threshold defined as the **cumulative total dose** of isotretinoin over the initial course of therapy. The recommended target cumulative dose of isotretinoin that needs to be reached to optimize long-term treatment success is 120–150 mg/kg.
Response of lesions	Pustules are cleared earlier than papules or nodules
Site	Lesions localized on the face, upper arms and legs tend to clear more rapidly than trunk lesions
Onset	After **2–4 weeks** of treatment, a **50%** regression of the pustules can be expected. In most cases, isotretinoin yields skin improvement in 3 months
Seborrhoea	Reduction: Starts at **7 days** of therapy majority of cases by 4 weeks Recovery: **4 months** after therapy Sebostatic effect lasts for **4 months**
Repeat course	1/3 require treatment within 2 years of stopping Relapses within 2 years Wait for **8 weeks** after stopping the therapy before a second course
Relapse	Can occur in 1/3 of cases and may require a repeat course of isotretinoin Most common cause is *subtherapeutic* dose
	Stainforth JM et al.: 22.7% :repeated course, 17% 2 courses, 5% 3 courses White GM et al.: 61% needed retreatment for acne, with 22.9% a second course of oral isotretinoin Azoulay L et al.: 41% relapse of AV, with 26% second course
	Treatment of relapse Topical therapy alone (16–21%), topical therapy and oral antibiotics (3.3–27%), or at least one repeat course of oral isotretinoin (16–23%)

Combination with interferon alfa-2a (Roferon-A, Roche) 3 million units subcutaneously three times for 8 weeks has also been tried but the results are similar to oral isotretinoin.

Rosacea

Initial dose of 10 mg/day (0.3 mg/kg/day) followed by continuous 'microdoses' as low as 20–30 mg per week for 4–6 months has results better than doxycycline.

Darier's Disease

Dose: 0.2 mg/kg/body weight/day, which may be increased up to 1 mg /kg/body weight/day. Clearance may take 2–4 weeks. A low dose maintenance therapy is required.

Hidradenitis Suppurativa and Dissecting Cellulitis of the Scalp

A higher dose is required (1–2 mg/kg daily) but the results are not satisfactory. In dissecting cellulitis 1 mg/kg daily with rifampicin has been tried.

Lupus Erythematosus

Discoid lupus erythematosus (DLE): The hyperkeratotic form responds in a dose of 1 mg/kg daily, with response within 4 weeks in the majority of patients. The drawbacks to the use of systemic retinoid in cutaneous lupus, apart from their known adverse side effects, appears to include the following:

1. A higher and more rapid recurrence rate upon discontinuation of therapy than seen with other commonly used systemic agents such as methotrexate. In cases of recurrence, implementation of a low maintenance dose might be a consideration.
2. There is a relative contradiction in cutaneous lupus associated Sjogren's syndrome due to preexisting keratoconjunctivitis sicca.
3. Expense: Isotretinoin and acitretin are both significantly more expensive than methotrexate, hydroxychloroquine, and prednisone.

Pityriasis Rubra Pilaris

Dose: 1–1.5 mg/kg/body weight/day is given for several weeks to achieve resolution of the lesions. This is followed by a lower dose as maintenance therapy for 4–6 months.

Lichen Planus

Generalized hypertrophic or oral erosive lichen planus: 1 mg/kg/day. Usually given in combination with steroids.

Skin Cancer

Currently, bexarotene is the only oral retinoid with FDA approval for treating advanced CTLC. However, isotretinoin and acitretin have also been successfully utilized. They are most often implemented in combination therapy with a variety of agents including chemotherapy, total skin electron beam (TSBE), PUVA, and INF-α2, in patients with CTCL (stages I–IV).

Isotretinoin/INF- α combination therapy has also proved promising in the treatment of advanced SCC skin cancer, achieving success rates between 17 and 68%. A recent small case study also reported that isotretinoin (1mg/kg daily) in combination with daily radiotherapy, resulted in a rapid reduction in tumor size in three patients with either extensive basal cell carcinoma (BCC) or SCC.

Drug Interaction

Increased dry skin: Topical benzoyl peroxide and topical tretinoin.

Pseudotumor cerebri: Tetracycline, doxycycline, minocycline.

(Oral tetracyclines in combination with isotretinoin should be avoided, as both can lead to benign intracranial hypertension. These are likely to be ***rare*** idiosyncratic reactions attributable to each drug in its own right, but there are reports in the literature suggesting there could theoretically an additive effect by combining the two).

Increased levels of isotretinoin: Vitamin A, tetracycline, doxycycline, minocycline, gemfibrozil, macrolides, azoles.

Reduced levels of isotretinoin: Alcohol, rifampin, rifabutin, phenytoin, phenobarbital, carbamazepine.

Isotretinoin may increase levels of: Cyclosporin.

Isotretinoin may decrease levels of: Progestin-only contraceptives, carbamezapine.

Methotrexate levels may increase, when used concomitantly.

Increased risk of bone loss: Systemic steroids, phenytoin.

Special Considerations

Isotretinoin should be given with a fatty meal.

There are no reports of cumulative toxicity from using repeat courses and tachyphylaxis has not been noted.

Decreased tolerance to contact lenses.

Should be avoided in patients with pre-existing hypertriglyceridemia or in those at risk of developing hyper-

triglyceridemia. Use of fish oil containing eicosapentaenoic acid is a useful adjunct in such cases *(See Appendix)*.

Patients receiving isotretinoin should not donate blood during, or for **1 month** after stopping therapy.

Isotretinoin is contraindicated in patients with hepatic impairment, hyperlipidemia and hypervitaminosis A.

Excessive exposure to sunlight and ultra violet (UV) light should be avoided.

Dizziness, drowsiness and visual disturbances may occur rarely and could affect the performance of skilled tasks such as driving.

Wax depilation should be avoided in patients receiving retinoids since they cause increased skin fragility and facial and leg erosions have occurred.

Aggressive chemical dermabrasion and cutaneous laser treatment should also be avoided for a period of 5–6 months.

In case of acne fulminans, discontinuation or reduction of the isotretinoin dose along with systemic corticosteroids is advised.

Side Effects

The side effects are reversible and dose-related (Table 12.5). A study has found that only 1.5% of the patients had serum triglyceride levels above 400 mg%. No laboratory abnormalities were a cause for discontinuation of treatment. Though, this is not a labeled advise but published evidence suggests that the laboratory tests need not be repeated except in groups at risk, such as diabetics and patients with known familial hypertriglyceridemia. The side effects are listed from common to the rare side effects. An overview of the preventive strategies is listed in Table 12.6.

Dermatological

Common: Dryness of the mucous membranes and skin, cheilitis, epistaxis, conjunctivitis, localized exfoliation, pruritus, erythematous rash and skin fragility. Cutaneous xerosis occurs in less than one-half of patients taking isotretinoin, but is more common in patients with a history of atopy. Acne can exacerbate at the beginning of isotretinoin treatment.

Rare: Acne fulminans, hair thinning (occasionally irreversible), hirsutism, photosensitivity, changes in skin pigmentation, paronychia, nail dystrophy, pyogenic granuloma, increased sweating, vasculitis and reversible melasma.

Table 12.5: Overview of side effects of isotretinoin

Class	*Details*
Acute adverse effects	**Mucocutaneous** ■ Xerosis with pruritus ■ Cheilitis ■ Dry mucosa (mouth, eyes, nose and epistaxis) ■ Skin fragility ■ Retinoid dermatitis ■ Palmoplantar peeling ■ Photosensitivity ■ Blepharoconjunctivtis, corneal ulceration ■ *Stickiness sensation* (palms or soles) ■ Granulation tissue and pyogenic granulomas-like lesions ■ Telogen effluvium (alopecia), hair thinning ■ Nail fragility with softening, paronychia, onycholysis ■ *Staphlococcus aureus* infection
Systemic	■ Arthralgias ■ Anorexia, nausea, diarrhea, abdominal pain ■ Headache, pseudotumor cerebri (rare) ■ Fatigue, lethargy, irritability ■ Reduced night vision ■ Blurred vision, photophobia, keratitis ■ Bone: DISH syndrome osteoporosis, epiphyseal closure, periosteal thickening ■ Depression, suicidal ideation (rare and controversial) ■ Toxic hepatitis (rare) ■ Pancreatitis secondary to hypertriglyceridemia (rare) ■ Hyperuricemia with gout (rare) ■ Menstrual irregularities (rare)
Laboratory abnormalities	■ Elevated liver function tests (transient, minor) (ASAT, ALAT, alkaline phosphatase, LDH, billirubin) ■ Hyperlipidemia, hypertriglyceridemia, increased cholesterol, VLDL and LDL, decreased HDL ■ Elevated CPK ■ Leukopenia (bexarotene) ■ Thrombocytosis, thrombocytopenia ■ Hypercalcemia (rare)

Ocular

Common: Dry eyes, decreased dark adaptation, ocular sicca, decreased tolerance to contact lenses. These side effects generally resolve within 1 month or on discontinuation of the drug.
Rare: Corneal opacities (does not adversely affect vision), blurred vision and colour vision disorders, impaired night vision (reversible), photophobia, keratitis, blepharoconjunctivitis, myopia.

Musculoskleteal

Common: Arthralgia, myalgia, and back pain.

Table 12.6: Side effects of isotretinoin and their management

Adverse effect	*Incidence*	*Comments*
Teratogenicity		Isotretinoin is contraindicated during pregnancy
Mucocutaneous		
▪ Dry lips	96%	Apply lip salve or petrolatum
▪ Facial dermatitis	55%	Apply noncomedogenic moisturizer (gel based)*
▪ Dry nose	51%	Apply nasal lubricant. Epistaxis usually mild
▪ Dry skin, pruritus, desquamation, irritant dermatitis	20–50%	Pruritus usually secondary to dry skin; peeling of palms and soles; eczematous changes: moisturize or apply hydrocortisone 1% ointment
▪ Conjunctivitis	19%	More common in contact lens users. Use artificial tears
▪ Hair loss	13%	Dose related and usually reversible. If severe, decrease or stop treatment. Persistent in 0.5% of patients treated
▪ Impetiginization	7.5%	Staphylococcal impetiginization should be suspected when severe cheilitis, nasal vestibulitis, dermatitis develops. Treat with topical or oral antibiotics
▪ Photosensitivity	1–5%	Minimize sun exposure; majority of patients have no trouble taking isotretinoin during summer
Arthralgia and myalgia	15–20%	Usually transient or episodic and dose related to exercise; nonsteroidal anti-inflammatory agents are rarely required
Headache	5–16%	Usually mild and requires no treatment. If severe and associated with impaired concentration and blurred vision, check for pseudotumor cerebri (0.5% incidence). Stop and restart at a lower dose when better. Avoid concurrent use of tetracycline
Depression/mood swing	Uncommon	Caution is required in patients with a history of severe depression. Patients should be monitored for mood changes during therapy
Ophthalmic impaired night vision	Unknown	Rarely persists. Warm patients to be careful when driving at night

*Sebamed clear gel/Zitmoist gel

Rare: Arthritis, osteoporosis and tendinitis. Hyperostosis and calcinosis have also occurred, particularly in patients treated with high doses of isotretinoin over long periods for keratinization disorders. Premature closure of the epiphyses has occurred in children treated with isotretinoin. High-dose isotretinoin for a period of over two years has been shown to induce skeletal hyperostoses and anterior spinal ligament calcification. Bone abnormalities in children, particularly premature closure of the epiphyses, is associated with high isotretinoin doses (>1 mg/kg/day), vitamin A supplementation and long-term treatment. If bone abnormalities occur, they may not resolve upon cessation of treatment. However in the short courses of relatively high-dose of therapy for acne, there does not appear to be any significant risk of skeletal effect.

Reversible myopathy with muscle pain, weakness and raised creatine kinase concentrations has been described. Rarely, rhabdomyolysis and myoglobinuria have been described.

Serum Lipids

Common: A **reversible** derangement of lipid profile has been consistently reported. In most cases, it does not warrant intervention but in late onset, persistent acne, it is relevant to assess for risk factors and decide interventions if needed. These alterations depend on the dose and duration of the treatment and generally start during the first 6 weeks (1–2 months) of treatment and normalize to baseline *2–4 weeks* after *discontinuation* of the drug of treatment.

The common finding seen is an *increase* in **VLDL, TG** and reduction of HDL. In some cases, they can be transient, possibly due to the hepatic adaptation of the organism to the drug impact on metabolism that is reflected by transient alterations in transaminase levels. Retinoids probably cause hyperlipidemia by interfering with lipid clearance. A study found that there was an increase in triglycerides in 44% and in total cholesterol in 31% of patients. Recent studies have pointed out that in isotretinoin induced hypertriglyceridemia, apoE gene alleles e2 and e4 are commonly associated and these patients are at a risk for future development of the metabolic syndrome. Logically normolipemic patients may be genetically protected against the development of metabolic syndrome.

Triglycerides (level **>300–500** mg/dL) is managed with weight reduction, increased physical activity, and a low-fat, low-carbohydrate, low-alcohol diet. Oral fish oils are an useful adjunct.

For triglyceride levels >**500** mg/dL reduction of the retinoid dose, with an addition of systemic agent (fibric acid derivative, a statin, or niacin), is advisable.

Triglycerides >**800–1000** mg/dL can cause pancreatitis and the therapy should be stopped.

The guidelines that dictate ideal LDL levels and therapeutic interventions are detailed in the *appendix*.

Liver

Common: Increase in hepatic enzymes is common occurring in 15% of patients and typically return to normal despite continued therapy. Circulating levels of alkaline phosphatase, lactic dehydrogenase and bilirubin may also become elevated during retinoid therapy.

Liver function abnormalities, mostly mild, usually occur 2–8 weeks after initiation of starting therapy and they return to normal within another 2–4 weeks, *despite* continued therapy. Transaminase elevations to greater than *three times* the upper limit of normal should lead to discontinuation of retinoid therapy.

Rare: Hepatic fibrosis, necrosis, cirrhosis.

Hematological

Common: Anaemia, thrombocytopenia and neutropenia.

Rare: Agranulocytosis, increase in blood sugar.

Psychiatric

Mood changes, psychotic symptoms, depression, sustained dreaming and suicidal behaviour have occurred in patients treated with oral isotretinoin. A large body of evidence suggests that the high background prevalence of psychiatric illness among adolescents in general, and among patients with acne, lack of clear cause and effect mechanism suggest that there is no strong evidence for an association between isotretinoin use and depression or suicidal behavior. In spite of this, monitoring for depression and other psychiatric effects has been advised for all patients receiving isotretinoin.

Gastrointestinal Tract

Gastrointestinal tract (GIT): Though reports of inflammatory bowel disease have been reported they are not common. It is believed that isotretinoin should be used with caution in patients with a history of inflammatory bowel disease or symptoms suggestive of the condition and those who might be at increased risk because of a family history.

Cardiovascular System

Rare: Myocardial infarction, stroke, pulmonary embolism, cardiac arrhythmias, such as sinus tachycardia with right branch bundle block atrial tachycardia.

Central Nervous System

Rare: Papilloedema, visual disturbances, headache, and nausea and vomiting. Stray reports of Guillain-Barré syndrome have been published.

Respiratory System

Rare: Exercise-induced wheezing, eosinophilic pleural effusion and worsening asthma.

Others

Complete loss of taste, ejaculatory failure and irregular menses.

Monitoring

It is reasonable to discontinue laboratory monitoring (other than pregnancy testing) after 8–12 weeks if laboratory results remain normal *and* the dose is constant. This applies to all tests except pregnancy testing. A method of monitoring is provided in Table 12.7.

1. **Pregnancy test**: Monthly and one month after stopping therapy.
   Guidelines for pregnancy monitoring:
   - Pregnancy testing is mandatory pre- and 5 weeks post-therapy
   - The treatment should ideally start on **day 3** of the menstrual cycle
   - Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before starting therapy
   - The second pregnancy test should be done during the first *5 days* of the menstrual period immediately preceding therapy
   - For patients with amenorrhea, the second test should be done at least *11 days* after the last act of unprotected sexual intercourse
   - Each month of therapy, the patient must have a negative result from a urine or serum pregnancy test
   - Must commit to two forms of contraception (at least one primary) for at least 1 month prior to initiation during therapy and one month after therapy
   - **Primary contraception:** Tubal ligation, vasectomy, IUCD, OC pills.
   - **Secondary contraception:** Latex condoms.

Table 12.7: Monitoring of patients on isotretinoin

Base line	*Follow-up*	
	Interval	*Duration **
Pregnancy test (2 pregnancy tests before isotretinoin therapy. Therapy should be initiated on the 2nd of next normal menstrual cycle or ≥11 days after the last unprotected intercourse)	Monthly	Till end of therapy
Lipid (blood lipid determinations should be performed before isotretinoin is adminstered and then continued at intervals, until the lipid response to isotretinoin is established, which usually occurs within 4 weeks)	Weekly	Till 1 month Then 3 monthly
LFT	Monthly	Till end of therapy
Blood sugar (if diabetic)	Monthly	Till end of therapy
Eye evaluation (history of cataracts or retinopathy)	If symptomatic	
CPK (if severe muscle pain)		
Bone evaluation (baseline X-rays of wrists, ankles or thoracic spine in children or on anticipated long-term therapy)	If symptomatic	

Abbreviations: LFT, Liver function test; CPK, Creatine phosphokinase
* When isotretinoin is used for a 20-week acne course, it is reasonable to discontinue laboratory monitoring (other than pregnancy testing) after 8–12 weeks if laboratory results remain normal and the dose is constant (Lee YH et al)
Lipid:12-hour fast and a 36-hour abstinence from ethanol

Clinical problems relating to the implementation of this approach include, difficulties in females with irregular menses, potential lack of continuity of treatment due to potential unavailability of patient and/or healthcare workers as well as forgotten tests. These factors may all contribute to early cessation and/or partial treatment, resulting in ineffective management and associated financial burden on healthcare systems. Given potential side effects of oral contraceptives, it may not always be appropriate to insist on all patients regardless of pregnancy risk using specific contraceptives.

2. **Liver function and fasting blood lipids:** Start of therapy, after the first month and thereafter as appropriate. (EU directive: baseline, 1 month into therapy and 3-monthly throughout treatment).
3. **Blood glucose:** This should be monitored throughout treatment in patients who either have or are predisposed to diabetes mellitus.
4. **Skeletal survey:** Optional.

Special Groups

Pregnancy: X

Lactation: X

Liver failure: Avoid

Kidney Failure

Severe renal impairment being treated with oral isotretinoin for acne should be started at a lower dose, such as 10 mg daily. It may be gradually increased up to 1 mg/kg daily as tolerated.

Children

Although, the European directive suggests isotretinoin should not be used below 12 years of age, up to 0.5 mg/kg/day has been used successfully in a number of neonates or juveniles with acne that have not responded to all appropriate topical or oral therapy. Isotretinoin liquid capsules can be opened and the contents mixed with a drink or soft food. One report described freezing the capsule so that it could be cut more easily to the required dose, which could then be concealed in food.

NOVEL ISOTRETINOIN VARIANTS

Isotretinoin-Lidose: Several formulations of oral isotretinoin are available. Several generic AB-ISO products are available based on the PK profile of Acc-ISO. Lidose-ISO is a nongeneric formulation that exhibits a unique PK profile.

The main pharmacological property of Lidose-ISO is a markedly greater GI absorption when administered on an *empty stomach*. As the PK profile of Acc-ISO demonstrated a greater than 60% mean increase in bioavailability when ingested with a HF/HC (high fat/high cholesterol) meal as compared to a fasted state, concern has been raised regarding how dietary factors may affect long-term treatment success with this type of isotretinoin. The PK profile of Lidose-ISO is likely to reduce the risk that decreased bioavailability related to dietary factors may adversely modify the therapeutic benefit of ISO, especially long-term remission of acne.

The ***micronized*** isotretinoin in India has been touted to enable a lower dose (0.5 mg/kg/d) comparable to the 1 mg/kg/d dose, but the original study on this, did not focus on this except as a data on file. It is safer but also slower to act than the conventional isotretinoin preparation.

FURTHER READING

Books/Reveiw

1. Anne-Marie Thielen, Jean-Hilaire Saurat. Retinoids. In: Bolognia Jean L, Jorizzo, Joseph L, Schaffer JV (eds). Dermatology: 2-Volume Set, 3 rd edition. Elseiver. 2012.
2. Ganceviciene R, Zouboulis CC. Isotretinoin: State of the art treatment for acne vulgaris. J Dtsch Dermatol Ges. 2010;8 Suppl 1:S47-59.
3. Layton AM. Disorders of the sebaceous glands. In: Burns DA, Breathnach SM, Cox NH, Griffiths EM (eds). 2010 Blackwell Publishing Ltd.
4. Lowe NL. When systemic retinoids fail to work in psoriasis. In: Saurat JH, (ed). Retinoids: 10 Years on. Basel: Karger. 1991;341-9.
5. Nickle SB, Peterson N, Peterson M. Updated physician's guide to the off-label uses of oral isotretinoin. J Clin Aesthet Dermatol. 2014;7(4):22-34.
6. On SC, Zeichner J. Isotretinoin updates. Dermatol Ther. 2013;26(5):377-89.
7. Patton TJ, Ferris LK. Systemic retinoids. In: Wolverton SE. (ed). Comprehensive dermatologic drug therapy. 3rd edition. Elseiver. 2013.
8. Sweetman, Sean Martindale. The Complete Drug Reference, Thirty-seventh edition. Pharmaceutical Press, 2011.

Journals

1. Alcalay J, Landau M, Zucker A. Analysis of laboratory data in acne patients treated with isotretinoin: Is there really a need to perform routine laboratory tests? J Dermatolog Treat. 2001;12(1):9-12.
2. Apalla Z, Karakatsanis G, Papageorgiou M, Kastoridou C, Chaidemenos G. A case of atrophoderma vermiculatum responding to systemic isotretinoin. J Dermatol Case Rep. 2009;3(4):62-3.
3. Azoulay L, Oraichi D, Berard A. Isotretinoin therapy and the incidence of acne relapse: A nested case-control study. Br J Dermatol. 2007;157:1240-8.
4. Barnes CJ, et al. A practical approach for the use of oral isotretinoin for infantile acne. Pediatr Dermatol. 2005;22:166-9.
5. Blasiak RC1, Stamey CR2, Burkhart CN. High-dose isotretinoin treatment and the rate of retrial, relapse, and adverse effects in patients with acne vulgaris. JAMA Dermatol. 2013;149(12): 1392-8.
6. Cardamakis EK, Kotoulas IG, Dimopoulos DP, Stathopoulos EN, Michopoulos JT, Tzingounis VA. Comparative study of systemic interferon alfa-2a with oral isotretinoin and oral isotretinoin alone in the treatment of recurrent condylomata accuminata. Arch Gynecol Obstet. 1996;258(1):35-41.
7. Cyrulnik AA, Viola KV, Gewirtzman AJ, et al. High-dose isotretinoin in acne vulgaris: Improved treatment outcomes and quality of life. Int J Dermatol. 2012;51(9):1123-30.
8. Del Rosso JQ. Face to face with oral Isotretinoin. J Clin Aesthet Dermatol. 2012;5(11):17-24.

9. Dispenza MC, Wolpert EB, Gilliland KL, Dai JP, Cong Z, Nelson AM, et al. systemic isotretinoin therapy normalizes exaggerated TLR-2-mediated innate immune responses in acne patients. J Invest Dermatol. 2012;132(9):2198-205.
10. Georgala S, Katoulis AC, Georgala C, Bozi E, Mortakis A. Oral isotretinoin in the treatment of recalcitrant condylomata acuminata of the cervix: A randomized placebo controlled trial. Sex Transm Infect. 2004;80(3):216-8.
11. Lumsden KR, Nelson AM, Dispenza MC, Gilliland KL, Cong Z, Zaenglein AL, et al. Isotretinoin increases skin-surface levels of neutrophil gelatinase-associated lipocalin in patients treated for severe acne. Br JDermatol. 2011;165(2):302-10.
12. Marsden JR. Effect of dietary fish oil on hyperlipidaemia due to isotretinoin and etretinate. Hum Toxicol. 1987;6:219-22.
13. Nelson AM, Zhao W, Gilliland KL, Zaenglein AL, Liu W, Thiboutot DM. Temporalchanges in gene expression in the skin of patients treated with isotretinoin provide insight into its mechanism of action. Dermatoendocrinol. 2009;1(3):177-87.
14. Rodondi N, Darioli R, Ramelet AA, et al. High risk for hyperlipidemia and the metabolic syndrome after an episode of hypertriglyceridemia during 13-cis retinoic acid therapy for acne: A pharmacogenetic study. Ann Intern Med. 2002;136:582-9.
15. Sardana K, Garg VK. Low-dose isotretinoin in acne vulgaris: A critical review. Br J Dermatol. 2011;165(3):698-700.
16. Stainforth JM, Layton AM, Taylor JP, et al. Isotretinoin for the treatment of acne vulgaris: Which factors may predict the need for more than one course? Br J Dermatol.1993;129:297-301.
17. Strauss JS, et al. Isotretinoin therapy for acne: Results of a multicenter dose-response study. J Am Acad Dermatol. 1984; 10(3):490-6.
18. White GM, Chen W. Recurrence rates after first course of isotretinoin. Arch Dermatol. 1998;134:376-8.

APPENDIX

Table 1: LDL goals and treatment cutpoints: Recommendations of the NCEP Adult Treatment Panel III

Risk category	LDL goal (mg/dL)	LDL level at which to initiate lifestyle changes (mg/dL)	LDL level at which to consider drug therapy (mg/dL)
High-risk: CHD or CHD risk equivalents (10-year risk > 20%)	<100 (optional goal: < 70 mg/dL)	≥100	≥100 (<100: consider drug options)
Moderately high risk: 2+ risk factors (10-year risk 10% to 20%) (Cardamakis EK et al.)	<130	≥130	≥130 (100–129; consider drug options)

Moderate risk: 2+ risk factors (10-year risk <10%)	<130	≥130	≥160
Low-risk: 0–1 risk factors	<160	≥160	≥190 (160–189: LDL-lowering drug optional)

Table 2: Slow responders to isotretinoin

Causes	*Incidence*
Macrocomedones	70% (light cautery or hyfrecation)
Hyperandrogenism † Post-isotretinoin flare** Poor absorption Differences in receptor sensitivity Colonization with *Staphylococcus aureus* Severe acne Unusual variants	25%
Unknown	5%

*erythromycin 1 g daily or trimethoprim 200–300 mg twice daily. ** oral steroids may be required (e.g. 0.5–1.0 mg/kg/day for 2–3 weeks) † polycystic ovarian syndrome

ACITRETIN

Classification

Acitretin is a second-generation aromatic retinoid and is an active metabolite of the precursor drug, etretinate.

Chemical Class

Retinoids.

Mechanism of Action

Acitretin activates all retinoic acid receptor subtypes to alter gene transcription.
It normalizes proliferation and differentiation.

The drug has an anti-angiogenic and anti-inflammatory properties. This includes modulation of T-cell responses, inhibition of chemotactic responses and activation of polymorphonuclear leukocytes, which may contribute to their therapeutic effects.

Pharmacology

Absorption and Distribution

Acitretin is absorbed from the gastrointestinal tract and peak plasma concentrations have been obtained 1–5 hours after oral doses.

Bioavailability after a single dose is about 60–70%, but this can vary considerably; bioavailability may be increased by dosages with food.

Acitretin is highly bound to plasma proteins. It is metabolized to 13-cis-acitretin.

Acitretin is excreted as metabolites in bile and urine and is distributed into breast milk.

Acitretin is completely cleared from the body approximately one month after discontinuing therapy.

Etretinate has also been detected in the plasma of some patients after doses of acitretin which has a half life of about 120 days.

Clinical use in Dermatology

FDA Approved: Psoriasis

Others

- Actinic keratosis
- Cutaneous malignancies/chemoprevention
- Darier's disease
- Ichthyosis
- Keratodermas
- Lichen planus
- Lichen sclerosus et atrophicus
- Lupus, cutaneous
- Pityriasis rubra pilaris.

Usage Guidelines

Women with childbearing potential must not consume ethanol during and up to 2 months after cessation of acitretin therapy. In female patients of nonreproductive potential and in males, this conversion of acitretin to etretinate is not a clinically important issue.

Psoriasis

This is an ideal drug for psoriasis and the duration of therapy depends on the response and the concomitant therapy. The lack of immunosuppressive effects makes it a useful drug but the onset of action is slow. The best results have been obtained in acral or generalized (von Zumbusch) pustular psoriasis, in which acitretin is considered to be a first-line therapy. The lesions of both localized and generalized pustular psoriasis, as well as those of erythrodermic psoriasis, cleared more rapidly with etretinate or acitretin monotherapy than with most other therapies.

Monotherapy

1. **Chronic plaque:** 25–75 mg/d (8–24 weeks).
   Although complete clearance of plaques is achieved in only about 30% of treated patients, a significant improvement is obtained in an additional 50%. About 20% of patient do ***not*** respond to acitretin. One of the main reasons for treatment interruption is an initial worsening of the disease with an increase in erythema and/or the extent of involvement.
   The initial dose is 0.5 mg/kg/d which can be increased to 1 mg/kg/d as tolerated. The recommended initial dose, for psoriasis, is between 25 and 50 mg daily which can be increased in 10 mg increments until a clinical response is achieved. Most patients require a 50–75 mg for a satisfactory response. Effects start at 4–6 weeks with a full effect achieved by 3 months.
   For maintenance the dose can be reduced to 10 mg daily or 25 mg alternate day.
2. **Nail psoriasis:** 0.2–0.3 mg/kg/day (6 months).
3. **Human immunodeficiency virus:** It has no immunosuppressive properties, and therefore, may be used as a monotherapy for psoriasis associated with human immunodeficiency virus (HIV) infection.
4. **Pustular psoriasis:** It is the drug of choice with similar dosing as for chronic plaque psoriasis. Analysis of 385 cases of generalized pustular psoriasis (GPP) revealed that *retinoid* treatment was effective in 84% of patients, *methotrexate* in 76% of patients, *cyclosporine* (CsA) in 71% of patients, and oral psoralen plus ultraviolet A (*PUVA*) in 46% of patients (Ozawa A). Localized pustular psoriasis of the palms and soles also responds very well to retinoid therapy (Lassus A).

Combination Therapy

1. **Re-UVB/Re-PUVA:** Retinoids have been combined with BB-UVB/PUVA/NB-UVB and home tanning units.
   Acitretin with broadband UVB (ReUVB) has been evaluated in randomized, controlled studies (Ruzicka T). It has been shown that there is significant improvement in patients receiving acitretin plus UVB therapy compared to patients receiving UVB therapy alone, with significantly shorter total treatment times and UVB doses in the patients receiving acitretin. Similar findings were also seen in patients receiving narrowband UVB and acitretin. Acitretin with PUVA (Re-PUVA) has been shown in formal studies to improve the efficacy of PUVA while reducing the PUVA dose required for clearance (Saurat JH).

Initiate low-dose (*25 mg*) acitretin *2 weeks* prior to the initiation of phototherapy. The initial dose of UV light should be *lower* than the dose assigned for the skin type (Tanew A). The therapy can be continued till response or for 12 weeks. Alternatively, if a patient is on a stable dose of UV, the UV dose should be *lowered* by 30–50% approximately 7 days after starting acitretin. The cumulative radiation exposure required to produce a remission is also significantly lower with Re-PUVA, reducing the risk of PUVA-induced carcinogenesis which is UVA dose-dependent.

2. **Immunosuppressant:** It can be used with methotrexate or cyclosporine but there is a risk of cumulative side effects with both the drugs.

   Sequential regimen: Use first a rapidly acting drug (cyclosporine), followed by a one month transitional phase to acitretin. This is followed by tapering off of cyclosporine over 3–4 months. This type of sequential regimen takes advantage of cyclosporine's rapid onset of action and acitretin's excellent long-term safety profile.

   The use of the drug with **methotrexate** is strictly **off label:** Acitretin 25 mg daily or alternate days with 7.5–25 mg of methotrexate weekly for an average of 12 months.
3. **Biologicals:** It has been used in combination with etanercept 25 mg once weekly. There are reports of its use with other biologicals also but this is not yet an approved combination. In a randomized trial comparing etanercept 25 mg twice weekly, acitretin 0.4 mg/kg daily, and the combination of etanercept 25 mg once weekly and acitretin 0.4 mg/kg daily, the combination of acitretin with etanercept 25 mg once weekly was superior to acitretin alone and was equivalent to etanercept 25 mg twice weekly, with similar safety profiles (Gisondi P).
4. **Pioglitazone:** In diabetic patients, acitretin (25 mg) can be combined with pioglitazone (15 mg).
5. **Calcipotriol:** Acitretin in combination with calcipotriol has been found to be superior to monotherapy. The dose of acitretin is increased from 10–20 mg to 40 mg a day with concomitant topical therapy.

Chemoprevention of Malignancy

Systemic retinoids have also been studied as preventative agents in patients with genetic susceptibility to skin malignancies, including patients with xeroderma pigmentosum and nevoid basal cell cancer syndrome. Though there is some evidence that retinoids may prevent nonmelanoma skin cancer (NMSC), the effects of retinoids do not persist on discontinuation.

Darier's Disease

Though isotretinoin is preferred, acitretin can be initiated at 30 mg/day for the first 4 weeks, and adjusted to 10–50 mg for the next 12 weeks.

Hyperkeratotic Palmoplantar Dermatitis (Keratoderma)

In a dose of 25–50 mg daily, the drug has been found to be better than topical betamethasone/salicylic acid ointment. A therapy of 1-2 months is ideal and can be maintained by topical medications.

Ichthyosis

(Lamellar ichthyosis, non-bullous and bullous ichthyosiform erythroderma, and Sjögren-Larsson syndrome).

Retinoids have been used successfully in most ichthyosis with the *exception* of autosomal dominant ichthyosis vulgaris. In lamellar ichthyosis, they are the preferred drug. Bullous congenital ichthyosiform erythroderma (BCIE) and congenital ichthyosiform erythroderma (CIE) also respond moderately well, although higher doses of the retinoids in BCIE may lead to worsening skin fragility and a flare of bullous lesions.

Dosage regimens vary from 0.77–1.07 mg/kg/day to 0.6 mg/kg/day for 2–12 months. The dose can be tapered down to 0.5 mg/kg per day but monitoring for potential side effects is advisable, as in most cases children are affected.

Lichen Planus

It is used for wide spread, hypertrophic or erosive lesions in a dose of 30 mg/day for 8 weeks.

Lichen sclerosus et Atrophicus (Vulva)

Suggested dose is 20–30 mg for 16 weeks.

Cutaneous Lupus Erythematosus

Though, a dose of 50 mg/day is useful in the hyperkeratotic variant, a useful method is to combine it with HCQS 400 mg. In other forms of cutaneous LE, HCQS is a letter option.

Pityriasis Rubra Pilaris

A dose of 10–20 mg (1mg/kg/day) is successful in 70% of cases. Combination with phototherapy can also be considered.

Adverse Effects

The adverse effects are largely similar to isotretinoin and the salient side effects will be covered here. Very few serious side

effects have been reported as the duration of therapy does *not* exceed 6 months in most cases.

Common

Dermatological: Acitretin may cause dose-related cheilitis and nasal dryness, although at doses currently used most patients do not have these symptoms. It also causes cutaneous xerosis and a sensation of 'sticky skin,' especially on the palms.

Hair loss: This is a dose-related effect and is reversible. It starts 2 months after either discontinuation of therapy or with a significant dose reduction. Women seem to have a more noticeable hair loss.

Bone: Regular monitoring for bone changes is an issue faced by clinicians, but it has been shown that with an average dose of acitretin of 25 mg for more than 1 year does not lead to DISH. Thus, only in cases of worsening arthritis or skeletal symptoms a regular X-ray is advised.

Lipids: It leads to dose-dependent serum triglyceride elevation in approximately 20–40 percent of patients and hypercholesterolemia in approximately 10–30%. The guidelines for stopping therapy are similar to that of isotretinoin.

Liver functions: Elevation of AST and ALT occur in 30.5% and 27.3% of patients. Most of these reverse on stopping therapy and severe hepatitis is uncommon.

Rare

Capillary leak syndrome. There are rare reports of capillary leak syndrome associated with acitretin. This leads to generalized edema and weight gain, hemorrhagic lesions, rhabdomyolysis, dyspnea, pulmonary infiltrates, pleural effusion, hypotension and oliguria.

Monitoring

The monitoring is similar to isotretinoin. It is inadvisable to use it in females in the reproductive age group unless a **3 year** post therapy contraception can be ensured.

Lipid: Baseline lipid profile. Repeat every 1–2 weeks for 4–8 weeks, then every 6–12 weeks.

Liver: Baseline LFTs. Repeat every 1–2 weeks until stable, then every 6–12 weeks.

Diabetic patient: Blood sugar monitoring.

Females: Baseline pregnancy test. Repeat monthly, avoid pregnancy for three years following discontinuation.

Long-term therapy: Consider yearly X-rays of wrists, ankles or thoracic spine with *long-term* retinoid therapy. Based on the symptoms, an ophthalmological examination may be advised.

Special Considerations

Recommendations vary in different countries but pregnancy should be avoided for at least 2 (Europe) to 3 years (USA) after treatment has been withdrawn.

Patients should not donate blood for at least 1–3 years after stopping therapy.

Female patients should avoid alcohol during treatment with acitretin and for 2 months after stopping treatment.

Drug Interactions

Alcohol: The consumption of alcohol has been associated with the formation of etretinate in patients taking acitretin. However, the presence of alcohol is not essential for this transformation to take place and etretinate has also been detected in a patient taking acitretin who did not drink alcohol. It is not clear what quantity of ingested alcohol is required for the re-esterification of acitretin to etretinate. Thus, licensed product information warns that alcohol must not be consumed by female patients during acitretin therapy and for 2 months after stopping, to avoid the formation of etretinate and associated prolonged risks of teratogenicity.

Increased serum levels of acitretin: Azole antifungals, macrolides, tetracyclines, vitamin A.

Decreased serum levels of acitretin: Anticonvulsants, antituberculosis drugs.

Increased drug levels of: Cyclosporin.

Decreased drug levels of: Progestin-only contraceptives.

Prolonged teratogenic potential of acitretin: Alcohol (alcohol converts acitretin to etretinate).

Increased risk of hepatotoxicity: Methotrexate.

Special Groups

Pregnancy: X

A study conducted by the manufacturer revealed that the vast majority of offspring born to mothers who had been exposed to acitretin within 2 years prior to conception had no malformations typical of retinoid embryopathy. Nevertheless there is a small theoretical risk of fetal malformation if conception occurs within 3 years of discontinuing therapy.

Children

Acitretin is not generally considered suitable for use in children. But in ichthyosis, it is often the only modality that has any disease modifying capability. If deemed necessary an

oral dose of 500 micrograms/kg once daily (occasionally up to 1 mg/kg daily for limited periods) has been suggested, but the maximum daily dose should not exceed 35 mg.

The British National Formulary (BNF) suggests that these doses may be used under expert supervision for children aged 1 month to 12 years for the treatment of severe extensive psoriasis resistant to other forms of therapy, palmoplantar pustular psoriasis, severe congenital ichthyosis, and Darier's disease. The *method* of administration is either by opening the capsules and adding the medicines in a oily dietary medium.

Lactation

Acitretin was distributed into the breast milk of a woman treated with oral acitretin for psoriasis. Although, the estimated amount of acitretin that would be consumed by a breast-fed infant was only 1.5% of the maternal dose, the authors considered that the toxic potential of acitretin to the infant justified its avoidance. Licensed product information also recommends that breastfeeding women should not be given acitretin. The American Academy of Pediatrics, however, has found no mention of clinical effect on the infant, and considers the maternal use of acitretin to be usually compatible with breastfeeding.

Renal

The pharmacokinetics of acitretin are reported to be altered in patients with chronic renal failure but neither acitretin nor its 13-*cis* metabolite are removed by hemodialysis.

Hepatic

Dose modification is required in case of elevation of values 3X that of normal.

FURTHER READING

1. Gisondi P, et al. Combining etanercept and acitretin in the therapy of chronic plaque psoriasis: A 24-week, randomized, controlled, investigator-blinded pilot trial. Br J Dermatol 2008;158(6):1345-9.
2. Lassus A, Geiger JM. Acitretin and etretinate in the treatment of palmoplantar pustulosis: A double-blind comparative trial. Br J Dermatol. 1988;119(6):755-9.
3. Ozawa A, et al. Treatments of generalized pustular psoriasis: A multicenter study in Japan. J Dermatol. 1999;26(3):141-9.
4. Ruzicka T, et al. Efficiency of acitretin in combination with UV-B in the treatment of severe psoriasis. Arch Dermatol. 1990;126(4): 482-6.
5. Saurat JH, et al. Randomized double-blind multicenter study comparing acitretin-PUVA, etretinate-PUVA and placebo-PUVA in the treatment of severe psoriasis. Dermatologica. 1988;177(4):218-24.

6. Tanew A, et al. Photochemotherapy for severe psoriasis without or in combination with acitretin: A randomized, double-blind comparison study. J Am Acad Dermatol. 1991;25(4):682-4.

BEXAROTENE

Mechanism of Action

Bexarotene is an agonist at the R × R, which is involved in the regulation of cell differentiation and proliferation.

Clinical Use

- CD30 + large-cell lymphoma
- Cutaneous T-cell lymphoma
- Hand dermatitis
- Lymphomatoid papulosis
- Metastatic breast carcinoma
- Non–small cell lung carcinoma
- Parapsoriasis
- Renal cell carcinoma.

Usage Guidelines

Oral: Begin 300 mg/m ^{2}/d, may increase to maximum of 400 mg/m ^{2}/d after 8 weeks of nonresponse.

CTCL – Mycosis Fungoides and Sézary Syndrome

Refractory to at least one previous systemic therapy. Dose (300 mg/m^2). Overall response rates of 48%, with a complete response rate of 4%.

Chronic Hand Eczema

Although not currently approved for this indication in the United States, it is undergoing phase III studies for use in the treatment of chronic hand dermatitis.

Monitoring

1. **Baseline:** Serum pregnancy test, complete blood count, liver function tests, fasting lipid profile, renal function, thyroid-stimulating hormone, thyroxine, urinalysis (if renal disease, diabetes, proteinuria, hypertension), eye exam (if history of cataracts).
2. **Fasting lipid profile:** 1–2 weeks/ 2–4 weeks, then monthly for 3–6 months, then 3 monthly.
3. **Complete blood count, liver function, renal function, thyroid-stimulating hormone, thyroxine:** Monthly for 3–6 months, then 3 monthly.
4. Serum pregnancy test (monthly).

Special Considerations

Pregnancy, hypersensitivity to drug/class, vitamin A supplementation, diabetics on insulin, gemfibrozil.

Drug Interactions

Increased levels of: Diethyltoluamide (DEET; insect repellent).

Increased drug levels of bexarotene: Ketoconazole, itraconazole, erythromycin, gemfibrozil, grapefruit juice.

Decreased drug levels of bexarotene: Rifampin, phenytoin, phenobarbital, inducers of cytochrome P450 3A4.

Adverse Effects

The important side effects are pancreatitis, leukopenia, agranulocytosis, hypothyroidism.

Common

Hypertriglyceridemia, hypercholesterolemia, central hypothyroidism, headache, asthenia, rash, nausea, diarrhea, infection, edema, abdominal pain, dry skin, fatigue, constipation, cheilitis.

Hematologic Effects

In CTCL studies, up to 43% of patients had reversible *leukopenia* (1000–3000 WBC/mm^3). Elevations in serum triglycerides and/or cholesterol seen in 79% of patients. Statins and fenofibrate, a fibric acid derivative, should be started. Gemfibrozil is to be avoided.

Thyroid Effects

They are seen in **80%** of patients taking the medication for CTCL. Decrease in both TSH and circulating thyroid hormone. Thus, low-dose levothyroxine should be started in all patients with monitoring of the free thyroxine level.

Rare

Hepatitis, pancreatitis, photosensitivity, leukopenia, muscle spasm, anemia, pneumonia, confusion, subdural hematoma, liver failure, chills, chest pain, candida, hypertension, angina, syncope, hypoproteinemia, hyperglycemia, change in weight, arthralgia, myalgia, bone pain, depression, agitation, ataxia, neuropathy, pharyngitis, rhinitis, dyspnea, cough, hypoxia, acne, alopecia, dry eyes, visual field defects, keratitis, otitis externa, hematuria, urinary incontinence, dysuria, breast pain.

ALITRETINOIN

This drug is being tried for chronic hand dermatitis. It has been shown to improve the condition in a dose of 10–30 mg daily. The response rates, defined as a physician's global assessment (PGA) of clear or almost clear of 28% and 48%, respectively, have been reported. A higher dose has been tried with better results (40 mg/53%).

RETINOIC ACID METABOLISM BLOCKING AGENTS

Retinoic acid metabolism blocking agents (RAMBAs) inhibit catabolism of a*t*RA by P450 enzymes in the CYP26 family, thereby raising the intracellular levels of endogenous a*t*RA in the skin and other targeted tissues. This limits systemic exposure and the potential for toxicity, and a*t*RA levels return to the physiologic range within 24 hours of discontinuing these medications.

Liarozole, an imidazole derivative without antifungal properties, is a RAMBA with low isoenzyme specificity that also inhibits P450-mediated pathways of steroid biosynthesis. *Talarozole* (R115866), a triazole derivative, is a more selective and highly active CYP26 enzyme inhibitor.

Both topical and oral forms of liarozole and talarozole have been developed, but they are not currently available in the US. However, **liarozole** has been granted orphan drug status for *congenital ichthyosis* by the European Commission and the FDA, and a randomized controlled trial showed that oral liarozole had equal efficacy to acitretin but greater tolerability in patients with moderate-to-severe forms of ichthyosis. Preliminary studies of **talarozole** have shown potential benefit for *plaque-type* psoriasis and *acne*.

13
CHAPTER

Vasoactive Drugs

Kabir Sardana

VASODILATOR DRUGS

This includes a plethora of drugs that work in various conditions including hypertension. The various classes of drugs are listed below in Figure 13.1. Even though ACE inhibitors are used in dermatology in scleroderma to prevent renal crisis, we will focus on other classes of drugs in this chapter.

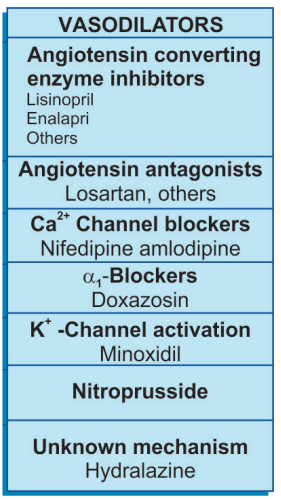


Fig. 13.1: Overview of vasodilator drugs

Calcium-channel Blockers (Nifedipine/Diltiazem)

DEPIN cap	Nifedipine 5 mg
DEPIN cap	Nifedipine 10 mg
DEPIN cap	Nifedipine 20 mg (Retard)

DILZEM CD cap	Diltiazem 90 mg
DILZEM CD cap	Diltiazem 120 mg
DILZEM CD cap	Diltiazem 180 mg
DILZEM SR tab	Diltiazem 90 mg
DILZEM tab	Diltiazem 30 mg
DILZEM tab	Diltiazem 60 mg

The tone of vascular smooth muscle is determined by the cytosolic Ca^{2+} concentration. This is increased by α_1-adrenoceptor activation (resulting from sympathetic tone), which triggers Ca^{2+} release from the sarcoplasmic reticulum via the second messenger inositol-1,4,5-trisphosphate. There are also receptor-operated cation channels that are important because the entry of cations through them depolarizes the cell, opening voltage-dependent (L-type) Ca^{2+} channels and causing additional Ca^{2+} to enter the cell. The calcium antagonists (e.g. nifedipine, amlodipine) bind to the L-type channels and, by blocking the entry of Ca^{2+} into the cell, cause relaxation of the arteriolar smooth muscle. This reduces the peripheral resistance and results in a fall in blood pressure. The efficacy of calcium antagonists is similar to that of the thiazides and ACE inhibitors. Their most common side-effects are caused by excessive vasodilatation and include dizziness, hypotension, flushing and ankle edema.

Mechanism of Action

Calcium-channel blockers prevent the transport of Ca^{2+} across the plasma cell membrane of smooth muscle cells. Nifedipine has also been shown to increase RBC deformability as well as synergistic platelet anti-aggregation activity via PGI 2 *in vitro*.

Absorption and Distribution

Calcium-channel blockers are generally well absorbed orally but have a variable bioavailability (50–70% for nifedipine, 20–40% for diltiazem, and 50–88% for amlodipine). Peak plasma levels after oral administration are reached at 30 minutes with diltiazem, 1–2 hours with nifedipine, and 7–8 hours with amlodipine. These drugs are largely protein bound. Nifedipine and amlodipine are principally excreted via the kidney, whereas 60–65% of diltiazem is excreted via the feces after extensive deacetylation. The plasma half-life for nifedipine and diltiazem is 4 hours, whereas the plasma half-life of amlodipine is much greater, at 35 hours after a single oral dose.

Uses

Treatment with *nifedipine* can be initiated at **10 mg TDS or 30 mg** once daily of sustained-release preparations. In India the 20 mg retard is available. The maximum dose is 90 mg daily of a sustained-release form of nifedipine. Longer-acting preparations are generally preferred.

Diltiazem treatment should be commenced at **60 mg three times daily**, increasing to 120 mg three times daily if

tolerated. *Amlodipine* dosage is usually initiated at 5 mg once a day and can be increased to 10 mg once a day. Intralesional verapamil hydrochloride is given in 2.5 mg/mL, with most reports using 0.5–5 mL, depending on the size of the lesions treated.

Recently, *topical nifedipine* has been tried for Raynauds phenomenon and periocular wrinkles.

1. Raynaud's Phenomenon, Systemic Sclerosis, Chilblains

The agent of choice for Raynaud's phenomenon is nifedipine. Nifedipine has been shown in double-blinded controlled studies to be effective in the treatment of primary and secondary Raynaud's phenomenon. Nifedipine is also advantageous owing to its demonstrated *in vivo* antiplatelet effects in patients with systemic sclerosis. It is also useful in recalcitrant chilblains and was found in one trial to be superior to diltiazem for this purpose. Other dihydropyridine calcium-channel blockers have also been used successfully for Raynaud's phenomenon, including nicardipine, amlodipine, felodipine, and isradipine.

Among the nondihydropyridine agents, diltiazem has also been shown in randomized controlled trials to be effective in the treatment of primary and secondary Raynaud's phenomenon.

2. Calcinosis Cutis

The results of diltiazem in the treatment of calcinosis cutis, are variable.

3. Wound Healing

Nifedipine and amlodipine have been shown to enhance wound healing in mouse models. The calcium-channel blockers improved skin tensile strength in an incision wound model, and wound contraction in an excision wound model.

4. Keloids

Verapamil injected *intralesionally* has been used with some success to treat both Peyronie's disease and keloids/hypertrophic scars. The drug is usually combined with other measures and is not superior to intralesional triamcinolone.

5. Chronic Anal Fissures

Both oral and topical forms of the calcium-channel blockers diltiazem and nifedipine have been used for the nonsurgical treatment of chronic anal fissures.

6. Cyclosporine-induced Hypertension

In patients who develop hypertension while on cyclosporine therapy, several calcium-channel blockers are considered first-line for managing this complication. Because of both metabolic properties (regarding interactions via the CYP3A4 pathway, and renal blood flow preservation), both nifedipine and isradipine have been deemed appropriate for these patients.

Side Effects

Adverse effects are frequent but rarely require cessation of therapy, with dosage reduction alone typically sufficient to reduce the adverse effect. Most of the adverse effects are due to vasodilation, and include dizziness, headache, peripheral edema (ankle or pedal), nausea, and flushing.

Diltiazem and amlodipine have similar, but *less severe* adverse effects than nifedipine.

Rarely, gingival hyperplasia, facial and truncal telangiectasia, new onset or exacerbation of psoriasis, photosensitivity reactions, subacute cutaneous lupus erythematosus, gynecomastia, erythromelalgia, and oral ulcers have been seen. Photodistributed hyperpigmentation has been reported from diltiazem.

BIBLIOGRAPHY

1. Foti C, Quaranta D, et al. Study on the effectiveness of a nifedipine gel for treatment of Raynaud?s phenomenon. J Biol Regul Homeost Agents. 2006;20(3-4):59-65.
2. Innocenti M, Ramoni S, Doria C, Antropoli C, Garbagna N, Grossi E, Veraldi S. Treatment of periocular wrinkles with topical nifedipine. J Dermatolog Treat. 2010;21(5):282-5.

PROPRANOLOL (Ciplar 10 mg, 20 mg)

Propranolol is a synthetic, β-adrenergic receptor-blocking agent that is classified as nonselective blockers because it blocks both β_1 and β_2 adrenergic receptors. Chronotropic, inotropic, and vasodilator responses decrease proportionately when propranolol blocks the β-receptor site, resulting in a decrease in heart rate (HR) and blood pressure (BP).

Mechanism of Action

The mechanism of action of propranolol on infantile hemangioma (IH) is yet to be clearly defined. Some of the proposed *hypotheses* include vasoconstriction, decreased renin production, inhibition of angiogenesis, and stimulation of apoptosis.

Absorption and Distribution

Propranolol is highly lipophilic and undergoes first-pass metabolism by the liver with only ~ 25% of oral propranolol reaching the systemic circulation. Multiple path ways in the cytochrome P450 system are involved in propranolol metabolism, making clinically important drug interactions a potential issue.

Uses (Approved/Unapproved)/Dosage

Propranolol had previously been used in pediatric patients primarily for the treatment or prevention of cardiac arrhythmias, hypertension, out flow obstructions in congenital heart disease,and hypertrophic cardiomyopathy. Its antihypertensive effects result from decreased HR, decreased cardiac contractility, inhibition of renin release by the kidneys,and decreased sympathetic tone.

FDA Approved	Hemangioma

Hemangioma

The FDA approval for this drug was based on a study published in NEJM. Though a comprehensive protocol for initiation has been suggested, probably the only side effect of consequence is bradycardia. Table 13.1 describes the method of initiation and continuation of propanolol.

Inpatient hospitalization: Infants ≤8 weeks of gestationally corrected age, or any age infant with inadequate social support, or any age infant with comorbid conditions affecting the cardiovascular system, the respiratory system including symptomatic airway hemangiomas or with a need for blood glucose maintenance.

PHACE syndrome: This syndrome present in one-third of infants with large, facial hemangiomas; it is characterized by large, segmental hemangiomas of the head and neck and congenital anomalies of the brain, heart, eyes, and/or chest wall. Arterial anomalies of the head and neck are the most common noncutaneous manifestation of PHACE syndrome, and acute ischemic stroke is a known complication.

PHACE must be thoroughly evaluated with MRI/magnetic resonance angiography of the head and neck and cardiac imaging to include the aortic arch before considering propranolol. If imaging results place a patient into a higher risk category for stroke, consultation and comanagement with neurology is appropriate. If the potential benefits of propranolol outweigh the risks, the consensus group recommends use of the lowest possible dose, slow dosage

Table 13.1: Overview of proponalol use in hemangioma

Before starting propranolol*	i. HR, BP and SpO_2 ii. Clinical photography iii. ECHO and ECG in selected patients **ECG:** If the HR is below normal for age. History of arrhythmia or arrhythmia on examination **ECHO:** Patients with history, symptoms or signs of cardiovascular disease, including patients with suspected high output heart failure Patients with large segmental hemangioma of the face and neck and suspected PHACE syndrome	
Dosage regime	Week 1	1 mg/kg/day divided into three equal doses
	Week 2	2 mg/kg/day divided into three equal doses
	PHACE syndrome	0.5 mg/kg/day and very cautious increase of the dose in small increments until MRI excludes arterial anomalies of head and neck
	FDA approval is for a 3 mg per kilogram per day for 6 months	
Review	4–6 weeks after starting treatment, then 3–4 monthly	
Increments	Increments greater than 0.5 mg/kg/day should include monitoring of HR and BP for 2 h	
Treatment stopping	Usually at **12–14 months** of age but can be longer Gradual dose reduction over **2–4 weeks**	

* Propranolol can be commenced while the investigations/results are pending, in most cases a heart rate is sufficient

titration upward, close observation, including inpatient hospitalization in high-risk infants, and 3 times daily dosing to minimize abrupt changes in systolic BP (Table 13.1).

Drug Interaction

Increase blood levels/ toxicity	Inhibitors of CYP2D6: Amiodarone, cimetidine (but not ranitidine), delavudin, fluoxetine, paroxetine, quinidine, and ritonavir Inhibitors of CYP1A2: Imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton, zolmitriptan, and rizatriptan
Decrease blood levels/ Decrease efficacy	Inducers of hepatic drug metabolism: Rifampin, ethanol, phenytoin, and phenobarbital

Special Considerations

Contraindications to Propranolol Therapy
Cardiogenic shock

Sinus bradycardia
Hypotension
Greater than first-degree heart block
Heart failure
Bronchial asthma
Hypersensitivity to propranolol hydrochloride.

Cardiac Monitoring

A. Not all cases require ECG, but ECG should be part of the pretreatment evaluation in any child when
   1. The HR is below normal for age :
      a. Newborns (<1 month old), <70 beats per minute,
      b. Infants (1–12 months old), <80 beats per minute, and
      c. Children (>12 months old): 70 beats per minute.
   2. There is family history of congenital heart conditions or arrhythmias (e.g. heart block, long QT syndrome,sudden death), or maternal history of connective tissue disease.
   3. There is history of an arrhythmia or an arrhythmia is auscultated during examination.

B. Monitoring of BP is advised on therapy. Cutoff values are suggested as below:
   Newborn: <57 mm Hg or 64 mm Hg (Auscultation)
   6 months: <85 mm Hg or 65 mm Hg (Auscultation)
   1 year: <88 mm Hg or 66 mm Hg (Auscultation)

Hypoglycemia

Blood glucose is *not* measured routinely, unless the patient is having signs or symptoms of hypoglycemia. Propranolol should be administered during the *daytime* hours with a *feeding* shortly after administration. Parents should be instructed to ensure that their child is fed regularly and to avoid prolonged fasts.

In otherwise healthy children, the risk of hypoglycemia is age-dependent and begins after 8 hours of fasting in children of 0–2 years of age. Infants <6 weeks should be fed at least every 4 hours, between 6 weeks and 4 months of age should befed at least every 5 hours, and >4 months of age should be fed at least 6–8 hours. Propranolol should be discontinued during intercurrent illness, especially in the setting of restricted oral intake.

Side Effects

The most frequently reported serious complications are asymptomatic hypotension or hypotension; pulmonary symptoms related to direct blockade of adrenergic bronchodilation; hypoglycemia or hypoglycemic seizure; asymptomatic bradycardia; and hyperkalemia.

The most commonly reported nonpotentially life-threatening complications are sleep disturbances, including nightmares, somnolence, cool or mottled extremities, diarrhea, and gastroesophageal reflex/upset.

Common

Bradycardia and Hypotension

This effect peaks around 2 hours after an oral dose.

Hypoglycemia

Symptomatic hypoglycemia and hypoglycemic seizures have been reported in infants with IH treated with oral propranolol. These cases occurred in both new-borns and toddlers but were often associated with poor oral intake or concomitant infection. The mechanism through which propranolol-induced hypoglycemia develops is **not** completely understood. Non-selective β-blockers, such as propranolol, may block catecholamine-induced glycogenolysis, gluconeogenesis, and lipolysis, predisposing to hypoglycemia.

Clinical Features

Mild hypoglycemia produces symptoms associated with counterregulatory epinephrine action, including *sweating, shakiness, tachycardia, anxiety, and hunger*. With propranolol-induced β-adrenergic blockade, early symptoms may be masked. Therefore, because *sweating* is not typically blocked by β-blockers, this may be a more reliable symptom for diagnosis. More severe hypoglycemia produces symptoms of neuroglycopenia,including lethargy, stupor, poor feeding,seizures, apnea, loss of consciousness,and hypothermia.

Most of the reported patients who developed hypoglycemia were prescribed relatively low doses (1.25 – 2.0 mg/kg/day), suggesting that hypoglycemia associated with propranolol may **not** be dose-dependent. Patients with IH may be at increased risk if they have received or are concomitantly receiving treatment with *corticosteroids*, because adrenal suppression may result in loss of the counterregulatory cortisol response and increase the risk of hypoglycemia. Children, infants, and especially preterm infants appear to be at higher risk for this hypoglycemia as their glucose utilization rates are threefold higher in the fasting state and their glycogen stores are lower.

Bronchospasm

Bronchial hyperreactivity, described as wheezing, bronchospasm, or exacerbation of asthma/bronchitis, is a recognized side effect of propranolol as the result of its direct blockade of adrenergic bronchodilation. Thus, the use of propranolol in the setting of known reactive airway disease must be considered cautiously. The development of bronchial hyperreactivity in the setting of an acute viral illness in patients on propranolol has necessitated temporary discontinuation of therapy.

Hyperkalemia

Hyperkalemia (without electrocardiographic changes) was reported in 2 children on propranolol for IH. The cause of the hyperkalemia is not known, but the authors postulate that it was tumor lysis from the large ulcerated IH combined with impaired potassium uptake into cells as the result of beta blockade.

Rare

CNS

In adult patients there is evidence that propranolol use is associated with central nervous system (CNS) effects. Impairment to short- and long-term memory, psychomotor function, sleep quality and mood with relatively low doses and durations of treatment have been reported.

In children, though this has not been studied, it suggests that the drug should be used for cases with ulceration, impairment of a vital function or risk of permanent disfigurement and for a limited duration, and the benefits of treatment should be weighed carefully against potential adverse events before treatment is initiated.

Monitoring of Propranolol

Laboratory tests	Base line	Follow-up
BP	Yes	▪ BP and HR immediately before the dose and every 30 min for 2 h (Weight >3.5 kg) ▪ BP and HR immediately before the dose and every 30 min for 4 h (Weight <3.5 kg)
HR	Yes	
Thyroid function test	Yes (Liver hemangioma Parotid hemangioma PHACE syndrome)	
Full blood count	Yes (Bleeding hemangioma)	
Liver function tests	Yes (For liver hemangioma)	
ECHO		
MRI* (Brain/spine)	Yes	
Abdominal USG**	Yes	

* Large segmental hemangioma of head and neck with suspected PHACE syndrome; Plaque hemangioma in lumbosacral area crossing the midline or perianal/perineal hemangioma extending into gluteal cleft

**More than 10 cutaneous hemangiomas Perianal and perineal hemangioma crossing the midline and/or extending into gluteal cleft

BIBLIOGRAPHY

1. Langley A, Pope E. Propranolol and central nervous system function: potential implications for paediatric patients with infantile haemangiomas. Br J Dermatol. 2015;172(1):13-23.
2. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med. 2015;372(8):735-46.

SILDENAFIL (Suhagra/Suhagra Force) (Sildenafil 25 mg, 50 mg)/(Sildenafil 50 mg/ Dapoxetine 30 mg)

Mechanism of Action

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective ***inhibitor*** of cGMP specific phosphodiesterase type 5 **(PDE5)** in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore, *sexual stimulation is required* in order for sildenafil to produce its intended beneficial pharmacological effects.

Absorption and Distribution

Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes of oral dosing. When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in t_{max} of 60 minutes and a mean reduction in C_{max} of 29%.

Biotransformation

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% that of the parent drug.

Elimination

The total body clearance of sildenafil is 41 l/h with a resultant terminal phase half-life of 3–5 h. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administered oral dose). A combination with dapoxetine is useful in the indicator.

Uses (Approved/Unapproved)

1. Treatment of men with **erectile dysfunction**, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. A combination with dapoxetine is useful in this indication.
   In order for sildenafil to be effective, sexual stimulation is required.
2. **PSS:** Sildenafil has been successfully used in the treatment of systemic sclerosis-related Raynaud's. It is also useful for treating digital ulcerations. In systemic sclerosis and severe digital ulcerations, combined therapy with sildenafil 12.5 mg daily plus 125 mg daily of bosentan (an endothelin-1 antagonist) resulted in complete healing.
3. Sildenafil 50 mg daily has been reported to accelerate healing of chronic and nonhealing skin **ulcerations** in patients with antiphospholipid antibody syndrome.
4. An open-labeled study has used the drug in chidren in a dose ranging from 30–60 mg for 20 weeks in cases of lymphatic malformations (Danial C).

Dosage

Use in Adults

The recommended dose is **50 mg** taken as needed approximately **one hour** before sexual activity. Based on efficacy and tolerability, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is **100 mg.** The maximum recommended dosing frequency is once per day. If Sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state.

Drug Interaction

- Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as **ketoconazole, erythromycin, cimetidine**). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered

concomitantly with CYP3A4 inhibitors, a starting dose of **25 mg** should be considered
- Coadministration of sildenafil with **ritonavir** is not advised
- Concomitant administration of strong CYP3A4 inducers, such as **rifampin**, is expected to cause greater decreases in plasma concentrations of sildenafil
- **Nicorandil** is a hybrid of potassium channel activator and nitrate. Due to the nitrate component, it has the potential to result in a serious interaction with sildenafil
- Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals
- Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its coadministration with nitric oxide donors or nitrates in any form is therefore contraindicated
- Pooling of the following classes of antihypertensive medication: diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally acting), adrenergic neurone blockers, calcium-channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment.

Special Considerations

1. Cardiovascular Risk Factors

a. Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decrease in blood pressure. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g. aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

b. Sildenafil potentiates the hypotensive effect of nitrates.

c. Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of sildenafil without sexual activity.

2. **Priapism:** Agents for the treatment of erectile dysfunction, including sildenafil, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma or leukemia).

   Prolonged erections and priapism have been reported with sildenafil in post-marketing experience. In the event of an erection that persists longer than *4 hours*, the patient should seek immediate medical assistance.
3. Concomitant use with other PDE5 inhibitors or other treatments for erectile dysfunction

   The safety and efficacy of combinations of sildenafil with other PDE5 Inhibitors, or other pulmonary arterial hypertension (PAH) treatments containing sildenafil, or other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.
4. **Effects on vision:** Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors. Cases of **non-arteritic anterior ischemic optic neuropathy**, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors. Patients should be advised that in the event of any sudden visual defect, they should stop taking sildenafil and consult a physician immediately
5. **Women:** Sildenafil is not indicated for use by women.

Side Effects

The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, hot flush, visual disturbance, cyanopsia and vision blurred.

It has been reported to precipitate PPD (Koçak AY) and more seriously melanoma (Li WQ).

Special Groups

Elderly Patients

Dosage adjustments are not required in elderly patients (≥ 65 years old).

Patients with Renal Impairment

The dosing recommendations described in 'use in adults' apply to patients with mild to moderate renal impairment (creatinine clearance = 30–80 mL/min).

Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 mL/min) a 25 mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg up to 100 mg as necessary.

Patients with Hepatic Impairment

Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis), a 25 mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg up to 100 mg as necessary.

Pediatric Population

Sildenafil is not indicated for individuals below 18 years of age.

Use in Patients Taking Other Medicinal Products

With the exception of ritonavir for which co-administration with sildenafil is not advised a starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors

In order to minimize the potential of developing postural hypotension in patients receiving α-blocker treatment, patients should be stabilized on α-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered.

BIBLIOGRAPHY

1. Ambach A, Seo W, Bonnekoh B, Gollnick H. Low-dose combination therapy of severe digital ulcers in diffuse progressive systemic sclerosis with the endothelin-1 receptor antagonist bosentan and the phosphodiesterase V inhibitor sildenafil. J Dtsch Dermatol Ges. 2009;7(10):888-91.
2. Brueckner CS, Becker MO, Kroencke T, et al. Effect of sildenafil on digital ulcers in systemic sclerosis: analysis from a single centre pilot study. Ann Rheum Dis. 2010;69(8):1475-8.
3. Danial C, Tichy AL, Tariq U, Swetman GL, Khuu P, Leung TH, et al. An open-label study to evaluate sildenafil for the incident melanoma in US men: a prospective cohort study. JAMA Intern Med. 2014;174(6):964-70.
4. Koçak AY, Akay BN, Heper AO. Sildenafil-induced pigmented purpuric dermatosis. Cutan Ocul Toxicol. 2013;32(1):91-2.
5. Li WQ, Qureshi AA, Robinson KC, Han J. Sildenafil use and increased risk of treatment of lymphatic malformations. J Am Acad Dermatol. 2014;70(6):1050-7.

BOSENTAN (62.5 mg/125 mg)

Mechanism of Action

Bosentan is a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (ET_A and ET_B) receptors. Bosentan decreases both pulmonary and systemic vascular resistance resulting in increased cardiac output without increasing heart rate.

The neurohormone endothelin-1 (ET-1) is one of the most potent vasoconstrictors known and can also promote fibrosis, cell proliferation, cardiac hypertrophy and remodeling, and is proinflammatory. These effects are mediated by endothelin binding to ET_A and ET_B receptors located in the endothelium and vascular smooth muscle cells. ET-1 concentrations in tissues and plasma are increased in several cardiovascular disorders and connective tissue diseases, including pulmonary arterial hypertension, scleroderma, acute and chronic heart failure, myocardial ischemia, systemic hypertension and atherosclerosis, suggesting a pathogenic role of ET-1 in these diseases. In pulmonary arterial hypertension and heart failure, in the absence of endothelin receptor antagonism, elevated ET-1 concentrations are strongly correlated with the severity and prognosis of these diseases.

Absorption and Distribution

Absorption

In healthy subjects, the absolute bioavailability of bosentan is approximately 50% and is not affected by food. The maximum plasma concentrations are attained within 3–5 hours.

Distribution

Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

Biotransformation and Elimination

After a single intravenous dose of 250 mg, the clearance was 8.2 L/h. The terminal elimination half-life ($t_{1/2}$) is 5.4 hours.

Upon multiple dosing, plasma concentrations of bosentan decrease gradually to 50–65% of those seen after single dose administration. This decrease is probably due to autoinduction of metabolizing liver enzymes. Steady-state conditions are reached within 3–5 days.

Bosentan is eliminated by biliary excretion following metabolism in the liver by the cytochrome P450 isoenzymes, CYP2C9 and CYP3A4. Less than 3% of an administered oral dose is recovered in urine.

Dosage

Adults

In adult patients, dose should be initiated at a dose of **62.5 mg twice daily** for **4 weeks** and then increased to the maintenance dose of **125 mg twice daily**.

Uses (Approved/Unapproved)

1. Treatment of **pulmonary arterial hypertension** (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in:
   - Primary (idiopathic and heritable) pulmonary arterial hypertension
   - Pulmonary arterial hypertension secondary to scleroderma without significant interstitial pulmonary disease
   - Pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology.

   Some improvements have also been shown in patients with pulmonary arterial hypertension WHO functional class II.
2. It is also indicated to reduce the number of new **digital ulcers** in patients with systemic sclerosis and ongoing digital ulcer disease (Nagai Y et al.). It has also been used for lower extremity ulcers in scleroderma (Naert A).

   Treatment should only be initiated and monitored by a physician experienced in the treatment of systemic sclerosis.

   The dose should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily. Controlled clinical study experience in this indication is limited to 6 months.
3. A recent report suggests that the drug can be used to prevent neoangiogenesis in resistant **PWS.** A dose of 62.5 mg twice daily 1 day before the PDL irradiation and continued for 14 days was used with encouraging results in one patient (Taquin H).

Drug Interaction

Bosentan is an inducer of the cytochrome P450 (CYP) isoenzymes CYP2C9 and CYP3A4. *In vitro* data also suggest an induction of CYP2C19.

1 Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan (see ketoconazole). The influence of CYP2C9 inhibitors on bosentan concentration

has not been studied. The combination should be used with caution.

2. **Fluconazole and other inhibitors of both CYP2C9 and CYP3A4:** Concomitant administration with fluconazole, which inhibits mainly CYP2C9, but to some extent also CYP3A4, could lead to large increases in plasma concentrations of bosentan. The combination is not recommended. For the same reason, concomitant administration of both a potent CYP3A4 inhibitor (such as ketoconazole, itraconazole or ritonavir) and a CYP2C9 inhibitor (such as voriconazole) is not recommended.
3. **Cyclosporine A:** Coadministration of cyclosporine A (a calcineurin inhibitor) is contraindicated.
4. **Glibenclamide:** Coadministration of bosentan 125 mg twice daily for 5 days decreased the plasma concentrations of glibenclamide (a CYP3A4 substrate) by 40%, with potential significant decrease of the hypoglycemic effect.
5. **Rifampicin:** Coadministration in 9 healthy subjects for 7 days of bosentan 125 mg twice daily with rifampicin, a potent inducer of CYP2C9 and CYP3A4, decreased the plasma concentrations of bosentan by 58%, and this decrease could achieve almost 90% in an individual case.
6. **Lopinavir+ritonavir (and other ritonavir-boosted protease inhibitors):** Coadministration of bosentan 125 mg twice daily and lopinavir + ritonavir 400 + 100 mg twice daily for 9.5 days in healthy volunteers resulted in initial trough plasma concentrations of bosentan that were approximately 48-fold higher than those measured after bosentan administered alone.
7. **Sildenafil:** Coadministration of bosentan 125 mg twice daily (steady state) with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63% decrease in the sildenafil AUC and a 50% increase in the bosentan.

Side Effects

The most frequent adverse reactions are headache (11.5%), edema/fluid retention (13.2%), abnormal liver function test (10.9%) and anemia/hemoglobin decrease (9.9%).

Liver Function

Elevations in liver aminotransferases, i.e. aspartate and alanine aminotransferases (AST and/or ALT), associated with bosentan are dose dependent.

Treatment with bosentan has been associated with dose-dependent elevations in liver aminotransferases and decreases in haemoglobin concentration

BIBLIOGRAPHY

1. Naert A, De Haes P. Successful treatment with bosentan of lower extremity ulcers in a scleroderma patient. Case Rep Med. 2013;2013:690591.
2. Nagai Y, Hasegawa M, Hattori T, Okada E, Tago O, Ishikawa O. Bosentan for digital ulcers in patients with systemic sclerosis. J Dermatol. 2012;39(1):48-51.
3. Taquin H, Lacour JP, Le Duff F, et al. Treatment of resistant port-wine stains with bosentan and pulsed dye laser: a pilot prospective study. J Eur Acad Dermatol Venereol. 2015; Aug 24. doi:10.1111/jdv.13275.

14
CHAPTER

Psychotropic Agents

Kabir Sardana

PSYCHOTROPIC DRUGS

Though it may seem at first glance that psychotropic drugs are under the purview of psychiatrists, in reality as patients presenting to dermatologist rarely agree to go to a psychiatrist, we tend to be the first and in most cases the last medical professional providing point of care advice. Moreover there are many other uses of these drugs. Of all the drugs the most important probably are antidepressants.

The dermatological presentation can either be in the form of primary psychiatric disorders, which is decidedly uncommon and difficult to diagnose or a dermatological manifestations. These can range from delusions of parasitosis to common conditions like neurotic excoriations, prurigo, dysmorphophobia and acne excoriee.

Some of the other off-label indications include premature ejaculation, neuropathy, neuralgia and glossodynia. The use of SSRI in pruritus and doxepin in urticaria are probably the most commonly prescribed off-label indications.

Classification

Psychopharmacological therapy may be indicated in some cases of primary or secondary psychiatric disorders and comorbidities (Table 14.1).

Indications for Psychopharmacological Therapy in Dermatology

1. **Primary psychiatric disorders with reference to the skin:** In addition to delusional disorders, these include compulsive disorders, somatoform disorders, and psychogenic itching, in which skin changes are secondary events.
2. **Secondary psychiatric disorders due to dermatoses:** These comprise secondary psychiatric disorders due to a cutaneous disease, in which the dermatosis is the stressor causing a psychopathological response. The symptoms develop following the model of an adjustment disorder, with depression or/and anxiety as a consequence of

Table 14.1: Indications of Psychotropic Drugs in Dermatology

Disorders	*Class*	*Examples*
Psychiatric diseases (delusional -- parasitosis, hypochondriacal delusions, and others)	Antipsychotics (neuroleptics)	**1st choice:** Aripiprazole, risperidone, quetiapine, olanzapine **2nd choice:** pimozide
Depressive disorders	Antidepressants	**1st choice SSRI:** Citalopram, fluoxetine, sertraline, paroxetine, venlafaxine **2nd choice:** Tricyclic antidepressants: doxepin
Anxiety and panic disorders		**Acute/transient:** Benzodiazepines **Chronic:** **1st choice:** Buspirone **2nd choice:** Doxepin, paroxtenine **3rd choice:** Benzodiazepines
Compulsive disorders		**1st choice:** SSRIs: paroxetine, escitalopram, sertraline, citalopram, fluoxetine, fluvoxamine **2nd choice:** Tricyclic antidepressant: clomipramine

dealing with the dermatosis, which may make psychopharmacotherapy necessary.

3. **Comorbidities:** These involve juxtaposition of psychiatric disorder and dermatosis. A clear delineation between the former groups (2 and 3) is not always possible.

Therapy with psychopharmaceuticals has some important caveats that determine the variable use:

1. An identical psychopharmaceutical drug may act differently in different patients.
2. A medication from the same group may act differently in the same patient.
3. A medication dose differs from patient to patient (titration).
4. The selection and indications of a psychopharmaceutical should be made on the basis of the side effects profile.

Overview of Common Psychiatric Afflictions

1. Anxiety Disorder

In general, there are two broad categories of antianxiety medications:

- **Quick-acting** benzodiazepines
- **Slow-acting** non-benzodiazepines that are neither sedating nor dependency-provoking.

The prototypical fast-acting benzodiazepine is **lorazepam.** Usually, 0.5–2 mg every 6–8 hours on an "as needed" basis can be used to control acute anxiety. As with all benzodiazepines, addiction can develop with long-term use. Thus, the duration of treatment should be limited to no more than *4 weeks*. This amount of time is usually adequate for treatment of anxiety related to acute situational stressors. Sedation is usually the only adverse effect encountered when lorazepam is used for such a short period of time, and this usually subsides after several days of treatment or can be controlled by dosage adjustment.

If a patient has chronic anxiety, the use of a non-benzodiazepine such as **buspirone** is preferable. This medication can be used for long-term maintenance because it is non-sedating and does not produce dependency. In this respect, it is much safer to use than benzodiazepines. Because the onset of action may be delayed for 2–4 weeks after initiating therapy, buspirone is not useful in acute anxiety. The recommended initial dose is 15 mg daily (usually divided into three doses). To achieve an optimal therapeutic response, the dosage may be increased by 5 mg a day every 2 to 3 days, up to a maximum of 60 mg a day if needed.

Antidepressants (see below) such as paroxetine (20–50 mg/day), sertraline (25–200 mg/day), fluoxetine (10–60 mg/day), escitalopram (10–20 mg/day), low-dose doxepin (≤50 mg/day), and venlafaxine extended release (75–150 mg/day) have also been shown to be useful for the treatment of chronic anxiety.

2. Depression

The numerous available antidepressants have similar efficacy rates of approximately 60–80%. The initial response to antidepressants usually begins **2–3 weeks** after the therapeutic dose is reached, and at least **6 weeks** of full-dose treatment is generally required before full therapeutic effectiveness is achieved. The US FDA requires that antidepressants have a black box warning noting an increased risk of suicidal thoughts and behavior (particularly during the first 1–2 months of therapy) in patients <25 years of age.

The tricyclic antidepressant that is most often used by dermatologists is doxepin. Doxepin is well suited for depressed patients with neurotic excoriations because, in addition to its antidepressant effects, it is a very powerful H_1 receptor antagonist that can help break the itch–scratch cycle. For control of pruritus, a dosage of 10–25 mg at bedtime would be appropriate. To treat depression, this starting dose is increased by 10–25 mg every 1–2 weeks as tolerated, up to a therapeutic range of 100-300 mg daily (lower for elderly or small individuals). The most common adverse effect is sedation. Other side effects of doxepin are similar to those of other tricyclic antidepressants, including cardiac conduction

abnormalities, weight gain, orthostatic hypotension, and anticholinergic effects (e.g. dry mouth, blurry vision, constipation, urinary retention).

SSRIs represent the most widely prescribed class of antidepressants and the first-line treatment for depression. They include fluoxetine, paroxetine, sertraline, escitalopram and citalopram. These drugs are as effective as the tricyclic antidepressants but have a more favorable side-effect profile because they do not affect the cholinergic and histaminic receptors. The most common adverse effects are gastrointestinal symptoms such as nausea and diarrhea. As with all antidepressants, the clinical response is gradual. Patients showing no improvement in 6–8 weeks should be switched to another SSRI or to an agent from another class of antidepressants, such as venlafaxine or bupropion.

3. Psychosis

The psychodermatologic conditions that typically require treatment with an antipsychotic medication are forms of somatic-type delusional disorder, most often **delusions of parasitosis**. Traditionally, the treatment of choice for delusions of parasitosis has been **pimozide.** Careful titration of this medication is needed to ensure its safe use. Pimozide is usually started at a dose of 1 mg daily, which is increased by 1 mg every 1–2 weeks until the optimal clinical response is achieved, usually at 4–6 mg daily.

Although there have been reports of sudden death (presumably of cardiac cause) in patients with chronic schizophrenia who were treated with high-dose pimozide (>10 mg/day), there is less evidence for clinically significant cardiac effects at the lower doses used for psychodermatologic conditions. Since pimozide can potentially cause arrhythmias by prolonging the Q–T interval, an electrocardiogram should be performed before and after initiating treatment in patients with a history of cardiac conduction abnormalities. It has been debated whether an electrocardiogram is warranted for lower-dose pimozide therapy in young, healthy patients with no history of cardiac problems. The patient's medications should be reviewed in order to identify any potential drug–drug interactions. For example, agents that inhibit the P450 CYP3A4 enzyme system (e.g. macrolide antibiotics, azole antifungals, HIV protease inhibitors; also grapefruit juice) can increase serum levels of pimozide, and some other medications (e.g. certain quinolones) also prolong the Q–T interval.

Most patients with delusions of parasitosis can be successfully tapered off pimozide after 2–6 months of therapy. Because this drug differs from haloperidol only by one methyl group, extrapyramidal side effects, such as stiffness or a feeling of inner restlessness called akathisia (manifested

outwardly by difficulty remaining still and fidgeting or pacing) are possible. Benztropine (1–2 mg up to four times daily) or diphenhydramine (25 mg up to four times daily) can be used to treat extrapyramidal side effects.

"Atypical" antipsychotic medications with more favorable side-effect profiles (e.g. fewer extrapyramidal symptoms, lack of Q–T prolongation) are now the most frequently prescribed medications for the treatment of psychosis. These drugs include risperidone, **olanzapine**, quetiapine, **aripiprazole**, ziprasidone and lurasidone. This group of medications appears to be as effective as the older antipsychotics for various psychotic disorders and may prove useful and safe for **somatic-type delusional disorder,** although the optimal dosage range for the latter condition has not been established. Additional side effects of pimozide and (to a lesser degree) some atypical antipsychotic agents include anticholinergic symptoms (see above), increased prolactin, and weight gain.

4. Obsessive–Compulsive Disorder

Several psychodermatologic disorders have OCD-like features, including trichotillomania, onychotillomania, neurotic excoriations and acne excoriée. The **SSRIs** (see above) are the first-line treatment for OCD.

OCDs often require a *higher* dose of SSRIs and take *longer* to respond to therapy than depression. The initial response may appear at 4–8 weeks and a maximal response may take as long as 20 weeks. A 10–12-week trial with an SSRI at a therapeutic dosage for OCD is necessary to confirm a failure to respond. Once a therapeutic response is achieved, treatment should be continued for 6 months to a year.

ANTIPSYCHOTICS

These drugs primarily work on the D2 receptors. Though most dermatologists use pimozide, there are better and safer drugs that should be used. Thus these second generation, or atypical antipsychotics, will be discussed in brief as they are invariably the first choice in most disorders (Table 14.2).

Treatment of Dermatologic Conditions with Underlying Psychotic/Delusional Functioning

Neuroleptics are medications that influence thought processing and experience. Target symptoms of neuroleptics are the *psychotic* symptoms: visual, auditory, and tactile hallucinations; delusions; paranoid ideation; ideas of reference; states of psychomotor excitation; reduction of psychotic anxiety; decreased affective intensity; and, in general, deceptive perceptions.

Table 14.2: Classification of antipsychotics

Drug Class	
First-generation Antipsychotics	Perphenazine **Promethazine** (Phenargan) Chlorpromazine Haloperidol **Pimozide**
Second-generation Antipsychotics	Risperidone **Olanzapine** (Oleanz) Quetiapine Risperidone **Aripiprazole** (Arpizol) Amisulpride
Long-acting/high potency preparations	Fluphenazine Haloperidol decanoate Thiothixene
Uses	■ Schizophrenia and schizoaffective disorder ■ Acute manic and mixed episodes of bipolar disorder ■ Major depression with psychosis ■ Delusional disorder ■ Delirium ■ Dementia ■ Mental retardation ■ Developmental disorders (e.g. autism) ■ Huntington's disease ■ Tourette's syndrome ■ Substance-induced psychoses (psychostimulants, phencyclidine, levodopa, steroids)

(Drugs in bold have been used for dermatological disorders)

They work by blocking the (D2) dopamine receptors in the mesolimbic projection (tegmentum to nucleus accumbens) and decreasing the activity of the pathway postulated to be responsible for the psychotic symptoms (Table 14.2).

First-generation antipsychotic agents, also called conventional agents, are remarkably effective in decreasing psychotic symptoms. They are also effective at blocking other postsynaptic dopamine D2 receptors widely distributed in the brain, causing numerous side effects, which are the reason that most psychiatrist do not prefer using these agents. The side effects include, intense extrapyramidal rigidity and excitation (akathisia), tardive dyskinesia, hyperprolactinemia/galactorrhea and menstrual cycle disturbance, marked worsening of the already existent apathy, withdrawal, and slow psychic functioning. Neuroleptic malignant syndrome is a rare side effect and is more frequent with high doses or rapid titration. It is characterized by, hyperthermia (>38°C), change in mental status, diaphoresis, muscle rigidity and tachycardia.

Pimozide, a 1st-generation antipsychotic, is still used as numerous reports have been published on the use of pimozide in dermatology patients. But the newer neuroleptics with fewer extrapyramidal motor side effects should be used in dermatology (Table 14.2). These so-called atypical neuroleptics are characterized by the fact that their effect is more *specific* and produces *fewer* extrapyramidal and cortical withdrawal side effects than the 1st-generation or conventional neuroleptics. Neuroleptic antihistaminics such as **promethazine** are especially indicated in psychomotor excitation and anxious agitation. Due to their often good antiallergic/antihistaminic effect, they are sometimes the choice in patients with urticaria and atopic dermatitis.

Risperidone, aripiprazole, ziprasidone, and quetiapine are the drugs of first choice in psychiatric disorders with psychotic functioning. These atypical neuroleptics have a low and favorable side effects profile and thus better acceptance on the patient's part. Due to the rarity of patients with delusional diseases, there are no broad controlled studies on the newer antipsychotic drugs but only isolated case reports and empirical treatment observations in the area of dermatology.

The duration of treatment and the dose must be determined in each individual case. The duration should be at least ***1 month*** until the onset of action. In responders, therapy should be given for ***6*** months and may sometimes be necessary over a period of years.

The dermatological disease with underlying psychotic/confusional functioning most frequently **observed in** dermatology is **delusion of parasitosis (DP)**, initially called acrophobia. The complete disappearance of DP often ***can not*** be achieved even with adequate drug therapy. Improvement and transition of a serious DP to a less intense form can be considered therapeutic success or the goal of therapy, and can often mean clear stabilization and social integration of the patient. In DP, depending on the seriousness of the underlying psychosis, only 30–50% remission is likely.

Chemistry

Antipsychotic drugs bind to numerous neurotransmitter receptor subtypes like dopamine, norepinephrine, epinephrine, acetylcholine, serotonin, and histamine. They act to antagonize the endogenous ligands at these receptors. Both therapeutic and extrapyramidal side effects can be attributed to the antagonism of dopamine at D2 receptors, with actions at the other neuroreceptors associated with various other side effects.

The typical antipsychotics have been described as being of high (e.g. haloperidol), low (e.g. chlorpromazine), and mid (e.g. loxapine) potency on the basis of their degree of affinity for D2 receptors and their therapeutic dose range.

Atypical antipsychotics are characterized by generally lower affinities for D2 receptors and relatively greater affinities for serotonin (5-hydroxytryptamine) 5-HT 2A receptors in particular, but also for noradrenergic receptors (1 and 2), muscarinic acetylcholine receptors, histamine, and other dopamine (DA) subtype receptors.

Mechanism of Action

The therapeutic actions of antipsychotic drugs are generally attributed to antagonism of DA receptors, particularly the D 2 subtype. Atypical antipsychotics, with their lower D 2 receptor affinities and broader spectrum of pharmacologic properties, also antagonize 5-HT 2A receptors, giving possible therapeutic advantages and a superior motor side effect profile.

Drugs Overview

1. Risperidone

(Respidon 1,2,3,4 mg)
Risperidone is a well-tolerated neuroleptic with a relatively low side effects profile. It can especially be successfully used in elderly patients with, when possible heart disease and, if appropriate, electrocardiography (ECG) control are taken into account.

Dose: The initial dose of risperidone (Risperdal) in dermatology is 0.5–1 mg daily with a slow dose increase every 5–7 days until a maximum dose of 4–6 mg is attained.

Side effects: The side effects include dizziness, sedation, hypotension, weight gain, constipation, abdominal pain, possible decompensation of diabetes, hyperglycemia (frequent and dose-dependent), anxiety, extrapyramidal rigidity, akathisia, hyperprolactinemia and restlessness. Risperidone can also minimally prolong the QT interval on ECG. Tachycardia and sexual dysfunction may also be seen.

2. Quetiapine

(Quell 25,50,100 mg)
They are preferred in use in ***elderly*** patients, including patients with brain diseases (***dementia***).

Dose: Treatment is begun with 25 mg twice daily and can be increased to a dose of 150–800 mg/day.

Side effects: Fatigue, sedation, weight gain, mild anticholinergic symptoms, dizziness, hypotension, and tachycardia occur in rare cases. Dry mouth, constipation, and abdominal

pain may be seen. Orthostatic dysregulation is also possible. The drug increases diabetes risk and dyslipidemia.

3. Olanzapine

(Oleanz Rapi tab 2.5, 5, 7.5, 10, 15, 20 mg)
This drug is very ***well tolerated,*** but is often discontinued, especially by younger patients, because of its anticholinergic effects and pronounced ***weight gain.***

Dose: The initial dose is 5 mg/day, and further increases and titration are done to a dose range of 5–20 mg per day.

4. Aripiprazole

(Arpizol 5,10,15,20 mg)
This drug is ***well tolerated*** and has ***minimal*** anticholinergic effects but is discontinued at times because of its activating effects, particularly at low doses. It is also the atypical neuroleptic associated with ***less*** weight gain. It is my preferred drug of choice as an antipsychotic.

Dose: The initial dose is 5 mg/day, with further increases and titration to a dose range of 15–30 mg per day. Antipsychotic effects may be present in low dosages of 5–10 mg/day, but at times side effects and activation are prominent with low dosage.

Side effects: Anticholinergic effects such as dizziness, sedation, orthostatic hypotension, nausea, occasional vomiting, extrapyramidal akathisia (rare), constipation, and insomnia may occur, and there is frequently minimal or no weight gain.

5. Pimozide

Larap, Mozep, Monozide, Medip, Neurap, Notic, Orap (1 mg/2 mg).

Pimozide is an antipsychotic drug of the diphenylbutylpiperidine class.

Pharmacology

Bioavailability: 50%.

Metabolism/Excretion: Pimozide undergoes hepatic metabolism, and the resultant metabolites are excreted primarily in the urine. Some fecal excretion occurs, however.

After administration, 6–8 hours are needed to achieve peak serum levels. Although the plasma half-life of pimozide is reported as being 29 hours.

Clinical Uses

Delusion of Parasitosis

Treatment of the somatic delusions associated with delusions of parasitosis has been primarily with pimozide. In contrast to schizophrenia, in which hallucinations and delusions coexist with other affective and cognitive deficits, delusions

of parasitosis often is the only psychiatric symptom presents; however, it may coexist with other psychiatric disorders.

Although no comparative studies exist between pimozide and other antipsychotic agents in the treatment of delusions of parasitosis, pimozide is considered the treatment of choice. Other atypical antipsychotic drugs have been used with success, and it is my opinion that they should be preferred as they have a better side effect profile.

Dosage

Induction: Pimozide should be started at doses of 1 to 2 mg/d with increases in dose of 1–2 mg occurring from every other day to every week. Maximum dose is 4–6 mg.

Clinical improvement often is evident, with doses in the range of ***2–4 mg/d.*** Doses may be divided initially; however, pimozide is designed to be given *once a day*. Doses should be increased until the patient experiences improvement or unacceptable adverse effects occur.

Maintenance: After there has been adequate relief on a stable pimozide dose, treatment should continue for at least 1 additional month.

Tapering: The drug is then tapered by 1-mg decrements in dose on a weekly basis till the minimum effective dosage is arrived at. Some patients may require 2–5 months of treatment to obtain relief; approximately 50% of these patients experience a complete remission.

Others require intermittent treatment. Episodic treatment may minimize the risk of tardive dyskinesia.

Psychogenic Excoriation

2 mg two or three times daily.

Post-herpetic Neuralgia

2 mg two or three times daily.

Dermatitis Artefacta

If there is clinical evidence of a psychotic process, pimozide could be considered empirically in resistant cases.

Lichen Simplex Chronicus

In resistant cases benzodiazepines, amitriptyline, **pimozide**, and doxepin have been used to treat neurotic excoriations and severe neurodermatitis.

Others

It has also been used for body dysmorphic disorder, metastatic melanoma, trichotillomania, and trigeminal and postherpetic neuralgia.

Drug Interaction

1. Pimozide can potentiate the central nervous system depressant effects of psychotropic drugs, such as alcohol, barbiturates, narcotic analgesics, other antipsychotic medications, and antihistamine.
2. Drugs that may prolong the QT interval should not be coadministered with pimozide; these include TCAs and antiarrhythmic drugs.
3. Diuretics and other drugs that cause hypokalemia may augment cardiotoxic effects of pimozide.
4. Antipsychotic drugs, including pimozide are known to reduce the seizure threshold. Antiepileptic medications may require dosing adjustments when taken with pimozide.

Side Effects

There are many potential side effects of pimozide, including ventricular arrhythmias and extrapyramidal side effects. These effects usually occur with higher doses (e.g. >6 mg/d). Thus, at dermatological doses, they are almost never seen.

EPS

1. Among extrapyramidal side effects, *akathisia i*s the most common. Akathisia is characterized by subjective and objective restlessness. The incidence of akathisia is about 20–40% in patients treated with antipsychotic drugs in general and usually occurs within the first month of treatment. Acute dystonic reactions, usually presenting within the first week of treatment, include dysphagia, ophthalmoplegia, midline muscle cramps, and pharyngeal and lingual spasms. Reduction in drug dose or coadministration of antimuscarinic drugs, such as benztropine or trihexyphenidyl, can counteract dystonia. Diphenhydramine also can be effective in treating akathisia.
2 *Parkinson-like* symptoms, including masklike facies, tremor, cogwheel rigidity, bradykinesia, and postural changes, are extrapyramidal side effects associated with antipsychotic drug use. These symptoms usually occur secondary to dopamine receptor blockade. Generally occurring within the first month, these symptoms can be treated with benztropine or trihexyphenidyl.
3 *Tardive dyskinesia* and tardive dystonia are chronic forms of extrapyramidal side effects. Tardive-dyskinesia is a movement disorder with choreoathetoid movements, including smacking of lips or cheeks, intermittent

protrusion of tongue, chewing movements, uncontrolled movements of arms or legs. It is irreversible in about 50% of those affected and may be exacerbated after a reduction in antipsychotic drug dose or antimuscarinic treatment. Tardive dyskinesia can develop during withdrawal from antipsychotic therapy but generally tends to be self-limited.

Risk factors for this problem include age greater than 50 years, previous experience of severe extrapyramidal side effects, and intermittent dosing of antipsychotic.

4 *Neuroleptic malignant syndrome.* Hyperpyrexia and muscle rigidity are characteristic signs of the neuroleptic malignant syndrome. There is only one report of this syndrome occurring in a patient treated with pimozide. The neuroleptic malignant syndrome is treatable with the calcium-channel blocker, dantrolene.

Cardiovascular System

Pimozide can increase the QT interval, induce T-wave changes, and cause U-wave abnormalities in the ECG of some patients.

Others

In comparison with other antipsychotic drugs, pimozide has less sedation potential. With the exception of mild dry mouth, constipation, and blurry vision, the anticholinergic effects of pimozide are minimal. Menstrual irregularities and galactorrhea also may occur occasionally with this drug.

Monitoring

Antipsychotics are monitored as per Table 14.3.

Table 14.3: Monitoring of antipsychotics

Baseline	*Follow-up*	*Interval*
Weight	Yes	3 m
Body mass index	Yes	3 m
Blood pressure	Yes Specially in elderly	3 m
Fasting glucose >100 prediabetic, >125 diabetic	Yes	3 m
Lipid profile	Yes	6 m
Prolactin level (with risperidone)		

A baseline **ECG** and serial ECGs should be obtained during pimozide use, because of its association with

cardiac conduction abnormalities. Dose increases should be discontinued when the QT interval is greater than 0.47 second or there is a QT interval increase of 25% or more above the baseline. The risk of cardiac conduction difficulties in patients with normal cardiac functioning is *minimal* in those receiving ***less*** than 20 mg/d.

DEPRESSIVE DISORDERS

A general indication for the use of antidepressants/psychopharmaceuticals is recommended to the dermatologist if, during the course of the dermatosis, depressive symptoms are part of or a dominant feature of the skin disease.

Depressive symptomatology can be detected with standard instruments, self-assessment questionnaires, and classic history and mental status examinations. In several dermatologic conditions, mood disorders can be present. Depressive episodes may be part of several mood disorders, and distinguishing the mood disorders to which the depressive episode belongs allows the clinician to implement the appropriate treatment decision. Following the DSM-IV-TR, truly depressive disorders (i.e. major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified) are distinguished from bipolar disorders by the fact that the patient has no history of ever having had a manic, mixed, or hypomanic episode, allowing a more liberal treatment with antidepressants. Major depressive episodes can also be present in bipolar disorders (i.e. bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified). In these cases, treatment with antidepressants can precipitate a manic or hypomanic episode. Therefore, mood stabilizers are the main pharmacological medication, whereas antidepressants need to be used with extreme caution.

Dermatological conditions with possible underlying, concurrent, or reactive depressive episodes are detailed in Box 14.1. Indications for antidepressants in primary psychiatric disorders when depression is underlying or concurrent are given in Box 14.2.

Antidepressants increase the concentration of serotonin and interact usually in the synaptic cleft with the serotonergic and noradrenergic system, which plays a decisive role in not only depression but also in anxiety and compulsive disorders. The classic tricyclic antidepressants amitriptyline, imipramine, and desipramine (Table 14.4) are rarely used in dermatology (with the exception of postherpetic neuralgia) because of their anticholinergic or extrapyramidal side effects.

In the treatment of depression, prescription of SSRIs and, only rarely, tricyclic antidepressants (such as doxepin) is

Box 14.1: Skin disorders with depressive symptoms

Atopic dermatitis
Prurigo diseases
Psoriasis
Alopecia areata
Chronic urticaria
Trichotillomania
Skin-picking syndrome (neurotic excoriations)
Compulsive disorders
Somatoform disorders
Hypochondriacal disorders
Body dysmorphic disorders
Cutaneous dysesthesias
Idiopathic forms of pruritus

Box 14.2: Indication for antidepressants in psychaitric disorders with depression

Delusional parasitosis
Compulsive disorder
Dermatitis artefacta (trichotillomania, acne excoriée)
Impairment of impulse control
Psychogenic pruritus/dysesthesias/pain syndrome—somatoform disorders with depression
Somatization disorders with depression
Body dysmorphic disorders

currently the treatment of choice. The target symptom of the antidepressant is primarily a mood-lightening effect, as well as relief of anxiety, a calming, drive-increasing, or drive-suppressing effect, and a decrease in compulsive disorders. Thus, three different complexes of depressive target symptoms can be differentiated:

1. Anxious agitated symptoms
2. Psychomotor-inhibited disorder
3. Vital impaired mood and somatic disorder.

As the onset of action is delayed, up to ***6 weeks*** may elapse before a mood-lightening effect is observed. The danger of suicide is increased if drive increases before the mood change is effected. The patient can then perhaps muster the energy to attempt suicide, which he or she could not do earlier because of apathy. Extreme caution is required here. Compulsive disorders and other primary psychiatric dermatoses may also be included in the expanded main indications for antidepressants.

Antidepressants

The use of antidepressants in the treatment of depression remains the best-understood medications; however, there is a growing list of other indications for antidepressants including panic disorder (PD), obsessive–compulsive disorder (OCD), bulimia and posttraumatic stress disorder (PTSD).

Table 14.4: Overview of antidepressants

Drug class	*Drugs dosages and salient indications*
MAOIs	Phenelzine
Amine tricyclics (TCAs)	a. Amitriptyline tablets (mg): 25, 50, 75, 100, 150 150 mg b. Imipramine tablets (mg): 10, 25, 50 Capsules (mg): 75, 100, 125, 150 c. Nortriptyline capsules (mg): 10, 25, 50, 75 **(PHN)** d. Desipramine tablets (mg): 10, 25, 50, 75, 100, 150 150 mg e. Doxepin capsules (mg): 10, 25, 50, 75, 100, 150 **(pruritus)**
SSRIs (Selective serotonin reuptake inhibitors)	a. Fluoxetine tablets (mg): 10, 20, 40 **(Less agitation/less drive)** Delayed release capsules: 90 mg b. Sertraline tablets (mg): 25, 50, 100 **(Agitation = lack of drive)** c. Paroxetine tablets (mg): 10, 20, 30, 40 **(More agitation/less drive)** Paroxetine controlled release Controlled release tablets (mg): 12.5, 25, 37.5 40 mg d. Citalopram tablets (mg): 10, 20, 40 e. Escitalopram tablets (mg): 5, 10, 20
Norepinephrien-dopamine reuptake inhibitors	Bupropion tablets (mg): 75, 100 Trazadone
SNRI Serotonin Norepinephrine Reuptake Inhibitors	a. Venlafaxine tablets (mg): 25, 37.5, 50, 75, 100 (Depression, Anxiety) (DALIUM) b. Duloxetine tablets (mg): 20, 30, 60 (**Depression**, anxiety psychosis) (Dulojoy)
Mixed serotonin/ noradrenaline antagonists	Mirtazapine **(Depression + Pain/Pruritus)** tablets (mg): 15, 30, 45
Mixed serotonin antagonist/reuptake inhibitors	Nefazodone tablets (mg): 50, 100, 150, 200, 250

Pharmacology

The first antidepressant was the monoamine oxidase inhibitor (MAOI), iproniazid, initially licensed as an antituberculosis drug. This was soon followed by the tricyclic antidepressant(TCA), imipramine.

A new direction in antidepressant pharmacology began in 1987 with the discovery and marketing of fluoxetine, the first antidepressant selective for serotonin reuptake blockade. Beyond selective serotonin reuptake inhibitors (SSRIs), the latest offerings in antidepressant pharmacology include agents that act at multiple neurotransmitter levels. In evaluations of the many antidepressants available, the focus has generally been on the agent's side-effect profile and ease of administration. Despite many efforts in this area,

there is no conclusive evidence to demonstrate the clinical superiority of any one group of agents.

Mechanisms of Action

All known antidepressants affect monoamine neurotransmision.

MAOIs inhibit the activity of monoamine oxidase, resulting in a decrease in the breakdown of dopamine, serotonin, and norepinephrine in the synapse, thus increasing the amount of these neurotransmitters available for release and synaptic transmission. MAOIs are highly effective antidepressants and anxiolytics but are ***rarely*** used due to dietary restrictions that must be adhered to in order to avoid tyramine-induced hypertensive crises.

TCAs block presynaptic reuptake of norepinephrine(NE) and serotonin (5-HT) to various degrees. Several are related by metabolism; thus, the tertiary amines amitriptyline and imipramine are metabolized to the secondary amines nortriptyline and desipramine, respectively. All act through reuptake inhibition and are generally selective for the norepinephrine transporter; several, however, have equal or greater affinity for the serotonin transporter. Though effective, their ***nonselective actions*** on cholinergic, histaminergic, and presynaptic adrenergic receptors resulted in a number of side effects.

SSRIs were first introduced in the late 1980s, and rapidly eclipsed the TCAs as the drugs of choice for depression. There are subtle differences between compounds, mainly in terms of their half-life, their potency for reuptake inhibition, and their affinity for some other receptors. As SSRIs more selectively affect reuptake, with few effects on the adrenergic, histaminergic, and cholinergic systems, side effects have been reduced.

Several other **second-generation agents**, sometimes referred to as "atypical antidepressants", were introduced during the same period as the SSRIs. These include bupropion, which seems to exert primarily a dopaminergic effect, and trazodone, which is structurally related to the TCAs but has a primary serotonergic mechanism.

The so-called **third-generation antidepressants** include serotonin–norepinephrine reuptake inhibitors (**SNRIs**–venlafaxine, milnacipran and duloxetine), **mixed serotonin antagonist/reuptake inhibitors** (nefazodone and trazodone) and the **mixed serotonin/noradrenaline antagonist** mirtazapine.

SNRIs have equal affinity for the norepinephrine and serotonin transporter. Though, like several of the TCAs, *venlafaxine* has multiple receptor effects, it is relatively *free* of the anticholinergic and antihistaminic side effects that are common with the TCAs.

The **mixed serotonin/noradrenaline antagonist** mirtazapine is unique in that it appears to work primarily through specific receptor blockade of the alpha-2-autoreceptors on presynaptic noradrenergic neurons, enhancing noradrenergic output. This class may exert a similar effect toward autoreceptors on serotonin neurons. Antagonism of 5-HT 2 and 5-HT 3 receptors may also concentrate the effect of serotonin on 5-HT 1A receptors.

Indications

It is primarily used in depression and anxiety disorders

Particularly good efficacy has been described for SSRIs, in addition to depression and compulsive disorders, **dermatitis para-artefacta** with impaired impulse control (trichotillomania, acne excoriée) and other factitious disorders with transition to compulsive symptomatics. SSRIs are also very effective in **body dysmorphic** disorders. There is evidence for slow but continued improvement in symptoms for many months after initiation of treatment; medication should therefore be tried for up to **four** months if the patient shows a partial response.

Obsessive–Compulsive Disorder (OCD)

SSRIs show strong evidence of effectiveness in the treatment of OCD and are considered the first-line treatment option in this disorder; all agents appear equally effective. The recommended starting dose is the same as that for depression, although higher doses (60–80 mg of fluoxetine) may be required for adequate response.

Good efficacy has been reported with fluoxetine, sertraline, paroxetine, fluvoxamine, and escitalopram. The indication and selection of the specific medication in compulsive disorders depends on the desired side effect spectrum of the drug.

Generalized Anxiety Disorder (GAD)

Several agents have shown efficacy in this disorder. Good evidence exists for the use of SSRIs, venlafaxine, nefazodone and mirtazapine. Both TCAs and MAOIs have also shown moderate effectiveness; MAOIs also show efficacy in other anxiety disorders.

Body Dysmorphic Disorder (BDD)

SSRIs have also shown efficacy in the treatment of BDD. It may be at least partially responsive to TCA medications, particularly those selective for serotonin. Moderate evidence exists for the use of MAOIs.

Pain Disorders

It has been known for over 40 years that antidepressants possess analgesic properties independent of their mood effects. Medications that possess both *norepinephrine and 5-HT reuptake* blocking properties are often useful in treating pain disorders. Ascending corticospinal monoamine pathways appear to be important in the endogenous analgesic system. In addition, chronic pain conditions are commonly associated with major depression. **TCAs** continue to be commonly used for some of these conditions, and **SNRIs** are increasingly used. The SNRI ***duloxetine*** was the first antidepressant to secure FDA approval for the treatment of pain associated with **diabetic neuropathy** and **fibromyalgia**. A dose of 40 mg daily has been found to be effective in trigeminal neuralgia.

Other SNRIs, e.g. desvenlafaxine and milnacipran, are being investigated for a variety of pain conditions from postherpetic neuralgia to chronic back pain.

Premenstrual Dysphoric Disorder

Approximately 5% of women in the childbearing years will have prominent mood and physical symptoms during the late luteal phase of almost every cycle; these may include anxiety, depressed mood, irritability, insomnia, fatigue, and a variety of other physical symptoms. These symptoms are more severe than those typically seen in premenstrual syndrome (PMS) and can be quite disruptive to vocational and interpersonal activities. The SSRIs are known to be beneficial to many women with PMDD, and **fluoxetine** and **sertraline** have been approved for this indication. Treating for 2 weeks out of the month in the luteal phase may be as effective as continuous treatment. The rapid effects of SSRIs in PMDD may be associated with rapid increases in pregnenolone levels.

Other Uses for Antidepressants

Antidepressants are used for many other on- and off-label applications.

Enuresis in children is an older labeled use for some TCAs, but they are less commonly used now because of their side effects.

The SNRI *duloxetine* is approved in Europe for the treatment of ***urinary stress incontinence***.

Although serotonergic antidepressants are commonly associated with inducing sexual adverse effects, some of these effects might prove useful for some sexual disorders. For example, SSRIs are known to delay orgasm in some patients. For this reason, SSRIs are sometimes used to treat ***premature ejaculation***. This includes *dapoxetine* and *paroxetine.*

How to Choose an Antidepressant?

The choice of an antidepressant depends first on the indication. Not all conditions are equally responsive to all antidepressants.

The choice of an antidepressant for the treatment of depression rests primarily on practical considerations, such as cost, availability, adverse effects, potential drug interactions, the patient's history of response or lack thereof, and patient preference. Other factors, such as the patient's age, gender, and medical status may also guide antidepressant selection. At present, SSRIs are the most commonly prescribed first-line agents in the treatment of both MDD and anxiety disorders. Their popularity comes from their ease of use, tolerability, and safety in overdose. Other agents, including the SNRIs, bupropion, and mirtazapine, which are also reasonable first-line agents for the treatment of MDD.

1. Older patients are particularly sensitive to the anticholinergic effects of the TCAs.
2. There is some suggestion that female patients may respond to and tolerate serotonergic better than noradrenergic or TCA antidepressants. Women may have slower gastrointestinal absorption than men due to less gastric acid and slower gastric emptying. A woman's volume of distribution differs as well, given her increased ratio of adipose tissue to lean body mass. Water retention associated with the menstrual cycle may also affect the volume of distribution. Oral contraceptives can alter the hepatic metabolism of TCAs.
3. Patients with narrow-angle glaucoma may have an exacerbation with noradrenergic antidepressants, whereas bupropion and other antidepressants are known to lower the seizure threshold in epilepsy patients.
4. Bupropion, ***mirtazapine,*** and nefazodone are the antidepressants with the ***least*** association with sexual side effects and are often prescribed for this reason. The primary indication for mirtazapine is in the treatment of major depression. However, its strong antihistamine properties have contributed to its occasional use as a hypnotic and as an adjunctive treatment to more activating antidepressants.
5. TCAs and SNRIs appear to be useful in the treatment of pain conditions, but other antidepressant classes appear to be far less effective.
6. SSRIs and the highly serotonergic TCA, clomipramine, are effective in the treatment of OCD, but noradrenergic antidepressants have not proved to be as helpful for this condition.

7. Ethnic and racial factors: African-Americans may be more likely than those of European descent to be slow metabolizers of antidepressant due to possible genetic differences in metabolic enzyme expression; a growing number of studies suggest that African-Americans will have higher plasma levels per dose of antidepressant. This has been primarily demonstrated with TCAs; data with SSRIs are lacking. Some data suggest that Asians are slower to metabolize nortriptyline than other groups.
8. Comorbidities patients with renal impairment may require dose adjustment for many antidepressants; ***fluoxetine and sertraline*** appear to be the exception. Liver disease can increase levels of TCAs—blood levels should be monitored.
9. SSRIs are extensively metabolized in the liver and lower doses should be given in hepatic-impaired patients. Nefazodone is not indicated due to association with hepatic injury.
10. Pregnant women and nursing mothers: Clinicians must consider whether the potential benefits of treatment justify the potential risk to the fetus. The risks of untreated depression are well-described, and the risks of medication treatment during pregnancy and lactation are less well known. In general, studies have not shown increases in fetal malformations from antidepressant exposure. Reports of withdrawal syndromes among neonates have led some experts to recommend tapering and discontinuing antidepressants 10–14 days before the mother's due date. Antidepressants are excreted in varying degrees in breast milk, so breastfeeding in antidepressant-treated women should be done with caution.
11. For patients with mixed patterns of ***depression, agitation, and anxiety***, *doxepin* may be the first choice, followed by *paroxetine*, escitalopram, or *venlafaxine*.
12. Overall, antidepressant initial therapy is administered for **2–3 weeks** before an optimal therapeutic dose range is found. Maximal- dose therapy should be administered for 6 weeks before efficacy.
13. The duration of therapy for the first appearance of disease is **6–9 months** on average and 5 years for the first relapse, lifelong with a second relapse.
14. A single dose may be administered if insomnia or sedation occurs as a side effect. If insomnia occurs under medication, the dose should be taken in the morning. If the dominant side effect is fatigue, the entire dose should be taken in the evening.

15. If there is no adequate improvement in symptoms after 4–6 weeks or if pronounced side effects have occurred, a different substance group should be selected as an alternative.

TRICYCLIC ANTIDEPRESSANTS

In addition to their antidepressants and antihistaminic effects, the TCAs have analgesic properties. Of the various uses of TCAs, the applications in dermatologic practice include treatment of pruritus secondary to urticaria and dermatitis with doxepin and postherpetic neuralgia (PHN) with amitriptyline.

Pharmacology

Absorption/excretion: The TCAs are a highly lipid-soluble group of compounds which are absorbed rapidly and almost completely in the gastrointestinal tract. Intestinal absorption is followed by a large first-pass effect in the liver. The first-pass effect is variable among the TCAs, resulting in a great range in bioavailabilities seen with oral administration of these drugs. Hepatic metabolism consists of oxidative demethylation, hydroxylation, and subsequent conjugation of metabolites to make them more water soluble and expedite urinary, biliary, and fecal excretion. The highest level of excretion occurs in the urine.

Peak levels: After absorption, peak plasma levels are reached in 2–4 hours. TCAs are highly protein bound in serum and tissues and poorly dialysable.

Mechanisms of Action

The mode of action depends to a large extent on the receptor specificity of drug (Table 14.5).

Table 14.5: Receptor specificity of antidepressants

	ACh M	*A1*	*H1*	*5-HT2*	*NET*	*SERT*	
Doxepin	2+	3+	3+	1+	1+	1+	Good for pruritus/ urticaria
Nortriptyline	1+	1+	1+	1+	2+	1+	Neuralgia
Fluoxetine						3+	Safe/less side effects
Paroxetine	1+					3+	Safe/less side effects
Mirtazapine			3+	1+	1+		Safe with a potent effect in itch disorders
Venlafaxine					1+	2+	

ACh M, acetylcholine muscarinic receptor; A1, alpha1-adrenoceptor; H1, histamine1 receptor; 5-HT2, serotonin 5-HT2 receptor; NET, norepinephrine transporter; SERT, serotonin transporter

1. TCAs competitively inhibit neuronal NE and 5-HT presynaptic transporters, which results in increased synaptic concentrations of these neurotransmitters. Over time, however, synaptic NE and 5-HT receptors are down-regulated. Downregulation of synaptic amine receptors includes presynaptic receptors responsible for regulating the release of 5-HT and NE.
2. The *antihistaminic* effects of the TCAs, particularly doxepin, have made them useful in treating pruritic conditions often refractory to traditional antihistamines. Doxepin has a 56-fold greater affinity for HI receptor compared with those of hydroxyzine and a 775-fold greater affinity for H1, receptors compared with diphenhydramine. In addition to its blockade of histamine H1, receptors, doxepin antagonizes histamine H2, receptors. Doxepin has 6 times the affinity for H2, histamine receptors compared with cimetidine, an H receptor blocker.
3. The mechanisms of *analgesic* effects of the TCAs are less clear than those associated with its antidepressive and antihistamine effects. The TCAs have been used in the treatment of neuropathic pain, such as occurs in postherpetic neuralgia and diabetic peripheral neuropathy. Hyperexcitability is induced centrally in the dorsal horn of the spinal cord. This central hyperexcitability leads to distribution of the pain beyond the regional pain distribution of the damage nerve. The hyperalgesia associated with neuropathic pain is mediated by NMDA receptor activation and its subsequent cascade of events. It has been shown that amitriptyline is a partial NMDA receptor antagonist; and NMDA receptor modulation also has been suspected in the analgesic effects of studies with imipramine. The most plausible mechanism of analgesia of the TCAs may involve their ability to block voltage-dependent sodium channels.

Adverse Effects

Based on the position of their side-chain amine, TCAs can be separated into two general classes: tertiary amines (e.g. amitriptyline, imipramine, and doxepin) and secondary amines (e.g. desipramine and nortriptyline).

The secondary amines, nortriptyline and desipramine, are active metabolites of amitriptyline and imipramine. Secondary amines produce fewer anticholinergic, neurologic, cardiac, and antihistaminic effects compared with the side effect profile of the tertiary amine. Because TCAs can interact with many different classes of neurotransmitter receptors, they display a variety of untoward effects based on the

receptor antagonized. TCA toxicity is related to dose and depends on the rate of drug elimination. The presence of slow and fast hepatic TCA metabolizers results in the wide range of steady-state TCA plasma levels among different patients taking similar drugs.

Muscarinic: Blurred vision, dry mouth, sinus tachycardia, constipation, induction or aggravation of narrow angle glaucoma cognitive dysfunction. Anticholinergic effects can be especially troublesome in the elderly.

α1-Adrenergic: Postural hypotension, dizziness, drowsiness, reflex tachycardia

Blockade of α,-adrenergic receptors can result in orthostatic hypotension. In healthy individuals without cardiac disease, the incidence of orthostatic hypotension is estimated to be 2% to 3%. The incidence of orthostatic hypotension increases to 50%, however, in patients with heart failure.

Dopamine D2: Extrapyramidal movement disorders

The incidence of extrapyramidal syndromes and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) occurs rarely with TCA use.

Histamine (HI): Sedation, weight gain

Na^+-K^+ channel: Cardiovascular problems, e.g., arrhythmia

The most disturbing effect of the TCAs is cardiac conduction changes. Conduction abnormalities, such as QT prolongation, T-wave inversion, and other ventricular conduction defects, can occur during treatment in patients with a pre-existing cardiac conduction abnormality.

Dermatologic side effects occur occasionally with TCA use, including photosensitivity, papular eruptions, urticaria, petechiae, pruritus, and pathologic sweating. Among the TCAs, amitriptyline is associated most commonly with urticaria.

Special Population

Elderly patients are prone to certain problems associated with TCA therapy not commonly seen in younger patients, including changes in cognition, such as mild confusion, deficits in recent memory, and development of delirium.

Use of TCAs in older patients has been associated with an increased risk of hip fracture.

Monitoring

In the elderly, in patients with cardiovascular disease, and in children, strict monitoring guidelines should be followed.

1. Baseline laboratory studies should include LFT and KFT
2. Cardiovascular assessment, including blood pressure and ECG, should be undertaken to assess potential orthostatic hypotension and cardiotoxicity. The ECG should be performed as a baseline and periodically during treatment.
3. Glaucoma testing and plasma TCA monitoring may be necessary in selected cases.

Doxepin

Spectra (10 mg, 25 mg)

Doxepin is a tertiary amine used in treatment of neurotic excoriations, chronic urticaria, and generalized pruritus. In addition to its antidepressive effects, doxepin exerts strong antihistaminic effects, making it a potent antipruritic agent in urticaria. Although the antipruritic and sedative effects of doxepin occur promptly, the antidepressive effects may take 2 weeks for clinical improvement to be observed. The antidepressant effects of doxepin may be important in dermatologic conditions associated with depression.

Dermatological Uses

Indications of Doxepin

Frequent indications	Prurigo (doxepin is the ideal drug for depressive patients with prurigo) Dermatoses with significant itching (pruritus sine materia) Breaking through the itching–scratching and pain–depression cycles
Other possible indications	Skin-picking syndrome (neurotic excoriations) Disorders of impulse control: ■ Compulsive disorders ■ Anxious-agitated complaint patterns ■ Functional organ complaints ■ Somatization disorders

This drug has a broad indication spectrum: Endogenous, psychogenic, or somatogenic depression with anxious, agitated presentation as well as functional organ complaints resulting from masked depressions, chronic states of pain, and also withdrawal symptoms from sedatives, alcohol, and drugs.

In dermatology, it is suitable for use especially because of its antihistaminergic effect, which is both sedative and antipruritic, making it an effective treatment in pronounced pruritus. Other indications include lichen simplex chronicus in association with a depressive disorder or in cholinergic urticaria because of the intensive H1 antihistamine effect. Doxepin is capable of successfully breaking through the itching–scratching and itching–depression cycles as well as

an existing pain–depression cycle in depressive patients. In agitated depression, the sedation may be a desired side effect in defining the indication.

In urticaria, it is an excellent adjunct as it blocks both H1 and H2 receptors, even though some experts advise updosing of 2nd generation antihistamines, it must be pointed out that this is **not** a FDA approved indication and unlike allergic rhinitis where the foremost concern is lack of sedation, in urticaria the patients have difficulty in sleeping, thus it makes sense to give doxepin which has a sedative potential.

Dosages

Doxepin usually is started with low doses and titrated upward.

Initial dose: The initial dose is usually **25 mg** at bedtime with 25-mg dose increments every 5–7 days until the therapeutic range of 100 to 200 mg at bedtime is achieved. Dose titration every 5–7 days is based on the 5- to 7-day period needed for serum doxepin levels to reach equilibrium.

In most dermatological conditions **10 mg/day** is a good starting point in most indications and causes less sedation For pruritus, the effective dose usually is in the range of 10–100 mg. Initial doses of 10 mg/d may be indicated in the elderly.

Special Considerations

There is great individual variability in plasma concentrations seen in patients taking similar doses of doxepin. If a patient fails to respond to usual doses of doxepin, serum doxepin levels can be obtained.

Adverse Effects

Sedation, malaise, orthostatic hypotension, weight gain, and anticholinergic side effects, such as dry mouth may occur and sometimes lead to discontinuation by the patient.

Particular attention must be paid to a possible cardiac repolarization impairment. An ECG should be performed prior to therapy to control prolonged QT intervals and also later to record arrhythmias under doxepin.

The dermatologist should not undertake doxepin therapy if the patient has a history of manic-depressive disorders, but should use an alternative medication or request a liaison consult. There is a risk of suicide and overdosing.

Amitriptyline and Nortriptyline

Sensival (Nortriptyline)

Tryptomer (Amitriptyline 25 mg, 75 mg) SR (50 mg)

Libotryp: (Amitriptyline 12.5/25 mg + Chlordiazepoxide)

Amitriptyline has been a popular treatment for neuropathic pain syndromes, including PHN and painful diabetic neuropathy. In dermatology, it is suitable for use in *cutaneous pain syndromes* such as glossodynia and postherpetic neuralgia as well as other cutaneous sensory complaints including burning, stabbing, biting, or tingling.

Dosages

Amitriptyline

10–25 mg/d and increased by 10–12.5 mg/d every 2–5 days to a daily dose of approximately 75 mg. Not all patients with PHN respond to amitriptyline therapy.

Nortriptyline

Start with 10 mg/d in patient older than over age 65 and 20 mg/d in patients younger than age 65. The dose should be increased by 10–20 mg/d/week till appropriate relief is experienced or intolerable side effects appear.

PHN

Amitriptyline is useful in a dose of 12.5–150 mg/d with an average daily dose of 65 mg/d. Similar analgesic effects were found in amitriptyline and nortriptyline and thus as the two are equally efficacious in treating pain, the attenuated side-effect profile associated with nortriptyline use favours its use.

Amitriptyline may *prevent* PHN in patients with acute herpes zoster. A dose of 25 mg suffices and can reduce PHN in 50–75% of patients.

In those who do not respond, other TCAs have shown some efficacy in relieving pain in PHN which includes desipramine and maprotiline can relieve the pain in PHN patients.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The SSRIs were developed to offer antidepressant therapy without the side effects seen commonly with TCAs and monoamine oxidase inhibitors (MAOIs). As with all antidepressants, SSRIs are highly lipophilic. The popularity of SSRIs stems largely from their ease of use, safety in overdose, relative tolerability, cost (all except escitalopram are generically available), and broad spectrum of uses. They are the preferred drug for most psychodermatological disorders (Boxes 14.1 and 14.2) and as can be seen in Table 14.4, they can have multiple actions and can help in various other psychiatric disorders.

Pharmacology

They undergo extensive hepatic metabolism and have half-lives of 18–24 hours. Fluoxetine is an exception because norfluoxetine, an active metabolite of fluoxetine, has a half-life of 7–15 days. The long half-life of norfluoxetine results in a longer period required for eliminating the drug. All SSRIs are excreted in the urine as inactive conjugated metabolite Each drug in this group exhibits high affinity for the neuronal serotonin 5-HT transporter. Despite the high specificity for the 5-HT transporter, the SSRIs have low affinities for other neurotransmitter receptors.

An overview of common drugs in the dose is given below as ready reckoner.

1. Fluoxetine (Fludac 10, 20, 60 mg)

Indication: Depression, compulsive disorder.

Dose: Fluoxetine should be started at a dose of 10 mg daily, followed by slow adequate dose finding. A higher dose is often necessary in compulsive disorders. Fluoxetine leads more often than the other SSRIs to cause *anxiety disorders and insomnia*.

2. Paroxetine (Pari CR 12.5,25,37.5)

Indication: Depression, compulsive disorder, panic, generalized anxiety disorder, and sociophobia, as well as post-traumatic stress disorders. Paroxetine is well tolerated.

Dose: The dose in depression is 20 mg/day; in compulsive disorders, it is often 50 mg/day.

3. Sertraline

Indication: Depression

Dose: Sertraline (daily dose 25–200 mg) increases activity less than fluoxetine does and is less sedating than paroxetine.

4. Escitalopram

Indication: Depression, panic disorder, interferon alpha-induced depression (malignant melanoma). Escitalopram is especially effective for concurrency of a depressive disorder and a panic disorder.

Dose: The dose is 10–30 mg daily.

Clinical Uses in Dermatology

The SSRIs are drugs of first choice in the treatment of a variety of psychiatric disorders, including major depressive disorder, general anxiety, and obsessive-compulsive disorder (OCD). Many of these conditions are associated with *cutaneous* manifestations. These include body dysmorphic disorders, dermatitis artefacta, excoriated acne, neurotic excoriations, and trichotillomania.

The selection of the right SSRI depends on the desired side effect and thereby primarily on the ratio of agitation to lack of drive. Three groups can be differentiated:

A. Less agitation/more lack of drive
- Therapy option: stimulation ++
- First choice: escitalopram , *fluoxetine* (Fludac)

B. Agitation equals lack of drive
- Therapy option: little sedation, little increase of drive
- First choice: *sertraline* (Sertil)

C. More agitation/less lack of drive
- Therapy option: sedation ++
- First choice: *paroxetine* (Pari-CR)

1. OCD

SSRI doses in OCD spectrum of diseases may be higher than doses needed in treating depression or anxiety. SSRIs used in OCD may take 8 weeks to work; maximal responses could take 20 weeks. To avoid sedation the drug should be taken at bedtime. Taking the drug with meals may help to decrease gastrointestinal discomfort.

2. Psychogenic excoriations

Fluoxetine: 15–20 mg X 6 weeks (max dose 80 mg/d)
Sertraline 25–50 mg/d of sertraline, titrating to doses of 100–200 mg/d.

3. Body dysmorphic disorder

Fluoxetine 50 mg /day.

If a patient fails with one SSRI, he or she may respond to another drug in the same class or by augmentation with the anxiolytic buspirone or the antipsychotic drug pimozide. Pimozide also has been used in clomipramine resistant or SSRI-resistant body dysmorphic disorder, particularly of the severely delusional type.

4. Raynauds phenomenon

Fluoxetine (20–60 mg/day) has been compared with nifedipine and found to be equally effective as treatment for primary or secondary Raynaud's phenomenon.

5. Pruritus

Pruritus associated with malignancies: Paroxetine (20 mg/d), sertraline (75-100 mg/d).
Cholestatic/Drug induced pruritus: Sertraline (75–100 mg/d)
Nocturnal pruritus: Mirtazapine (15–45 mg).

6. Trichotillomania

Although the SSRIs are inconsistent in treating trichotillomania, evidence that they help in some individuals coupled with a good side-effect profile makes them reasonable drugs to use. Serotonin reuptake inhibitor augmentation is by using the antipsychotic drugs pimozide, and risperidone.

Drug Interactions

The SSRI class of drugs is associated with numerous drug interactions, which depend on the specific SSRI involved.

1. Citalopram has the *lowest* potential of such interactions among the SSRIS.
2. Fluoxetine increases level of alprazolam, phenytoin, diazepam, carbamazepine.
3. Paroxetine is a potent inhibitor of CYP2D6.
4. Similar to citalopram, *sertraline* is reported to have few drug interaction.

Side Effects

In contrast to the TCAs, SSRIs usually do not cause orthostatic hypotension, are less likely to elicit anticholinergic effects, and are safe in the treatment of depression in patients with heart disease.

a. Common

Nausea, headache, nervousness, insomnia, fatigue, and sexual dysfunction.

The sexual dysfunction associated with SSRI use includes decreased libido, ejaculatory delay, and anorgasmia. In this case, the antidepressant group should be changed; for example to non-SSRIs, or to supplementary therapy with peripherally active substances, such as the phosphodiesterase inhibitors sildenafil and vardenafil.

Weight loss from decreased appetite is seen in some patients, particularly in those who are obese.

b. Rare

EPS

These include parkinsonian movements, restlessness, and dystonic reactions, but are seen infrequently with SSRI use.

SIADH

SIADH, especially in the elderly is diagnosed by repetitive serum sodium level determinations. The symptoms of SIADH include weight gain, lethargy, and delirium.

Risk factors for SIADH secondary to SSRI use are age greater than 65 years, concomitant use of diuretics, and smoking. If antidepressant-induced SIADH is encountered, discontinuation of the drug and reinitiation at a lower dose is possible. Alternatively, switching to another antidepressant may be indicated.

Withdrawal Syndrome

This is characterized by flu-like symptoms, such as dizziness, nausea, paresthesias, tremor, anxiety, and dysphoria. This syndrome typically occurs within 1 week of stopping the drug. The withdrawal syndrome can be minimized by tapering the dose gradually; it is less likely to occur with fluoxetine because of the longer half-life of its active metabolite, norfluoxetine, which allows for a self-tapering effect.

NON-SSRI DRUGS

A group of antidepressants comparable with respect to indication and efficacy to the SSRIs are the non-SSRIs; a heterogeneous group of medications that may lead the way in the future because of their more specific mode of action.

The main ***advantage*** may lie in a better side effects spectrum with respect to lack of impairment of sexual function. However, the sometimes pronounced ***weight gain*** may be a disadvantage.

1. Mirtazapine

Mirtazapine is an antidepressant that antagonizes presynaptic $\alpha 2$-adrenergic auto- and heteroreceptors that are responsible for controlling the release of norepinephrine and serotonin (5-HT). It is also a potent antagonist of postsynaptic 5-HT 2 and 5-HT 3 receptors. Mirtazapine is also a potent H1 antagonist, which is associated with the drug's sedative effects.

This unique mechanism of action preserves antidepressant efficacy but minimizes many of the adverse effects common to heterocyclic antidepressants and SSRIs. Mirtazapine, like bupropion, is one of the few antidepressants *not* commonly associated with sexual side effects. It has a tetracyclic chemical structure and belongs to the piperazino-azepine group of compounds.

Pharmacology

Mirtazapine has an onset of clinical effect in 2–4 weeks, similar to other antidepressants. It has an elimination half-life of 20–40 hr, allowing once-daily administration at bedtime.

Dosage

PO for depression **15** mg/day at bedtime initially, increasing at 1–2-week intervals to a maximum of **45** mg/day.

Indication

Single case reports show good efficacy in patients with glossodynia. In general, it appears to be the antidepressant of choice in depression with the presence of significant physical pain. Mirtazapine is the only non-SSRI drug that has been used as an *antidepressant, anxiolytic, and antipruritic agent.* Of note, all the previously mentioned psychotherapeutic medications have a period of "therapeutic lag" of as long as 2–4 weeks before their effect is evident.

a. Pruritus

Medications that can be used to treat pruritus with comorbid depression and/or anxiety include selective serotonin reuptake inhibitors (SSRIs), noradrenergic selective serotoninergic antidepressant (NaSSA) and tricyclic antidepressants (TCAs). The SSRI antidepressants and anxiolytics that have been used to treat pruritus consist of paroxetine, sertraline, fluvoxamine, and fluoxetine. The use of TCAs, namely amitriptyline and doxepin, in psychiatry is limited nowadays in view of the better efficacy and safety profile of the SSRIs.

Adverse Reactions

Sedation, increased appetite, and weight gain are the most frequent side effects. Sedation is most frequent at lower doses (15 mg) and decreases in frequency with increasing dosage. Although two cases of agranulocytosis occurred in clinical trials, no specific or additional blood count monitoring is required.

Mirtazapine has minimal cardiovascular and anticholinergic effects and essentially lacks adverse GI effects, insomnia, and sexual dysfunction.

Mirtazapine is a substrate for several CYP450 enzymes including 2D6, 3A4, and 1A2. Consequently, drugs that inhibit these isozymes may raise mirtazapine levels. However, mirtazapine is not an inhibitor of these enzymes.

The sedating effects of mirtazapine may be additive with those of CNS depressants such as alcohol and benzodiazepines.

2. Venlafaxine

Venlafaxine (Dalium) is a selective serotonin/noradrenalin reuptake inhibitor (SNRI) in this group, which is nonanticholinergic and nonsedating.

Indication

Venlafaxine is an antidepressant for treatment of depression and accompanying *anxiety disorders and agitation*. Apart from doxepin, a therapy attempt can be made with venlafaxine as second choice, with good efficacy in patients with such mixed disorders. Venlafaxine is one of the newest serotonin antagonists and noradrenalin reuptake inhibitors and has an antidepressant effect comparable to the SSRIs.

Dose

The dose should begin at 37.5 mg or one half tablet and can be increased at 3-day intervals to 150–225 mg/day (Dalium 25,37.5,75 mg)

Side Effects

Venlafaxine has a favorable side effect spectrum. Most frequent are nervousness, hypertension, and insomnia. Impaired sexual function reportedly occurs in only 10% of treated patients. Concurrent administration with MAO inhibitors is contraindicated.

ANXIETY AND PANIC DISORDERS

Anxiety disorders are characterized by excessive worry, tension, agitation, and restlessness, which may be treated by psychotherapy, pharmacotherapy, or combination therapy of psychotherapy with psychopharmaceuticals.

Tranquilizers are medications that, in their target symptoms, relieve anxiety and tension and also have sedative and sleep-promoting effects. When used as an anxiolytic, the other properties are considered desired side effects (sedation) or undesired side effects (concentration impairment).

The transition from anxiolytic to hypnotic (sedative) is usually fluid and dose dependent and also depends on half-life. The speed at which an active metabolite becomes available is decisive for the profile of action. The tranquilizers primarily include substances in the groups of benzodiazepines, nonbenzodiazepines (buspirone), plant-based sedatives, and low-strength neuroleptics.

In defining the indication for therapy of anxiety disorders, differentiation must be made in the first place between transient, brief, stress-related anxiety disorders and chronic anxiety disorders. Chronic anxiety disorder must be distinguished from a transient anxiety disorder (lasting up to a few weeks) or an acute panic attack in defining the indication for drug treatment.

Also in selecting the psychopharmaceutical, the habituation potential must be taken into account if long-term therapy is planned.

BENZODIAZEPINES

Benzodiazepines are used in anxiety disorder—both generalized anxiety disorders as well as acute anxiety disorders and panic disorders. Whether the effect of the benzodiazepine is anxiolytic, sedating, or sleep-inducing depends largely on the dose administered. Diazepam is a good lipid-soluble medication that is quickly absorbed and thus can develop its efficacy rapidly in acute anxiety disorder.

The benzodiazepines are differentiated on the basis of their efficacy (potency) and half-life (Table 14.5.) Benzodiazepines with longer half-lives should be used especially in persistent states of excitation in order to prevent recurrence between doses. Benzodiazepines with shorter half-lives are primarily used for sleep disorders.

When benzodiazepines are withdrawn, real withdrawal symptoms may occur, with primarily vegetative symptoms including convulsions and psychotic episodes. These must be distinguished from the rebound phenomenon (restlessness, anxiety, insomnia). Due to a tolerance development with reduced efficacy at the same dose, there may be a recurrence of the initial symptoms that originally led to the medication's use. Other side effects are erectile dysfunction, reduced, libido, impaired concentration, inability to drive, alcohol intolerance, and paradoxical excitation, especially in the elderly with brain-organic diseases.

1. Alprazolam

Stresnil (Melatonin 3 mg, Alprazolam 0.25 mg/0.5 mg)

Indication: Anxiety disorder; states of tension and excitation, such as in acute stress-dependent hyperhidrosis. Alprazolam often produces an antidepressive effect.

Dose: Alprazolam 1–2 mg/day. For dermatological patients with generalized anxiety disorders, lower initial doses are often sufficient.

Side effects: Due to the *addiction* potential, use should be limited to 3–4 weeks. The medications are also taken by drug addicts and have an addiction potential.

2. Diazepam

Indication: Rapid efficacy in immediate treatment of acute anxiety or panic disorders, especially in intravenous administration. Diazepam (Valium) has a half-life of 20–40 h and thus also has good efficacy in chronic anxiety and states of excitation.

Dose: Diazepam 5–20 mg/day.

Side effects: Because of the *addiction* potential, use should be limited to 3–4 weeks.

NONBENZODIAZEPINES

Buspirone

Buspin 5 mg/10 mg

Indication: If drug therapy should be required in treatment of anxiety disorder for more than 4–6 weeks, nonbenzodiazepines should be used, for which buspirone (Buspar) is the first choice. This is a partial serotonin 5-HT receptor agonist and D2 blocker, which permits safe long-term therapy with sufficient anxiolytic effect and little sedative effect.

Advantage: Hardly any withdrawal symptoms or habituation

Disadvantage: Late onset of effect.

Dose

It must be remembered that buspirone shows a therapeutic effect only after 2 weeks. This is a problem in the case of acute anxiety symptoms. The buspirone dose of 5 mg should be administered three times daily, and a maximum of 60 mg/day (mean dose 30 mg/day) should not be exceeded.

Side Effects

Usually there are only mild side effects such as headache and nausea.

Hypnotics

In some cases, insomnias are predominant in the complaint symptoms of depressive or anxiety disorders. In certain patient groups, hypnotics may show sufficiently good therapeutic success. The habituation potential must be kept in mind.

Hypnotics from the group of nonbenzodiazepines, such as zolpidem, should be used as therapy of first choice. The hypnotics of second choice are mostly benzodiazepines with a short half-life in order to induce sleep but avoid drowsiness the following morning. Brotizolam, temazepam, nitrazepam, and lormetazepam, which should be used only for short times, belong to this group (Table 14.6).

Miscellaneous Drugs Useful in Anxiety Disorders

As an alternative to buspirone, doxepin and paroxetine can be used in anxiety disorders.

1. Doxepin for treatment of chronic anxiety disorders, whereby usually 50 mg or less per day is administered.

Table 14.6: Overview of anxiolytic drugs

Short- to middle-acting benzodiazepine	Lormetazepam	HL 8–12 h	1 mg/day	Impaired sleep with frequent waking periods and trouble falling asleep again
	Brotizolam	HL 4–9 h	0.125–0.25 mg/day	Trouble falling asleep and sleeping through the night
Middle-length benzodiazepine	Alprazolam	HL 10–14 h	1–2 mg/day initial dose 3–4 times 0.125–0.25 mg/day	Acute and chronic states of tension, excitation, and anxiety Additionally, low antidepressant efficacy
	Lorazepam	HL 12–15 h	1–5 mg/day	Short-term treatment of anxiety, tension, excitation, and sleep impairments, especially in the presence of other somatic diseases
Long-acting benzodiazepines	Diazepam	HL 20–40 h	5–20 mg/day	Acute and chronic states of anxiety, tension, and excitation
Nonbenzodiazepine	Zolpidem	Different agonist of the GABA Receptors HL 2–3 h	8 mg/day	Short-term treatment of insomnias (trouble falling asleep)
	Buspirone	HL 2–3 h Late onset of action after 2–4 weeks	5–30 mg/day	Chronic anxiety Inner restlessness States of tension

Doxepin is nearly as effective as diazepam but without the corresponding side effect spectrum.
2. Paroxetine can be used as another attempt, at a dose of 20–50 mg/day.
3. Doxepin should be preferred for patients with mixed presentations of anxiety and depression, or a therapy attempt can be made with venlafaxine.
4. **Beta-blockers:** Beta-receptor blockers do not belong to psychopharmaceuticals in the actual sense, but they show very good efficacy in vegetative symptoms of psychiatric disorders, especially anxiety disorders. Their advantage lies in a lack of central nervous system (CNS) side effects such as Impaired concentration and sedation.

Indications: Flushing and sweating are among the special indications and migraine, hypertensive crises, hyperventilation and respiratory distress, feeling of constriction in the chest, tremors, muscular tics, feeling of weakness, and nausea and vomiting. Special use can also be justified in so-called stage fright. Beta-receptor blockers such as propranolol or oxprenolol may be helpful in situational anxiety (such as fear of examination).

Dose: Often, 10–20 mg propranolol is sufficient.

Caution is required in known heart disease, asthma, and allergies (wasp sting allergy); these conditions are thus possible contraindications, and side effects, including erectile dysfunction and reduced reaction capacity, must be taken into account.

BIBLIOGRAPHY

1. Antidepressant Agents: Basic and Clinical Pharmacology. 11th Edn. New delhi. Tata McGraw Hill.
2. Drug Therapy of Depression and Anxiety Disorders. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th ed.
3. Handbook of Psychiatric Drugs Jeffrey A. Lieberman and Allan Tasman © 2006 John Wiley & Sons, Ltd. ISBN: 0-470-02821-1.
4. Harth W, Gieler U, Tausk FA, Kusnir D. Clinical Management in Psychodermatology. Springer-Verlag Berlin Heidelberg. 2009.
5. Lorenzo CR, Koo J. Pimozide in dermatologic practice: a comprehensive review. Am J Clin Dermatol. 2004;5(5):339-49. Review.

15

CHAPTER

Nutritional Supplements

Kabir Sardana

INTRODUCTION

For some dermatologic diseases which are chronic with no definitive cure, patients often try alternative treatments to prevent onset, reduce symptom severity, or prevent reoccurrence of a disease. Dietary modification, through supplementation and exclusion, is an extremely popular treatment modality for patients with dermatologic conditions. It is, therefore, important for dermatologists to be aware of the growing body of literature pertaining to nutrition and skin disease to appropriately inform patients on benefits and harms of specific dietary interventions.

Herein I address the role of nutrition in alopecia psoriasis, atopic dermatitis, urticaria, and bullous diseases and specific dietary modifications as an adjunct or alternative to conventional therapy. This is followed by a focus on common nutritional supplements in dermatology.

NUTRITIONAL AGENTS AND ALOPECIA

The role of various nutritional supplements in alopecia has been based on studies in malnutrition and in apparently normal people they may not have a role. Also a large number of studies have been done on mice, dogs and shep. But it must be understood that in a large number of individuals various fad diets and eating habits may predispose them to nutritional defects that may affect the hair growth. Though ferritin levels as a surrogate marker for alopecia has been hotly debated, most experts give it credence, and I use a >30 μg/L cut off to intervene, though some use a cut off of 10 μg/L.

Supplying sufficient nutrients to microorgans such as the hair follicle and sebaceous glands is as important as acquiring the nutrients. The long and winding road to the skin and hair starts with ingestion, digestion, and absorption of nutrients. Hair growth and maintenance are in part linked to vitamin B and folate assimilation through the gastrointestinal tract. Hair growth potential is optimum when specific parameters for biochemical variables such as red blood cell (erythrocyte) generation are in place. These include erythrocyte and serum

folate concentrations within the normal range, serum vitamin B_{12} levels of 300–1,000 ng/L, hemoglobin levels >13.0 g/dL, and serum ferritin concentrations of 70 ng/mL (Rushton 2002). Here it is important to note that excessive levels of vitamins can itself hamper iron absorption and levels of vitamin B_{12} (ng/L) >1500 and folic nmol/L >45 can actually cause alopecia (Rushton 1990). A study that is rarely quoted is pertinent which exammed the various factors and evaluated total proteins, calcium, copper, iron, iodine, magnesium, manganese, phosphorus, potassium, selenium, zinc, omega 3 and omega 6. A control group matched for age, gender and metabolic profile was established. On multivariate analysis, only a *protein* intake was directly associated to alopecia, odds ratio of 1.5 (1.06–2.3) p = 0.02. Significantly this may be more important than the vitamin (El Fékih N) in the diet.

We will now address the main nutrients implicated in hair loss and discuss their role, though it must be appreciated that the effect on alopecia depends on multiple androgenic and genetic factors and the role of nutrients is largely restricted to chronic telogen effluvium (CTE).

Iron

Women can develop alopecia from iron deficiency as the result of the blood loss that occurs in delivery that can add to postpartum alopecia. Nevertheless, alopecia in women can also be a consequence of decrease in iron reserves. This is not uncommon in women that have heavy menses and do not eat red meat or have vegetarian diets (Olsen EA). When iron deficiency develops, the synthesis of ferritin by the liver ceases.

Ferritin that was located in growing follicles is released to serum to support other organ function, such as the bone marrow. As a consequence of this loss of ferritin, the follicles go into telogen phase. Ferritin levels less than 40 ng/mL (90 pmol/L) are associated with an increase of telogen phase. When the levels are between 40 ng/mL and 70 ng/mL (90 and 156 pmol/L), an excess of telogen hair loss is also observed (Olsen FA). Only when serum levels are greater than 70 ng/mL the hair is in normal anagen phase. Other authors paradoxically have confirmed that low serum levels of ferritin have an influence in female androgenetic alopecia (FAGA) and in alopecia areata but *not* in telogen effluvium or total or universal alopecia areata (Kantor).

In India, its my opinion that iron levels have a heightened importance because of the large number of patients who have a vegetarian diet and thus are iron deficient, as non-heme iron has a poor absorption. Women with sideropenic anemia need iron, but it also will be necessary in the treatment of female pattern hair loss (FPHL) in women on a vegetarian diet.

Amino Acids

The amino acids *proline* and *lysine* along with *ascorbic* acid from the diet are linked to a healthy dermis, where hair follicles reside. With increased age, dermal proteins (collagen and elastin) begin to degrade. Ascorbic acid is a water-soluble vitamin that acts as a reducing agent required for synthesis of healthy collagen fibers through hydroxylation of proline and lysine. More commonly, it protects the body against damage caused by free radicals.

The bioavailability of *L-lysine* is restricted primarily to *meat, fish, and eggs;* consequently reducing the consumption of these foods could result and in a negative balance. While the body could make up any shortfall from the muscle reserves, it could arguably prioritize their availability for the essential tissues leaving nonessential tissue such as scalp hair compromised. Adding the essential amino acid L-lysine (1.5–2 g/day) to their existing iron supplementation resulted in a significant ($P < 0.001$) increase in the mean serum ferritin concentration (Rushton 2002a). This highlights the importance of serum ferritin levels in regard to hair loss and the role of L-lysine. As previously mentioned in women without systemic inflammation or other underlying disorders, serum ferritin levels <30 ng/mL are strongly associated with telogen hair loss (Moeinvaziri 2009).

Taurine 150 mg was said to improve hair density (Collin, C). Another preparation (Innéov Lab) containing taurine (75 mg), polyunsaturated fatty acids (omega-3 plus omega-6 195 mg), vitamins C (15 mg) and E (2.5 mg), lycopene (0.5 mg), plant polyphenols (140 mg), and zinc (7.5 mg) was recently used for the treatment of hair loss. Compared to placebo, hair loss was considerably reduced and hair density and quality increased.

The other amino acids, have not been linked to alopecia, even though most companies extol their virtues and debate on their finer aspects in their pharmaceutical discourses. This includes *cystine* and *cysteine* which may help in nail maturation, but *not* in hair loss.

Gelatin

Gelatin is produced by acid hydrolysis of collagen, the main sources of which are dermis, tendons, and bones. More than half a century ago, it was suggested that large amounts of gelatin increase the cystine content of nails, which may reflect keratin formation and cross-linking. Gelatin contains 84–86% of protein and 2–4% of mineral salts. It is rich in glycine (24%), proline (14%), and hydroxyproline (10%), but *poor* in essential and particularly in sulfur-containing amino acids: cystine <0.1%, methionine <1%. However, hair and

nails do not contain collagen or gelatin, thus its role in hair loss is debatable.

Botanical Antiandrogens

One of the primary enzymes involved in androgen metabolism is 5α-reductase, which converts testosterone to dihydrotestosterone. The latter is biologically active on androgen-sensitive hair tissue. Interestingly, there are a number of commonly used food/herbal products that have 5α-reductase properties. Green tea and Saw Palmetto are two such products.

Green tea catechins have been demonstrated to inhibit testosterone conversion (Hiipakka, 2002). Flavonoids from natural products that are potent inhibitors of the *type 2* 5α-reductase include *myricetin, quercetin, baicalein, and fisetin*. *Biochanin A*, *daidzein, genistein, and kaempferol* (Hiipakka 2002).

Fats and Essential Fatty Acids

Dietary fats and fatty acids have been shown to modulate skin especially in hyperinflammatory conditions such as eczema and atopic dermatitis (Boelsma 2001). In particular, the consumption of omega-3 and omega-6 fatty acids for the management of inflammation is well documented (Fu et al. 2001).

Importantly the omega-6 essential fatty acids (EFAs) is derived from linoleic acid and present in vegetables and red meat; and the omega-3 EFAs derived from alpha-linolenic acid and present in oily fish and marine animals. The ideal ratio should be 5 : 1 (linoleic : alpha-linolenic acid). In unresponsive scaling dermatoses including that of the scalp problems it might be worth considering trying an EFA supplement if the subject's diet is low in fish oil or red meat; unfortunately, there is no routine investigation available to assess this. Though a leading brand in India has used Borage oil, there is no documented published literature of this helping in alopecia.

Trace Elements

Trace element nutrition is the most studied aspect of hair as it relates to nutrition. Zinc, copper, magnesium, and selenium have been examined for their effects on hair biology. In alopecia areata, *serum zinc* levels are significantly ***decreased*** in subjects who are resistant to standard treatment when compared to control subjects. Of particular note, copper and magnesium levels were elevated in this study but not significantly (Bhat 2009).

Zinc is an essential micronutrient for human metabolism; it is a cofactor for more than 100 enzymes, facilitates protein

folding, and helps regulate gene expression. Manifestations of zinc deficiency in the skin include nail dystrophies and hair abnomalities. It should be noted that zinc level determination is controversial, and many factors play into an inaccurate zinc level determination in hair—mainly the use of zinc pyrithione in shampoos. Additional studies examining the role of trace elements in alopecia found that there are statistically significant differences in the serum copper content in alopecia areata and alopecia universalis patients (Mussalo-Rauhamaa 1986). *Copper* is the key mineral in an enzyme called lysyl oxidase, which participates in the cross-linking of elastin fibers in the dermis. A combination of collagen and elastin is essential for tissues such as blood vessels and for a functional matrix in the dermis. It should be noted that with most trace elements megadoses inhibit the very biology they are supposed to assist. Thus is the case with *selenium.* High doses of ingested selenium have been documented to have adverse effects in natural killer cell activity, hepatotoxicity, gastrointestinal disturbances, and nail and hair loss.

In clinical practice, though the true frequency of mineral deficiency, like Zn, in women with CTE in the UK is around 0.5% and much lower than previously thought. Correcting Zn deficiency may not resolve CTE (Rushton 2002). If the level of zinc is equal to that of iron then iron uptake is significantly decreased, thus a ratio of 3 : 1 (Fe : Zn) is desirable to prevent competitive interference. One should therefore be alert to patients taking excessive amounts of nutritional supplements. In such individuals, elevated red cell folic acid concentrations are found where folic acid is present in their supplementation regimen.

Vitamins

Symptoms of *biotin* deficiency in skin include dermatitis and hair loss (Zempleni 2008). Biotin is one of the most widely used vitamins for hair as it is said to promote healthy hair growth and protect against dryness presumably through long-chain fatty acid incorporation into the cuticle, but sufficient evidence is lacking. It also increases the elasticity of the hair's cortex, preventing breakage. One reason to believe in this action comes from the effect of biotin on fatty acid metabolism. Biotin is a cofactor for acetyl-CoA carboxylase, which catalyzes the rate-limiting step in fatty acid elongation (Zempleni 2008).

Interestingly *vitamin B_{12}* levels may be low in patients taking CPA (cyproterone acetate). In women being treated with oral CPA and EE 2, concurrent oral vitamin B_{12} supplementation (100–200 μg/day) maintained serum B_{12} concentrations above 300 μg/L. Assessing the vitamin B_{12} concentration before starting CPA therapy with subsequent

follow-up at 4 months is advisable. In the diet, vitamin B_{12} is only found in meat, chicken, fish and eggs.

Phytoestrogens

Phytoestrogens are plant compounds that are structurally and functionally similar to mammalian estrogens. The 3 main classes found in the human diet are isoflavones (daidzein, genistein, and glycitein), lignans (enterodiol and enterolactone), and coumenstans. The primary food sources of **isoflavones** are *soy and soy products*, and sources for **lignans** *are cereals, flaxseed, and berries*. Plasma concentrations of phytoestrogens in Europeans are low compared with Asian populations.

Soybean proteins have been used in East Asia for centuries. Women working in soy-processing factories were known for their silky and light skin, which was thought to be due to the high amount of soy phytoestrogens. Also the hair quality was believed to be improved by soy. This has recently been supported by another mechanism of soy ingredients, an anti-alopecia activity of the immunostimulatory soy peptide soymetide-4. This effect is probably due to prostaglandin E2 (PGE_2), which is produced after activation of COX by soymetide-4 and might suppress apoptosis of hair matrix cells and etoposide-induced alopecia by activating NF-kappaB (Tsuruki T).

Conclusion

There are numerous compounds that have been used for hair loss some which are healthy, like pumpkin seed oil and green tea and some which have no proven utility like, silicon, selenium, fluorides and Gingko biloba. A common practice by many looking to correct nutritional deficiencies is to supplement for what is believed to be a loss of critical nutrients. Excessive intake of nutritional supplements may cause hair loss and are not recommended in the absence of a proven deficiency (McLaren 1993).

Apart from *Iron, L-lysine, protein and possibly soy extract*, little in vivo human data exists for the rest of the agents used for hair loss. Thus more research directed at the biological aspects of hair growth will be needed to unlock the secrets behind the role of nutrition in hair growth.

BIBLIOGRAPHY

1. Bhat YJ. Trace element levels in alopecia areata. Indian J Dermatol Venereol Leprol. 2009;75(1):29-31.
2. Collin C, Gautier B, Gaillard O, Hallegot P, Chabane S, et al. Protective effects of taurine on human hair follicle grown in vitro(1). Int J Cosmet Sci. 2006;28:289-98.

3. El Fékih N, Kamoun H, Fazaa B, El Ati J, Zouari B, Kamoun MR, Gaigi S. [Evaluation of the role of dietary intake in the occurrence of alopecia]. Rev Med Liege. 2010;65(2):98-102.
4. Hiipakka RA. Structure-activity relationships for inhibition of human 5alpha-reductases by polyphenols. Biochem Pharmacol. 2002;63(6):1165-76.
5. Kantor J, Kessler LJ, Brooks DG, Cotsarelis G. Decreased serum ferritin is associated with alopecia in women. J Invest Dermatol. 2003;121:985-8.
6. McLaren DS. Fat soluble vitamins. In: Garrow JS, James WPT, (Eds). Human nutrition, dietetics. 9th ed. Edinburgh: Churchill Livingstone; 1993. pp. 208-38.
7. Moeinvaziri M. Iron status in diffuse telogen hair loss among women. Acta Dermatovenerol Croat. 2009;17(4):279-84.
8. Mussalo-Rauhamaa H. Element concentrations in serum,erythrocytes, hair and urine of alopecia patients. Acta Derm Venereol. 1986;66(2):103-9.
9. Olsen EA. Female pattern hair loss. J Am Acad Dermatol. 2001; 45:S70-S80.
10. Rushton DH, Ramsay ID, James KC, Norris MJ, Gilkes JJ. Biochemical and trichological characterization of diffuse alopecia in women. Br J Dermatol. 1990;123(2):187-97.
11. Rushton DH. Causes of hair loss and the developments in hair rejuvenation. Int J Cosmet Sci. 2002a;24(1):17-23.
12. Rushton DH. Nutritional factors and hair loss. Clin Exp Dermatol. 2002;27(5):396-404.
13. Rushton DH, Ramsay ID. The importance of adequate serum ferritin levels during oral cyproterone acetate and ethinyl oestradiol treatment of diffuse androgen-dependent alopecia in women. Clin Endocrinol (Oxf). 1992;36:421-7.
14. Tsuruki T, Takahata K, Yoshikawa M. Anti-alopecia mechanisms of soymetide-4, an immunostimulating peptide derived from soy beta-conglycinin. Peptides. 2005;26:707-11.
15. Zempleni J. Biotin and biotinidase deficiency. Expert Rev Endocrinol Metab. 2008;3(6):715-24.

NUTRITIONAL AGENTS AND PSORIASIS

Psoriasis is a chronic disease of abnormal keratinocyte proliferation and differentiation, as well as localized and systemic inflammation. The pathogenesis is multifactorial, allowing for multiple therapeutic options, including vitamin A and D derivatives, corticosteroids, ultraviolet light phototherapy, and immunosuppressive agents. Biologic therapies that target cytokines, including tumor necrosis factor alpha (TNF-α), interleukin (IL)-12, IL-23, and IL-17, are now of particular importance in the therapeutic ladder of intervention.

The association of various dietary factors and psoriasis, however, cannot be ignored. In particular, the association between obesity and psoriasis deserves further consideration. The clinical course of psoriasis can be affected by dietary caloric modifications; and intake of antioxidants, ω-3 polyunsaturated fatty acids (PUFAs), alcohol, vitamin A and vitamin D derivatives, gluten, and inositol.

Obesity: The associations between obesity and psoriasis are numerous; however, more study on the effects of calorie restriction, weight loss, and the mechanisms of response to different treatments in obese patients is needed to more effectively counsel patients on diet modification.

Antioxidants

Antioxidants could potentially help in counteracting the oxidative stress that may play a role in the pathogenesis of psoriasis. Diets rich in fresh fruits, vegetables, and their antioxidants may help reduce the risk for developing psoriasis.

A case-control study linked increased consumption of carrots, tomatoes, and fresh fruit, as assessed by patient questionnaires, with a significantly decreased risk for psoriasis (Naldi et al.). Other antioxidants have been considered in the treatment of psoriasis, including selenium, coenzyme Q, and vitamin E. Selenium and vitamin E supplementation for 8 weeks led to an increase in antioxidant enzyme (glutathione peroxidase) levels in patients with psoriasis who showed decreased glutathione peroxidase levels at the start of the study (Juhlin L).

Fish Oil

Fish oil has known beneficial effects when used as either a monotherapy or adjuvant therapy for treatment of psoriasis and its comorbidities.

Intravenous (IV) formulations of eicosapentaenoic acid (EPA) and docosahexaenoic acid given over 10 to 15 days produced consistent and dramatic improvements in PASI scores; however, the significant cost of IV therapy and inpatient treatment severely limits its use on a wide scale (Grimminger F). Although blinded and controlled trials of oral fish oil as monotherapy containing either 1.8 or 3 g of EPA taken daily for 2 to 4 months yielded suboptimal results, supplementing phototherapy or systemic retinoids with oral fish oil did produce a greater therapeutic response than either therapy alone. (Bjorneboe A).

Gluten-free Diet

Investigators have shown that adoption of a gluten-free diet in patients with psoriasis who have elevated anti-gliadin antibodies and/or celiac disease may result in improvement in psoriasis (Michaelsson G). Based on this information, it may be useful to screen psoriasis patients with bowel symptoms for autoantibodies so that both the potential underlying celiac disease and psoriasis can receive appropriate treatment.

Vitamin D

Systemic vitamin D complexes with the vitamin D receptor, translocates to the nucleus, and binds responsive DNA elements, ultimately regulating calcium homeostasis, the immune system, and cellular proliferation and differentiation. The effect of vitamin D supplementation in patients with psoriasis with vitamin D deficiency is unclear, as randomized controlled trials are lacking. A recent case-control study conducted in Spain demonstrated that patients with psoriasis indeed have lower 25-hydroxyvitamin D [25(OH)D] levels than controls and also are more likely to have 25(OH)D deficiency (Orgaz-Molina J).

Conclusion

Dietary modifications alone are unlikely to cure psoriasis in most patients but weight loss, dietary changes to improve comorbidities, limitation of alcohol consumption, ingestion of antioxidants, avoidance of gluten in patients with anti-gliadin antibody positivity, may help in ameliorating psoriasis in certain populations.

BIBLIOGRAPHY

1. Bjorneboe A, Smith AK, Bjorneboe GE, Thune PO, Drevon CA. Effect of dietary supplementation with n-3 fatty acids. Br J Dermatol. 1988;118:77-83.
2. Juhlin L, Edqvist LE, Ekman LG, Ljunghall J, Olsson M. Blood glutathione peroxidase levels in skin diseases: Effect of selenium and vitamin E treatment. Acta Derm Venereol (Stockh). 1982;62:211-4.
3. Mayser P, Mrowietz U, Arenberger P, et al. ω-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis: Results of a double-blind, randomized, placebo-controlled, multicenter trial. J Am Acad Dermatol. 1998:539-47.
4. Michaelsson G, Gerden B, Hagforsen E, et al. Psoriasis patients with antibodies to gliadin can be improved by a gluten-free diet. Br J Dermatol. 2000;142:44-51.
5. Naldi L, Parazzini F, Peli L, Chatenoud L, Cainelli T. Dietary factors and the risk of psoriasis. Results of an Italian case-control study. Br J Dermatol. 1996;134:101-6.
6. Orgaz-Molina J, Buendia1-Eisman A, Arrabal-Polo MA, Ruiz JC, Arias-Santiago S. Deficiency of serum concentration of 25-hydroxyvitamin D in psoriatic patients: A case-control study. J Am Acad Dermatol. 2012 [Epub].

NUTRITIONAL AGENTS AND ATOPIC DERMATITIS

At present, dietary avoidance or supplementation during pregnancy and lactation is not recommended as research has been inconclusive in establishing clinical benefit in

AD and there is concern regarding safety during this critical developmental period for infants. Probiotics have shown the most favorable results and may be beneficial in preventing AD. Stronger studies, however, are required before incorporation into standard practice. Definite conclusions about the effect of breastfeeding in either preventing or delaying the onset of AD are difficult to make. Studies suggest that exclusive breastfeeding for 3 to 4 months may be beneficial in preventing AD by mothers of infants with a family history of atopy.

Hydrolized Formula

Although not supported by the Cochrane review, a more recent meta-analysis, including 18 studies, found decreased incidence of AD until 3 years of age with use of this formula (Alexander DD). Fewer studies evaluate the role of the hydrolyzed formulas in established AD. A recent double-blind RCT studied the effect of a hydrolized formula in 113 infants with mild to moderate AD. Results showed that the severity of AD and number of flare-ups were significantly reduced at week 12 (Jin YY). Studies on soy formula have not been conclusive, and therefore, use in infants in prevention of AD is not currently recommended.

Delayed Introduction of Solid Foods

A landmark study, in 1989, suggested an association between atopy and introduction to solid foods *before 6 months* and to *allergy-associated foods,* such as milk, eggs, and fish *before 2 years* of age. The study showed a reduction in allergic manifestations at 12 months in the group avoiding solids and allergy-causing foods compared with the group without restrictions (Zeiger RS). There is little evidence to support avoiding solid foods beyond 6 months. A prospective cohort study followed 642 infants to 5.5 years found no data to recommend delaying solid foods after 6 months. Instead, they showed a significant increased risk for AD with delayed introduction of certain allergy-associated foods including egg (Zutavern A).

One hypothesis accounting for this is that there is a "critical window," likely between *4 and 6 months*, in which exposure to food antigens *must occur* in order to develop tolerance. Lack of exposure during this period may lead to sensitization and increased risk for food allergy and AD (Prescott SL).

The data, thus far on the optimal timing to introduce solid foods into the infants' diet, remain somewhat inconclusive. In accordance with current AAP guidelines, introducing a variety of solids between 4 and 6 months of age may allow for appropriate development of tolerance and decrease risk for food allergy and AD.

Exclusions

At this time, dietary exclusions, with the exception of cases of food allergy, are *not* recommended. There is concern that patients with AD may develop an underlying nutrient deficiency, because patients with AD have been shown to consume significantly lower quantities of dairy products, fish, egg, fruits, and tree nuts. Dietary supplementation with essential nutrients rather than dietary elimination may be required.

Fish Oil

A meta-analysis including six double-blind RCTs showed no benefit of fish oil in the primary prevention of eczema; however, they suggested that use may be valuable in reducing the severity of established AD (Anandan C). Although there is some conflicting evidence as to whether fish oil can aid in the prevention of AD, more convincing data exist to support its supplementation to reduce clinical symptoms and severity of established AD (Bjørneboe A).

Probiotics/Prebiotics

Probiotics, living microorganisms that provide health benefits to the host, may have therapeutic potential in AD. Gastrointestinal (GI) microflora is involved in processing enteric antigens; their absence results in increase antigen uptake, and thereby, risk for allergic sensitization to a variety of food substances. In patients with cow's milk allergy, intact milk protein up-regulates the immune system resulting in release of proinflammatory cytokines. Intestinal lactobacilli have been shown to process intact cow's milk protein into tolerogenic peptides. In addition to processing antigens, certain microflora, particularly *Lactobacillus* and *Bifidobacteria*, have been shown to increase anti-inflammatory cytokines, TGF-β and IL-10, in children with AD. It is thought that probiotics exert their effect by altering composition of local microflora and modulating inflammatory processes in the GI tract.

Studies of probiotic supplementation in AD have been equivocal, with data supporting and refuting their use (Taylor AL Kalliomäki M). Studies of probiotic supplementation in *treatment* of established AD has produced less successful results than *prevention* studies. Although probiotics may be beneficial, particularly in primary prevention of AD, the evidence is not yet sufficient to substantiate their use in standard practice.

Prebiotics are nondigestible food products that can stimulate growth or activity of nonpathogenic bacteria in the colon. The most common form of prebiotics is

oligosaccharides such as inulin and oligofructose. Although more widely recognized in the treatment of inflammatory bowel disease, a few studies have evaluated the use of prebiotics in AD.

BIBLIOGRAPHY

1. Alexander DD, Cabana MD. Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. J Pediatr Gastroenterol Nutr. 2010;50:422-30.
2. Anandan C, Nurmatov U, Sheikh A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. Allergy. 2009;64:840-8.
3. Bjørneboe A, Søyland E, Bjørneboe GE, Rajka G, Drevon CA. Effect of dietary supplementation with eicosapentaenoic acid in the treatment of atopic dermatitis. Br J Dermatol. 1987;117:463-9.
4. Jin YY, Cao RM, Chen J, et al. Partially hydrolyzed cow's milk formula has a therapeutic effect on the infants with mild to moderate atopic dermatitis: a randomized, double-blind study. Pediatr Allergy Immunol. 2011;22:688-94.
5. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet. 2001;357:1076-9.
6. Prescott SL, Smith P, Tang M, et al. The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. Pediatr Allergy Immunol. 2008;19:375-80.
7. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. J Allergy Clin Immunol. 2007;119(1):184-91.
8. Zeiger RS, Heller S, Mellon MH, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. J Allergy Clin Immunol. 1989;84:72-89.
9. Zutavern A, von Mutius E, Harris J, et al. The introduction of solids in relation to asthma and eczema. Arch Dis Child. 2004;89:303-8.

DIET AND URTICARIA

Urticaria is a common dermatologic problem with a lifetime prevalence of approximately 20%.

The pathogenesis is not yet fully understood, and a triggering factor can be identified in only 10% to 20% of cases. Many patients with chronic urticaria attribute their symptoms to food intolerance. Food products including *wheat, dietary fats, and alcohol* are thought to play a role in the development of urticarial lesions (Beltrani VS). Research also has identified many pseudoallergens, natural and artificial, that induce and/or aggravate urticaria via a non-IgE-mediated pathway.

Wheat

Although atopic dermatitis occurs mainly in children, chronic urticaria and wheat-dependent exercise-induced anaphylaxis (WDEIA) are mostly found in adults. WDEIA is part of a larger entity of *food-dependent, exercise-induced anaphylaxis* (FDEIA), where ingestion of a specific food before physical exercise triggers anaphylaxis.

Symptoms of FDEIA include pruritus, urticaria, angioedema, dyspnea, hypotension, and shock, which are indistinguishable from those in classic IgE-mediated anaphylaxis. Patients with FDEIA have IgE antibodies to an offending food, yet food ingestion alone fails to elicit symptoms. Common triggering foods include '*celery*, *shellfish*, *peanut*, *tree nuts*, and *tomato*'.

A frequent cause, however, is *wheat* (Inomata N). The water-salt-insoluble component of wheat, gliadin, is rich in glutamine residues and becomes modified by the intestinal enzyme, tissue transglutaminase (tTg). tTg has been implicated in the development of WDEIA.

Pseudoallergens

The term pseudoallergen is used to describe a stimulus that provokes histamine or cutaneous mast cell degranulation via a *nonimmunologic* pathway (i.e. not IgE mediated). It has been estimated that 1 to 3% of patients with chronic urticaria exhibit pseudoallergic reactions (Di Lorenzo G). Pseudoallergens include, but are not limited to, *artificial preservatives and sweeteners, food dyes, aromatic compounds in some natural foods (e.g. tomatoes, herbs), and phenolic substances (salicylic acid, p-hydroxybenzoic acid, anethole, ethyl vanillin, citron oil, and orange oil).*

After a period of general restriction, patients can be challenged with more select pseudoallergens and begin to add foods back into their diet that do not provoke urticaria.

Prospective interventional studies have reported improvement of chronic urticaria symptoms in 28 to 73% of participants adopting a pseudoallergen-free diet (Magerl M). Double-blind, placebo-controlled oral challenges with individual pseudoallergens, the current gold standard for diagnosing food allergy, yield reproducible urticaria symptoms following a pseudoallergen-free diet in only 1 to 19% of patients (Di Lorenzo G).

Because patients differ in terms of the specific pseudoallergens that trigger urticaria, symptom diaries and oral food challenges are useful in determining whether an ingredient or additive plays an exacerbating role. Interestingly, after several months of dietary avoidance, many patients can return to a normal diet without experiencing

reoccurrence of urticaria. In contrast to medications, a pseudoallergen-free diet may be curative rather than symptom suppressing (Magerl M).

Artificial food additives are thought to play a greater role in chronic urticaria afflicting *children*, whereas *natural* pseudoallergens evoke more sensitivity among *adults*.

Artificial Pseudoallergens

A variety of artificial pseudoallergens have been identified, primarily in the form of *preservatives and dyes* 1 (tartrazine, sodium benzoate, BHT, Sunset Yellow FCF, Food Red 17, Amaranth, Ponceau 4 R, Erythrosine, Brillant Blue FCF) as well as *additives* such as monosodium glutamate and sweetners (saccharin) (Mikkelsen H).

Natural Pseudoallergens

Although artificial pseudoallergens have received significant attention, there also is increasing awareness of the role of natural pseudoallergens in urticaria (Zuberbier T). They include *natural food dyes*, such as annatto extract, salicylates, and aromatic compounds, found in high concentrations in several types of *fruits, vegetables,* and *spices.* Unlike artificial pseudoallergens, quantities of naturally occurring pseudoallergens are difficult to estimate as they vary considerably in each fruit or vegetable depending on its type, age, and place of origin.

Natural pseudoallergens pose a challenge in the management of urticaria because of the difficulty of avoiding all foods containing these ingredients. Testing to determine the natural pseudoallergens to which the patient is sensitive can help in developing a dietary regimen. Although complete elimination is not possible, lowering consumption of certain natural pseudoallergens may help to ameliorate symptoms of urticaria.

Probiotics

Intestinal microbiota play an important role (particularly at an early age when the mucosal barrier and immune system are still immature) in the development of food allergy and food allergen-associated urticaria. Probiotics, when given in infancy, may address the root cause by preventing allergic sensitization to foods, which can subsequently manifest with urticaria.

Natural Remedies

Although the spines of the stinging nettle plant cause burning urticaria upon penetration, a tea made from the leaves of stinging nettle has been used for the treatment of many inflammatory conditions including hives themselves.

Flavonoids such as quercetin have been shown to inhibit the release of histamine in *in-vitro* mast cells. Supplementation with quercetin 500 mg three times daily may reduce symptoms. Other flavonoids such as luteolin have been shown to decrease the allergic cytokines IL-4 and IL-13 (Kawai M). *Curcumin* and *pycnogenol,* other members of the flavonoid family, may provide some relief from urticaria at doses of 500 mg three times daily and 300 mg daily, respectively.

Conclusion

Only about half of patients with chronic urticaria are willing to treat their symptoms with medications. Dietary modification, including a trial of a gluten-free diet; reduced alcohol consumption; elimination of salicylates; and avoidance of artificial sweeteners, food dyes, citrus oils, and aromatic and phenolic compounds is a cost-effective and likely effective method for these motivated patients.

Other considerations include keeping a food journal, screening for *H. pylori*, and trialing several nutritionals that support the intestinal immune system (glutamine, probiotics, and B_{12}), as well as managing mast cell degranulation and symptoms (stinging nettle tea, vitamin C, flavonoids, yogurt, chickweed, peppermint, and stress-reducing modalities). But it must be pointed out that a pseudoallergen elimination diet may be of limited utility in the majority of chronic urticaria patients (Rajan JP).

BIBLIOGRAPHY

1. Beltrani VS. An overview of chronic urticaria. Clin Rev Allergy Immunol. 2002;23:147-69.
2. Di Lorenzo G, Pacor ML, Mansueto P, et al. Food-additive-induced urticaria: a survey of 838 patients with recurrent chronic idiopathic urticaria. Int Arch Allergy Immunol. 2005;138:235-42.
3. Di Lorenzo G, Pacor ML, Mansueto P, et al. Food-additive-induced urticaria: a survey of 838 patients with recurrent chronic idiopathic urticaria. Int Arch Allergy Immunol. 2005;138: 235-42.
4. Inomata N. Wheat allergy. Curr Opin Allergy Clin Immunol. 2009;9: 238-43.
5. Kawai M, Hirano T, Higa S, et al. Flavonoids and related compounds as anti-allergic substances. Allergol Int. 2007;56:113-23.
6. Magerl M, Pisarevskaja D, Scheufele R, Zuberbier T, Maurer M. Effects of a pseudoallergen-free diet on chronic spontaneous urticaria: a prospective trial. Allergy. 2010;65:78-83.
7. Mikkelsen H, Larsen JC, Tarding F. Hypersensitivity reactions to food colours with special reference to the natural colour annatto extract (butter colour). Arch Toxicol Suppl. 1978;1:141-3.
8. Rajan JP, Simon RA, Bosso JV. Prevalence of sensitivity to food and drug additives in patients with chronic idiopathic urticaria. J Allergy Clin Immunol Pract. 2014;2:168-71.

9. Zuberbier T, Edenharter G, Worm M, et al. Prevalence of adverse reactions to food in Germany—a population study. Allergy. 2004;59:338-45.

DIET AND BULLOUS DISORDERS

Pemphigus (Pemphigus Vulgaris, Foliaceus, Paraneoplastic Pemphigus, and IgA Pemphigus)

A variety of substances (tannins, thiols, phenols, isothiocyanates, phycocyanins) in different foods are believed to potentially play a role in the induction of pemphigus in genetically predisposed individuals based on the similarity of their chemical structure to drugs known to induce the disease (Tur E). Additionally, environmental factors such as the high tannin content in water is believed to play a role in endemic pemphigus in populations of Amazonian Brazil and India (Kaimal S).

A list of foods containing these substances includes *garlic, leek, chives, onion, mustard (thiols), black pepper, red chilies, mango, pistachio, cashews, aspartame, food additives (phenols), cassava, yucca, guarana, betel nuts, raspberry, cranberry, blackberry, avocado, peach, ginger, ginseng, tea, red wine, coffee, spices, eggplant (tannins), mustard, horseradish, cauliflower (isothiocyanates) and Spirulina platensis alga (phycocyanins)*.

Pemphigus induced by contact with phenolic compounds (tincture of benzoin, phenol peels, phenol-based cleaning agent) has been reported. High consumption of foods containing **phenols** (mango, cashews, pistachio, black peppers) and **tannins** has been proposed to explain the early age of onset and high incidence of pemphigus in Indian patients (Brenner S). No case reports of pemphigus induced by isothiocyanates (mustard, horseradish, kale, cauliflower) have been reported to date, although they are believed to be similar to thiol-containing compounds.

Bullous Pemphigoid

No dietary factors have been implicated in the induction of bullous pemphigoid. There is only one case report of nickel-free diet associated with cessation of dyshidrosiform pemphigoid, as well as the suggestion of gluten sensitivity in some bullous pemphigoid patients, although no reports of bullous pemphigoid improving with a gluten-free diet.

Linear IgA Disease

Gluten-sensitivity may be present in linear IgA disease patients. In one case report, gluten restriction in the presence of an underlying gluten-sensitive enteropathy resulted in

resolution of linear IgA disease, with recurrence when gluten was reintroduced. In another study, of four patients with linear IgA disease and intestinal biopsy changes consistent with gluten-sensitive enteropathy, only 2 responded to a gluten-free diet (Egan CA, Leonard JN).

Dermatitis Herpetiformis

Gluten

The role of gluten and gluten-free diet in patients with dermatitis herpetiformis (DH) is well established. A gluten-free diet has been shown to result in resolution of enteropathy, decreased or lack of requirement for medications, protective effects against development of lymphoma, and a general feeling of well being (Garioch JJ).

A long-term gluten diet also has been shown to decrease the intensity of skin IgA fluorescence. In a recent report comparing dapsone and a gluten-free diet to a gluten-free diet alone, patients with severe DH on a gluten-free diet alone had improvement in symptoms comparable with the dapsone with gluten-free diet group after 18 months of treatment (Nino M).

Cross contact of oats with other gluten-containing cereals (wheat, barley, rye) may cause contamination, therefore, purity of oats is important to consider when introducing oats to a gluten-free diet, though oats by itself do not cause DH.

Other factors implicated include milk, iodides and selenium.

BIBLIOGRAPHY

1. Brenner S, Ruocco V, Ruocco E, et al. In vitro tannin acantholysis. Int J Dermatol. 2000;39:738-42.
2. Egan CA, Smith EP, Taylor TB, Meyer LJ, Samowitz WS, Zone JJ. Linear IgA bullous dermatosis responsive to a gluten-free diet. Am J Gastroenterol. 2001;96:1927-9.
3. Garioch JJ, Lewis HM, Sargent SA, Leonard JN, Fry L. 25 years' experience of a gluten-free diet in the treatment of dermatitis herpetiformis. Br J Dermatol. 1994;131:541-5.
4. Kaimal S, Thappa DM. Diet in dermatology: revisited. Indian J Dermatol Venereol Leprol. 2010;76:103-15.
5. Leonard JN, Griffiths CE, Powles AV, Haffenden GP, Fry L. Experience with a gluten-free diet in the treatment of linear IgA disease. Acta Derm Venereol. 1987;67:145-8.
6. Nino M, Ciacci C, Delfino M. A long-term gluten-free diet as an alternative treatment in severe forms of dermatitis herpetiformis. J Dermatolog Treat. 2007;18:10-2.
7. Tur E, Brenner S. Contributing exogenous factors in pemphigus. Int J Dermatol. 1997;36:888-93.1

DIET AND ACNE

The current status of the relation between diet and acne is unclear and under debate. On one hand, the American Academy of Dermatology (AAD) published recommendations (Strauss et al. 2007) suggesting that caloric restriction has no benefit in the treatment of acne and that there is insufficient evidence to link the consumption of certain "food enemies" to acne (http://www.skincarephysicians.com.acnenet acne_and_diet.html). On the other hand, recent clinical studies have suggested a rather close relation between diet and acne (Smith et al. 2007).

Eventhough, some authors have linked milk with acne, I have seen scores of patients who take milk and have no acne. Though, IGF-1 is increased in patients on a high glycemic diet, why this effect does not occur in all patients, especially after they have a resolution of acne is inexplicable. Also the argument linking high glycemic diet with acne, hinges on the role of insulin, and may be relevant to the persistence of acne. But the lack of acne in diabetics is still inexplicable and is an argument against the insulin hypothesis.

Vitamin A

Oral administration of isotretinoin (13-cis-retinoic acid) and topical application of its isomers and natural retinoids (e.g. tretinoin) are used as anti-acne therapies. 13-cis-retinoic acid (RA) is the only drug that targets all four pathogenic factors of acne and is the most efficient drug so far in regard to sebum suppression. 13-cis-RA is a retinoid that potentially derives from the metabolism of vitamin A. Although several websites state that it is found in small quantities naturally in the body without citing a reference (Vahlquist 1999), we know that at least the natural isomers of RA also affect the disease.

The superlative effect of isotretinoin, a vitamin A derivative, is a good argument of the role of nutrients in acne, though the quantity required of oral vitamin A is extremely high to individually effect a treatment response.

Essential Fatty Acids

There are two fatty acids in our body that are essential and cannot be synthesized by human cells: linoleic acid (18:2, D9,12) and linolenic acid (18:2, D9,12,15). These are important nutrients that need to be obtained from the diet, which is why they are referred to as essential fatty acids. These two essential nutrients are precursors to the omega-6 (γ-linoleic acid) and omega-3 fatty acid (α-linolenic acid) families, respectively, a family of metabolites that are involved in numerous important physiological processes, including inflammation.

Numerous studies have revealed that clinical imbalances of specific essential fatty acids are associated with a variety of skin problems, such as dry, itchy, scaly skin, which is a hallmark sign of fatty acid deficiency. More relevant to this is a publication that suggested that the sebum of acne patients is relatively deficient in *linoleic* acid (Downing et al. 1986). A recent nutritional clinical study (De Spirt et al. 2009) in two groups of women who consumed flaxseed (omega-3 fatty acid) or borage oil (omega-6) for 12 weeks revealed that the daily ingestion of 2.2 g total fatty acids with alpha-linolenic acid and linoleic acid (LA) as major constituents in the flaxseed oil group and linoleic and gamma-linolenic acid in the borage oil group, demonstrated skin benefits. Skin irritation, changes in skin reddening, and blood flow were diminished in both groups compared to the placebo group, providing evidence that skin properties can be modulated by intervention with dietary fats.

The fact that Western diets are often deficient in the longer-chain omega-3 fatty acids and their precursor alpha-LA raises an additional issue for this discussion. It is known that the ratio of omega-6 to omega-3 fatty acids in a typical Western diet ranges from about 10:1 to 20:1 versus a ratio of 3:1–1:1 in a non-Western diet or in primitive, non-industrialized populations. These findings were the foundation for population studies that revealed that non-Western diets correlated with the absence of acne (Cordain et al. 2002).

A number of studies have suggested that *inflammatory markers* correlate with an increase of the *omega-6/omega-3* ratio (Kris-Etherton et al. 2000). The omega-6 fatty acids are thought to induce more proinflammatory mediators and have been associated with the development of inflammatory acne (Zouboulis, 2001). On the other hand, intake of high levels of omega-3 fatty acids is linked with decreases in inflammatory factors (James et al. 2000). In addition, there are epidemiological studies demonstrating that increasing the intake of omega-3 fatty acids through a diet rich in seafood results in lower rates of inflammatory disease (Kris-Etherton et al. 2000).

Thus in essence diets rich in fresh *vegetables, fish, flaxseed oil, DHA/EPA*, which are all rich in omega-3 EFA can have a salutary effect on acne. Supplements (MAXEPA) can also reduce the lipid abnormalities of isotretinoin in acne.

Essential Elements

Another class of nutrients that derives from the diet includes minerals such as zinc, copper, selenium, and iron, which known to influence anti-inflammatory and proinflammatory enzymes (e.g. desaturases and lipoxygenases). We have shown the superlative effects of zinc in acne, specially with the methionine based zinc (Sardana K).

High Glycemic Diet

It has been reported that people living in the Kitavan Islands (off the coast of Papua New Guinea) and the Aché hunter-gathers of Paraguay do not suffer from acne and that it is associated with their low-glycemic diet, consisting mainly of fresh vegetables, fruits, and lean proteins (Cordain et al. 2002). This conclusion is in agreement with the latest studies (Smith et al. 2007) on low-glycemic diets.

In brief, one prospective cohort study (Smith et al. 2007) found a valid association between high-glycemic-index foods and longer acne duration, whereas low-glycemic-index diet had a reduced acne risk. The work of Smith et al. (2007) focused on the glycemic load, insulin sensitivity, hormonal mediators, and acne. The investigators reported that foods with a high glycemic index contribute to acne by elevating serum insulin concentrations (which may stimulate sebocyte proliferation and sebum production), suppress SHBG concentrations, and raise androgen concentrations. On the contrary, low glycemic index foods increased SHBG and reduced androgen levels, which is important because high SHBG levels were associated with less acne severity. Recently, Spencer et al. (2009) and Bowe et al. (2010) summarized 27 relevant studies: 21 were observational, and 6 were clinical trials and concluded that although there is compelling evidence for the association of acne and high-glycemic-load diets, there is weak evidence for an association between dairy product ingestion and acne.

A recent study has used metformin and a low calorie diet and has shown an improvement in acne lesions (Fabbrocini G), though extrapolating this data on low calorie diet in India, where teenagers often have a wayward eating habit, can be deleterious and can lead to malnutrtition.

Conclusion

There are still questions unanswered about the association of diet and acne (Sardana K). This include, why is that not all obese individuals have long-term acne as most people who are obese demonstrate insulin resistance? In addition, if insulin resistance is associated with acne, everyone who suffers from diabetes type 2 would be expected to have acne, which would be prolonged and persistent than others, a clinical finding that is not seen.

Nevertheless, a high glycemic load seems to be associated with the occurrence of acne, and a recommendation for a low-glycemic load diet cannot harm the affected population. How bad could it be when such a diet, which includes a variety of fruits and vegetables, lean protein, and healthy fats, can also protect against cardiovascular disease, type 2 diabetes, metabolic syndrome, and even obesity?

Thus, it is a good common sense advise to tell patients to avoid processed foods, cheese, simple carbohydrates and increase the intake of EFA of the omega-3 kind. Whether national recommendations differ, is not relevant here as if a clinician can make a difference in the eating patterns of patients a lot more good than harm can be achieved.

BIBLIOGRAPHY

1. Bowe WP, Joshi SS, Shalita AR. Diet and acne. J Am Acad Dermatol. 2010; 63(1):124-41. Epub 2010 Mar 24. Review.
2. Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton SB, Brand-Miller J. Acne vulgaris: a disease of western civilization. Arch Dermatol. 2002;138(12):1584-90.
3. Downing DT, Stewart ME, Wertz PW, Strauss JS. Essential fatty acids and acne. J Am Acad Dermatol. 1986;14(2 Pt 1):221-5.
4. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. Am J Clin Nutr. 2000;71 (1Suppl):343S-8. Review.
5. Kris-Etherton PM, Taylor DS, Yu-Poth S, Huth P, Moriarty K, Fishell V, et al. Polyunsaturated fatty acids in the food chain in the united states. Am J Clin Nutr. 2000;71(1 Suppl):179S-88. Review.
6. Sardana K, Madan A. Diet and Acne. In: Sardana K (Ed). Clinical Approach to Acne vulgaris. 1st edition. 2015.94.
7. Smith RN, Mann NJ, Braue A, et al. The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. J Am Acad Dermatol. 2007;57:247-56.
8. Smith RN, Mann NJ, Braue A, et al. The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. J Am Acad Dermatol. 2007b;57:247-56.
9. Spencer EH, Ferdowsian HR, Barnard ND. Diet and acne: a review of the evidence. Int J Dermatol. 2009;48(4):339-47. Review.
10. Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, et al. American Academy of Dermatology/American Academy of Dermatology Association. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007;56(4):651-63. Epub 2007 Feb 5. Review.
11. Vahlquist A. What are natural retinoids? Dermatology. 1999;199 (Suppl) 1:3–11. Review.
12. Zouboulis CC. Is acne vulgaris a genuine inflammatory disease? Dermatology. 2001;203(4):277-9.

NUTRITIONAL SUPPLEMENTS AND SKIN

Nutritional supplements are possible the most common prescribed medication and its use is rarely guided by a therapeutic rationale. There is a possibility of excess supplementation though with water-soluble vitamins most of them are excreted in the urine.

Here we will discuss first, iron salt, vitamins, antioxidants, EFA and then focus on the clinical uses in major dermatological conditions. Zn has been discussed elsewhere. The other minerals are not being discussed as they have a minor role in skin disorders.

ORAL IRON

Iron is one of the most commonly prescribed agents in India and in dermatological practice, it is often prescribed for telogen effluvium eventhough its role has not been defined beyond doubt in this condition.

Absorption and Distribution

Iron is distributed in active metabolic and storage pools. Total body iron is about 3.5 g in healthy men and 2.5 g in women; the difference relates to women's smaller body size, lower androgen levels, and dearth of stored iron because of iron loss due to menses and pregnancy.

The distribution of body iron in an average man is Hb, 2100 mg; ferritin, 700 mg (in cells and plasma); hemosiderin, 300 mg (in cells); myoglobin, 200 mg; tissue (heme and nonheme) enzymes, 150 mg; and transport-iron compartment, 3 mg.

Iron absorption: Iron is absorbed in the duodenum and upper jejunum. Absorption of iron is determined by the *type* of iron molecule and by what other substances are ingested. Iron absorption is best when food contains heme iron (meat). Dietary nonheme iron must be reduced to the ferrous state and released from food binders by gastric secretions. Nonheme iron absorption is reduced by other food items (e.g. vegetable fiber phytates and polyphenols; tea tannates, including phosphoproteins; bran) and certain antibiotics (e.g. tetracycline). *Ascorbic* acid is the only common food element known to increase nonheme iron absorption.

Of about **15 mg/day** of dietary iron, adults absorb only **1 mg,** which is the approximate amount lost daily by cell desquamation from the skin and intestines. In iron depletion, absorption increases, although the exact signaling mechanism is not known; however, absorption rarely increases to > 6 mg/day unless supplemental iron is added. Children have a greater need for iron and appear to absorb more to meet this need.

Iron transport and usage: Iron from intestinal mucosal cells is transferred to *transferrin*, an iron-transport protein synthesized in the liver; transferrin can transport iron from cells (intestinal, macrophages) to specific receptors on erythroblasts, placental cells, and liver cells. For heme synthesis, transferrin transports iron to the erythroblast

mitochondria, which insert the iron into protoporphyrin for it to become heme. Transferrin (plasma half-life, 8 days) is extruded for reutilization. Synthesis of transferrin increases with iron deficiency but decreases with any type of chronic disease.

Iron storage and recycling: Iron not used for erythropoiesis is transferred by transferrin, an iron-transporting protein, to the storage pool; iron is stored in 2 forms, *ferritin* and *hemosiderin*. The most important is ferritin (a heterogeneous group of proteins surrounding an iron core), which is a soluble and active storage fraction located in the liver (in hepatocytes), bone marrow, and spleen (in macrophages); in RBCs; and in serum. Iron stored in ferritin is readily available for any body requirement. Circulating (serum) ferritin level parallels the size of the body stores (**1 ng/mL = 8 mg of iron in the storage pool**). The 2nd storage pool of iron is in hemosiderin, which is relatively insoluble and is stored primarily in the liver (in Kupffer cells) and in bone marrow (in macrophages).

Because iron absorption is so limited, the body recycles and conserves iron. Transferrin grasps and recycles available iron from aging RBCs undergoing phagocytosis by mononuclear phagocytes. This mechanism provides about 97% of the daily iron needed (about 25 mg of iron). With aging, iron stores tend to increase because iron elimination is slow.

Iron deficiency: Deficiency develops in stages. In the first stage, iron requirement exceeds intake, causing progressive depletion of bone marrow iron stores. As stores decrease, absorption of dietary iron increases in compensation. During later stages, deficiency impairs RBC synthesis, ultimately causing anemia.

Stages of iron deficiency: Laboratory test results help stage iron deficiency anemia.

Stage 1: It is characterized by decreased bone marrow iron stores; Hb and serum iron remain normal, but **serum ferritin level falls to < 20 ng/mL**. The compensatory increase in iron absorption causes an **increase in iron-binding capacity** (transferrin level).

Stage 2: Erythropoiesis is impaired. Although the transferrin level is increased, the serum iron level decreases; transferrin saturation decreases. Erythropoiesis is impaired when **serum iron falls to < 50 µg/dL (< 9 µmol/L) and transferrin saturation to < 16%. The serum ferritin receptor level rises (> 8.5 mg/L).**

Stage 3: Anemia with normal-appearing RBCs and indices develops.

Stage 4: Microcytosis and then hypochromia develop.

Stage 5: Iron deficiency affects tissues, resulting in symptoms and signs.

Uses

Iron Deficiency

Symptoms caused by iron deficiency include fatigue, lack of energy, loss of appetite, and increased susceptibility to infections. From a dermatological perspective, the iron-deficiency state can lead to dry skin, brittle hair, hair loss, rutted fingernails (Beau's lines), inflammation of the oral mucosa and tongue, pruritus, chronically sustained inflammation, dermatitis herpetiformis, and photodermatitis as well as changes in the overall appearance such as pallor and blue sclerae (Sato 1991).

Pruritus

One of the many causes of puritus is iron deficiency with or without accompanying anemia. A finnish study revealed that men and women who have low serum hemoglobin and ferritin concentrations suffer significantly more often from pruritus than people with normal iron values (Takkunen 1978).

Iron and Hair

In the presence of iron deficiency, the hair appears lusterless, dry, brittle, and spliced. It may be due to impaired keratin production (Sato 1991). The major cause of hair loss in women before the age of 50 is poor nutrition, which affects about 30% of women. Increased and persistent hair shedding (chronic telogen effluvium, or CTE) as well as reduced hair volume are the principal changes that occur. The main cause appears to be depleted iron stores accompanied by suboptimal intake of the essential amino acid l-lysine (Rushton et al. 2002). As early as the 1960s, the role of iron as an etiological factor in diffuse hair loss in nonanemic women with an iron deficiency was demonstrated (Hård 1963). More recent studies succeeded in a significant decrease in hair shedding as well as in the percentage of hair in the telogen phase in women with CTE after supplementation with *72 mg iron* and **1.5 g l-lysine** daily for 6 months. In these studies, a significant increase in the mean serum ferritin concentration was found in the treated groups.

This implies that there is a minimum ferritin concentration required to optimize treatment in those with diffuse hair loss. Although the exact level of serum ferritin that should be reached is still not fully resolved, 70 mg/L seems to be the level to achieve. The amount of supplementation or dietary change needed to maintain this serum ferritin concentration is the subject of continuing research. According to a preliminary

analysis of data, a daily iron supplement of 24–48 mg seems to be needed by menstruating women, with a lower level required in postmenopausal women (Rushton et al. 2002).

Kantoer at al. analyzed the iron levels in females with alopecia and found that the mean ferritin level (ng per mL) in patients with *androgenetic alopecia* and alopecia areata were statistically significantly lower than in normals without hair loss but the mean ferritin levels in patients with *telogen effluvium* and *alopecia areata totalis/universalis* were not significantly lower than in normals. Rasheed on the contrary found an association with alopecia and found that there was a correlation with hair loss and a serum ferritin cut-off value for TE and FPHL was 27.5 and 29.4 μg/L, respectively and could be used as a surrogate marker for alopecia.

The practice at the Cleveland Clinic Foundation is to screen male and female patients with both cicatricial and noncicatricial hair loss for iron deficiency. Although this practice is not evidence based per se, they believe that treatment for hair loss is enhanced when iron deficiency, with or without anemia, is treated. In clinical practice, I do not intervene with iron supplements if the ferritin levels >30 μg/L. Paradoxically, a study by Olsen et al. found that though iron deficiency is common in women, but not increased in patients with FPHL or CTE compared with control subjects. It is pertinent to note that most of the studies have been done from the west and in India, iron deficiency (ID) is a bigger problem, with possibly different cut off levels.

Iron and Nails

Brittle and rutted fingernails (Beau's lines) are often observed with moderate iron deficiency. In advanced cases, the nails have an even, plain, spoon-shaped, convex structure, predominantly, but not exclusively, the index and middle fingers. As these characteristically spoon-shaped nails are not seen in other conditions, this is an infallible indication for iron deficiency. Recovery takes a long time after introducing therapy (Sato 1991).

Dosage

The oral dose of elemental iron for iron-deficiency anemia should be 100 to 200 mg daily. It is customary to give this as dried ferrous sulfate, 200 mg (65 mg elemental iron) three times daily; for prophylaxis of iron-deficiency anemia, a dose of ferrous sulfate 200 mg once or twice daily may be effective.

Iron content in different iron preparations

Iron salt	*Amount*	*Content of ferrous iron*
Ferrous fumarate	200 mg	65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous sulfate	300 mg	60 mg
Ferrous sulfate, dried	200 mg	65 mg

Therapeutic response: The hemoglobin concentration should rise by about 100–200 mg/100 mL (1–2 g/L) per day or 2 g/100 mL (20 g/L) over 3–4 weeks. Anemia should be corrected within 2 months. A subnormal response suggests continued hemorrhage, underlying infection or cancer, insufficient iron intake, or, very rarely, malabsorption of oral iron.

When the hemoglobin is in the reference range, treatment should be continued for a further **3 months** to replenish the iron stores. Epithelial tissue changes such as atrophic glossitis and koilonychia are usually improved, but the response is often slow.

Compound Preparations

Preparations containing iron and folic acid are used during pregnancy in women who are at high risk of developing iron and folic acid deficiency. It is important to note that the small doses of folic acid contained in these preparations is inadequate for the treatment of megaloblastic anemias. Some oral preparations contain ascorbic acid to aid absorption of the iron but the therapeutic advantage of such preparations is minimal and cost may be increased.

There is no justification for the inclusion of other ingredients, such as the B group of vitamins (except folic acid) for pregnant women.

Modified-release preparations of iron are licensed for once-daily dosage, but have no therapeutic advantage and should not be used. These preparations are formulated to release iron gradually; the low incidence of side-effects may reflect the small amounts of iron available for absorption as the iron is carried past the first part of the duodenum into an area of the gut where absorption may be poor.

Side Effects

Gastrointestinal irritation can occur with iron salts. Nausea and epigastric pain are dose-related, but the relationship between dose and altered bowel habit (constipation or diarrhea) is less clear.

Oral iron, particularly modified-release preparations, can exacerbate diarrhea in patients with inflammatory

bowel disease; care is also needed in patients with intestinal strictures and diverticular disease.

Iron preparations taken orally can be constipating, particularly in older patients and occasionally lead to fecal impaction.

If side-effects occur, the dose may be reduced; alternatively, another iron salt may be used, but an improvement in tolerance may simply be a result of a lower content of elemental iron. The incidence of side-effects due to ferrous sulfate is no greater than with other iron salts when compared on the basis of equivalent amounts of elemental iron.

BIBLIOGRAPHY

1. Hård S. Non-anemic iron deficiency as an etiological factor in diffuse loss of hair of the scalp of women. Acta Derm Venereol. 1963;43:562-9.
2. Kantor J, Kessler LJ, Brooks DG, Cotsarelis G. Decreased serum ferritin is associated with alopecia in women. J Invest Dermatol. 2003;121(5):985-8.
3. Olsen EA, Reed KB, Cacchio PB, Caudill L. Iron deficiency in female pattern hair loss, chronic telogen effluvium, and control groups. J Am Acad Dermatol. 2010;63(6):991-9.
4. Rasheed H, Mahgoub D, Hegazy R, El-Komy M, Abdel Hay R, Hamid MA, et al. Serum ferritin and vitamin D in female hair loss: do they play a role? Skin Pharmacol Physiol. 2013;26(2):101-7.
5. Rushton DH, Norris MJ, Dover R, Busuttil N. Causes of hair loss and the developments in hair rejuventation. Int J Cosmet Sci. 2002;24:17-23.
6. Sato S. Iron deficiency: structural and microchemical changes in hair, nails, and skin. Semin Dermatol. 1991;10(4):313-9.
7. Takkunen H. Iron-deficiency pruritus. JAMA. 1978;239(14):1394.
8. Trost LB, Bergfeld WF, Calogeras E. The diagnosis and treatment of iron deficiency and its potential relationship to hair loss. J Am Acad Dermatol. 2006;54(5):824-44.

FAT-SOLUBLE VITAMINS

VITAMIN D

Vitamin D is a fat-soluble vitamin manufactured by the body when exposed to sunlight. The inhibition of vitamin D manufacture by sunscreens and sun avoidance has been a controversial topic in the popular media, with some advocating discontinuing sunscreen use and deliberate sun exposure to prevent vitamin D deficiency. One cup of milk supplies 25% of the recommended daily allowance of vitamin D in adults; however, the current recommended daily allowances are probably too low.

Vitamin D is a hormone essential for regulation of calcium and phosphorous metabolism (Fig. 15.1). Vitamin D activates bone osteoclasts to mobilize calcium and phosphorus,

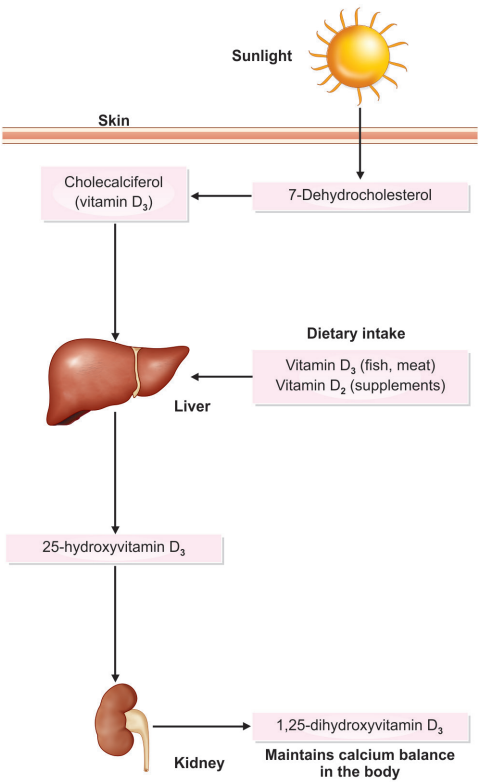


Fig. 15.1: A diagrammatic overview of vitamin D synthesis and metabolism

and stimulates enterocyte calcium channel synthesis to enhance calcium absorption. It can be obtained through dietary sources as ergocalciferol (vitamin D_2) or endogenous synthesis as cholecalciferol (vitamin D_3). Fish and fish oils have the greatest amount of vitamin D available, but egg, liver, shiitake mushrooms, and fortified products, such as milk and orange juice, are additional dietary sources.

Recommended daily intake ranges from 200 to 600 IU, depending on age.

Vitamin D Synthesis in Skin (Fig. 15.1)

Vitamin D, the precursor of the biologically active vitamin D metabolite 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] can be absorbed from the diet or synthesized in skin under the influence of UVB radiation from 7-dehydrocholesterol (7-DHC). All in all, nine enzymatic reactions are involved in the photochemical cutaneous synthesis of vitamin D. Whereas vitamin D_2 (ergocalciferol) can be found in plants, vitamin D_3 (cholecalciferol) is photochemically synthesized under the influence of UVB radiation in the skin of animals and humans.

The biologically active vitamin D metabolite $1,25(OH)_2$ D, or calcitriol, which circulates in the blood, is synthesized from vitamin D by a well-characterized biochemical reaction cascade.

First, it is hydroxylated in the liver in the C-25 position by a cytochrome P450 enzyme, the vitamin D-25-hydroxylase (CYP27A1), before it is hydroxylated a second time in the kidney in the C-1 position by another cytochrome P450 enzyme, 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1). Production of 1,25-$(OH)_2D_3$ in the kidney is regulated by a feedback mechanism of the hormone itself as well as by parathyroid hormone, calcium, and cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-α (TNF alpha) (Holick 2007).

Recent in vitro trials and studies of anephric humans demonstrated that cultured human keratinocytes, monocytes, macrophages, osteoblasts, and prostate and colon cells, among others, express enzymatic machinery for the synthesis of 1,25$(OH)_2D_3$ (Bikle et al. 1986; Holick 2003, 2007). The keratinocyte is the only cell type known today that is able to synthesize 1,25$(OH)_2D_3$ from 7-DHC. According to our present knowledge 1,25$(OH)_2D_3$ has 100- to 1,000-fold higher biological activity than other natural vitamin D metabolites (Bikle et al. 1994).

Mechanism of Action

Inhibition of Proliferation and Induction of Differentiation in Keratinocytes

Numerous in vitro and in vivo studies have demonstrated dose-dependent effects of vitamin D analogs on cell proliferation and differentiation. At low concentrations <10 (–8) M, calcitriol promotes proliferation of keratinocytes in vitro; at higher pharmacological doses >10 (–8) M keratinocyte proliferation is inhibited (Gniadecki 1996).

In psoriatic skin, immunohistochemical and biochemical analysis have clearly shown antiproliferative and differentiation-inducing effects in epidermal keratinocytes along with treatment with vitamin D analogs in vivo (Reichrath et al. 1997). It is well known that these effects are at least in part genomic and mediated via vitamin D receptors (VDRs). The ability of calcitriol to regulate keratinocyte growth is closely linked to the expression of VDRs. The target genes of topical calcitriol that are responsible for its therapeutic efficacy in psoriasis are still unknown. Major candidates for calcitriol target genes that are responsible for the calcitriol-induced terminal differentiation in keratinocytes are distinct cell cycle-associated proteins (i.e. INK4 family), including p21/WAF-1 (Holick and Reichrath 1999).

Immunomodulatory Effects in the Skin (Fig. 15.2)

It has been demonstrated that various cell types involved in immunological reactions (e.g. monocytes, T and B

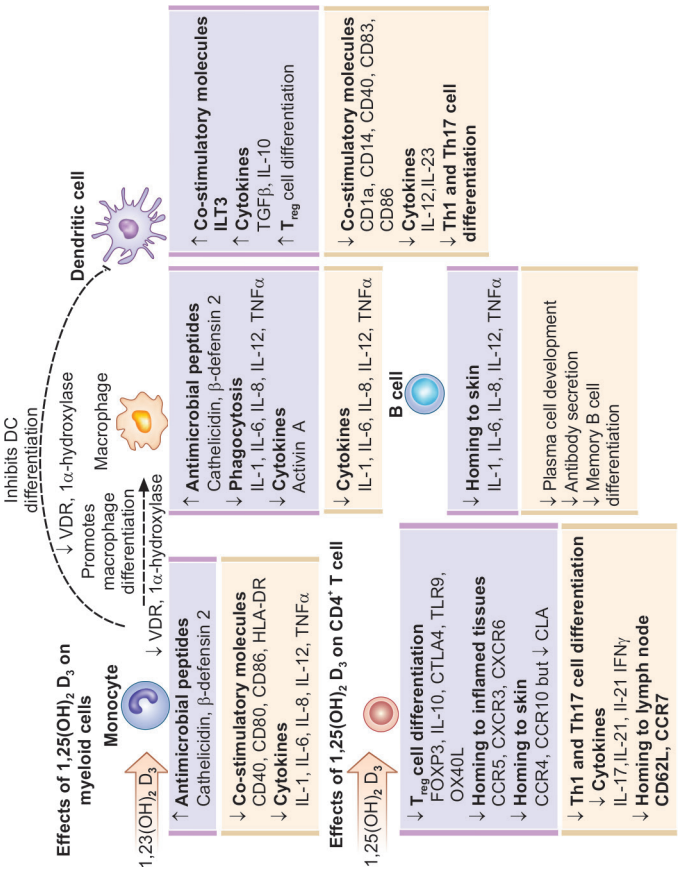


Fig. 15.2: Molecular and cytokine modulation by vit D_3 in the body

Source: Hart PH, Gorman S, Finlay JJ. Modulation of the immune system by UV radiation: more than just the effects of vitamin D? Nature Reviews Immunology. 2011;11:584-96.

lymphocytes, Langerhans cells) not only express VDR, they possess the enzymatic machinery (25-hydroxyvitamin D-1a-hydroxylase) for local synthesis of calcitriol (Holick 2007). Today, local synthesis of calcitriol in immune cells is considered to be of importance for the regulation and control of various immune responses. $1\alpha,25\text{-}(OH)_2D$ inhibits activation of T cells and induces the generation of $CD25^+/CD4^+$ regulatory T cells (Holick 2007). In dendritic cells, calcitriol inhibits maturation and induces a phenotype that promotes tolerance and inhibits immunity after stimulation with antigen. It also suppresses expression of major histocompatibility complex II (MHC II) molecules and of co-stimulatory molecules, including CD40, CD80, and CD86. Thus, production of interleukin-10 (IL-10) is stimulated and production of IL-12 inhibited, leading to suppression of T-cell activation (Griffin and Kumar 2003).

Thus vitamin D deficiency encourages the pathogenesis of many autoimmune diseases (e.g. diabetes mellitus type I) and that a sufficient vitamin D serum concentration reduces

the incidence of those diseases. At present, a connection between vitamin D and pathogenesis of atopic dermatitis and allergic contact dermatitis is being actively explored.

Other important effects of vitamin D_3 are a **cytoprotective, anti-apoptotic and antioxidant role.**

Dosage

The daily recommendation is 200 IU from birth to 50 years, 400 IU from 51 to 70 years, and 600 IU for 71 years and older. Only drinking milk is enriched with vitamin D. Cheese, yogurt, and ice cream are not required to include vitamin D enrichment; however, a new trend in some of the nutricosmetic yogurts, mentioned previously, is to add vitamin D. A few foods are rich in vitamin D, including fatty fish, such as salmon, sardines in oil, and mackerel, and fish oils, such as cod liver oil.

Vitamin D *deficiency* is considered to be present when serum 25(OH)D levels are **<20 ng/mL;** insufficiency between 20–30 ng/mL and sufficient when > 30 ng/mL (Hollis BW).

It has been reported that a requirement of **60,000–120,000 IU** per month is needed to achieve vitamin D level >30 ng/mL. This is the level at which calcium absorption from the gut is maximum (Heaney RP). Another study by Goswami et al. have reported correction of vitamin D level to normal after **8 weeks** of supplementation with weekly dose of **60,000 IU** (Goswami R). Both these studies highlight the need of regular supplementation of at least **2000 IU/day** of vitamin D supplementation to maintain normal vitamin D levels (Marwaha RK).

Vitamin D Deficiency in the Tropics

Thirty minutes of exposure of the skin over the arms and face to sunlight, without application of sunscreen, preferably between 10 am to 2 pm (as maximum ultraviolet B rays are transmitted during this time) daily is adequate to avoid vitamin D deficiency. It is essential to interpret bone mineral density (BMD) with vitamin D levels. Studies of BMD without knowing 25(OH)D status can be misleading.

Vitamin D deficiency is a common problem in India due to several factors:

- Changing *food* fads and *food habits* contribute to low dietary calcium and vitamin D intake
- High *fiber* diet containing phosphates and phytates which can deplete vitamin D stores and increase calcium requirement
- *Genetic* factors like having increased 25(OH)D-24- hydroxylase which degrades 25(OH)D to inactive metabolites
- With modernization, the number of hours spent indoor have increased thereby preventing adequate sun exposure. This is particularly true in the urban Indians

- Increased *pollution* can hamper the ultraviolet rays to adequately synthesize vitamin D in the skin
- Cultural and traditional habits prevalent in certain religions like *"Burqa"* and the *"pardah"* system in Muslims may be a cause
- Repeated and unplanned, unspaced pregnancies in dietary deficient patients can aggrevate vitamin D deficiency in the mother and the fetus

A summary of the status of vitamin D deficiency in India is given below (Harinarayan CV), based on a comprehensive meta-analysis.

- All studies uniformly point to **low** 25(OH)D levels in the populations studies **despite** abundant sunshine in our country
- All studies have uniformly documented **low dietary calcium** intake compared to Recommended Daily/Dietary Allowances (RDA) by Indian Council of Medical Research (ICMR)
- The vitamin D levels of children is very low in both urban and rural population studied
- In some of the studies it has been clearly shown that the 25(OH)D levels were directly proportional to the duration of exposure to **sunlight**. This is evident from the vitamin D status of rural population who were agricultural workers and had their chest and tarso exposed to sunlight compared to the urban population who were white collared workers. Hence, exposure to sunlight has positive effect on the vitamin D status of individuals
- Pregnant women and their newborn had low vitamin D status
- Residents of northern tip of India in Kashmir valley had low 25(OH)D levels
- **Indian paramilitary forces** who had dietary calcium well above the RDA and daily exercises in sunlight in the morning hours had better 25(OH)D levels compared to the civilian counterparts
- Dietary calcium supplementation had positive effect on 25(OH)D levels
- The effect of single course of loading doses of vitamin D (60,000 IU) does not have a lasting effect and a **maintenance dose** is needed long term. There is a need to evolve an Indian therapy protocol which is cost-effective. Vitamin D analogs have a narrow therapeutic window (should be avoided), while agents like calcirol sachets or bolus vitamin D injection have a wider therapeutic window (are more economical). Situations of hypervitaminosis D should be avoided
- Low 25(OH)D levels has its implications on lower peak bone mass and lower BMD compared to the west.

Implications of Low Vitamin D Status and Low Dietary Calcium Intake in India

- The prevalence of "sub-clinical 25(OH)D deficiency (hypovitaminosis D)" may be overlooked due to its vague clinical presentation (Fig. 15.1)
- It has important connotations in therapeutic aspect of the disease process. Vitamin D supplementation has to be considered in patients with osteoporosis (keeping in mind the hypovitaminosis D in majority of the population)
- The 25(OH)D levels and the dietary calcium pattern of the urban and rural population differs in the same region and different regions of our country. The dress code varies from latitude; season (winter/summer); religion (Purdhas in Muslims); the nature of work (white collar workers/ manual laborers), etc.
- There is an urgent need to revise the RDA of calcium and propose new guidelines for 25(OH)D for Indian population. Multicenter studies with a large sample size are required to generate normal standards and evolve those guidelines
- **Food fortification programs** have to be thought of in various parts of the country depending on their vitamin D status and dietary calcium intake
- The bone mineral density (BMD) measured in these populations could be incorrect. Early osteomalacia could co-exist with osteoporosis in the elderly population and can give fallacious BMD values misleading the diagnosis
- It may not be valid to extrapolate the normogram of BMD of the west to the Indian population (a nation with diverse culture, food habits, work culture and exposure to sunlight, especially when there are racial differences in BMD, vitamin D status, metabolism, etc.)
- Vitamin D insufficiency is associated with secondary hyperparathyroidism (SHPT), which is further amplified by inadequate calcium intake. Thus, in the background of low vitamin D levels and inadequate dietary calcium intakes, when an individual is exposed to the additional insult of an environmental toxin like fluoride, the clinical expression of the disease is altered. Various studies have shown that the effect of an environmental toxin like fluoride on bone mineral metabolism is severe and more complex in children with poor dietary calcium intake when compared to the children with adequate dietary calcium intake.

Other Causes of Vitamin D Deficiency

Conditions with fat malabsorption can predispose to vitamin D deficiency, including celiac disease, gastric bypass surgery, biliary atresia, cystic fibrosis, Crohn disease, pancreatic

Table 15.1: Features of vitamin D deficiency in children

Symptoms	Infants and adolescents	■ Seizures or tetany ■ Adolescents can complain of carpopedal spasm and limb pain
	Chronic vitamin D deficiency	■ Fraying and widening of the metaphysis, prominent costochondral joints (rachitic rosary), thinned bony cortex, and frontal bossing ■ Fractures, caries
Investigations		■ Hypophosphatemia ■ Hypocalcemia ■ Increased alkaline phosphatase ■ Increased parathyroid hormone (PTH) ■ Low levels of 25-hydroxyvitamin D

disease, and biliary disease. Liver disease, renal disease, and anticonvulsant drugs (phenytoin and phenobarbital) that interfere with vitamin D metabolism.

Inadequate diet from autism, food allergies, in adolescents, and in elderly or disabled individuals can inadvertently cause vitamin D deficiency. Premature infants have an inadequate store of vitamin D at birth and so have a greater requirement of dietary vitamin D than full-term infants to meet needs for growth (Table 15.1). Similarly, infants born to vitamin D-deficient mothers have inadequate stores at birth. In general, breast milk does not provide enough daily vitamin D in exclusively breastfed infants without sun exposure.

Uses

Psoriasis

Before launching clinical trials in 1985, MacLaughlin and associates reported that psoriatic fibroblasts were partially sensitive to the antiproliferative effects of $1,25(OH)_2D_3$ (MacLaughlin et al. 1985). This observation led these researchers to speculate that calcitriol may be effective in the treatment of hyperproliferative skin diseases such as psoriasis. The second line of investigation resulted from a clinical observation. In 1985, Morimoto and Kumahara reported that a patient who was treated orally with 1α-hydroxyvitamin D_3 for osteoporosis had a drastic remission of psoriatic skin lesions (Morimoto and Kumahara 1985). In a follow-up study, they demonstrated that almost 80% of 17 patients with psoriasis who were treated orally with 1α-hydroxyvitamin D_3 at a dose of 1.0 mg/day for up to 6 months showed clinically significant improvement (Morimoto et al. 1986).

Up to now, various studies reported that numerous vitamin D analogs, including calcitriol, calcipotriol, tacalcitol,

maxacalcitol, and beocalcidiol, are effective and safe for topical treatment of psoriasis, though in clinical practice, steroids still are written more often than vitamin D_3 analogs, at least in India.

Ichthyosis

A double-blind, bilaterally paired, comparative study showed the effectiveness of topical treatment with calcipotriol ointment on congenital ichthyoses (Lucker et al. 1994). Reduced scaling and roughness on the calcipotriol-treated side was shown in all patients with lamellar ichthyosis and bullous ichthyotic erythroderma of Brocq. The only patient with Comel-Netherton syndrome was treated and showed mild improvement, and the only patient suffering from ichthyosis bullosa of Siemens who was treated with calcipotriol did not show any change in severity on the calcipotriol-treated side compared to the vehicle-treated side.

Conversely patients with ichthyosis may develop vitamin D deficiency. Of the different clinical phenotypes of ichthyosis, both autosomal recessive congenital ichthyosis (ARCI) and epidermolytic ichthyosis (EI) were found to have significantly increased PTH, ALP and radiological rickets scores compared with common ichthyosis (Sethuraman G).

Scleroderma

Some case reports point at the efficacy of vitamin D analogs for the treatment of scleroderma. Humbert et al. (1993) reported that oral administration of calcitriol 1.0–2.5 mg/day alleviates skin involvement, probably by inhibiting fibroblast proliferation and dermal collagen deposition (Slominski A).

Vitiligo

A great variety of therapeutic agents are being used for the treatment of vitiligo, but treatment remains a challenge. Recent investigations indicate that vitamin D analogs may be efficient and safe in the treatment of vitiligo. Oral vitamin D_3 (vitamin D_3 35,000 IU once daily for 6 months) has been shown to achieve 25–75% repigmentation in a study (Finamor DC).

Vitamin D and Other Skin Diseases

A number of case reports have demonstrated positive effects of topical treatment with vitamin D analogs in a variety of skin diseases, such as transient acantholytic dermatosis (Grover's disease), inflammatory linear verrucous epidermal nevus (ILVEN), disseminated superficial actinic porokeratosis, pityriasis rubra pilaris, epidermolytic palmoplantar keratoderma of Vorner, and Sjögren-Larsson syndrome. These

promising observations will have to be further evaluated in clinical trials.

Side Effects

With so much said about vitamin D deficiency and insufficiency, one must be careful not to overenthusiastically overtreat vitamin D deficiency without actually monitoring vitamin D levels and land up with hypervitaminosis D. Hypercalcemia, constipation, decreased appetite, lethargy, dehydration, failure to thrive (in children), polyuria, polydipsia, nausea, vomiting, abdominal pain, nephrocalcinosis and headache can be the common clinical features of hypervitaminosis D. Preliminary reports also suggest that hypervitaminosis D due to an increased 1-alphahydroxylase activity seems to be a cause of the premature aging in mice.

Chronic ingestion of 50 to 100 times normal physiologic requirement of vitamin D (>40,000 IU/day) can lead to severe hypercalcemia. It requires prompt therapy in the form of intravenous fluids, oral prednisolone, restriction of calcium in diet and, some patients may require pamidronate infusion for reducing hypercalcemia.

BIBLIOGRAPHY

1. Bikle DD, Neumanic MK, Gee E, Elias P. 1, 25-dihydroxyvitamin D_3 production by human keratinocytes. J Clin Invest. 1986;78:557–66.
2. Finamor DC, Sinigaglia-Coimbra R, Neves LC, Gutierrez M, Silva JJ, Torres LD, et al. A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of vitiligo and psoriasis. Dermatoendocrinol. 2013. 1;5(1):222-34.
3. Gniadecki R. Stimulation versus inhibition of keratinocyte growth by 1,25-dihydroxyvitamin D_3: dependence on cell culture conditions. J Invest Dermatol. 1996;106(3):510-6.
4. Goswami R, Gupta N, Ray D, et al. Pattern of 25-hydroxyvitamin D response at short (2 months) and long (1 year) interval after 8 weeks of oral supplementation with cholecalciferol in Asian Indians with chronic hypovitaminosis D. Br J Nutr. 2008;100:526-9.
5. Harinarayan CV, Joshi SR. Vitamin D status in India—its implications and remedial measures. J Assoc Physicians India. 2009;57:40-8.
6. Heaney RP. Vitamin D depletion and effective calcium absorption. J Bone Min Res. 2003;18:1342.
7. Holick MF, Reichrath J. Clinical utility of 1,25-dihydroxyvitamin D_3 and its analogues for the treatment of psoriasis. In: Holick MF (Ed). Vitamin D: physiology, molecular biologic and clinical aspects. Totowa: The Humana Press Inc; 1999. pp. S357-73.
8. Holick MF. Vitamin D deficiency. NEJM. 2007;357:266-81.

9. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of Vitamin D insuffiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 2005;135:317-22.
10. Humbert P, Dupond JL, Agache P, Laurent R, Rochefort A, Drobacheff C, et al. Treatment of scleroderma with oral 1,25-dihydroxyvitamin D_3: evaluation of skin involvement using non-invasive techniques. Results of an open prospective trial. Acta Derm Venereol Stockh. 1993;73:449-51.
11. Lucker GP, van de Kerkhof PC, van Dijk MR, Steijlen PM. Effect of topical calcipotriol on congenital ichthyosis. Br J Dermatol. 1994;131:546-50.
12. MacLaughlin JA, Gange W, Taylor D, Smith E, Holick MF. Cultured psoriatic fibroblasts from involved and uninvolved sites have partial but not absolute resistance to the proliferation-inhibition activity of 1,25-dihydroxyvitamin D_3. Proc Natl Acad Sci USA. 1985;82:5409-12.
13. Manggau M, Kim DS, Ruwisch L, Vogler R, Korting HC. 1a,25-dihydroxyvitamin D_3 protects human keratinocytes from apoptosis by the formation of sphingosine-1-phosphate. J Invest Dermatol. 2001;117:1241-9.
14. Marwaha RK, Tandon N, Garg MK, et al. Vitamin D status in healthy Indians aged 50 years and above. J Assoc Physicians India. 2011;59:703-7.
15. Morimoto S, Kumahara Y. A patient with psoriasis cured by 1a-hydroxyvitamin D_3. Med J Osaka. Univ. 1985;35(3-4):51-4.
16. Reichrath J, Perez A, Chen TC, Kerber A, Bahmer FA, Holick MF. The effectiveness of topical 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2$ D_3) application in the treatment of psoriasis: an immunohistological evaluation. Acta Derm Venereol. 1997b;77:268-72.
17. Sethuraman G, Sreenivas V, Yenamandra VK, Gupta N, Sharma VK, Marwaha RK, et al. Threshold levels of 25-hydroxyvitamin D and parathyroid hormone for impaired bone health in children with congenital ichthyosis and type IV and V skin. Br J Dermatol. 2015;172(1):208-14.
18. Slominski A, Janjetovic Z, Tuckey RC, Nguyen MN, Bhattacharya KG, Wang J, et al. 20S-hydroxyvitamin D_3, noncalcemic product of CYP11A1 action on vitamin D_3, exhibits potent antifibrogenic activity in vivo. J Clin Endocrinol Metab. 2013;98(2):E298-303.

VITAMIN E

Natural vitamin E is the most important lipid-soluble, membrane-bound antioxidant in the body. As a free-radical quencher, vitamin E deactivates these aggressive radicals and terminates damaging chain reactions, protecting primarily the fatty components of cell membranes. Vitamin E is synthesized only in plants, so all animals require a nutritional source. The highest levels in the body are in fatty tissue where vitamin E is stored. Vitamin E is delivered to the skin by sebum (Podda et al. 1996; Thiele 2001).

As the stratum corneum is the outermost defense of the body, this layer is the first to absorb the oxidative stress of sunlight and pollution. Vitamin E is depleted by this exposure to both UV and to the ozone of environmental pollution, so its concentration is highest at the lower levels of the stratum corneum with a decreasing gradient outward. Thus, increasing the skin's surface concentration of vitamin E by topical application is especially important. The lipophilic structure of vitamin E enhances absorption and makes it cosmetically attractive for application as a moisturizer.

Metabolism

Several forms of vitamin E exist in natural dietary sources. The form found in mammalian tissues with by far the greatest biological activity is pure, nonesterified RRR-α-tocopherol (or d-α-tocopherol) with three methyl groups on the 6-chromal ring. *Humans* use predominantly α-*tocopherol* because a specific α-tocopherol transfer protein selectively transfers α-tocopherol into lipoproteins (Azzi et al. 2000). The other natural forms are β, γ, and δ, which contain only one or two methyl groups on the 6-chromal ring.

Synthetic vitamin E is *"dl"* or *"all-rac,"* a mixture of eight stereoisomers. These synthetic isomers are esterified (to acetates and succinates) for use in commercial vitamins and some topical formulations because the esters are far more stable. This ester must be hydrolyzed before there is any biological activity, a reaction that readily occurs in the stomach after oral ingestion or in cell and organ culture but is very slow after topical application. The skin has only a limited ability to cleave the esterified forms of vitamin E to the active free tocopherol form, so the antioxidant potential of the esters is minimal (Gensler et al. 1996). Furthermore, the all-rac form of vitamin E has been reported to cause allergic contact dermatitis and erythema multiforme when applied topically. No such adverse reaction has been reported with d-α-tocopherol.

Uses and Mode of Action

Ultraviolet Protection

Many studies have demonstrated protection from UV-induced damage to the skin by applying various topical vitamin E formulations. Various forms of topical vitamin E that are less metabolically potent when applied topically have demonstrated protection from the acute (Burke et al. 2000), UV-induced damage of inflammation (erythema, sunburn) and hyperpig- mentation (tanning) as well as protection from the chronic UV-induced damage of actinic keratosis and skin cancer.

The kind of preparation used is crucial and d-α-tocopherol and d-α-tocopheryl succinate were proven effective in protecting against all acute and chronic UV-induced damage, with d-α-tocopherol most effective for all parameters (i.e. decreasing sunburn, tanning, skin cancer incidence) (Burke et al. 2000).

The results tabulated below (Burke et al. 2000) show that topical d-α-tocopherol inhibited blistering sunburn by 73% and tanning by 40%. The topical ester *d-α-tocopheryl succinate* was more effective than oral vitamin E but less effective that the nonesterified topical d-α-tocopherol for both inhibition of acute sunburn and tanning (Burke et al. 2000).

Treatment	*Blistering sunburn(%)*	*Degree of tanning*
d-α-tocopherol lotion (5%)	27	1.93
d-α-tocopheryl succinate lotion (5%)	67	2.07
Oral d-α-tocopheryl acetate	73	2.43
Vehicle lotion	100	3.75

Cancer Prevention

A topical *d-α-tocopherol* was most effective in decreasing the incidence of UV-induced skin cancer, although all three forms of vitamin E were effective at earlier time points, with topical d-α-tocopheryl succinate almost as effective long term as topical d-α-tocopherol.

Melasma

A new formulation of vitamin E with *both* dl-α-tocopherol in lecithin and dl- α-tocopheryl ferulate in lecithin was found to inhibit the enzyme tyrosinase and to decrease melanogenesis in human melanoma cells (Ichihashi et al. 1999).

Photodamage

Clinically, vitamin E reverses photoaging dramatically, decreasing unattractive wrinkles and solar lentigos. The best effect is with *d-α-tocopherol* (5%) once daily for 4 months.

Combination

Vitamins C and E act synergistically in cells to provide antioxidant protection: Vitamin E is located in the cellular membranes, where it quenches free radicals, and vitamin C is plentiful in the neighboring aqueous cytoplasm. With a lower redox potential, vitamin C can reduce the oxidized vitamin E, thereby regenerating vitamin E activity and eliminating

the need for nutritional replacement (Chan 1993). In high doses, vitamin C with vitamin E can protect against UV-induced erythema in humans whereas either vitamin alone is ineffective (Fuchs and Kern 1998). Formulating l-ascorbic acid (15%) with α-tocopherol (1%) was found to give four-fold protection against UV-induced erythema.

BIBLIOGRAPHY

1. Azzi A, Breyer I, Feher M, et al. Specific cellular responses to alpha-tocopherol. J Nutr. 2000;131(suppl):369-75.
2. Burke DE, Clive J, Combs GF Jr, et al. The effects of topical and oral vitamin E on pigmentation and skin cancer induced by ultraviolet irradiation in Skh:2 hairless mice. Nutr Cancer. 2000;38:87-97. Published by Taylor and Francis, Ltd.
3. Chan AC. Partners in defense, vitamin E and vitamin C. Can J Physiol Pharmacol. 1993;71:725-31.
4. Fuchs J, Kern H. Modulation of UV-light-induced skin inflammation by d-α-tocopherol and L-ascorbic acid: a clinical study using solar simulated radiation. Free Radic Biol Med. 1998;25:1006-12.
5. Ichihashi M, Funasaka Y, Ohashi A, et al. The inhibitory effect of D L-alpha-tocopheryl ferulate in lecithin on melanogenesis. Anticancer Res. 1999;19:3769-74.
6. Podda M, Weber C, Traber MG, Packer L. Simultaneous determination of tissue tocopherols, tocotrienols, ubiquinols, and ubiquinones. J Lipid Res. 1996;37:893-901.
7. Thiele JJ. Oxidative targets in the stratum corneum: a new basis for antioxidative strategies. Skin Pharmacol Appl Skin Physiol. 2001;14:87-91.

CAROTENOIDS (VITAMIN A)

(Antoxid HC: **Beta carotene** 30 mg; **Selenium** 200 μg; **Zinc sulphate** 27.5 mg; **Manganese** 2 mg; **Copper** 1 mg.)

Carotenoids are derivatives of vitamin A and have found widespread use in nutricosmetics and in cosmeceuticals due to the established topical antiaging benefits associated with the prescription retinoid tretinoin. The carotenoids are a large family of orange-, red-, and yellow-appearing substances that perform vital antioxidant roles when ingested but are less well established as topical antioxidants. The currently popular nutricosmetic carotenoids include astaxanthin, lutein, and lycopene.

Dietary Carotenoids

Various classes are derived by modification of the basic structure (Fig. 15.3).

Carotenoids are divided into two major classes: carotenes and xanthophylls. The most common dietary **carotenes** include the acyclic *lycopene* and its biosynthetic *downstream* cyclic products β-*carotene* and α-*carotene*. **Xanthophylls**

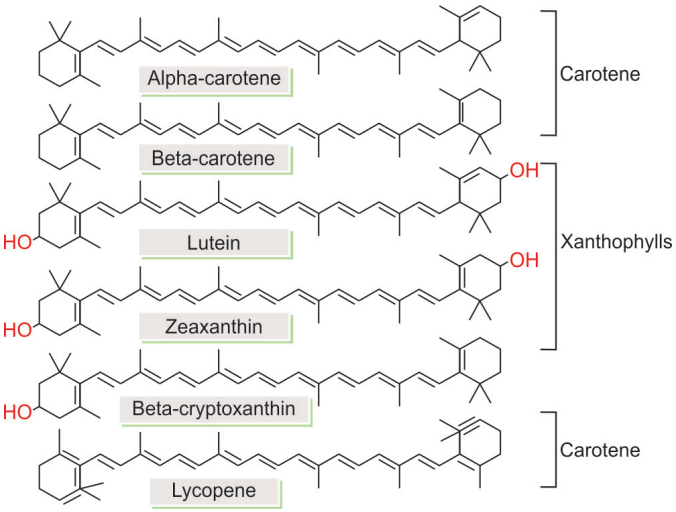


Fig. 15.3: A graphical representation of the carotenoids

are also known as oxycarotenoids due to the presence of at least one oxygen molecule in the structure. Xanthophylls are more hydrophilic than carotenes. **Lutein, zeaxanthin, and β-cryptoxanthin** represent the most common xanthophylls found in the human diet.

Because de novo synthesis of carotenoids is not possible, humans have to depend on dietary sources to obtain them. Carotenoids appear in shades of yellow and orange to red, and they are commonly found in fruits and vegetables of those colors. Orange fruits and vegetables (e.g. carrot, mango, orange-flesh sweet potato, apricots, squash) contain β-carotene, α-carotene, and b-cryptoxanthin, which are the three most common provitamin A carotenoids. On the other hand, green vegetables (e.g. spinach, kale, collard greens), are excellent sources of β-carotene, lutein, and zeaxanthin but have their colors masked by the presence of chlorophyll. Red fruits and vegetables (e.g. tomato, watermelon, guava, pink grapefruit) are rich sources of lycopene.

Being fat-soluble, β-carotene absorption is increased by fatty meals and processing, such as mashing, cooking, or pureeing. Its absorption is decreased by dietary fiber. It is stored in the liver and adipose tissue and excreted through the colon and sebaceous gland secretions in the skin. The recommended daily intake depends on age and gender, ranging from **400 to 1,300 µg**.

The main purpose of the existence of these pigments in plants is to preserve the photosynthetic complex by

protecting it against damage by solar UV. Indirect sources of carotenoids include seafood and enriched egg.

Metabolism

Absorption of carotenoids from a meal requires several processes, including (1) release of carotenoids from a food matrix, (2) incorporation into lipid droplets, (3) transfer to mixed bile salt micelles in the lumen of the small intestine, (4) uptake of carotenoid molecules across the apical surface of intestinal mucosal cells from bile salt micelles, (5) incorporation of carotenoids and their metabolites into chylomicrons, and (6) efflux of chylomicrons across the basolateral membrane into the lymphatic circulation (Fig. 15.4).

Carotenoids Biodistribution to Skin

Once carotenoids clear the intestinal epithelial barrier and reach the systemic circulation via lymphatics, deposition occurs in hepatic and extrahepatic tissues including skin. Carotenoids stored in hepatic tissues can also be mobilized for distribution to extrahepatic tissues in times of need. Skin

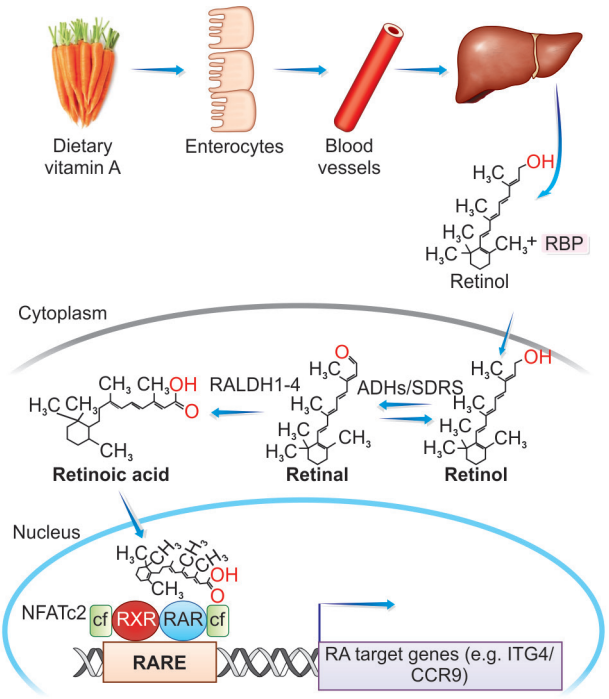


Fig. 15.4: Overview of RA metabolism and signaling. Dietary vitamin A is converted into retinal via alcohol dehydrogenase (ADHs) or short-chain dehydrogenase/reductase (SDRs) and then oxidized to RA by the RALDHs. RA acts by binding the nuclear receptors RAR and RXR to form a transcriptional complex with additional cofactors (CF; which may include NFATc2) that drives the transcription of RARE-containing genes

derived from subjects undergoing abdominoplasty suggests that apolar carotenoids (e.g. β-carotene, phytoene, lycopene) and their isomers constitute approximately 70% of the total pool; xanthophylls such as lutein and zeaxanthin are present at lower concentrations (Hata et al. 2000). However, it should be noted that dietary intake based on the availability of carotenoid-enriched foods and cultural traditions in different regions of the world may influence this profile.

Although stereoisomers of carotenoids mainly exist as the all-trans configuration in nature, cis isomers are also present in skin (Stahl et al. 1992). A high concentration of cis isomers in skin may be due to preferential uptake of cis isomers from the circulation, isomerization in biological systems after absorption, or both. Carotenoids exhibit a concentration gradient in the layers of skin with a higher amount in the dermis (inner layer) and lower levels in the stratum corneum (outer layer). Regional variations may also be observed in the skin carotenoid level; indeed, higher concentrations of total carotenoids are measured in skin of the *forehead*, *palm* of the hand, and *dorsal skin*, whereas lower levels are present in the arm and the back of the hand (Bayerl et al. 2003).

Occasionally, consumption of diets or supplementation containing more than 30 mg carotenoids per day for more than 4 weeks may result in yellowish discoloration of the skin, called carotenodermia. This condition is reversible, with the usual skin color restored upon cessation of the supplementation.

Deficiency States

Vitamin A intake can be inadequate (Table 15.2) in individuals with restrictive diets, such as those with eating disorders, vegans, and alcoholics. Autistic individuals are also at risk for vitamin A deficiency because of food refusal or restrictive dietary therapies.

Table 15.2: Features of vitamin A deficiency

Symptoms	Eye	Xerophthalmia, conjunctival xerosis, Bitot spots, (white keratinized lesions). With time, corneal xerosis progresses to corneal ulceration and keratomalacia
	Skin	Phrynoderma: Keratotic follicular papules on the anterolateral thighs and posterolateral upper arms which can spread to the extensor extremities, shoulders, abdomen,back, buttocks, and posterior neck. Xerosis is usually present
Treatment		Treatment is 50,000 to 200,000 IU vitamin A, with the dose depending on age and the schedule depending on clinical severity

Conditions associated with fat malabsorption, such as cystic fibrosis, pancreatic insufficiency, biliary disease, and bowel bypass surgery, also predispose to vitamin A deficiency.

Chronic diarrhea from celiac disease, inflammatory bowel disease, chronic intestinal infection, and colitis can result in decreased vitamin A absorption.

Defective hepatic storage in liver disease secondary to diabetes, cirrhosis, or thyrotoxicosis increases the risk of deficiency.

Uses of Carotene

- Erythropoetic protoporphyria
- Polymorphic light eruption
- Reduction of negative effects of phototoxic drugs
- Hydroa vacciniforme
- Solar urticaria
- Lupus erythematosus
- Vitiligo
- Acne excoriee
- Chloasma
- Multiple dysplastic nevi
- Skin aging

Beta-carotene is indicated in erythropoietic protoporphyria and other photosensitive diseases. Additionally, it might be used to reduce the negative effects of phototoxic drugs (Box above). For short vacation periods in regions with high UV exposure, beta-carotene (30 mg) is recommended, particularly in combination with alpha-tocopherol and ascorbic acid (Gollnik HPM). Smoking habits, alternative UV protection methods using textiles, and physical/chemical sunscreens should be discussed with the patient to ensure that long-term beta-carotene treatment is administered only after weighing the risks and benefits.

Photoprotection

Upon UV exposure, reactive oxygen species (ROS), which are constantly generated in skin, may be rapidly neutralized by nonenzymatic and enzymatic antioxidants substances. In consequence, cellular macromolecules (i.e. lipids, proteins, DNA) are protected from oxidation and a pro-oxidant/antioxidant balance is maintained, resulting in cell and tissue stabilization. Carotenoids such as β-carotene, lycopene, zeaxanthin, and lutein have potent antioxidant functionality and are among the most effective naturally occurring scavengers of single oxygen and peroxyl radicals (Cantrell et al. 2003).

A meta-analysis (Kopcke and Krutmann 2008) of seven studies demonstrated that **β-carotene** supplementation is

Table 15.3: Effect of β-carotene supplements on photoprotection

Intervention dose (source)	*Duration (weeks)*	*Results*
β-Carotene		
90 mg/day	3	No protection
15 mg/day (supplement)	8	No effect
180 mgl/day	10	MED increased
24 mg/day *(D. salina)*	12	Erythema less pronounced
24 mg/day *(D. salina)*	12	Erythema less pronounced
30 mg/day (supplement)	12	Erythema less pronounced
30 mg/day *(D. salina)*	8	MED increased
60 mg/day *(D. salina)*	8	
90 mg/day *(D. salina)*	8	
Lycopene		
16 mg/day (tomato paste)	10-12	Erythema less pronounced
10 mg/day (synthetic lycopene)	12	Erythema less pronounced
10 mg/day (tomato extract: Lyc-o-Mato)		
10 mg/day (beverage: Lyc-o-Guard-Drink)		
16 mg/day (tomato paste)	12	Erythema less
10.2 mg/day (synthetic)		Pronounced except for synthetic plycopene
Carotenoid mix		
Lycopene		
60 mg/day (p-carotene)+ 90 mg/day (canthaxanthin)	4	No protection
8 mg/day (p-carotene) + 8 mg/day (lycopene) + 8 mg/day lutein pronounced	12	Erythema less
5.1 mg/day (p-carotene, carrot juice)+ 10 mg (lycopene, synthetic)	10	Erythema less pronounced except for synthetic lycopene

Abbreviations: D. salina (Dunaliella salina) is a type of halophile green micro-algae; *MED, minimum* erythema dose.

efficient in providing sun protection against the development of sunburn (Table 15.3). The photoprotective effect is observed only in studies providing a daily dose of **20 mg** for a minimum of **10 weeks** of supplementation.

Lycopene has also been used for its photoprotective effect (Aust et al. 2005). Daily intake of **10 mg** of lycopene was provided from three sources: a synthetic lycopene, a tomato extract (Lyc-o-Mato), or a drink containing solubilized Lyc-o-Mato (Lyc-o-Guard-Drink). After **12 weeks** of supplementation, erythema formation induced by UV exposure was significantly lower with each of the three

lycopene treatments. Compared to week 0, the reductions were of 25%, 38%, and 48% for the synthetic lycopene, the tomato extract, and the drink, respectively.

Stahl and coworkers (Stahl et al. 2006) also demonstrated this effect in a study where four lycopene sources—tomato paste, lycopene-rich carrot juice, lycopene drink, synthetic lycopene—were used to supply lycopene (8.2–16.0 mg/day) to volunteers over a period of 10–12 weeks. The paste, juice, and drink- induced efficient photoprotection by 40%, 45%, and 50%, respectively. The synthetic lycopene showed a trend but it did not reach statistical significance (Stahl et al. 2006). Human intervention studies with a mix of carotenoids (i.e. β-carotene, lycopene, lutein) confirmed the photoprotective effect of carotenoids (Heinrich et al. 2003). Erythema development was diminished in subjects whose diets were supplemented with β-carotene (24 mg/day) or a carotenoid mixture consisting of β-carotene, lutein, and lycopene (8 mg each/day) for 12 weeks (Stahl et al. 2001).

Future Perspectives on Systemic Photoprotection by Carotenoids

Protection against UV-induced erythema, or sunburn, does *not* necessarily mean protection against *skin cancer*. Although evidence is available to support a role for dietary carotenoids (notably β-carotene, lutein, and lycopene) in protecting skin against sunburn development, it is not clear whether endogenous carotenoids can positively affect skin health by also interfering with UV-induced pathways that lead to DNA mutations, immune suppression, and skin cancer development.

The concept of endogenous dietary skin photoprotection is that it provides a systemic maintenance level at sensitive dermal and epidermal target layers—beyond those reached by topical and temporary coverage through the use of sunscreen. Although endogenous protection through individual dietary components (in terms of the sun protection factor) may be considerably lower than that achieved using topical sunscreens and take considerably longer to be reached, an increased lifelong overall systemic protection via dietary supply may contribute significantly to skin health and complement the use of sunscreens in protecting the skin against the damaging effects of solar UV exposure.

Aging, and Skin Cancer

Beta-carotene increases the immune defense by enhancing cytotoxicity of macrophages against tumor cells. It also increases lymphocyte production and T- and B- cell activity. By modulating immune defense, beta-carotene might have

an impact on carcinogenesis. In addition, beta-carotene may modulate skin carcinogenesis by a reduction of lipid peroxidation in human skin, either as a free radical scavenger or as a specific lipoxygenase inhibitor.

Clinical proof of its role in preventing cancer is *not* confirmed. Recently, it was shown that the daily use of oral beta-carotene (30 mg per day, n = 1621) for 4.5 years did not reduce the incidence of basal cell or squamous cell carcinoma; in contrast, daily *sunscreen use* resulted in a reduction in incidence of the latter (Green A).

Dysplastic Nevi

Patients with multiple nevi profit from long-term beta-carotene supplementation only in highly UV-exposed body sites in respect to a slower development of new nevi and a reduction of dysplastic nevi in comparison to controls (Bayerl C). The effect of beta-carotene on the reduced development of new melanocytic nevi on the lower arm and feet might be explained by a retardation of the presumed manifestation of damaged cells in these UV-exposed body sites.

BIBLIOGRAPHY

1. Bayerl C, Schwarz B, Jung EG. A three-year randomized trial in patients with dysplastic naevi treated with oral beta-carotene. Acta Derm Venereol. 2003;83:277-81.
2. Cantrell A, et al. Singlet oxygen quenching by dietary carotenoids in a model membrane environment. Arch Biochem Biophys. 2003;412(1):47-54.
3. Gollnik HPM, Hopfenmüller W, Hemmes C, Chun SC, Schmid C, Sundermeier K, et al. Systemic beta-carotene plus topical UV-sunscreen are an optimal protection against harmful effects of natural UV-sunlight: results of the Berlin-Eilath study. Eur J Dermatol. 1996;6:200-5.
4. Green A, Williams G, Neale R, et al. Daily sunscreen application and beta-carotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomized controlled trial. Lancet. 1999;354:723-9.
5. Hata TR. et al. Non-invasive Raman spectroscopic detection of carotenoids in human skin. J Invest Dermatol. 2000;115(3):441-8.
6. Heinrich U, et al. Supplementation with beta-carotene or a similar amount of mixed carotenoids protects humans from UV-induced erythema. J Nutr. 2003;133(1):98-101.
7. Kopcke W, Krutmann J. Protection from sunburn with beta-carotene-a meta-analysis. Photochem Photobiol. 2008;84(2):284-8.
8. Stahl W, et al. Lycopene-rich products and dietary photoprotection. Photochem Photobiol Sci. 2006;5(2):238-42.
9. Stahl, W. et al. Dietary tomato paste protects against ultraviolet light-induced erythema in humans. J Nutr. 2001;131(5):1449-51.

10. Stahl W, Sies H. Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans. J Nutr. 1992;122(11):2161-6.

VITAMIN K

Vitamin K is necessary for synthesis of several coagulation factors in the liver: factor II, factor VII, factor IX, factor X, protein C, and protein S.

Dietary vitamin K occurs as phylloquinone (vitamin K_1) and is found in green leafy vegetables, liver, brussel sprouts, lentils, plant oils, and soybeans.

Absorption and Distribution

It is absorbed through active transport in the upper small intestine. Gastrointestinal bacteria synthesize approximately 50% of daily vitamin K requirements as menaquinone (vitamin K_2) that is absorbed passively in the small intestine.

RDA: Age and gender determine adequate daily intake, which ranges from **2 to 120 μg**.

Deficiency States

Clinical vitamin K deficiency can be found in **five** clinical scenarios: decreased intake, fat malabsorption, antibiotic therapy, use of vitamin K-inhibiting medications, and neonates.

- **Diet:** Vitamin K deficiency can develop in individuals with limited diets, such as anorexics, elderly, and alcoholics, because of inadequate intake
- Vitamin K is a fat-soluble vitamin, so absorption is impaired by fat malabsorption syndromes, such as cystic fibrosis, liver disease, biliary atresia, α-1-antitrypsin deficiency, celiac disease, and Crohn disease
- Prolonged **antibiotic therapy** can eradicate intestinal bacteria that synthesize menaquinone. Coumadin inhibits vitamin K epoxide reductase, an important enzyme in vitamin K recycling. High doses of salicylates also inhibit vitamin K epoxide reductase. Cephalosporin antibiotics, phenytoin, isoniazid, cholestyramine, and rifampin can inhibit vitamin K metabolism.
- **Neonatal vitamin K deficiency bleeding** (VKDB), previously called **hemorrhagic disease of the newborn**, is classified as early, classical, or late. Neonates are born with a low vitamin K store because of poor transplacental transfer and lack of gastrointestinal bacteria for synthesis.

Early VKDB occurs during the first 24 hours of life and is typically seen in infants born to mothers who take medications

that interfere with vitamin K metabolism, such as those listed above. *Classical* VKDB occurs between days 2 and 7 of life in infants with inadequate intake or breastfed infants because vitamin K concentrations in breast milk are relatively low. *Late VKDB* occurs after day 8, most commonly between 3 and 8 weeks, in breastfed infants without vitamin K prophylaxis or those with underlying fat malabsorption diseases. Neonates have a natural nadir in vitamin K level after birth, with breastfed infants reaching a lower level than formula-fed infants even if given prophylactic vitamin K.

Clinical features: Vitamin K deficiency presents as areas of hemorrhage, purpura, and ecchymoses resulting from disruptions in the coagulation cascade. Cutaneous, gastrointestinal, genitourinary, and retroperitoneal bleeding is common.

Early VKDB commonly presents with cephalic (cephalhematoma, intracranial, scalp electrode sites), intrathoracic, intra-abdominal, umbilical, or gastrointestinal bleeding. Gastrointestinal and umbilical bleeding are most common in *classical VKDB,* but cutaneous, nasal mucosal, and postcircumcision bleeding can also occur. *Most late VKDB* presents with intracranial hemorrhage that can lead to severe neurologic damage and even death.

Investigations

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are *frequently* prolonged. Serum vitamin K levels can also be measured.

Treatment

Neonates routinely receive a single prophylactic intramuscular dose of 0.5 to 1.0 mg of vitamin K at birth. Acute bleeding secondary to vitamin K deficiency is treated with fresh frozen plasma or prothrombin complex concentrate. Bleeding and prothrombin time should improve within 1 hour. *Vitamin K deficiency* is treated with intramuscular phytonadione, *2 mg* in children and *5 to 10 mg* in adults.

WATER-SOLUBLE VITAMINS

VITAMIN B_2 (RIBOFLAVIN)

Riboflavin, in its biologically active forms, flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), is an essential cofactor in numerous metabolic and oxidation reduction reactions. It is also involved in conversion of pyridoxine phosphate to pyridoxal phosphate in vitamin B_6 metabolism.

Food: Milk, dairy products, organ meats, fatty fish, eggs, green leafy vegetables, whole grains, and enriched breads are dietary sources of riboflavin.

Recommended dietary allowance: The recommended daily intake ranges from 0.3 to 1.6 mg, depending on age and gender.

Deficiency States

Deficiency can be caused by inadequate dietary intake, malabsorption, and phototherapy.

Riboflavin deficiency is endemic in areas that depend on an unenriched cereal diet, such as rural India, China, and Iran. Breastfed infants of riboflavin-deficient mothers are at risk because breast milk riboflavin levels reflect maternal levels. Infants weaned to nonmilk products are also at risk. Concurrent protein-energy malnutrition confounds riboflavin deficiency because catabolic states increase the renal loss of riboflavin. Alcoholism, anorexia nervosa, advanced age, and adolescence are also risk factors for riboflavin deficiency because of inadequate intake. Medications such as chlorpromazine and other tricyclic medications can inhibit riboflavin transport in the small intestine. Malabsorption after bariatric surgery is another more recently described predisposing factor.

Clinical Features

Signs of chronic riboflavin deficiency present 3 to 5 months after the initiation of a riboflavin-deficient diet and are often described as *oro-oculo-genital syndrome*. In clinical practice often minor or incomplete variants of this clinical picture are often seen:

- *Angular stomatitis* begins as small papules at the corner of the mouth that enlarge, macerate, fissure, and bleed as it extends laterally from mucocutaneous junction
- *Cheilitis* presents as erythema, xerosis, and fissuring of the lips
- *Lingual papillae* are prominent in early glossitis, but eventually the papillae are lost and the entire tongue becomes smooth and magenta
- *A seborrheic* dermatitis-like eruption forms on the nasolabial folds, nasal ala, nasal bridge, forehead, cheeks, and posterior auricular area. In elderly individuals, this eruption involves facial creases, especially around the eyes and nose
- Plugging of the sebaceous glands can be seen around the nose

- Erythema, lichenification, and crusting of the *scrotum* can extend to involve the inner thighs and is more common than vulvar involvement. The dermatitis is more prone to develop in the inguinal area of infants and the perineal and buttock area of incontinent patients because it favors sites that are prone to chafing and minor trauma
- Ocular manifestations include photophobia, conjunctivitis, and corneal vascularization.

Treatment

Riboflavin treatment is 1 to 2 mg/d in infants and children or 10 to 20 mg/d in adults

VITAMIN B_3 (NIACIN)

Niacin (nicotinic acid) is converted into nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADPH), which are essential cofactors in hundreds of reactions in the human body.

Food source: It is readily found in meat, poultry, nuts, eggs, fish, dry beans, and fortified grains. Trigonelline, found in coffee, can also be converted to niacin by heat and acid. Therefore, coffee bean roasting can increase the niacin content of coffee beans. Maize and jowar (a grain consumed in India) contain niacin in an inaccessible form. The high leucine content of these two grains binds niacin and makes it unabsorbable.

Niacin can also be synthesized from dietary tryptophan, which requires vitamin B_2 and B_6. Approximately half of the body's niacin occurs through conversion from tryptophan: 60 mg of tryptophan is converted to 1 mg of niacin.

Recommended dietary allowance: The recommended daily intake is 13 to 20 mg, depending on age and gender.

Deficiency States

Niacin deficiency, **pellagra**, is endemic in areas with a high grain, low meat diet, including Africa, China, Indonesia, and India. In many countries, pellagra has become less common due to the fortification of rains and breads. Decreased dietary intake occurs in anorexia nervosa, other psychiatric disease, alcoholism, food allergies, and in impoverished individuals.

Impaired niacin and tryptophan absorption occurs in malabsorption syndromes, such as ulcerative colitis, Crohn disease, gastrostomy, gastrectomy, jejunoileitis, and gastrointestinal bypass. **Hartnup** disease is a rare autosomal recessive disorder with a defective monoamine and monocarboxylic amino acid transport system that results in malabsorption of tryptophan. **Carcinoid syndrome** can

cause pellagra through depletion of tryptophan stores. *Drugs* that cause deficiency include sulfonamides, anticonvulsants, antidepressants, azathioprine, and chloramphenicol.

Clinical Features

The classic tetrad of pellagra is dermatitis, dementia, diarrhea, and death. The dermatitis of pellagra is a bilateral, symmetric, eruption that is initially intermittently pruritic, edematous, burning erythema after sun exposure. With time, the eruption becomes fixed and may be associated with vesicles coalescing into bullae, eventually becoming sharply marginated, keratotic, hyperpigmented plaques. These often occur in areas susceptible to sun exposure, heat, and friction. The dorsal hands are most commonly affected. It can extend to the wrists and arms but has a sharp demarcation from normal skin, often in a glove distribution. The face has a symmetric butterfly distribution. Casal's necklace describes this dermatitis when on the upper chest and around the neck. Mucous membrane findings include cheilitis, glossitis, angular stomatitis, and oral or perirectal sores.

Gastrointestinal symptoms include nausea, vomiting, abdominal pain, and diarrhea. Neurologic manifestations include headache, irritability, anxiety, hallucinations, photophobia, depression, insomnia, and impaired memory.

Treatment

Treatment is with 500 mg of nicotinamide or nicotinic acid a day for several weeks. Symptoms should begin to improve in 24 hours, but cutaneous manifestations make take several weeks to resolve.

VITAMIN B_6

The three forms of vitamin B_6 are pyridoxine, pyridoxal, and pyridoxamine; the phosphorylated form of these three molecules are biologically active. It is a coenzyme for many enzymes, including those critical for decarboxylation and transamination of amino acids, fatty acid metabolism, neurotransmitter synthesis, and conversion of tryptophan to niacin.

The recommended daily intake ranges from 0.1 to 2 mg, depending on age and gender.

Absorption and Metabolism

Dietary vitamin B_6 is phosphorylated, so it needs to be hydrolyzed by intestinal phosphatases before absorption in the jejunum and ileum. At low concentrations, vitamin B_6 is actively transported into the cell but passively diffuses

at high concentrations. After transport to the liver, it is phosphorylated again and released back into the serum in its active phosphorylated forms. Vitamin B_6 is renally excreted.

Deficiency States

Vitamin B_6 deficiency is uncommon, but can occur with inadequate dietary intake, malabsorption, and certain medications. Elderly, malnourished, and anorexic individuals are at higher risk for developing deficiency. Alcoholics are particularly at risk because they are prone to poor diets at the same time that alcohol increases vitamin B_6 catabolism.

Conditions with malabsorption include Crohn disease and celiac disease. Medications can bind vitamin B_6 and increase excretion or decrease enzymatic activity. They include isoniazid, hydralazine, oral contraceptives, penicillamine, cycloserine, and theophylline.

Clinical Features

About 2 to 3 weeks after a vitamin B_6-deficient diet is initiated, a *seborrheic eruption* appears on the face, scalp, neck, shoulders, buttocks, and perineum. The **glossitis** is characterized by flattening of the filiform papillae, and redness, burning, and swelling of the tongue. The oral mucosa can be red with small ulcerations. Angular stomatitis and cheilitis may be present. A *pellagra-like dermatitis* with erythema, hyperpigmentation, and scaling has been reported. Neurologic symptoms have been observed, including somnolence, confusion, and peripheral neuropathy. A hypochromic, microcytic anemia also may develop.

Treatment

A therapeutic trial of vitamin B_6 can confirm the diagnosis. Symptoms should improve on 100 mg of pyridoxine a day. Discontinuation of any inciting medications is also an important component of therapy.

VITAMIN B_7

Biotin: Biotin is an essential cofactor for four carboxylase enzymes: acetyl-CoA carboxylase, which is involved in fatty acid synthesis and lipogenesis; pyruvate carboxylase, which is involved in gluconeogenesis; and propionyl-CoA carboxylase and 3-methylcrotonyl-CoA carboxylase, which are involved in amino acid catabolism. Biotin is obtained through dietary sources and through synthesis by intestinal bacteria.

Diet: Biotin sources include eggs, liver, walnuts, peanuts, mushrooms, cow's milk, and soybeans. Avidin is a

glycoprotein in egg whites that tightly binds biotin and prevents its absorption. Cooking eggs breaks this bond and allows biotin to be absorbed.

The recommended daily intake depends on age, ranging from 5 to 35 μg.

Absorption and Distribution

Pancreatic biotinidase releases biotin from dietary proteins and allows it to diffuse across the intestinal epithelium and bind to plasma proteins. Biotin travels to the liver, where holocarboxylase synthetase catalyzes its attachment to carboxylase enzymes. Biotinidase recycles biotin by releasing it from degraded carboxylases.

Deficiency States

1. *Multiple carboxylase deficiencies* represents a cause of biotin deficiency that are inherited in an autosomal-recessive fashion. Two forms have been identified with separate enzymatic deficiencies. The *neonatal,* or early onset form, presents in the first few weeks of life and is caused by holocarboxylase synthetase deficiency. *The juvenile,* infantile, or late-onset form, presents in infancy or early childhood and is the result of biotinidase deficiency.
   The clinical presentation of holocarboxylase synthetase deficiency is vomiting, hypotonia, lethargy, metabolic acidosis, and organic aciduria within the first weeks of life. A periorificial, intertriginous, and seborrheic distribution erythroderma-like dermatitis may be present but is not a consistent finding. There can be associated alopecia.
   Biotinidase deficiency presents with metabolic acidosis, organic aciduria, conjunctivitis, ataxia, encephalopathy, developmental delay, seizures, and sensorineural hearing loss. Periorificial dermatitis and alopecia are often seen. The metabolic encephalopathy is reversible after treatment is started. Sensorineural hearing loss is permanent but is preventable with early diagnosis and treatment. Immune deficiencies have also been reported and predispose these patients to secondary dermatitis infection.
2. *Acquired biotin deficiency* is *rare* because biotin is synthesized by intestinal bacteria and is also available through dietary sources. Most acquired deficiency is associated with excessive raw egg white intake, long-term total parenteral nutrition without biotin supplementation, and in patients with gastrointestinal malabsorption

conditions who take long-term antibiotics. Long-term use of anticonvulsants such as valproic acid, carbamazepine, and phenytoin have also been associated with biotin deficiency secondary to increased biotin catabolism or impaired liver function.

Clinical Features

Cutaneous symptoms of acquired biotin deficiency are similar to that of multiple carboxylase deficiency, but present 3 to 6 months after initiation of a deficient diet or raw egg rich diet. An erythematous, scaling, and crusting dermatitis begins around the eyes, nose, and mouth and progresses to involve other periorificial areas. Alopecia, glossitis, and conjunctivitis can be seen. Neurologic findings include irritability, lethargy, paresthesias, hypotonia, and myalgias.

Treatment

Acquired biotin deficiency is treated with 150 μg of biotin a day. Multiple carboxylase deficiency is treated with age appropriate biotin supplementation. Seizures, metabolic abnormalities, and cutaneous symptoms respond quickly, but hearing loss and vision changes can be permanent if treatment is not initiated early.

VITAMIN B_9 and B_{12}

Vitamins B_9 (folic acid, folate) and B_{12} are considered together because of the similarities in the clinical features related to their associated deficiency syndromes.

Vitamin B_9 is found in most foods but is most abundant in liver, grains, leafy green vegetables, and dried beans. As tetrahydrofolate, folate is essential for single-carbon transfers in amino acid, purine, and pyrimidine metabolism.

The recommended daily intake varies with age, ranging from 65 to 600 μg.

Deficiency States

Folate deficiency can occur in the context of inadequate intake from excessive boiling of cow's milk, an exclusive goat's milk diet, or alcoholism. Malabsorption secondary to surgical gastrectomy, celiac isease, and chronic diarrhea can cause folate deficiency. Antifolate medications include methotrexate, trimethoprim, oral contraceptives, and pyrimethamine; in addition, the antiepileptics phenobarbital and phenytoin can produce folate deficiency through induction of microsomal hepatic enzymes.

VITAMIN B_{12}

Animal products, particularly liver, eggs, milk, beef, and organ meats, represent the primary sources of vitamin B_{12} (cobalamin). After ingestion, gastric acid releases vitamin B_{12} from food proteins so it can bind to intrinsic factor in the duodenum. Most vitamin B_{12} entry is by specific receptors in the terminal ileum that take up the vitamin B_{12} -intrinsic factor complex, but approximately 1 to 5% of free cobalamin is absorbed by passive diffusion. Vitamin B_{12} dissociates from intrinsic factor in the enterocyte before binding to transcobalamin II to enter the portal circulation to reach target tissues.

Vitamin B_{12} is a critical coenzyme in two biochemical pathways in humans. Methylcobalamin is a coenzyme for the enzyme methyltransferase that methylates homocysteine to methionine, which is used in DNA, protein, and lipid metabolism. The second enzyme requires 5′-adenosylcobalamin to catalyze the enzyme methylmalonyl coenzyme A (CoA) mutase that converts methylmalonic acid to succinyl-CoA, which is used in fat and carbohydrate metabolism.

The recommended daily intake depends on age, ranging from 0.4 to 2.8 μg.

Deficiency States

Causes of vitamin B_{12} deficiency include inadequate intake, malabsorption, and inborn errors of transport or metabolism. The elderly, individuals with psychiatric disorders, vegans, and breastfed infants of vegans are at risk of deficiency because of inadequate intake. Malabsorptive states can be caused by:

- Decreased gastric acid secretion (chronic proton pump inhibitors, H_2 histamine receptor blockers), which leaves more food-bound B_{12}
- Decreased intrinsic factor (pernicious anemia, atrophic gastritis, after gastrectomy)
- Microbial competition in the gut (bacterial overgrowth)
- Impaired absorption (Whipple disease, Crohn disease, celiac disease, Zollinger-Ellison syndrome).

Clinical Features

The body is able to store large amounts of vitamin B_{12}, so symptoms of deficiency often take 3 to 6 years to develop.

1. The primary manifestation of both folate and vitamin B_{12} deficiency is megaloblastic anemia and hypersegmented neutrophils.

2. Mucocutaneous manifestations include angular cheilitis, Hunter glossitis, hair depigmentation, and mucocutaneous hyperpigmentation. Cutaneous hyperpigmentation can be diffuse and symmetric, a finding that can resemble Addison disease or present as localized macules. The most commonly affected areas are the hands, nails, face, palmar creases, flexural regions, and pressure points. Pigmentation of the oral mucosa can also be seen.
3. An atrophic, red, and painful tongue, with atrophy of the filiform papillae characterizes Hunter glossitis. Hair depigmentation can occur and be localized or diffuse.
4. A distinguishing clinical feature between folate and vitamin B_{12} deficiency is the neurologic manifestations of vitamin B_{12} deficiency, which may precede hematologic symptoms. Classically, vitamin B_{12} presents with subacute combined degeneration of the dorsal and lateral spinal column. Symptoms include generalized weakness with paresthesias that progress to ataxia and symmetric loss of vibration and proprioception, which is worse in the lower extremities. Untreated, severe weakness, spasticity, paraplegia, and incontinence eventually develop. Other neurologic findings include apathy, somnolence, irritability, memory loss, dementia, and psychosis.

Treatment

Folate deficiency is treated with oral supplementation of 1 to 5 mg of folate daily while addressing any underlying causes of deficiency. Exclusion of concurrent vitamin B_{12} deficiency is critical before initiating folate supplementation, because hematologic symptoms of vitamin B_{12} deficiency will improve, but neurologic symptoms will progress without correction of the underlying vitamin B_{12} deficiency. Oral or parenteral vitamin B_{12} of 1 mg of cyanocobalamin weekly for 1 month can treat vitamin B_{12} deficiency.

VITAMIN C

Vitamin C is an essential cofactor for proline hydroxylase in collagen formation. Hydroxylation of proline residues on each procollagen molecule is necessary for triple-helix formation of mature collagen. Without hydroxylation, the resulting molecule is unstable and unable to assemble into a rigid triple-helix structure, which is vital to vascular wall strength and hair formation.

Vitamin C aids osteoblast formation of bone and osteodentin formation of teeth. It is an essential cofactor in carnitine synthesis, which may explain the fatigue associated with vitamin C deficiency. Vitamin C is involved in synthesis of catecholamines, such as dopamine and norepinephrine,

and deficiency can result in behavioral and mood changes. As an antioxidant, vitamin C decreases urinary folic acid excretion by preventing oxidation of folate into forms that are easily excreted. It also increases dietary iron absorption by reducing iron from its ferric to ferrous state.

The value of vitamin C oral supplementation is theoretically to maintain the body reservoir of 1500 mg, which is rapidly depleted when the body is exposed to ultraviolet (UV) light. Some researchers believe that natural dietary sources of vitamin C, such as vegetables and citrus fruits, are the best method of restoring body reserves. But the poorly ripened fruits now sold in grocery stores are deficient in vitamin C and believe that synthetic vitamin supplementation is important.

Vitamin C (l-ascorbic acid) is the body's major aqueous phase antioxidant and is vital for life. Humans and other primates (and the guinea pig and Indian bat) cannot synthesize their own vitamin C, as do most other animals, including insects. In fact, animals synthesize very large quantities of vitamin C. A 130-lb goat manufactures 13 g of vitamin C daily, equal to 200 times the FDA human requirement (Puling 1987). Furthermore, animals can make up to ten times this normal amount when under stress (Puling 1987), suggesting the importance of vitamin C supplementation to human physiology.

Vitamin C, also known as ascorbic acid, is used both orally and topically for skin benefits. Topically, ascorbic acid is used in cosmeceuticals for hyperpigmentation because it interrupts melanogenesis by interacting with copper ions to reduce dopaquinone and blocks dihydrochinindol-2-carboxyl acid oxidation. Orally, nutricosmetic formulations use vitamin C, in the form of L-ascorbic acid, to function as an antioxidant by scavenging and quenching free radicals and by regenerating vitamin E from its radical form. That vitamin C is necessary for wound healing is well established.

Active l-ascorbic acid is such an excellent antioxidant that it is inherently unstable, turning brown as it is oxidized to **dehydroascorbic acid** when exposed to air. Therefore, the shelf life of most formulations containing pure vitamin C is short, so other forms of vitamin C are usually used for topical application in lotions, creams, serums, and patches to overcome the problem of instability. However, these more ***stable*** esterified derivatives (*ascorbyl-6-palmitate and magnesium ascorbyl phosphate* whose structures) are *not* well absorbed (Darr et al. 1992) and are only minimally metabolized by the skin to the active, free acid form. To achieve results, the formulation must contain *l-ascorbic acid* in a high enough concentration (*at least 10%*), be stable, and be at an *acidic pH*—less than the pKa (4.2) of vitamin C (Darr, et al. 1992) (The optimal pH is 3.5).

Food sources: Citrus fruits, strawberries, tomatoes, green leafy vegetables, and potatoes are sources of vitamin C. Vitamin C is vulnerable to heat and oxidation, so cooking, processing, and preserving fruits and vegetables significantly decrease their available vitamin C content.

The recommended daily intake depends on age and gender, ranging from 40 to 120 mg.

Absorption and Distribution

When it is absorbed in the first two-thirds of the small intestine, the percentage of absorbed vitamin C decreases as the intraluminal concentration increases. Vitamin C is not stored but is renally reabsorbed.

Mechanism of Action

1. Vitamin C has been proven to be **photoprotective**. Vitamin C does not absorb light in the UV spectrum, so vitamin C is itself not a sunscreen. However, as an antioxidant vitamin C deactivates UV-induced free radicals and decreases UVB erythema by 52% (Darr et al. 1992). This protection has been confirmed histologically.
2. Topical vitamin C is also directly **anti-inflammatory**. Laser resurfacing (with the older CO_2 lasers) causes redness for at least 3–4 months after treatment. With vitamin C applied before and after laser surgery, this redness of inflammation was markedly decreased afterward, and healing took only 2 months (Alster and West 1998). Topical vitamin C can also be used effectively to treat the inflammation of rosacea (Bergfeld and Pinnell 1996), though metronidazole is a better option.

   The mechanism of this anti-inflammatory action has been researched *in vitro* with human cells in vitamin C-enriched media. Decreased activation of the transcription factor nuclear factor kb (NF-kb), the factor responsible for many proinflammatory cytokines such as tumor necrosis factor-alpha (TNFa), and interleukins IL-1, IL-6, and IL-8, was demonstrated (Carcamo et al. 2002).
3. By directly decreasing inflammation, postinflammatory **hyperpigmentation** can also be reduced. Vitamin C is itself an excellent depigmentating agent because it inhibits the enzyme tyrosinase, which is required for melanin production. Kameyama et al. (1996) demonstrated suppression of melanin formation by inhibiting tyrosinase in melanocytes and melanoma cells using **10% magnesium-l-ascorbyl-2 phosphate** applied to human skin. Significant lightening of melasma and of lentigenes was observed in 19 of 34 patients (Kameyama et al. 1996).

4. Perhaps the most important action of vitamin C on the skin is direct stimulation **of collagen** synthesis. Vitamin C is an essential cofactor for the two enzymes required for collagen synthesis, prolyl hydroxylase (which makes the collagen molecule stable) and lysyl hydroxylase (which crosslinks the collagen to give structural strength) (Kivirikko and Myllyla 1996). By enhancing collagen synthesis, vitamin C can directly correct the collagen loss that causes wrinkles.

   Thus, supplementing the skin with extra vitamin C not only combats the collagen destruction due to photodamage, it can correct the loss (of about 1% per year) which occurs with natural, intrinsic aging (after approximately 45 years of age). In contrast to the increased synthesis of collagen, other *in vitro* studies suggested that vitamin C may inhibit elastin biosynthesis by fibroblasts (Davidson et al. 1997). This might be advantageous in reducing the solar elastosis due to photodamage.
5. Topical vitamin C has also been shown to increase the synthesis of several specific **sphingolipids** of the skin surface (Uchida et al. 2001). With these lipids, vitamin C helps the natural moisturization of the skin as it enhances the protective barrier function.

Uses (Approved/Unapproved)

1. **Photodamage:** Because our skin is the organ that protects us from environmental free-radical stress, the presence of vitamin C is extremely important. Exposure to sunlight and environmental pollution depletes vitamin C from the center layers of the skin. Even minimal UV exposure of 1.6 minimal erythema dose (MED) decreases the level of vitamin C to 70% of the normal level, and exposure to 10 MED decreases the vitamin C to only 54% (Shindo et al. 1994). Exposure to ozone at a dose of 10 parts per million in city pollution decreases the level of epidermal vitamin C by 55% (Thiele et al. 1997). Vitamin C is often used in conjunction with vitamin E is used to treat photodamage skin
2. **Pigmented purpuric dermatises PPD:** Oral rutoside and ascorbic acid may be an efficient and well-tolerated treatment for PPD. Early treatment is recommended to achieve best clinical outcome (Schober SM).
3. **Melasma/PIH:** Though studies have been published on its *in vitro* action, for an *in vivo* action at least 15% of the stabilized form should be used for a substantial effect.

Deficiency States

Vitamin C deficiency is uncommon in developed countries but can result from inadequate dietary intake in certain populations. Factors that place the elderly and men who live alone at risk include poor access to fresh produce, limited finances, reclusiveness, and dementia. Scurvy can develop in individuals on fad diets or in those with true or perceived food allergies if their limited diets does not include fruits and vegetables.

Limited intake can also result from medical conditions, including unsupplemented parenteral nutrition, anorexia nervosa, autism, and gastrointestinal diseases such as ulcerative colitis, Crohn's disease, gastrointestinal reflux, and Whipple disease.

Dialysis filters out water-soluble vitamin C from the serum, so renal failure patients are predisposed to scurvy. Tobacco decreases intestinal vitamin C absorption and increases its catabolism. Vitamin C deficiency in alcoholics is multifactorial, including decreased intestinal absorption and poor dietary intake.

Clinical Features

Clinical manifestations of scurvy develop 1 to 3 months after initiation of a diet deficient in vitamin C. The first signs are fatigue, malaise, and lethargy.

1. **Skin:** The first cutaneous sign is enlarged, hyperkeratotic hair follicles on the posterolateral aspects of the arms, which becomes generalized, especially on the buttocks and legs. A significant woody edema of the legs often also develops.
2. **Hair:** Abnormal hair development leads to fractured, coiled (corkscrew) hair, or hair bent in several places with a "swan neck deformity". Eventually, follicles become hemorrhagic, especially on the legs, where hydrostatic pressure is highest.
3. Oral changes occur most prominently in those with preexisting poor dentition. The gingiva become edematous, friable, and erythematous, with prominent shiny, red, smooth, swollen masses in the interdental papillae. Poorly formed, soft teeth are prone to infection. Later, tender, swollen, necrotic gums are prone to bleeding.
4. Ocular findings in scurvy include conjunctival varicosities, conjunctival hemorrhage, and intraocular hemorrhage.
5. Poor bone formation and hemorrhage into muscles and joints from osteopenia causes musculoskeletal complaints.

Characteristic findings in pediatric scurvy, or Barlow disease, include failure to thrive, irritability, and pain from

subperiosteal hemorrhage resulting in pseudoparalysis. Bowing of the long bones, a depressed sternum, and swelling of the costochondral junctions are seen on physical examination. Characteristic radiologic findings include healing metaphyseal corner fractures at the periphery of the zone of calcification, known as Pelkan spurs, increased density outlining the epiphyses (Wimberger ring), widening at the zone of calcification (white line of Frankl), and a transverse radiolucent band at the metaphysic (scurvy line or Trümmerfeld zone). Anemia is a common finding in scurvy and is caused by blood loss, folate deficiency, and iron deficiency.

Management

Measurement of serum ascorbic acid can diagnose scurvy if it is low (≤11 μmol/L), but can be inaccurate and falsely negative.

Serum ascorbic acid reflects recent dietary intake more than overall vitamin C status. Leukocyte ascorbic acid level is a more accurate measure of tissue and body vitamin C content, but testing is not widely available. Ascorbic acid levels need to be interpreted with consideration of inflammatory markers like C-reactive protein because ascorbic acid is transferred to leukocytes from the serum during inflammatory responses.

Diagnosis of scurvy can also be accomplished by an empiric trial of vitamin C supplementation.

Scurvy is treated with 100 to 300 mg ascorbic acid daily until symptoms resolve. Symptoms should respond quickly to supplementation. Fatigue and pain resolve in 24 hours, joint swelling resolves in days, ecchymoses resolve and gums heal in 1 to 2 weeks, and normal hair growth is visible by 4 weeks. Complete recovery should occur by 3 months.

BIBLIOGRAPHY

1. Alster T, West TB. Effect of vitamin C on postoperative CO_2- laser resurfacing erythema. Dermatol Surg. 1998;24:331-4.
2. Barrier formation in submerged human keratinocyte cultures. J Invest Dermatol. 2001;117:1307-13.
3. Bergfeld W, Pinnell S. Topical vitamin C. Dialogues in dermatology. Am Acad Dermatol. 1996;38:1.
4. Carcamo JM, Pedraza A, Borquez-Ojeda O, Golde DS. Vitamin C suppresses TNF alpha-induced NF kappa B activation by inhibiting I Kappa B alpha phosphorylation. Biochemistry. 2002;41:12995-30002.
5. Darr D, Combs S, Dunsten S, et al. Topical vitamin C protects porcine skin from ultraviolet radiation-induced damage. Br J Dermatol. 1992;127:247-53.
6. Davidson JM, Luvalle PA, Zoia O, et al. Ascorbate differentially regulates elastin and collagen biosynthesis in vascular smooth

muscle cells and skin fibroblasts by pretranslational mechanisms. J Biol Chem. 1997;272:345-52.
7. Kameyama K, Sakai C, Kondoh S, et al. Inhibitory effect of magnesium L-ascorbyl-2-phosphate (VC-PMG) on melanogenesis *in vitro* and *in vivo*. J Am Acad Dermatol. 1996;34:29-33.
8. Kivirikko KI, Myllyla R. Post-translational processing of procollagens. Ann NY Acad Sci. 1996;11:250-3.
9. Puling L. How to live longer and feel better. New York: WH Freeman; 1987.
10. Schober SM, Peitsch WK, Bonsmann G, Metze D, Thomas K, Goerge T, Luger TA, Schneider SW. Early treatment with rutoside and ascorbic acid is highly effective for progressive pigmented purpuric dermatosis. J Dtsch Dermatol Ges. 2014;12(12):1112-9.
11. Shindo Y, Wit E, Han D, Packer L. Dose response effects of acute ultraviolet irradiation on antioxidants and molecular markers of oxidation in murine epidermis and dermis. J Invest Dermatol. 1994;23:470-5.
12. Thiele JJ, Traber MG, Tsange KG, et al. In vivo exposure to ozone depletes vitamins C and E and induces lipid peroxidation in epidermal layers of murine skin. Free Radic Biol Med. 1997;23:85-91.
13. Uchida Y, Behne M, Quiec D, et al. Vitamin C stimulates sphingolipid production and markers of barrier formation in submerged human keratinocyte cultures. J Invest Dermatol. 2001;117(5):1307-13.

ANTIOXIDANTS

INTRODUCTION

Antioxidants are molecules capable of inhibiting the oxidation of other molecules. Although oxidation reactions are essential for life, they can also be damaging. All living organisms maintain complex systems of multiple types of antioxidants to protect their cells from oxidative damage. Antioxidants can also act as pro-oxidants, under certain circumstances. The efficacy and benefit of an antioxidant is, therefore, very much dependent on the delivery of the antioxidant to the organism.

ANTIOXIDANT SYSTEMS IN THE SKIN

Human skin is equipped with an array of antioxidants and enzyme systems to protect the cells from damaging effects of free radicals (Table 15.4, and Fig. 15.5).

Antioxidant molecules such as vitamin A, vitamin C, and vitamin E slow the process of aging either by preventing free radicals from oxidizing sensitive biological molecules or by reducing the formation of free radicals and quenching the already formed ROS.

In addition, enzymes such as superoxide dismutase (SOD), catalase, and glutathione (GSH) biosynthesizing enzymes protect the tissues from free radicals.

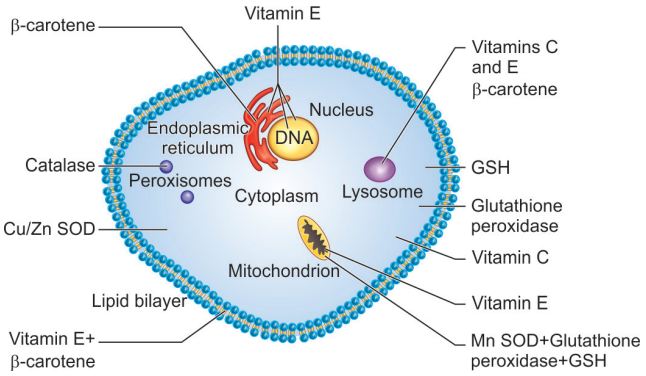


Fig. 15.5: Distribution of antioxidants and enzymes in the cell

Table 15.4: Overview of the antioxidant mechanism in the skin

Water-soluble antioxidant	Lipid-soluble antioxidant	Antioxidant enzyme system
Vitamin C (ascorbic acid)	Vitamin E and other tocopherol derivatives	Superoxide dismutase (SOD) Cu/Mn SODs
Glutathione	Ubiquinone (Co Q10)	Catalase
Lipoic acid (both water and lipid soluble)	Lipoic acid	Glutathoine peroxidase
Uric acid	Carotenoids (lycopene, lutein, beta Carotene, etc)	Glutathione S-transferase

The levels of these antioxidants, as well as antioxidant enzymes, are reduced by age and various environmental stresses such as UV exposure. Replenishing these antioxidants either by topical application or by dietary ingestion can protect skin from aging. The level of dietary or topical antioxidants achieved in the skin varies with the individual antioxidant and also with absorption and other factors.

Primary Antioxidants

Primary or free radical scavenging antioxidants inhibit oxidation via chain terminating reactions. Inhibition occurs via a transfer of a proton to the free radical species. Examples of primary antioxidant molecules include *GSH, alpha-tocopherol, vitamin E, ascorbic acid, or vitamin C*. GSH and ascorbic acid are water-soluble antioxidants, whereas vitamin E is membrane-bound and capable of intercepting free radical-mediated chain reactions (Fig. 15.5). They can also regenerate one another, thereby providing synergistic combinations when applied topically.

Secondary Antioxidants

Secondary antioxidants are often used in combination with primary antioxidants to yield synergistic stabilization effects.

They can regenerate the primary antioxidants and protect them from degradation. In human skin *lipoic acid,* (an organosulfur compound), which is an essential cofactor for many enzyme complexes, and can be considered as a secondary antioxidant. *Dihydrolipoic acid*, the reduced form of lipoic acid, is a potent antioxidant. It is able to regenerate (reduce) antioxidants such as GSH, vitamin C, and vitamin E. *N-acetyl cysteine*, a thiol compound that can regenerate GSH, is another example of a secondary antioxidant.

Protective Repair Enzymes and their Cofactors

Enzyme systems that *regenerate* antioxidants, such as GSH peroxidases, GSH reductase, glutathione S-transferases (GSTs), and other enzymes that directly *neutralize* ROS, such as SODs, catalase, and quinone reductase, form a group of antioxidant enzymes.

Many of these enzyme systems, for example, SODs [copper/zinc superoxide dismutase (CuZnSOD) and manganese superoxide dismutase (MnSOD)] are decreased in human aged skin. Enhancing the activities of these antioxidant enzyme systems, by providing their metal cofactors such as Cu, Mn, Zn and Se, can boost their activities and provide better antioxidant protection for skin.

Chelation Agents

Some compounds contribute to antioxidant defense by chelating transition metals and preventing them from catalyzing the production of free radicals in the cell. They all function by making several chemical bonds with metal ions, thus rendering them less reactive. The resulting complex is water soluble, allowing it to enter the bloodstream and be excreted harmlessly. Many antioxidants behave as pro-oxidants in the presence of metals such as Fe and Cu; therefore, chelating agents protect the antioxidants by chelating the toxic metal ions.

Categories of Cosmetic Antioxidants

Endogenous (Biological) Antioxidant Systems

In skin, the predominant antioxidant is vitamin C; vitamin C is the water-soluble vitamin that protects the aqueous phase of cells. The lipid phase including cell membranes and stratum corneum is protected by vitamin E. The activities of *catalase* and *GSH reductase* **increase** in the epidermis of photoaged and naturally aged skin. The concentrations of α-tocopherol, ascorbic acid, and GSH are generally *lower* in the epidermis of photoaged and aged skin.

Exogenously Supplied Antioxidants

A variety of antioxidants can be used in topical products. These include common vitamins such as vitamin C (ascorbic acid and its derivatives), vitamin E (tocopherol and its derivatives), coenzyme Q and its derivatives, and GSH and its precursors such as cysteine derivatives (N-acetylcysteine) and lipoic acid. In addition, *activators* of several enzymes systems that regenerate these antioxidants such as GSH peroxidases, GSH reductase, GSTs, and enzymes that *neutralize* ROS such as SODs, catalase, and quinone reductase are also used topically to "boost" antioxidant systems within skin.

Plant-derived Antioxidants

Plant-derived compounds such as *carotenoids* and *polyphenols* are an important group of compounds showing antioxidant properties. Polyphenolic compounds include tannins (gallic acid esters of glucose and other sugars) and phenylpropanoids such as lignins, flavonoids, and condensed tannins. The largest and best studied polyphenols are the flavonoids, which include several thousand compounds, among them the flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids.

Antioxidant Synergy

Although there are hundreds of naturally-occurring antioxidants, most of those currently used in the cosmetic industry are believed to work synergistically to regenerate and "enhance the power" of each other. The antioxidants that have been identified as working cooperatively have been referred to as network antioxidants. For example, after an antioxidant "disarms" a free radical by eliminating the odd number of electrons (by either adding or removing an electron), it is unable to function further as an antioxidant unless it is recycled. The **five** antioxidants that have been labeled as *network antioxidants* are *vitamins C and E, glutathione, lipoic acid, and Coenzyme Q10 (CoQ10)*.

Vitamin C or CoQ10 can recycle vitamin E, donating electrons to vitamin E to return the nutrient to its antioxidant state. Vitamin C and glutathione can be recycled by lipoic acid or vitamin C. These network antioxidants are being included in an increasing number of cosmetic preparations. It is likely that many antioxidants work synergistically, and that the term "network antioxidant" applies to many more antioxidants than the five identified as the "network."

INDIVIDUAL ANTIOXIDANTS

As most of these agents have discussed previously and a large number are used topically, we will give a general overview of these agents and their salient uses.

Fat-soluble Antioxidants

These are found in the lipophilic portion of the cell membrane and include vitamin E, carotenoids, and CoQ10. Further, idebenone, the synthetic analog of CoQ10, and food-derived lycopene are also fat-soluble antioxidants.

Vitamin E

Vitamin E has been used to treat or protect against various dermatologic conditions including skin cancer, dystrophic epidermolysis bullosa, discoid lupus erythematosus, yellow nail syndrome, granuloma annulare, atopic dermatitis, pemphigus, and lichen sclerosus et atrophicus, among others (Keller KL).

Results have varied just as widely as the range of diseases treated. In fact, some authors have reported that the use of oral vitamin E will reduce the side effects of retinoids; however, other studies have not shown this benefit. The most promising reason for research into the dermatologic use of vitamin E appears to be its antioxidant activity. The potency of vitamin E as an antioxidant can be increased through combination with other antioxidants. Vitamin E also appears to offer a ripe area for research into its potential for therapeutic benefit in the prevention and treatment of skin cancer and photoaging.

Coenzyme Q10 (Ubiquinone)

Coenzyme Q10 (CoQ10) is a naturally-occurring nutrient available through food consumption. The "Q" refers to its membership in the quinone family; the "10" identifies the number of isoprenoid units on its side chain. Fish and shellfish are good dietary sources of CoQ10. The current recommended oral dose is 90 to 150 mg daily; however, many physicians are recommending 200 to 400 mg/d.

CoQ10 is a fat-soluble compound found in all cells as part of the electron transfer chain responsible for energy production. It is estimated that CoQ10 provides 95% of the body's energy (ATP) requirements. CoQ10 has also been found to have antioxidant properties.

This has been used as an antiageing supplement which is based on a study, where oral supplementation of CoQ10 daily for 2 weeks was given and it was noted that levels of CoQ10 significantly increased in the epidermis, but not in the dermis. This probably is a prerequisite to the reduction of wrinkles and other benefits related to the potent antioxidant and energizing effects of CoQ10 in skin (Ashida Y).

Ageing has been associated with a functional loss of mitochondria. CoQ10 positively influences the age-affected cellular metabolism and enables to combat signs of aging

starting at the cellular level. As a consequence topical application of CoQ10 is beneficial for human skin as it rapidly improves mitochondrial function in skin *in vivo*. (Prahl S). The drug has also been noted to prevent skin cancer. Notably most expensive topical preparations contain this compound for its purported ant ageing effect.

Side Effects: Oral CoQ10 supplementation has been associated with a caffeine-like side effect and may cause nervousness or a jittery feeling. So as not to induce insomnia, it is recommended that CoQ10 should *not* be taken at night. Diarrhea, appetite loss, and mild nausea are among the other side effects reported. A report of a topical preparation causing vitiligo is a cause for worry specially in susceptible patients. This was consequent to the generation of hydrogen peroxide (H_2O_2) (Schallreuter KU).

Idebenone

Idebenone is the synthetic analog of CoQ10, penetrating the skin more efficiently because of its lower molecular weight. Idebenone has been shown to possess superior antioxidant capacity compared to CoQ10, tocopherol, kinetin, ascorbic acid, and lipoic acid in various *in vitro* and *in vivo* trials. (McDaniel D**)**.

Lycopene

Lycopene is a natural pigment synthesized by plants and microorganisms. Lycopene has been found to exhibit potent antioxidant properties. Because of its high number of conjugated double bonds, it demonstrates stronger singlet oxygen-quenching ability compared to alpha-tocopherol or beta-carotene.

Curcumin

Curcumin is a yellow pigment found in the root of the tropical turmeric plant, Curcuma longa, which belongs to the Zingiberaceae family. Turmeric consists of a water-soluble component, turmerin, and a lipid-soluble component, curcumin. Curcumin has been used for centuries in traditional Indian medicine for various treatments such as inflammatory conditions and other diseases. Turmeric tubers contain curcuminoids, of which curcumin I (diferuloylmethane) is most abundant, followed by curcumin II (6%) and III (0.3%). Curcumin has been shown to exhibit a broad array of biologic activities, such as anti-inflammatory, anticarcinogenic, an antioxidant, antimicrobial, and wound healing effect.

The molecular basis of these effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, adhesion

molecules, apoptotic genes, angiogenesis regulators, and other enzymes (Aggarwal BB, Surh YJ).

1. **Antioxidant and anti-inflammatory activities of curcumin:** Curcumin has been identified as a potent scavenger of a variety of ROS, including superoxide anion radicals, hydroxyl radicals, and nitrogen dioxide radicals (Conney AH). Also, curcumin has been shown to downregulate the production of the proinflammatory cytokines IL-1 and tumor necrosis factor-alpha, and to inhibit the activation of transcription factors NF-kB and AP-1, both regulating the genes for proinflammatory mediators and protective antioxidant genes. The antioxidant and anti-inflammatory properties of curcumin have been documented in mouse models, proving that curcumin has a beneficial effect against chemo- and photocarcinogenesis.
2. **Wound-healing effects of curcumin:** Sidhu et al. demonstrated that wound closure in curcumin-treated normal and genetically diabetic animals was significantly faster compared to controls. This enhanced healing effect was attributed to the improvement of neovascularization and reepithelialization, the increase of expression and production of transforming growth factor-1 and fibronectin, and the reduction of cell death by curcumin. Curcumin treatment has also improved collagen deposition and increased fibroblast and vascular density, enhancing both normal and impaired wound healing.
3. **Curcumin and skin cancer:** Curcumin has been demonstrated to inhibit carcinogenesis in several tumor model systems including skin neoplastic models (Limtrakul P). Its mechanism of action is not precisely known, but it is thought to inhibit initiation, promotion, and progression of cancer (Nagabhushan M).

Water-soluble Antioxidants

There are numerous agents in this class including silymarin, *Coffea arabica* and coffeeberry extract, *Polypodium leucotomos*, resveratrol, grape seed extract and Pomegranate, but most of them have mostly *in vitro* data with little human results.

Glutathione

Glutathione is the most abundant antioxidant in the network. A study has shown that reduced levels of antioxidant can be seen in acne vulgaris (Ikeno H). It is produced from the amino acids glutamic acid, cysteine, and glycine. Oral glutathione is not well absorbed into the body, so supplementation is difficult—it is not even available in cosmetic products.

Vitamin C

This drug is a known antioxidant that works in conjunction with vitamin E. There are multiple studies that demonstrate that mice treated with topical vitamin C have less erythema, fewer sunburn cells, and decreased tumor formation seen in treated skin after UV exposure. Its effect on collagen is known, but clinically, the relevance of these effects on collagen and elastin are limited. The decrease of inflammation can lead to a reduction of postinflammatory hyperpigmentation.

Though topical vitamin C has been used in melasma, PIH, stretch marks and postlaser erythema, they must be formulated properly and stored in airtight, light-resistant containers to be effective. Skinceuticals, Murad, and La Roche-Posay have formulated the most-effective vitamin containing products.

Green Tea

Green tea has been consumed as a popular beverage in Asian countries, in particular, and throughout the world for many years. It has recently gained greater popularity in Western nations, though, because of its purported antioxidant and anticarcinogenic effects. There are numerous *in vitro* and *in vivo* studies on the effects of green tea on the skin; in fact, green tea is one of the most studied antioxidants (Hsu S). Besides its antioxidant activity, green tea polyphenols possess anti-inflammatory and anticarcinogenic properties and modulate the biochemical pathways important in cell proliferation, when administered either topically or orally (Katiyar SK).

Polyphenols are a large, diverse family of thousands of chemical substances. There are four major polyphenolic catechins in green tea: **ECG** [(-) EpiCatechin-3-O-Gallate], **GCG** [(-) GalloCatechin-3-O-Gallate], **EGCG** [(-) EpiGalloCatechin-3-O-Gallate], and **EGC** [(-) Epi Gallo Catechin]. **EGCG** is the most abundant and biologically active component.

Polyphenols (*Classed by type and number of constituents)	
Phenols	Coumaric acid-derived lignins, kaempferol
Pyrocatechol	Catechin, quercetin, caffeic acid- and ferulic acid-derived lignins, hydroxytyrosol esters
Pyrogallol	Gallocatechins (EGCG), tannins, myricetin, sinapyl alcohol-derived lignins
Resorcinol	Resveratrol
Phloroglucinol	Most-flavonoids
Hydroquinone	Arbutin

EGCG is the main compound in green and white tea responsible for antioxidant activity. The most-effective

products contain 50–90% polyphenols. Such formulations are dark in color and look brown when they contain this high level of polyphenols. The Replenix line (not available in India) by Topix is an example of a product line with a high level of polyphenols.

The Fat- and Water-soluble Antioxidant

The sole network antioxidant known to be both water and lipid soluble is lipoic acid.

Alpha Lipoic Acid

Alpha lipoic acid (ALA) is an antioxidant agent used for the treatment and prevention of aging skin. It is different than the other antioxidants because it can be used as a superficial chemical peel to resurface the skin in a manner similar to glycolic acid. ALA is believed to have anti-inflammatory properties that may also make it useful in the treatment of postlaser erythema. This discussion will focus on the science and potential therapeutic applications of ALA in the cosmetic dermatology practice.

In 1951, it was first discovered that ALA acted as an antioxidant. It is both water- and lipid-soluble and, hence, has been termed the **"universal" antioxidant** (Kagan VE).

Dihydrolipoic acid (DHLA) is formed by reducing ALA. It has a more powerful antioxidative effect than does ALA. DHLA is very unstable, however, and would get oxidized in a matter of minutes after application to the skin. ALA has become popular because it is absorbed in a stable form and after it enters the cells, it is immediately converted to DHLA (Podda M).

Although ALA is available in topical cosmetic products and in formulations used for office peels, there are no published peer-reviewed clinical trials examining, the efficacy of these products.

Systemic administration: ALA can be used either topically or systemically. When systemically administered, it has been used to influence glucose control and prevent chronic hyperglycemia-associated complications such as diabetes mellitus, Alzheimer's disease, cataracts, HIV activation, and radiation injury. There is no currently established RDA but most proponents of ALA supplementation suggest 25 to 500 mg daily.

Antioxidative benefits: There are four principal antioxidative properties of ALA: metal chelating capacity, ability to scavenge ROS, ability to regenerate endogenous antioxidants, and the ability to repair oxidative damage.

Conclusion

Fruit and vegetables contain various antioxidants, which are also found in the human body and, more specifically, in the skin. Even in ancient times, it had been known that intake of fruit and vegetables is important for staying healthy, but it had not been possible to demonstrate that healthy food positively influences the course of disease as well (Darvin et al. 2006).

Intensive efforts had been undertaken to extract antioxidants from fruit and vegetables or to produce them synthetically. Analyzing the results of studies on plant extracts and synthetic antioxidants, a wide range of applications have been found that are deemed to support medical therapies. These studies, however, provided very different results on the action of antioxidants. The therapy of cancer patients, for example, was supported by treatment with antioxidants. Some studies revealed that the patients of the verum group (therapy with products containing antioxidants) died earlier than those of the placebo group as a consequence of carotenoid uptake (Gallicchio et al. 2008). Contrary to medical reports, almost no adverse effects have been observed when antioxidants were used in the field of cosmetology, except for isolated allergic reactions. This is due to the fact that the various antioxidants form protective chains in the human organism thus protecting themselves against the destructive action of free radicals. According to several studies, this protective network is more efficient as more components are contained in the antioxidant compound.

The best results were achieved when the composition and concentration of the antioxidants in food supplements were similar to those obtained by a healthy nutrition rich in fruit and vegetables. This is reasonable because the highest efficacy of the antioxidants could be obtained if they are administered at an amount similar to their physiological concentrations. For the application of single antioxidant components at high concentrations, there is a critical level. If this level is exceeded, these molecules can form radicals themselves. Unaware of this fact, various supportive treatments with antioxidants were carried out in the past based on the slogan, "the higher the level, the better the effect." Instead of reducing radical formation, this fatal error stimulated such formation, especially when single components were administered at high concentrations, which affected the course of the disease negatively (Darvin et al. 2006).

The situation is quite different when it comes to cosmetic treatments. In most cases, antioxidants are used as antiaging strategies; that is, the products are designed for long-term application. Most cosmetic products, therefore, contain significantly lower concentrations of antioxidants than products for supportive treatment with antioxidants. Based on the analysis of various studies, it can be stated

that the action of the antioxidants is more efficient as their composition and concentration correspond to the physiological conditions in the human body. In other words, the closer the supplementation resembles the intake of natural foods, the more efficient is the protective action of the antioxidative network. However, systemically applied antioxidants or antioxidant compounds in the form of tablets or drinks may contain much higher amounts of antioxidants than the ones that are usually taken up daily from food.

Most importantly the Indian diet contains some of the most powerful antioxidants and spices, including turmeric and tulsi, to name just two and the largely vegetable and fruit based diet in our country, is probably enough to tackle the antioxidant requirement.

I for one rarely, prescribe oral antioxidants, as there is little compulsive evidence that they can modulate the course of a skin disorder. With topical agents the formulation is the key to success which in most of the cases is inappropriate for effective use, notwithstanding this, perhaps there may be subtle parameters that may be affected by antioxidants, which may have some beneficial effects. This may account for the burgeoning prescriptions of antioxidants.

BIBLIOGRAPHY

1. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. 2003;23:363.
2. Ashida Y, Yamanishi H, Terada T, et al. CoQ10 supplementation elevates the epidermal CoQ10 level in adult hairless mice. Biofactors. 2005;25:175.
3. Conney AH, Lysz T, Ferraro T, et al. Inhibitory effect of curcumin and some related dietary compounds on tumor promotion and arachidonic acid metab olism in mouse skin. Adv Enzyme Regul.1991;31:385.
4. Darvin M, Zastrow L, Sterry W, Lademann J. Effect of supplemented and topically applied antioxidant substances on human tissue. Skin Pharmacol Physiol. 2006;19:238-47.
5. Gallicchio L, Boyd K, Matanoski G, Tao XG, Chen L, Lam TK, et al. Carotenoids and the risk of developing lung cancer: a systematic review. Am J Clin Nutr. 2008;88:372–83.
6. Hsu S. Green tea and the skin. J Am Acad Dermatol. 2005;52:1049.
7. Ikeno H, Tochio T, Tanaka H, Nakata S. Decrease in glutathione may be involved in pathogenesis of acne vulgaris. J Cosmet Dermatol. 2011;10(3):240-4.
8. Kagan VE, Shvedova A, Serbinova E, et al. Dihydrolipoic acid—a universal antioxidant both in the membrane and in the aqueous phase. Reduction of per- oxyl, ascorbyl and chromanoxyl radicals. Biochem Pharmacol. 1992;44:1637.
9. Katiyar SK, Ahmad N, Mukhtar H. Green tea and skin. Arch Dermatol. 2000;136:989.
10. Keller KL, Fenske NA. Uses of vitamins A, C, and E and related compounds in dermatology: a review. J Am Acad Dermatol. 1998;39:611.

11. Limtrakul P, Lipigorngoson S, Namwong O, et al. Inhibitory effect of dietary curcumin on skin carcinogenesis in mice. Cancer Lett. 1997;116:197.
12. McDaniel D, Neudecker B, Dinardo J, et al. Idebenone: a new antioxidant-Part I. Relative assessment of oxidativie stress protection capacity compared to commonly know antioxidants. J Cosmet Dermatol. 2005;4:10.
13. Nagabhushan M, Bhide SV. Curcumin as an inhibitor of cancer. J Am Coll Nutr.1992;11:192.
14. Podda M, Han D, Koh B, et al. Conversion of lipoic acid to dihydrolipoic acid in human keratinocytes. Clin Rec. 1994;42:41B.
15. Prahl S, Kueper T, Biernoth T, Wöhrmann Y, Münster A, Fürstenau M, et al. Aging skin is functionally anaerobic: importance of coenzyme Q10 for anti aging skin care. Biofactors. 2008;32(1-4):245-55.
16. Schallreuter KU. Q10-triggered facial vitiligo. Br J Dermatol. 2013;169(6):1333-6.
17. Sidhu GS, Mani H, Gaddipati JP, et al. Curcumin enhances wound healing in streptozotocin induced diabetic rats and genetically diabetic mice. Wound Rep Regen. 1999;7:362.
18. Surh YJ, Han SS, Keum YS, et al. Inhibitory effects of curcumin and cap saicin on phorbol ester-induced activa tion of eukaryotic transcription factors, NF-kappaB and AP-1. Biofactors. 2000; 12:107.

ESSENTIAL FATTY ACIDS

INTRODUCTION

Fat is perhaps the most diverse class of dietary macronutrients in regards to nutritional value and physiological effects. Currently, most people understand the differences between the good (unsaturated fat), bad (saturated fat) and ugly (*trans*-fat) fats. We know that oils derived from animal fat are not good for our health due to their high levels of saturated fat and cholesterol, and that oils derived from plants are generally good for our health due to their unsaturated fat content. However, not all unsaturated fats are healthy. Many plant seed oils such as *sunflower, peanut and corn oil* are rich in inflammatory polyunsaturated fatty acids (PUFAs) and devoid of anti-inflammatory PUFAs. On the other hand, some plant seed oils such as *canola and olive oil* have balanced PUFAs and are considered healthier. Therefore, it is important to distinguish between the types of PUFAs in dietary oils for optimal health (Fig. 15.6).

PUFAs are fatty acids that have two or more double bonds in each molecule. There are two types of PUFAs in dietary oil: omega-3 and omega-6, also known as ω-3 and ω-6. LA (18:2 ω-(6) and ALA (18:3 ω 3) represent the parent fats of the two main classes of PUFAs: the ω-6 (n-6) and the ω-3 (n-3) fatty acids, respectively.

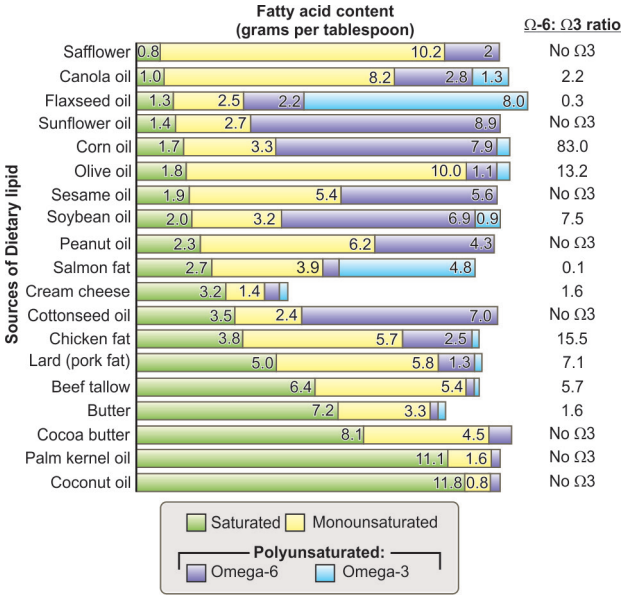


Fig. 15.6: A depiction of the MUFA and PUFA contents of common food items

The most common *omega-3 fatty acids* in the human diet are *ALA, EPA, and DHA* while the most common *omega-6* **fatty acids** are *LA and AA* (Table 15.5). The omega-3 fatty acid ALA and the omega-6 fatty acid LA are referred to as essential fatty acids because the body cannot synthesize them. Essential fatty acid deficiency can lead to dermatitis, stunted growth in infants and children, increased susceptibility to infection, and poor wound healing. In human cells, all long-chain omega-3 fatty acids are synthesized from ALA and all long-chain omega-6 fatty acids are synthesized from LA.

Long-chain omega-3 fatty acids (EPA and DHA) provide many health benefits with regard to their cardiovascular disease prevention properties and anti-inflammatory effects. DHA is also directly involved in visual and neuronal cell development. Adequate amounts of omega-6 fatty acids are also beneficial to human health since many bioactive signaling molecules, especially ones involved in immune response and cardiomyocyte (muscle cells) contraction, are derived from them. However, omega-6 fatty acids tend to be over-supplied while omega-3 fatty acids are under-supplied in modern Western diets due to industrialized food oil production. This overwhelming intake of *omega-6* leads to *hyperimmune* responses and interferes with the proper function of omega-3 fatty acids, causing detrimental effects associated with chronic cardiovascular diseases and inflammatory responses (Table 15.6).

Due to the opposing effects of omega-3 and omega-6 fatty acids, a healthy diet should contain a balanced omega-6:

Table 15.5: Overview of omega-3 and omega-6 fatty acids and their dietary sources

Types	*Abbreviation*	*Common name*	*Structure*	*Dietary sources*
Omega-3	ALA	α-Linolenic acid	C18 : 3	Oils: flaxseed, olive, canola
	EPA	Eicosapentaenoic acid	C20 : 5	Fish oil, marine algae
	DHA	Docosahexaenoic acid	C22 : 6	Fish oil, marine algae
Omega-6	LA	Linoleic acid	C18 : 2	Oils: corn, soybean, sunflower, peanut
	AA	Arachidonic acid	C20 : 4	Small amount in meat, dairy products and eggs

omega-3 ratio, ideally about 1:1. Modern Western diets exhibit omega-6:omega-3 ratios ranging between 15:1 to 17:1. Epidemiology and dietary intervention studies have concluded that while an exceptionally high omega-6:omega-3 ratio promotes the development of many chronic diseases, a reduced omega-6:omega-3 ratio can prevent or reverse these diseases. For example, a ratio of 4:1 was associated with a 70% reduction in mortality in secondary coronary heart disease prevention and a ratio of 2.5:1 reduced rectal cell proliferation in patients with colorectal cancer. A lower omega-6:omega-3 ratio in women was associated with decreased risk for breast cancer. A ratio of 2:1–3:1 suppressed inflammation in patients with rheumatoid arthritis, and a ratio of 5:1 had a beneficial effect on patients with asthma, whereas a ratio of 10:1 had adverse consequences.

Figure 15.6 shows the fatty acid composition as well as the omega-6:omega-3 ratio in common food sources. It is clear that *many plant seed oils contain no omega-3.* Long-term ingestion of these oils without supplementing omega-3 from other sources will gradually incur hyperimmune responses and associated chronic diseases. It is also clear that ***most*** animal-based fats are actually **well-balanced** with regard to the omega-6:omega-3 ratio (chicken fat is an exception), but due to the high percentage of saturated fat, consumption of animal fat still needs to be restricted in an appropriate amount.

Overall, **canola oil** has the most *balanced* fatty acid composition, not only due to a good omega-6:omega-3 ratio, but also because it contains a high percentage of monounsaturated fat which is beneficial to human health. **Olive oil**, although moderately high in the omega-6:omega-3

Table 15.6: The effects of omega-3 and omega-6 fatty acids on chronic diseases

Chronic diseases	*Risk factors*	*Comments*	*Omega-3*	*Omega-6*
Cardiovascular diseases	Arrhythmias (irregular heart beat)	Causes sudden cardiac death	Lowers	Increases
	Thrombosis (clot)	Leads to myocardial infarction or stroke	Lowers	Increases
	Atherosclerotic plaque	Leads to atherosclerosis	Lowers	Increases
	HDL	Good cholesterol	Increases	Lowers
	LDL	Bad cholesterol	Lowers	Increases
	Triglycerides	Cardiovascular risk factor	Lowers	Increases
Inflammatory responses	IL-1 (Interleukin 1)	Inflammation response	Lowers	Increases
	IL-6 (Interleukin 6)	Inflammation response	Lowers	Increases
	CRP (C-reactive protein)	Inflammation response	Lowers	Increases

ratio, also contains a high percentage of monounsaturated fat. Most importantly, olive oil also contains a high amount of antioxidants and the substance squalene that has been shown to have anti-cancer effects. Therefore, olive oil is another good choice of healthy food oil. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are obtained through breast milk and the oils of cold-water fish such as salmon, mackerel, sardines, herring, and rainbow trout.. **Flaxseeds oil** is also a rich source of omega-3.

Laboratory evaluation of EFA profiles can be obtained. Tissues preferentially metabolize PUFAs in this order: ω-3 > ω -6 > ω-9. When LA and ALA are not supplied by the diet, oleic acid (18:1 ω-9) serves as the substrate for PUFA generation, creating mead acid. An elevated mead acid (20:3 ω-9) level suggests a reduced blood level of ω-3 and ω-6 fatty acids, or essential fatty acid deficiency.

Dermatological Significance of EFA

Linoleic acid and its products serve as structural precursors for the important stratum corneum ceramides, and α-linolenic derivatives serve as immune modulators. Linoleic acid (LA) and its derivatives play a central role in the structure and function of the stratum corneum permeability barrier, defects of which are most notable in atopic dermatitis.

Derivatives of α-linolenic acid (ALA) can modulate the immune response of the epidermis by influencing T lymphocytes, acting on Toll-like receptors (TLRs), and activating caspase cascades that influence many inflammatory dermatoses, including *acne vulgaris, psoriasis, atopic dermatitis, systemic lupus erythematosus, and skin cancer.*

Finally, the ω-3s are ligands for an important class of transcription factors, the peroxisome proliferator-activated receptors (PPARs), which are important in lipid metabolism, sugar homeostasis, and insulin sensitization as well as inflammation, immune regulation, and skin barrier homeostasis. They also show promise as natural options for treating inflammatory skin disease and skin carcinogenesis, including melanoma.

The ideal homeostatic cellular concentration of ω-6: ω-3 is 3:1. (Ollis TE) In actual practice, this ratio is not always achieved due to multiple reasons

- Western diets. The intake of ω-6 fats is approximately 10 times greater than ω-3 fats. Furthermore, as a result of food processing and cooking, many ω-3 fats are lost or oxidized (Das UN).
- Enzyme competition. Both classes depend upon the same enzymes for the production of their long-chain derivatives. Given the abundance of ω-6s in the diet, EPA and DHA are

minimally produced; therefore, a balanced ratio of these fats is dependent on nutritional intake.

- Inefficiency of Δ 5 and Δ 6 desaturase enzymes. The production of long-chain derivatives of LA and ALA is dependent on these enzymes, but the process is quite inefficient, where only 5 to 10% of ALA is converted to EPA and 1% to DHA. Infants are even less capable of converting these fats due to immature enzyme activity and are dependent on dietary supply through breast milk.
- Western diet and disease. Saturated fats, trans-fats, fat-free diets, glucose-rich diets, alcohol, glucocorticoids, reduced insulin levels, protein deficiency, hypothyroidism and age also reduce the activity of the desaturase enzymes.

Thus, apart from the medical uses of these compounds extradietary supplemen tation of ω-3s is necessary to achieve

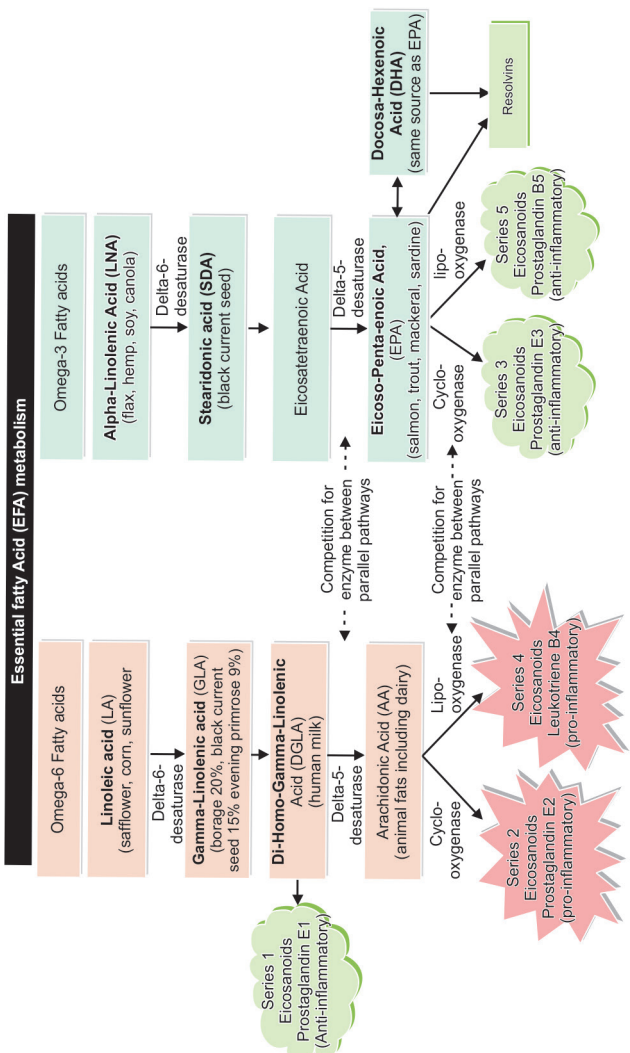


Fig. 15.7: Overview of EFA metabolism

a balanced ratio of ω-3: ω-6 fatty acids, especially in the cases of formula feeding, reduced cold-water fish intake, abundant alcohol consumption, diabetic states, protein deficiency, and aging.

Absorption and Distribution

PUFAs Metabolism

Once consumed from the diet and inside human cells, PUFAs are stored in the phospholipids of the cell and organelle membranes or in glycerides and phospholipids of lipid bodies in human cells. When needed, these fatty acids are released from phospholipids by PLA2 (phospholipase A2) and are further converted to signaling molecules. Shorter chain PUFAs, LA and ALA, can be further processed to produce longer carbon chains and more double bonds by the same set of enzymes (elongases and desaturases). However, omega-3 and omega-6 fatty acids are not inter-convertible in human and animals. All the longer chain products derived from omega-3 fatty acids remain omega-3, and omega-6 derivatives remain omega-6 (Fig. 15.7).

For example, AA (omega-6) can be synthesized from LA (omega-6), but not from ALA (omega-3) in the human body. Similarly, DHA (omega-3) and EPA (omega-3) can be synthesized from ALA (omega-3), but not from LA (omega-6). In addition, both types are also precursors of (and share the enzymes to produce) signaling molecules that work through cell surface receptors like the GPCRs (G protein coupled receptors) as well as through nuclear hormone receptor transcription factors directly to regulate processes related to cardiovascular function and inflammation response.

PUFA-derived Signaling Molecules

Overall, the signal molecules derived from omega-6 are proarrhythmic (irregular heart beat or muscle contraction) and proinflammatory while the signal molecules derived from omega-3 are antiarrhythmic and anti-inflammatory (Table 15.7).

Most of the signal molecules derived from PUFAs are eicosanoids, the 20-carbon atom ('eicosa' means 20 in Greek) signal molecules shown in Table 15.7, except for RVD and NPD1 which are DHA derived 22-carbon atoms signaling molecules. All of these signaling molecules are autocrines or paracrines that act locally on the cells or in the vicinity of the cells where they are manufactured. They activate different pathways either through GPCRs (G protein coupled receptors) on the cell surface or through nuclear hormone receptor transcription factors directly. Some of the signaling

Table 15.7: Effects of omega-3 and omega-6 derived signaling molecules

Types	*AA (ω-6) Derived*		*EPA and DHA (ω-3) Derived*	
	Molecules	*Function*	*Molecules*	*Function*
Prostaglandins	PGE_2	Proarrhythmic	PGE3	Antiarrhythmic
	PGI_2	Proarrhythmic	PGI3	Antiarrhythmic
Thromboxanes	TXA2	Platelet activator	TXA3	Platelet inhibitor
	TXB2	Vasoconstriction	TXB3	Vasodilatation
Leukotrienes	LTB4	Proinflammatory	LTB5	Anti-inflammatory
	LTC4	Proinflammatory		
	LTE4	Proinflammatory		
Lipoxin	LXA4	Anti-inflammatory		
Resolvins	RVD	Anti-inflammatory	RVE1	Anti-inflammatory
	NPD1	Anti-inflammatory		

molecules are generated in most of the cells while others are cell type specific. The same signaling molecules can bind to different GPCRs to activate totally opposite pathways. For example, prostaglandin PGE_2 causes bronchoconstriction (the constriction of airways in the lungs) when it binds to the receptor EP1 whereas the same molecule causes bronchodilation (the relaxation of the airways in the lungs) when it binds to the receptor EP2. Therefore, the effect of one signaling molecule on a whole body depends on its interaction with many other factors. A combination of different signaling molecules, different cell types and different GPCRs dictate the exact physiological effect (Fig. 15.7).

a. **Prostaglandins:** The *omega-6* fatty acid AA derived PGI2 (also known as prostacyclin) and PGE_2 have *pro-arrhythmic* effects, whereas the *omega-3* fatty acid EPA-derived prostaglandins PGI3 and PGE3 are *anti-arrhythmic* (Lin et al. 1997).
b. **Thromboxanes:** Named for their roles in thrombosis, the formation of blood clot, thromboxanes are a vasoconstrictor and facilitate platelet aggregation. Thromboxane-2 series TXA2 and TXB2, produced by activated platelets, have prothrombotic properties, stimulating activation of new platelets as well as increasing platelet aggregation. Whereas the *omega-3* fatty acid EPA derived TXA3 and TXB3 has opposite effect. The TXB2-mediated platelet aggregation and vasodilation is also inhibited by EPA-derived prostaglandins.
c. **Leukotrienes:** The *omega-6* fatty acid derived *LTB4* is a potent chemotactic agent for leukocytes. It increases vascular permeability, induces release of lysosomal enzymes and accelerates reactive oxygen species production. It also leads to the production of inflammatory cytokines like TNF-α, IL-1 and IL-6. The leukotrienes LTC4, LTD4 and LTE4 increase vascular permeability and promote hypersensitivity. These 4-series leukotrienes are believed to be responsible for hypersensitivity reactions that are involved in asthma, psoriasis, allergic rhinitis, gout, rheumatoid arthritis, adult respiratory distress syndrome, neonatal pulmonary hypertension, and inflammatory bowel disease. The *omega-3* fatty acid derived LTB5 blocks biosynthesis of the LTB4 thereby exhibiting *anti-inflammatory* effects.
d. **Lipoxins** (LX) are derived from the omega-6 fatty acid AA and manufactured in leukocytes. There are two types of lipoxins, LXA4 and LXB4. Both types inhibit chemotaxis of polymorphonuclear leukocytes and may have roles in inflammation and wound healing. LXA4 appears to oppose some leukocyte responses to leukotrienes. For

example, the binding of LXA4 to polymorphonuclear leukocytes inhibits chemotactic responses and degranulation induced by LTB4. By competing for receptor sites, LXA4 inhibits vasoconstriction induced by LTD4. By inhibiting neutrophil and eosinophil migration and adhesion, lipoxins act as anti-inflammatory signaling molecules. The anti-inflammatory effect of LXA4 is unusual in the sense that most of the omega-6 fatty acid derived eicosanoids are proinflammatory.

e. **Resolvins** are omega-3 fatty acid derived compounds, so named because they were first encountered in resolving inflammatory exudates. Neuroprotectins are resolvins first discovered in brain tissue. The resolvins have strong anti-inflammatory effects in addition to some immunoregulatory activities at picomolar to nanomolar concentrations. They are part of the molecular mechanisms that contribute to removal of inflammatory cells and restoration of tissue integrity once the need for the inflammatory response is over. The neuroprotectins appear to operate in the same way as the resolvins in brain tissue.

At the cellular level, it is characterized by edema, accumulation of leukocytes, and then by accumulation of monocytes and macrophages. Leukotrienes (especially LTB4) and prostaglandins (PGE_2 and PGD_2) derived from omega-6 fatty acid AA are actively involved in the early stages of the inflammatory process. As tissues return to health, resolvins and lipoxins promote resolution of inflammation through removal of leukocytes together with cellular debris.

COX and LOX Enzymes

The key enzymes that are responsible for the production of signaling molecules from PUFAs are COX (cyclooxygenases) and LOX (lipoxygenases) (Fig. 15.7).

There are two Cox isozymes in the human body: COX-1 and COX-2. COX-1 is considered a ***constitutive*** enzyme, being found in most mammalian cells. COX-2 is an **inducible** enzyme, becoming abundant in activated macrophages and other cells at sites of inflammation. Both COX-1 and COX-2 convert the omega-6 fatty acid AA to the prostaglandin-2 series and thromboxane-2 series molecules and the omega-3 fatty acids, EPA and DHA, to the prostaglandin-3 and thromboxane-3 series and resolvins (Fig. 15.7).

Both COX-1 and COX-2 are the targets of nonsteroidal anti-inflammatory drugs (NSAIDs). The anti-inflammation medicine aspirin, which irreversibly inhibits COX-1 more than COX-2, causes the reduction of inflammation, analgesia (relief of pain), the prevention of clotting, and the reduction

of fever through the decreased production of prostaglandins and thromboxanes.

Lox is a family of enzymes that convert the omega-6 fatty acid AA to leukotriene-4-series and lipoxins. These same enzymes also convert the omega-3 fatty acids EPA to leukotriene-5-series and DHA to resolvins (Fig. 15.7). The two major isozymes of Lox are 5-lipoxygenase and 15-lipoxygenase. The former is responsible for the synthesis of leukotrienes in myeloid cells and the later lipoxins in leukocytes. The asthma treatment drugs, zileuton and montelukast, and the antiparasite drug, diethylcarbamazine, are lipoxygenases inhibitors.

A unique feature about resolvin synthesis is that both Cox and Lox enzymes are involved. In the presence of aspirin, the enzyme COX-2 is acetylated. The acetylated COX-2, which can no longer convert omega-6 fatty acid AA, converts the omega-3 fatty acid EPA or DHA into the substrates for 15-Lox, which further converts the substrates into resolvins. In the absence of aspirin, 15-LOX can still convert EPA and DHA to resolvins through similar pathways for lipoxin biosynthesis. Without aspirin, most of the COX activity devoted to omega-6 fatty acid AA metabolism results in limited resolvin synthesis. Therefore, it is reasonable to believe that dietary supplementation of *omega-3 fatty acids,* taken together *with aspirin,* may ameliorate the clinical symptoms of many inflammatory disorders by regulating the time course of resolution via the production of resolvins.

MECHANISM OF ACTION

Skin Barrier

Linoleic acid (LA) is the most abundant fatty acid in the epidermis. Importantly, it is also the precursor to ceramides, a major component of the extracellular lipid matrix that forms the stratum corneum permeability barrier (SCPB). There are essentially three components of the SCPB: the extracellular lipid matrix, the cornified envelop, and dense keratin fibrils aggregated by filaggrin. The extracellular lipid matrix is composed of ***50% ceramides, 25% cholesterol, and 15% free fatty acids*** (Wertz PW). Lipids, enzymes, and antimicrobial peptides (β-defensin 2) are packaged into lamellar bodies in the upper stratum spinosum and stratum granulosum. Extrusion of lamellar bodies into the extracellular space signals the cross-linking of the cornified envelop proteins loricrin, involucrin, and trichohyalin by transglutaminase. The extracellular lipid matrix coats the cornified envelop proteins, forming a strong, water-impervious lamella. Defective SCPB results when mutations occur in the proteins and enzymes that are important in this complex process or when lipid levels are reduced.

An acid environment is critical for the functioning of acid sphingomyelinase and β-glucocerebrosidase involved in the production of ceramides. This is facilitated by the catabolism of filaggrin, which yields the polycarboxylic acids pyrrolidine carboxylic acid and trans-urocanic acid that help maintain an acidic pH (Elias PM).

Monounsaturated and saturated fatty acids can be synthesized within the epidermis. PUFAs must be obtained from the diet. Labeling experiments have shown that dietary fatty acids and cholesterol are delivered to the stratum corneum. Fatty acid transport proteins present in keratinocytes are more selective for PUFAs than monounsaturated fatty acids. When dietary PUFA is deficient, oleic acid takes its place, resulting in abnormal stratum corneum permeability and appearance. Insufficient LA also yields less ω-hydroxyceramide, an important anchoring lipid connecting the extracellular lipid matrix to the cornified envelop. Therefore, PUFA insufficiency results in increased transepidermal water loss (Meguro S, Schurer NY).

PPAR Receptors and EFA

There are three PPAR isoforms: PPAR-α, PPAR-β/Δ, and PPAR-γ. They are members of the nuclear receptor family that partner with the retinoic acid X receptor to fulfill their functions. Their primary role has been in cardiovascular medicine and endocrinology as lipid regulators and insulin sensitizers. PPAR-γ is particularly notable because it has strong anti-inflammatory properties. DHA and EPA, are known as "reversible agonists" of PPAR-γ, so higher concentrations are required for receptor activation. Perhaps the improvement in psoriasis observed with intravenous EPA and DHA occurs through this mechanism.

TLR Receptors and ω-3 Fatty Acids

The TLRs are a fairly recently identified group of receptors that are present on many cells, including keratinocytes, monocytes, Langerhans cells, dermal dendritic cells, and intestinal epithelial cells. The TLRs are involved in the first-line recognition of pathogens. They are pattern-recognition receptors that recognize certain pathogen-associated molecular patterns expressed by microbes. TLRs communicate signals of tolerance from recognized commensals or, when danger is sensed, elicit inflammatory responses leading to dendritic cell maturation and activation of adaptive responses.

DHA and EPA have been shown, through the consumption of fish oil, to ***reduce*** the proinflammatory signals derived from TLR-2 in human monocytes. In addition, DHA has been

shown to inhibit TLR-4, the receptor for lipopolysaccharide (Lee JY).

Immune-modulating Roles of ω-3 fatty Acids in the Epidermis and Skin Disease

DHA and EPA are not major constituents of the epidermis, which is likely a reflection of insufficient dietary consumption or increased cellular utilization. Unlike LA, which plays a major structural role in the epidermis and SCPB, ω-3 fatty acids appear to play an immune-modulating role.

EPA has been shown to reduce the expression of intercellular adhesion molecule-1, reduce T-lymphocyte proliferation, and dampen delayed-type hypersensitivity. Diets supplemented with fish oil can lead to altered phospholipid profiles in the epidermis. A prominent enzyme in the epidermis, 15-lipoxygenase, converts PUFAs into anti-inflammatory mediators that can reduce the production of leukotriene B4, a potent inflammatory and antimicrobial mediator derived from the proinflammatory enzyme 5-lipoxygenase on arachidonic acid.

INDICATIONS

Hypertriglyceridemia (FDA Approved)

Epanova (omega-3 carboxylic acids)

- **New drug for** hypertriglyceridemia.
- Indicated as an adjunct to diet in patients with severe hypertriglyceridemia (i.e. TG >500 mg/dL).
- Approval based on data from the EVOLVE (Epanova for lowering very high triglycerides) trial, which showed a significant decrease in non-HCL-C, ratio of total cholesterol to HDL-C, VLDLs, Apo-C phospholipase A2 and arachidonic acid over a 12-week period in patients with TGs >500 mg/dL.
- **Mechanism:** Omega-3 polyunsaturated fatty acid (PUFA) in free fatty-acid form; thought to inhibit acyl CoA:1,2-diacylglycerol acetyltransferase: may increase mitochondrial and peroxisomal beta-oxidation in the liver: may decrease hepatic lipogenesis.
- **Dosage:** 2–4 g PO once daily; individualize dose according to response and tolerability.

Off Label Indication

Atopic Dermatitis

Despite an incomplete pathogenic puzzle, lipid and other nutritional treatments may help facilitate maturation of the

permeability barrier and reduce the risk of AD. Nutritional modulation likely begins during gestation, as the risk for AD is encountered as early as in the in utero period. Low levels of arachidonic acid in cord blood have been associated with the risk of dermatitis (Galli E, Beck M).

Arachidonic acid is the precursor to series-4 leukotrienes and lipoxins in addition to series-2 prostaglandins (Fig. 15.7). Prostaglandin E_2 (PGE-2), an arachidonic acid derivative, appears to be involved in the generation of regulatory T cells, which are important in reducing inflammatory responses. Trans-fatty acids, derived from the hydrogenation of vegetable oils found in margarine, shortening, and baked goods, inhibit the Δ-5 and Δ-6 desaturase enzymes that are necessary for the conversion of LA and ALA to long-chain products.

Concentrations of PUFAs, both cis- and trans-isomers, in cord blood correlate with maternal serum concentrations. An inverse relationship was found between infant trans-fatty acids and arachidonic acid and DHA concentrations in serum. Arachidonic acid levels positively correlated with gestational length. Reducing the intake of trans-fatty acids during pregnancy may help reduce the risk of AD by increasing the concentration of arachidonic acid in infant serum. In addition, an increased gestational period likely gives the epidermis more time to mature, decreasing the chances of microbial invasion.

Supplementation with ω-6 in AD: The premise behind the use of evening primrose oil, as source of γ-linolenic acid (GLA) in AD comes from studies that showed reduced levels of GLA and dihomo-GLA (DGLA) and higher levels of LA in affected patients, suggesting that a defect in the Δ-6 desaturase enzyme was at work. Many reviews showed a benefit, but some were not as promising (Biagi PL). The most recent meta-analysis on this issue deduced that evening primrose oil is effective in a subset of patients with atopic dermatitis and elevated immunoglobulin (Ig) E levels (Morse NL).

AD, Biologic Lipids, and Other Nutrients

Many current treatments for AD are effective at reducing inflammation and improving the texture of the skin, but they may also be hampering maturation of the skin barrier, creating a cycle of disease. For instance, bleach baths, although helpful in reducing the burden of *Staphylococcus aureus* on the skin surface, are likely to prevent both acid sphingomyelinase and β-glucocerebrosidase that require an acid pH from producing ceramides.

The enzymes involved in lipid uptake and synthesis are up-regulated during acute barrier disruption and cholesterol

synthesis is increased. If ample lipid can be supplied to the epidermis, exogenous acids or enzyme sources may help convert these fats into ceramides. Healing of the SCPB after acute barrier disruption is also dependent on a graded calcium concentration from the stratum granulosum to the stratum corneum. Occlusive *petrolatum,* although seemingly controlling transepidermal water loss, impedes the calcium concentration gradient and prevents the extrusion of lamellar bodies that are important in barrier maturation and repair. Fewer lamellar bodies means less antimicrobial peptide necessary to combat pathogenic organisms like S aureus. Topical *steroid* application inhibits TLR-3, a signaling molecule important in combating viruses. Genetic defects in the SCPB in AD will make its maturation incomplete.

Applying more physiologic lipids would likely lead to greater healing as lipid mixtures are incorporated into nascent lamellar bodies (Mao-Qiang M). Understandably, a mixture of *ceramide, cholesterol,* and *free fatty* acids was therefore very effective in the treatment of severe atopic lesions (Sugarman J). Whether or not these topical preparations are available, increasing the dietary consumption of beneficial fatty acids like LA and GLA in conjunction with nutritional modalities, while maintaining an acidic environment of the stratum corneum, would likely be of benefit. A 2006 analysis found oral ceramide supplementation improved skin symptoms and allergic responses in atopic children when given at 1.8 g/day for 2 weeks (Kimata H). Wheat germ also contains ceramide precursors, yet the allergic nature of this substrate may limit its utility in some patients.

AD and ω-3 Fatty Acids

Use of ω-3 fats in pregnancy has been scrutinized, and fish oil supplementation during pregnancy was associated with improvements in clinical severity in AD at 1 year (Denburg J).

Early nutrition is highly important for infant development, especially for development of the immune system. In fact, thymic density of breastfed infants is nearly twice that of infants who receive formula. Many studies have shown that breastfeeding has a protective effect on the development of AD (Gdalevich M). This again is likely a reflection of maternal nutrition, because an increased incidence of AD was found in infants consuming breast milk rich in saturated fat and diminished ω-3 fats (Hoppu U). This argues for the importance of DHA and EPA in early life. Breast milk also contains other factors that protect against AD, including epidermal growth factor, which stimulates keratinocyte growth and migration (Gibbs S). This has led the US Food and Drug Administration to include the long-chain fatty acids, DHA and arachidonic acid, in infant formulas.

Psoriasis and ω-3 Fatty Acids

Supplementation with fish oil has produced varied results in psoriasis, depending on the method of administration. Improvement has *not* been seen with topical application or oral supplementation. Improvement was seen when administered ***intravenously*** in a randomized, double blind trial of patients hospitalized with plaque-type psoriasis (Mayser P).

Patients were given a combination of 4.2 g of EPA and DHA each vs an ω-6 preparation. Improvements in erythema, scaling, inflammatory infiltrate, and body surface area were observed. It appears that *higher* doses, and likely *longer* treatment periods, are necessary for the effects of EPA and DHA to be evident. The intravenous administration of 4.2 g likely equates to double or triple the dose orally. Fish oil supplementation was also shown to reduce the hyperlipid emia and nephrotoxicity associated with retinoid and cyclosporin therapy, respectively (Allen BR).

Skin Cancer and ω-3 Fatty Acids

DHA and EPA have protective effect on colorectal cancer and also enhance the effect of chemotherapeutic drugs. DHA and EPA were shown to have a proapoptotic effect on colorectal cancer cells by activation of intrinsic and extrinsic caspase cascades.

With regard to skin carcinogenesis, ultraviolet radiation is a known carcinogen. One study found that individuals supplemented with 4 g of EPA daily had an increased sunburn threshold, reduced p-53 expression, and fewer strand breaks in peripheral blood leukocytes (Rhodes LE).

Systemic Lupus Erythematosus and ω-3 Fatty Acids

Omega-3 FA increase the sunburn threshold with EPA supplementation and may beneficial for patients with SLE. Results of one study showed DHA and EPA levels were reduced in these patients (Mohan IK).

Acne Vulgaris

In acne, sebocytes are known to express TLR-2 and TLR- 4 constitutively. *Propionibacterium acnes* can activate TLR-2 on macrophages, leading to IL-12 and IL-8 production and neutrophil recruitment. Inflammation can be perpetuated by keratinocytes by *P. acnes* induction of TLR-4 (not typically expressed on keratinocytes) and TLR-2 activation. EPA and DHA may therefore be helpful in modulating this inflammation. While DHA and EPA may be functioning to

control inflammation, other antimicrobial fatty acids at the skin surface are trying to eliminate *P. acnes*.

Lauric acid is an antimicrobial fatty acid found in coconut oil and breast milk. It is also produced by sebaceous glands and is a stimulator of TLR-2. This fat, when applied topically, reduced the numbers of *P. acnes* colonies at the epidermal surface and was nontoxic to sebocytes (Nakatsuji T). Oral supplementation with DHA and EPA could then serve as a perfect adjunct to this potential antiacne drug by modulating inflammation and irritation.

Omega-3FA supplements can stabilize the expected increase in triglyceride levels during isotretinoin therapy in patients with preexisting hypertriglyceridemia. A study found that patients who did not use ω-3FA supplements experienced a mean increase of 49% in triglyceride levels during treatment, whereas patients using ω-3FA supplements only experienced a mean increase of 13.91% (Krishna S). This finding could be clinically significant as adjunctive treatment with ω-3FA could permit maximal therapeutic doses, without causing lipid abnormalities.

Stasis Dermatitis and Decubitus Ulcers

It is believed that EPA and DHA has an effect of stimulate blood circulation, increase the breakdown of fibrin, a compound involved in clot and scar formation and improving blood flow. In peripheral arterial disease, EPA-E and DHA-E induced a marked improvement in endothelial function. They have a vasoprotective effect, providing improving elastic properties of the arteries by preventing fibrosis. With decubitus, peripheral vascular endothelial function decreases, and as a result of blood stagnation, the intercellular adhesion molecule-1 (ICAM-1) and the vascular cell adhesion molecule-1 (VCAM-1) are expressed. EPA-E and DHA-E attenuate the expression of inflammatory cytokines such as this VCAM-1. A report of the use of omega-3FA in two cases of refractory pressure ulcers and stasis dermatitis, highlight its utility in this refractory disorder (Nagai K).

Conclusion

Linoleic acid, γ-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid are vital to optimum wellness and healthy skin. Poor maternal nutrition, infancy, consuming a Western diet, age, and diabetic states are conditions where increased dietary intake is required and nutritional supplementation is essential to restore the balance of ω-6: ω-3 fatty acids. As we have discussed, these fatty acids and their synthetic derivatives serve important and diverse roles in

the structural maintenance and immunologic balance of the epidermis and may aid in the healing of many dermatoses.

BIBLIOGRAPHY

1. Allen BR. Fish oil in combination with other therapies in the treatment of psoriasis. World Rev Nutr Diet. 2001;66:436-45.
2. Beck M, Zelczak G, Lentze MJ. Abnormal fatty acid composition in umbilical cord blood of infants at high risk of atopic disease. Paediatr. 2000;89:279-84.
3. Biagi PL, Bordoni A, Masi M, et al. The effect of gamma-linolenic acid on clinical status, red cell fatty acid composition and membrane microviscosity in infants with atopic dermatitis. Drugs Exp Clin Res. 1994;14:285-90.
4. Das UN. Essential fatty acids: biochemistry, physiology and pathology. Biotech J. 2006;1:420-39.
5. Denburg J, Hatfield H, Cyr M, et al. Fish oil supplementation in pregnancy modifies neonatal progenitors at birth in infants at risk of atopy. Pediatr Res. 2005;57:276-81.
6. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. J Allergy Clin Immunol. 2008;121:1337-43.
7. Galli E, Picardo M, Chini L, et al. Analysis of polyunsaturated fatty acids in newborn sera: a screening tool for atopic disease? Br J Dermatol. 1994;130:752-6.
8. Gdalevich M, Mimouni D, David M, Mimouni M. Breastfeeding and the onset of atopic dermatitis in childhood: A systematic review and meta-analysis of prospective studies. J Am Acad Dermatol. 2001;45: 520-7.
9. Gibbs S, Pinto ANS, Murli S, Huber M, Hohl D, Ponec M. Epidermal growth factor and keratinocyte growth factor differentially regulate epidermal migration, growth and differentiation. Wound Rep Regen. 2009;8:192-203.
10. Hoppu U, Rinne M, Lampi A, Isolaurie E. Breast milk fatty acid composition is associated with development of atopic dermatitis in the infant. J Pediatr Gastroenterol Nutr. 2005;41:335-8.
11. Kimata H. Improvement of atopic dermatitis and reduction of skin allergic responses by oral intake of konjac ceramide. Pediatr Dermatol. 2006;23:386-9.
12. Krishna S, Okhovat JP, Kim J, Kim CN. Influence of ω-3 fatty acids on triglyceride levels in patients using isotretinoin. JAMA Dermatol. 2015;151(1):101-2.
13. Lee JY, Plakidas A, Lee WH, Heikkinen A, Chanmugam P, Bray G, Hwang DH. Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. J Lipid Res. 2003;44:479-86.
14. Mao-Qiang M, Brown BE, Wu-Pong S, Feingold KR, Elias PM. Exogenous nonphysiological vs physiological lipids. Divergent mechanisms for correction of permeability barrier dysfunction. Arch Dermatol. 1995;131:809-16.
15. Mayser P, Mrowietz U, Arenberger P, et al. Omega-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis:

Results of a double-blind, randomized, placebo-controlled, multicenter trial. J Am Acad Dermatol. 1998;38:539-47.
16. Meguro S, Arai Y, Masukawa Y, Uie K, Tokimitsu I. Relationship between covalently bound ceramides and transepidermal water loss (TEWL). Arch Derm Res. 2000;292:463-8.
17. Mohan IK, Das UN. Oxidant stress, anti-oxidants and essential fatty acids in systemic lupus rythematosus. Prostaglandins Leukot Essent Fatty Acids. 1997;56:193-8.
18. Morse NL, Clough PM. A meta-analysis of randomized, placebo-controlled clinical trials of efamol evening primrose oil in atopic eczema. Where do we go from here in light of more recent discoveries. Curr Pharma Biotech. 2006;7:503-24.
19. Nagai K, Matsumaru K, Hirai I, Takae Y, Andoh K. New therapy using omega-3-Acid ethyl esters for decubitus ulcers and stasis dermatitis: a case report. Iran Red Crescent Med J. 20145;16(12):e19500.
20. Nakatsuji T, Kao MC, Fang JY, et al. Antimicrobial property of lauric acid against *Propionibacterium acnes:* its therapeutic potential for inflammatory acne vulgaris. J Invest Dermatol. 2009;129:2480-8. 451.
21. Ollis TE, Meyer BJ, Howe PR. Australian food sources and intakes of omega-6 and omega-3 polyunsaturated fatty acids. Ann Nutr Metab. 1999;43:346-55.
22. Rhodes LE, Shahbakhti H, Azurdia RM, et al. Effect of eicosapentanoic acid an omega-3 polyunsaturated fatty acid, on UVR-related skin cancer risk in humans: An assessment of early genotoxic markers. Carcinogenesis. 2003;24:919-25.
23. Schurer NY, Stremmel W, Grundmann JU, et al. Evidence for a novel keratinocyte fatty acid uptake mechanism with preference for linoleic acid: comparison of oleic acid and linoleic acid uptake by cultured human keratinocytes, fibroblasts and a human hepatoma cell line. Biochin Biophys Acta. 1994;1211:51-60.
24. Sugarman J, Parish LJ. A topical lipid-based barrier repair formulation (EpiCeram ™ cream) is high effective monotherapy for moderate-to severe pediatric atopic dermatitis. J Invest Dermatol. 2000;115:414-20.
25. Wertz PW. Biochemistry of human stratum corneum lipids. In: Elias PM, Feingold KR (Eds). Skin barrier. New York: Taylor & Francis; 2006. p. 33-42.

16

CHAPTER

Analgesics

Kabir Sardana

INTRODUCTION

This is a class of drug that is widely used in various pain disorders and neuropathies and a working knowledge with their applications is given in this chapter.

The "pain experience" involves more than just the sensation of pain. Pain activates many areas of the brain that interact, resulting in the pain experience, which will differ among individual patients. The three components of the pain experience include (i) sensory/discriminative, (ii) affective/emotional and (iii) evaluative/cognitive.

The sensory/discriminative component of pain provides information on the intensity, location and quality of the pain. These pathways consist of peripheral receptor activation, axon depolarization and ascending pathways to the cortex for processing. The ascending pathways that carry impulses from the nociceptor to the sensory cortex also give off fibers to brain stem structures and deep brain structures. Activation of these structures in the brain stem and deep brain will stimulate emotional and sympathetic responses from the individual, leading to the emotional/affective component of pain. Finally, ascending pain pathways also send projections to the forebrain structures where the pain is processed on a cognitive and evaluative level, explaining why patients respond differently to pain based on culture, gender and past experiences.

The main neurotransmitter in primary afferents is the excitatory amino acid **glutamate.** Activation of **nociceptors** causes the release of glutamate from presynaptic terminals in the spinal cord dorsal horn; this release acts on the ionotropic glutamate receptor amino-3-hydroxy-5-methylisoxazole-4-proprionic acid postsynaptically to cause rapid depolarization of dorsal horn neurons and, if threshold is reached, action potential discharge.

PAIN CLASSIFICATION

Pain can be mechanistically divided into **four** classifications: Nociceptive, inflammatory, functional and neuropathic.

Nociceptive pain is *transient* pain in response to a noxious stimulus that activates high threshold afferents. Nociceptive pain serves a protective function. **Inflammatory pain** is the spontaneous hypersensitivity to pain that occurs in response to tissue damage and inflammation (e.g., postoperative pain, trauma, arthritis). **Functional pain** is hypersensitivity to pain resulting from abnormal central processing of normal input (e.g., pathologic irritable bowel syndrome).

ANALGESICS

The efficacy of analgesics is dependent on the pain mechanism. **Primary analgesics** are more efficacious in *nociceptive and inflammatory* pain, whereas **adjuvant agents** are more efficacious in *neuropathic and functional pain*. Pain is mediated through both peripheral and central mechanisms and often more than one mechanism of pain is active in a given patient. Thus, the use of two or more agents with differing mechanisms increases the likelihood of interrupting pain signals and relieving pain. Pharmacologic agents for the management of chronic pain are divided into primary analgesics, which have intrinsic analgesic properties, and adjunct analgesics, which may have primary analgesic properties in neuropathic pain (NeP) but usually enhance the analgesic effects of primary analgesics when used in non-neuropathic pain syndromes (Table 16.1).

A. Antidepressants

Antidepressants have long been used for the treatment of chronic pain. In the past, they were more often chosen to improve mood rather than to treat pain because of coexisting anxiety and depression. After separate studies showed improved pain control in patients without depression, as well as in patients with depression without improvement in mood, it was realized that these medications have independent analgesic actions. Further, improvement in pain is seen earlier and at lower doses than improvements in depression, also demonstrating this analgesic efficacy. The FDA in the United States has now approved selective SNRIs for

Table 16.1: Classification of analgesics

Primary analgesics	*Adjunct analgesics*
Acetaminophen	Tricyclic antidepressants
Nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors	Serotonin-norepinephrine reuptake inhibitors
Opioids	Anticonvulsants
	Muscle relaxants
	Topical agents

fibromyalgia, diabetic peripheral neuropathy and chronic musculoskeletal pain.

1. Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are considered first-line agents in the treatment of chronic NeP and fibromyalgia. All TCAs have shown fairly equal efficacy within the class. TCAs are usually divided into tertiary amines (amitriptyline, imipramine, and doxepin) and secondary amines (nortriptyline and desipramine). Nortriptyline and desipramine are demethylated in the liver from amitriptyline and imipramine, respectively. The ***tertiary amines*** tend to block the reuptake of serotonin **more** than norepinephrine, and the secondary amines are more selective in their inhibition of norepinephrine uptake.

It is recommended that tricyclics should be started at the lowest dose possible and titrated slowly. A typical starting dose for amitriptyline, nortriptyline, or desipramine is as low as 5–10 mg before bedtime. Doses can be increased by the same amount as the starting dose approximately every 7 days. Studies have shown improved analgesia with amitriptyline in the range of 25–50 mg, but some studies have gone as high as 200 mg. Response should be seen within 3–4 weeks. When these medications are stopped, it is recommended that they be reduced by 25% per week to decrease side effects (Table 16.2).

Table 16.2: Common antidepressants used for pain relief

Drug	*Amitriptyline*	*Desipramine**	*Doxepin*	*Imipramine*	*Nortriptyline*
Half-life	9–27 hours	7–60 hours	6–8 hours	6–18 hours	28–31 hours
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
Excretion	Urine	Urine	Urine	Urine	Urine
Protein binding	≥90%	90–92%	80–85%	60–95%	93–95%
Therapeutic dose/day	10–150 mg	10–150 mg	10–150 mg PO	10–200 mg	10–150 mg
Administration	qhs or 2 times/day	qhs or 2 times/day	qhs or 2–3 times/day	qhs or 2 times/day	qhs or 2–3 times/day
Titration	≥7 days/dose change	≥3 days/dose change	≥7 days/dose change	≥7 days/dose change	≥3 days/dose change

Side Effects

Unfortunately, side effects with all of the TCAs are common and can limit use, especially in the elderly and in patients with hepatic impairment. Side effects tend to be less with the secondary amines.

a. **Sedation** is common owing to its antihistamine effects but can be beneficial if there are sleep complaints.
b. **Anticholinergic** side effects, which include dry mouth, constipation, urinary retention and blurred vision, are also prevalent. Both anticholinergic and antihistamine side effects are dose dependent and can decrease with time; slow titration can improve compliance.
c. **Weight gain** and **sexual dysfunction** are frequently reported.
d. **Cardiac side effects** include orthostatic hypotension and dysrhythmias. Cardiac history should be reviewed and a baseline electrocardiogram (ECG) should be considered for patients over the age of 40.
e. **Seizure thresholds** are lowered. Risk of suicidal thinking and behavior is increased in children, adolescents and young adults up to the age of 24.

2. Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

The SNRIs, venlafaxine, duloxetine and milnacipran, have also shown analgesic properties. Together they have shown benefit in *painful diabetic peripheral neuropathy, NeP, fibromyalgia and, most recently, chronic musculoskeletal pain* (Table 16.3).

Table 16.3: Common SNRIs used for pain relief

	Venlafaxine	Duloxetine	Milnacipran
Half-life	5–7 hours	8–17 hours	6–8 hours
Metabolism	Hepatic	Hepatic	Hepatic
Excretion	Urine	Urine 70%, feces 20%	Urine
Protein binding	35%	≥90%	13%
Therapeutic dose/day	37.5–225 mg/day	20–60 g/day	12.5–200 mg/day
Administration	2–3 times	Daily	Twice daily
Titration	≥4–7 days/dose change	≥7 day/dose change	1–2 days/dose change

Venlafaxine, the first drug in this class, is an inhibitor of serotonin reuptake at low doses, and at higher doses it inhibits norepinephrine reuptake. This means that it acts more like an SSRI at lower doses and does not become an SNRI until higher doses, where more side effects occur. Venlafaxine has shown some effectiveness with polyneuropathy, including painful diabetic neuropathy and fibromyalgia, but all of these indications are off label. Doses range from 75 to 225 mg/day.

Duloxetine has been shown to be superior to placebo in *fibromyalgia* except for fatigue symptoms. Long-term benefit of 6 months has been shown with single daily doses of 60 or 120 mg per day of duloxetine for fibromyalgia. Starting doses are **20–30 mg** in the morning.

It has also been approved for *diabetic peripheral neuropathy* in the United States. It has been shown to be superior to placebo at doses between **60 and 120 mg per day** with this disorder, and patients typically respond within the first week. Lastly, duloxetine has also shown efficacy in treating chronic musculoskeletal *pain*, including discomfort from *osteoarthritis and chronic lower back pain*.

Side Effects

Side effects of all three of these SNRIs include nausea, dry mouth and constipation. Sexual side effects tend to be less than with SSRIs. Duloxetine should not be used with coexisting hepatic insufficiency. Milnacipran is not recommended for patients with end-stage renal disease but is unique in that it is not metabolized by cytochrome P450 isoenzymes.

Serotonin syndrome, caused by iatrogenic overstimulation of central and peripheral serotonin receptors, presents with neuromuscular hyperactivity, autonomic hyperactivity and altered mental status. It may occur abruptly and progress rapidly when these drugs are used at high doses or combined with other medications that stimulate serotonin.

These drugs can also impair platelet aggregation, particularly if used concomitantly with aspirin or NSAIDs. Dose-related increases in blood pressure have been reported and should be followed. SNRIs carry a black box warning in the United States for increased risk of suicidal thinking and behavior in children, adolescents and young adults under the age of 25. When these medications are discontinued, withdrawal symptoms have been reported. It is recommended that the dose be decreased by 25% per week to minimize these symptoms.

B. Anticonvulsants

Neuropathic pain is chronic pain initiated by nervous system lesions or dysfunction and maintained by a number of mechanisms. Excess stimulation of nociceptive pathways or damage to non-nociceptive pathways alters the balance between painful and nonpainful inputs so that pain results without nociceptor stimulation. Many of these mechanisms can be modulated by the anti-convulsants. First, nerve injury is reported to evoke spontaneous discharges from the cell bodies of myelinated fibers at the levels of the dorsal root ganglia.

With the exception of pregabalin and gabapentin, studies on the efficacy of the various anticonvulsants to treat pain have been inconsistent. **Pregabalin** is FDA approved to treat *postherpetic neuralgia (PHN), painful diabetic peripheral neuropathy (DPN) and fibromyalgia*; **gabapentin** is FDA

approved to treat PHN; **carbamazepine** is FDA approved to treat *trigeminal neuralgia*; and **valproic** acid and **topiramate** are FDA approved to treat *migraine headaches*.

1. Gabapentin

Classification

Anticonvulsant.

Mechanism of Action

Gabapentin is a *cyclohexane compound* that is structurally related to GABA; its mechanism of action is not known. Gabapentin does not interact with GABA receptors or alter the formation, release, degradation, or reuptake.

Pharmacology

Gabapentin has a *nonlinear bioavailability* with a reduction in absorption as the dose increases. This is the result of an active and saturable transport mechanism. Gabapentin 900 mg has 60% bioavailability, and a 3600 mg dose has only 33% bioavailability. More frequent delivery of smaller doses may improve bioavailability through the saturable transport mechanism.

It is less than 3% protein bound, and because of its high lipid solubility, it readily penetrates the CNS. Gabapentin is not metabolized and is excreted unchanged in the urine. Therefore, renal impairment will significantly increase the drug half-life.

Absorption and Distribution

Onset and Duration: Steady-state serum levels are attained in **1–2 days** in patients with normal renal function.

Fate: Rapidly absorbed and food has no effect on absorption. Absorption occurs via a saturable transport mechanism, so bioavailability decreases with dosages greater than 1.8 g/day; at this dosage it is 60%. The drug is not bound to plasma proteins.

Gabapentin is not appreciably metabolized but is eliminated unchanged in urine and normal renal function.

$T_{1/2}$: 4.8 ± 1.4 hours in adults with epilepsy and normal renal function.

Clinical use in Dermatology

1. **Neuropathic pain:** Current maximum FDA-approved dose to treat pain is 1800 mg/day.
2. **Partial seizures**

3. **Postherpetic neuralgia**
4. **Pruritus, brachioradial**

Usage Guidelines

Because of its nonlinear kinetics, titration of gabapentin to an effective dose can be prolonged with an average onset of 10–14 days after initiation.

Start at 300 mg po od day 1, then bd day 2, tds day 3. Stop at maximum dose of 3600 mg/d.

Neuropathic pain: 300–1200 mg po tid.

Postherpetic neuralgia, brachioradial pruritus: 300–600 mg po tds.

Monitoring

- CBC with differential and platelets, serum BUN and creatinine
- CNS side effects.

Special Considerations

- Take first dose at night
- Do not take gabapentin within 2 hours of an antacid
- Notify dentist or treating physician prior to surgery if taking this medication
- Avoid alcohol
- Avoid driving and other activities requiring mental alertness.

Drug Interactions

- **Drugs that decrease effect/toxicity of gabapentin:** Antacids
- **Drug that increases effect/toxicity of gabapentin:** Cimetidine.

Adverse Effects

Common: Dizziness (15%), ataxia (12%), fatigue, somnolence. **Serious:** Depression, leukopenia, bronchospasm, nystagmus, diplopia, pancreatitis, thyroid abnormalities, personality changes, poor coordination.

Special Populations

- **Pregnancy:** Category C.
- **Lactation:** No data available. Best to avoid.
- **Kidney disease:** Creatinine clearance 30–60 mL/min: 300 mg bid.; creatinine clearance 15–30 mL/min: 300 mg/d; creatinine clearance 15 mL/min: 300 mg qid

- **Liver disease:** None
- **Elderly:** Use with caution because of age-related decrease in renal function
- **Pediatric:** Safety and effectiveness have not been established in children <12 years.

2. Pregabalin

Pregabalin is not dependent on active transport for absorption and therefore has linear kinetics with bioavailability of about 90%. Unlike gabapentin, pregabalin absorption is independent of dose. It has negligible protein binding and readily penetrates into the central nervous system. Pregabalin is not metabolized and is excreted unchanged in the urine; therefore, renal impairment will significantly increase the drug half-life, and dose adjustments are required.

The effective dose of pregabalin is between 150 and 300 mg per day. Owing to the linear kinetics and high bioavailability, the effective dose can be achieved in **2–3 days**; therefore, onset is **faster** than with gabapentin.

Toxicity of Gabapentin and Pregabalin

Neither gabapentin nor pregabalin has any significant drug interactions, and protein binding is minimal. Because gabapentin and pregabalin have similar mechanisms of action, their side effect profiles are very similar. The most common side effects with at least more than twice the incidence of placebo in controlled trials were dizziness, somnolence, dry mouth, peripheral edema, blurred vision, weight gain and thinking abnormalities.

1. Dizziness and somnolence usually began shortly after initiation of therapy, and most cases resolved with continued dosing. Dizziness and somnolence are dose related and can be reduced with slow titration. This side effect can also be an advantage when administered at night in that it will improve sleep. Controlled studies with gabapentin and pregabalin have demonstrated improved sleep quality when compared with placebo.
2. Xerostomia (dry mouth) is dose dependent; however, it is usually mild and few withdrawals from clinical trials have resulted from this side effect.
3. Peripheral edema occurred in almost a third of subjects in clinical trials. It does not appear to be dose related, nor is it associated with any cardiovascular, renal, or hepatic abnormalities.
4. Blurred vision is dose related and usually resolves with continued use. It is not associated with any ocular abnormalities.

5. Weight gain has been reported to be as high as 8% of baseline weight but is not associated with any cardiac, renal, or hepatic abnormalities. A mildly increased appetite was reported in epilepsy and fibromyalgia trials.
6. Thinking abnormalities are typical of anticonvulsants and are consistent with the calcium channel modulation mechanism of these agents. Thinking abnormalities tend to be mild but can be bothersome enough in some patients to lead to discontinuation.
7. Anticonvulsants, including gabapentin and pregabalin, have approximately twice the risk of suicidal ideation over placebo. This increased risk is not age related and appears to occur at between 1 and 24 weeks of therapy. Patients should be warned of this side effect and instructed to contact their health care provider immediately if it occurs.
8. Studies with pregabalin have shown a mild PR interval prolongation that was not associated with increased risk of second- or third-degree atrioventricular block.
9. In controlled clinical trials of pregabalin, more patients reported euphoria as compared with placebo. In a follow-up drug likability study in recreational drug users of sedative-hypnotics, pregabalin subjects reported a "good drug effect," "high," and "liking" to a degree that was similar to 30 mg of diazepam. In addition, clinical studies showed withdrawal symptoms of insomnia, nausea, headache and diarrhea.

As with any anticonvulsant therapy, pregabalin and gabapentin should be withdrawn slowly over at least a week to avoid withdrawal symptoms.

OPIOIDS

Opioid analgesics are drugs that mimic endogenous opioid peptides by causing a prolonged activation of opioid receptors (usually μ-receptors). This produces analgesia, respiratory depression, euphoria and sedation. Pain acts as an antagonist of respiratory depression, which may become a problem if the pain is removed, e.g. with a lead anesthetic. Opioids often cause nausea and vomiting, and antiemetics may be required. Effects on the nerve plexuses in the gut, which also possess opioid peptides and receptors, cause constipation, and laxatives are usually required. Continuous treatment with opioid analgesics results in tolerance and dependence in addicts.

Some analgesics, such as codeine and dihydrocodeine, are less potent than morphine and cannot be given in equianalgesic doses because of the onset of adverse effects. As a result of this restriction in dosage, they are less likely, in practice, to produce respiratory depression and dependence. They are useful in controlling mild to moderate pain. We will

be discussing two drugs in detail while the rest are covered in brief below.

1. Codeine

This is a weak opioid analgesics and is used in 'mild-to-moderate' pain. They may cause dependence and are subject to abuse. However, they are less attractive to addicts because they do not give a good 'buzz'.

Codeine (methylmorphine) is well absorbed orally, but has a very low affinity for opioid receptors. About 10% of the drug is demethylated in the liver to morphine, which is responsible for the analgesic effects of codeine.

Side-effects (constipation, vomiting, sedation) limit the possible dosage to levels that produce much less analgesia than morphine. Codeine is also used as an antitussive and antidiarrheal agent.

Variation in metabolic efficiency is evident among ethnic groups. For example, Chinese individuals produce less morphine from codeine than do whites and are less sensitive to the effects of morphine.

2. Tramadol

Tramadol is a synthetic codeine analogue with a dual mechanism of action. Analgesia results through weak MOR agonism and inhibition of uptake of norepinephrine and serotonin.

Tramadol is 68% bioavailable after a single oral dose with about 20% protein binding. Its affinity for the opioid receptor is only 16000 than that of morphine. However, the primary O-demethylated metabolite of tramadol is two to four times as potent as the parent drug and may account for part of the analgesic effect. Tramadol is supplied as a racemic mixture, which is more effective than either enantiomer alone. The compound undergoes hepatic metabolism and renal excretion, with an elimination half-life of 6 hours for tramadol and 7.5 hours for its active metabolite. Analgesia begins within an **hour** of oral dosing and peaks within 2–3 hours. The duration of analgesia is about **6 hours**. The maximum recommended daily dose is 400 mg. Tramadol is also available in an extended 24-hour release preparation.

Physical dependence on and abuse of tramadol have been reported. Although its abuse potential is unclear, tramadol probably should be avoided in patients with a history of addiction. Because of its inhibitory effect on serotonin uptake, tramadol should not be used in patients taking MAO inhibitors and triptans. Seizures have been reported with

concomitant use of selective serotonin receptor inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and neuroleptics.

3. Tapentadol

(Dol Proxyvon 50 mg, 100 mg)
Tapentadol is a strong opioid with a dual mechanism of action, similar to tramadol. It is a strong MOR agonist and a serotonin and norepinephrine reuptake inhibitor. Because of its first-pass metabolism, its bioavailability is low (32%) and protein binding is low (20%). The metabolites of tapentadol are inactive. The half-life is approximately 4 hours.

Similar to tramadol, tapentadol is contraindicated in patients taking MAO inhibitors, triptans, SSRIs, SNRIs, TCAs and neuroleptics owing to risk of serotonin syndrome. There does not appear to be a risk of seizures, as is seen with tramadol. Tapentadol is currently available as an oral immediate-release and an extended-release preparation.

4. Naltrexone

Naltima (50 mg).
Naltrexone is an oral opiate receptor antagonist that is effective in the treatment of pruritus. For many years, naltrexone was used in the treatment of opiate drug addiction, which often is accompanied by generalized pruritus. Because the addiction is managed successfully with opiate antagonists, the itch often subsides; this is the basis for the use of naltrexone in pruritic conditions.

Classification

Narcotic (opioid) antagonist, long-acting.

Mechanism of Action

Competitive binding at opioid receptor sites reduces euphoria and drug craving without supporting the addiction.
Naltrexone works by antagonism of μ, K and delta opioid receptors.

Pharmacology

Onset of action: 5 min–1 hour; Duration: 24 hours.

Uses

FDA: Alcohol opioid addiction.
Off label use: Pruritus

It relieves pruritus associated with cholestatic liver disease, chronic renal failure, chronic urticaria and atopic

dermatitis. In case reports and case series, antipruritic efficacy of naltrexone has been reported in prurigo nodularis, mycosis fungoides, postburn pruritus, aquagenic pruritus, hydroxyethyl starch-induced pruritus and pruritus of unknown origin.

The pathophysiology of itching is believed to have two components, peripheral and central. Peripherally, itching occurs through the interaction of cutaneous chemical mediators (e.g. histamine) with unmyelinated C fibers. C fibers are primary afferent nerves responsible for detecting painful, mechanical and temperature-related stimuli. They travel from the skin to the spinal cord, where they synapse in the dorsal horn and eventually cross the midline to ascend in the spinothalamic tract.

The interaction of histamine with these neural pain-sensing pathways was thought to occur with C fibers responsible for mechanical and temperature detection. A new type of C fiber dedicated to the perception of itch has been described and is sensitive to histamine with variable sensitivity to heat and mechanical stimuli.

Itch also has a central component. The endogenous opioids (e.g., endorphins and enkephalins) and their receptor systems are important in modulating central pain and itch pathways. This central modulation has been attributed to opioid reaction at opiate class receptor

Dosage

Dose: Single 50 mg dose per day. Lower doses might be considered in elderly patients, although the drug usually is well tolerated in the elderly.

Tachyphylaxis may occur with this drug, generally after 1–9 months of treatment. Increasing the dose to 50 twice a day may be effective in these case. Alternatively, tachyphylaxis can be avoided by interrupting the dosing regimen for 2 days every week.

Drug Interaction

The effect of pain, cough, cold, or antidiarrheal medications may be less.

Drugs that increase effects/toxicity of naltrexone: Thioridazine.

Naltrexone decreases effects/toxicity of opioids used, such as antidiarrheals, analgesics or antitussives.

Monitoring

Baseline and serial liver function studies should be obtained while on naltrexone.

Evidence of suicidal tendency (higher risk in opiate abusers).

Signs of withdrawal: Muscle cramps, perspiration, rhinorrhea, nausea, diarrhea, abdominal cramps, restlessness, increased BP.

Side Effects

Common

Naltrexone generally is safe. The side-effect profile includes nausea and fatigue as the most commonly experienced problems with routine doses. Dizziness, flushing, drowsiness, headache, dry mouth, nightmares, myoclonus, increases in blood pressure, increased peripheral edema, skin rash and tremors have been associated with its use.

Rare

Liver toxicity, depression, suicide attempt or ideation and idiopathic thrombocytopenic purpura.

Laboratory abnormalities include elevation of serum transaminase levels (e.g., alanine aminotransferase) that appear to be dose dependent. This elevation is transient, however, and levels return to baseline slowly after discontinuation of the therapy. One study showed no toxicity associated with doses of naltrexone of 800 mg/d.

Transient mild withdrawal-like symptoms have been reported in non-opioid-dependent individuals taking naltrexone, including lacrimation, restlessness, yawning, gastrointestinal symptoms and increased heart rate and blood pressure. The opiate withdrawal effects observed in studies using naltrexone to treat pruritus were not significant enough to stop treatment. They were transient, appearing during the second day of treatment and decreasing within 3 days of treatment.

MANAGEMENT OF CHRONIC NEUROPATHIC PAIN

Because NeP can be severe and unrelenting, it is important to recognize and treat comorbidities, such as anxiety and depression. It is also important to recognize secondary treatment goals, such as improving sleep, ability to function and overall quality of life. However, treatment goals must be realistic. Caregivers should validate the patient's pain to gain their trust and should set realistic treatment goals. This is typically straightforward from the caregiver's point of view because most NeP states are based on well-defined injuries to the nervous system. The primary goal in most cases is to make the pain 'bearable' or 'tolerable'—**not** to eliminate the pain. Such goal setting can make a considerable difference in patient satisfaction when pharmacological treatments are instituted.

Table 16.4: Drugs used for neuropathic pain (NeP)

First line analgesic	Anticonvulsants	Gabapentin Pregabalin Carbamazepine
	Antidepressant agents (SNRIs)	Duloxetine Venlafaxine
Second-line analgesics		Tramadol Opioid analgesics
Third-line analgesics		Cannabinoids
Fourth-line analgesics	SSRIs	Citalopram Paroxetine Escitalopram
		Lamotrigine Topical lidocaine

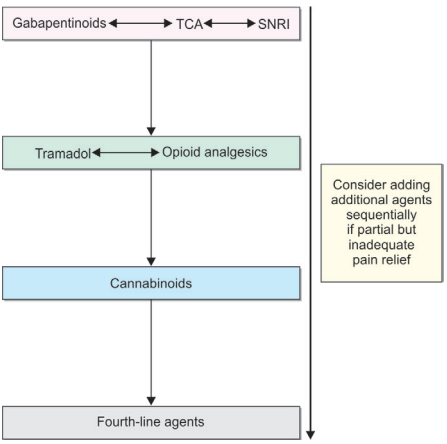


Fig. 16.1: An updated algorithm for the pharmacological management of NeP

The various drugs used are given below (Table 16.4), and detailed overview is given in Table 16.5, but most clinicians combine agents. Combining ≥2 analgesic agents in the management of NeP is an attractive option because combination pharmacotherapy may improve analgesic efficacy and has the potential to reduce the overall side effect profile if synergistic effects allow for dose reductions of combined drugs. The majority of these studies evaluated the combination of an **opioid** with *gabapentin, pregabalin or a TCA,* the combination of **gabapentin and nortriptyline**, and various topical medications.

Stepwise Management (Fig. 16.1)

Duloxetine has been upgraded from a second-line to a first-line agent while **TCAs, gabapentinoids and SNRIs** have all been considered to be first-line agents in the management of chronic NeP.

TCAs have the advantage of low cost and once-daily dosing, but can produce drowsiness and significant anticholinergic

Table 16.5: Dosing regimens for selected agents in neuropathic pain

Agent	*Starting dose and titration*	*Usuai maintenance dose*	*Adverse effects*	*Comments*
Tricyclic antidepressants				
Amitriptyline	10–25 mg/day: Increase	10–100 mg/day	Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrythymia	Amitriptyline is more likely to produce drowsiness and anticholinergic side effects; contraindicated in patients with glaucoma, symptomatic prostatism and significant cardiovascular disease
Nortriptyline	Weekly by 10 mg/day		Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, armylhmia	
Desipramine				
Serotonin noradrenaline reuptake inhibitors				
Venlafaxine	37.5 mg/day; increase weekly by 37.5 mg/day	150–225 mg/day	Nausea, dizziness, drowsiness, hyperhidrosis, hypertension	Dosage adjustments required in renal failure
Duloxetine	30 mg/day; increase weekly by 30 mg/day	60–120 mg/day	Sedation, nausea, constipation, ataxia, dry mouth	Contraindicated in patients with glaucoma
Anticonvulsanls				
Gabapentin	100–300 mg/day: increase weekly by 100-300 mg/day	300–1200 mg three times daily	Drowsiness, dizziness, peripheral edema, visual blurring	Dosage adjustments required in renal failure and in elderty patients

Contd...

Contd...

Pregabalin	25–150 mg/day: increase weekly by 25–150 mg/day	150–300 mg twice daily	Drowsiness, dizziness, peripheral edema, visual blurring	Similar adjustments in renal failure
Carbamazepine	100 mg once daily: increase weekly by 100–200 mg/day	200–400 mg three times daily	Drowsiness, dizziness, blurred vision, alaxia, headache, nausea, rash	Drug of first choice for tic douloureux {idiopathic trigeminal neuralgia}; as an enzyme inducer, may interfere with activity of other drugs, such as warfarin; monitoring of blood counts and liver function tests recommended
Controlled-release opioid analgesics				
Morphine	15 mg every 12 h	30–120 mg every 12 hours	Nausea, vomiting, sedation, dizziness, urinary retention, constipation	Constipation requires concurrent bowel regimen; monitor for addiction
Oxycodone	10 mg every 12 h	20–60 mg every 12 hours		
Fentanyl	12–25 µg/h patch	25–100 µg/h patch		
Hydromorphone	3 mg every 12 h	6–24 mg every 12 h		
Others				
Tramadol	50 mg/day; increase weekly by 50 mg/day	50–100 mg four limes daily or 100–400 mg daily (controlled release)	Ataxia, sedation, constipation, seizures, orthostatic hypotension	May lower seizure threshold; use with caution in patients with epilepsy

Contd...

Contd...

Lidocaine		5% palches or gel applied to painful areas for 12 hours in a 24 hours period		Most useful for postherpetic neuralgia; has virtually no systemic side effects; lidocaine patches not available in Canada
Tetrahydrocannabinol/ cannabidiol (nabiximols)	1-2 sprays every 4 hours, maximum 4 sprays on day 1, titrate slowly	Two sprays four times daily	Dizziness, fatigue, nausea, euphoria	Approved in Canada for neuropathic pain associated with multiple sclerosis; causes positive urine drug testing for cannabinoids; monitor application site (oral mucosa)
Nabilone	0.25–0.5 mg at night; increase weekly by 0.5 mg/ day	3 mg twice	Dizziness, drowsiness, dry mouth	Approved in Canada for nausea and vomiting associated with chemotherapy. Does not test positive for cannabinoids on routine urine drug testing

side effects, including dry mouth, constipation and urinary retention, and are, thus, poorly tolerated in the elderly. **Secondary amine TCAs** (nortriptyline and desipramine) are better tolerated than **tertiary amine** TCAs (amitriptyline and imipramine) with comparable analgesic efficacy.

Gabapentin and pregabalin appear to be similar in their mechanisms of action and side-effect profiles, and allow for more rapid titration than antidepressant agents. Pregabalin carries the advantage of twice-daily dosing and linear pharmacokinetics relative to gabapentin. Gabapentinoids in general have few drug interactions, but are dependent on renal excretion and, therefore, require dosage reductions in patients with renal insufficiency.

If a TCA fails or is contraindicated, the use of a gabapentinoid or an SNRI, such as duloxetine, should be considered. If one of the latter agents provides only partial pain relief, it is reasonable to add the other agent because there is evidence that combination pharmacotherapy can be helpful.

When first-line medications fail or provide inadequate pain relief, *tramadol* or a conventional *opioid* analgesic may be useful as a **second-line treatment**. It is also reasonable to consider a short-acting opioid, such as codeine or oxycodone (sometimes combined with acetaminophen), for breakthrough pain during titration of a first-line agent if needed for severe pain. Controlled-release opioid analgesics are considered to be second-line agents in the management of NeP because of their extensive side-effect profile and the risk of opioid misuse, abuse and addiction leading to cautionary prescribing and monitoring. Although tolerance may occur to several of these side effects, there is very little tolerance to constipation and almost all patients placed on a controlled-release opioid analgesic require a bowel regimen with continued monitoring of bowel function.

The *cannabinoids* have now advanced **to third-line agents** in the management of chronic NeP based on increasing evidence of efficacy in multiple pain models including HIV neuropathy, post-traumatic and postsurgical NeP, painful diabetic neuropathy and spinal cord injury pain.

Fourth-line agents in the management of NeP include *methadone, tapentadol and anticonvulsants*, with lesser evidence of efficacy to drugs like lacosamide, lamotrigine and topiramate. *Topical lidocaine* has been relegated to fourth-line status because of conflicting evidence of efficacy except in the management of postherpetic neuralgia, for which it remains a second-line option.

17
CHAPTER

Miscellaneous Agents

Vikrant Choubey[1], Shankila Mittal[2], Isha Narang[3], Kabir Sardana

COLCHICINE (ZYCOLCHIN)[1]

Colchicine is an alkaloid obtained from the plant *Colchicum autumnale,* which is also known as meadow saffron or autumn crocus, and from other related species. The usage of the plant *Colchicum autumnale* was first described for joint pain and swelling in Egyptian literature "Ebers Papyrus" in 1500 BC. Colchicum plants were brought to America by Benjamin Franklin, who suffered from gout himself. The medical compound was first isolated in 1820 by the French chemists PS Pelletier and JB Caventou.

Mechanism of Action

It primarily works by inhibiting leukocyte migration, chemotaxis, mobility, adhesion and phagocytosis, and lactic acid production. Thus, it is primarily used in n*eutrophilic disorders*.

1. Colchicine and its analogs interfere with the growth of *microtubules* in nerve cells, ciliated cells, leukocytes and sperm. This is as it forms high-affinity complexes with tubulin and inhibits protein polymerization. Microtubule assembly and elongation are thus disrupted, limiting the chemotactic and phagocytic activity of *polymorphonuclear lymphocytes*. It also induces mitotic arrest and inhibits DNA synthesis.
2. Colchicine also suppresses *leukocyte function* by increasing the cellular cyclic adenosine monophosphate level and inhibiting lysosomal degranulation. Increases in the level of cyclic adenosine monophosphate release prostaglandin E, which further suppresses leukocyte function.
3. This drug reduces *procollagen* synthesis by impairing its cellular secretion. Collagenolytic activity is also enhanced with increased collagenase production.
4. Interferes with intercellular adhesion molecules, selectins, thus inhibiting T-lymphocyte activation and its adhesion to endothelial cells.
5. Finally, colchicine inhibits cell-mediated immune responses, by inhibiting immunoglobulin secretion,

interleukin-1 production, histamine release and HLA-DR expression.

Absorption and Distribution

Colchicine is readily absorbed from the gastrointestinal tract and peak concentrations occur in plasma by half-an-hour to two hours. Absorption is not affected by food. The kidney, liver and the spleen also contain high concentrations of colchicine, but it is apparently largely excluded from the heart, skeletal muscle and brain. It is partially deacetylated in the liver. Colchicine and its metabolites are excreted in the urine and feces.

Peak plasma levels are levels reached 30–120 minutes after oral administration. In plasma, 50% of colchicine is protein bound. The plasma t1/2 of colchicine is 9 hours, but the drug can be detected in leukocytes and in the urine for at least 9 days after a single dose.

Uses (Approved/Unapproved)

Tablet: 0.5 mg, 0.6 mg
Importantly, studies published from outside India usually mention a dose of 0.6 mg though in India, 0.5 mg is available.

FDA approved	Acute flares of gout Familial Mediterranean fever
Off label	**Autoimmune connective tissue disorders** Dermatomyositis Scleroderma **Neutrophilic dermatoses** Behcet's disease Sweet's syndrome **Vasculitis** Leukocytoclastic vasculitis **Bullous disorders** Dermatitis herpetiformis Epidermolysis bullosa acquisita Linear IgA disease Subcorneal pustular dermatosis **Papulosquamous disorders** Psoriasis **Others** Actinic keratosis ENL Erythema nodosum Fibromatosis Keloids Mid dermal elastolysis Pyoderma gangrenosum Recurrent aphthous stomatitis Renal amyloidosis secondary to ulcerative colitis

Doses of colchicine in some commonly used indications are given below. I use it preferentially for Palmoplantar pustulosis, amylodosis, aphthosis and vasculitis. A recent review has recommended its use for autoinflammatory diseases (Tripathi SV et al.), while another report has suggested it to be used for neutrophilic urticaria (Belani H et al.), though Anakinara is the preferred drug in this condition. As a thumb rule the drug is useful in cases where a neutrophilic dermatoses is suspected.

Dosage

Tablet: 0.5 mg, 0.6 mg
An overview of its dosage in common conditions is given in Box 17.1.

Box 17.1: Dosage of colchicine in common conditions

1. Amyloidosis: 2 mg/day
2. Aphthous stomatitis: 1.5–1.8 mg/day
3. Behçet's syndrome: 1–1.5 mg/day
4. Chronic bullous dermatosis: 0.5 mg twice daily
5. Dermatitis herpetiformis: 1.2–1.8 mg/day
6. Leukocytoclastic vasculitis: 0.6 mg twice daily
7. Palmoplantar pustulosis: 1–2 mg per day
8. Recurrent idiopathic plantar eccrine hidradenitis: 2 mg/day
9. Sweet's syndrome: 1.5 mg daily
10. Urticarial vasculitis: 2 mg/day

1. **Palmoplantar pustulosis** is a chronic pustular dermatosis closely related to psoriasis. Mori et al. described 32 patients who were given 1–2 mg per day of the drug. Partial or complete remission of pustule formation occurred in all but one patient after 2–8 weeks of therapy. The authors believe that colchicine suppressed leukocyte chemotaxis and blunted pustule development. Other studies have hown either minimal or no effect with the drug.
   In my opinion, if the condition is diagnosed correctly, the results are excellent. In fact, a patient who had recurrent pustules on the palms, is controlled on one tablet alternate day!
2. **Behçet's syndrome:** Colchicine is helpful for treating patients with Behçet's syndrome, perhaps by inhibiting leukocyte chemotaxis. Response rates of 60–70% have been described. Orogenital and ocular lesions are the most responsive (Mizushima Y et al.). Aktulga E et al. reported that doses of 1.5 mg per day were useful in controlling erythema nodosum and arthralgias associated with this disease. To date few controlled trials of colchicine in the treatment of Behçet's syndrome have been carried out, but a single double-blind study comparing this drug with

cyclosporine demonstrated that both medications were equally effective in reducing symptoms (Masuda K, et al.).

3. **Recurrent aphthous stomatitis:** Recurrent aphthous stomatitis affects 20% of the population. Colchicine, 0.6 mg three times a day, effectively induced disease remission in 3 patients (Ruah CB et al.). Katz et al. described 20 patients, who were given 1.5 mg/day. Pain and mean ulcer count decreased by 77% and 71%, respectively. All patients experienced relapse when the drug was discontinued.
   A recent review also recommends colchicine, pentoxifylline, or prednisolone as preferred agents for Aphthosis (Altenburg A et al.). In my practice, a combination of colchicines and pentoxyfylline is a good option, though in some the results of doxycyline are better. Of course nothing beats the response of steroids, though they cannot be used for a long time.
4. **Leukocytoclastic vasculitis and urticarial vasculitis:** Leukocytoclastic vasculitis is an inflammatory reaction in postcapillary venules and is characterized by neutrophil infiltration with leukocytoclasis. Several case reports have described the beneficial effects of colchicine in this condition (Plotnick S et al.).
   Callen (Callen JP) treated 13 patients with an initial dose of colchicine, 0.6 mg twice daily. Complete control in 9 patients and partial control in 3 patients was achieved. Response was usually rapid, occurring within the first week of treatment. Relapse was noted in several patients after drug withdrawal and rapid control occurred on resumption of the drug. Associated arthralgias responded. Cutaneous vasculitis in a C3-deficient patient was successfully treated with colchicine (Barash J et al.). The patient responded rapidly to 1 mg twice daily with immediate return of lesions on withdrawal of the drug.
   First-line systemic treatments for chronic, idiopathic CSVV include colchicine or dapsone, used singly or in combination. Recurrent, chronic, or severely symptomatic CSVV that does not respond to the aforementioned therapies may require initiation of an immunosuppressive agent, such as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, or rituximab (Goeser MR).
5. **Bullous disease:**
   CBDC (Chronic bullous dermatosis of children): One report describes a 3½ - year-old boy with chronic bullous dermatosis and glucose-6-phosphate dehydrogenase deficiency, who was prednisone dependent. Colchicine, 0.5 mg twice daily, was begun and the prednisone dose was reduced. The disease responded in 2 weeks without relapses (Zeharia A et al.).

EBA: Megahed and Scharffetter-Kochanek described the successful treatment of two patients with epidermolysis bullosa acquisita (EBA). After 2 weeks of colchicine, 2 mg daily, most mucosal and cutaneous lesions had resolved. At 6 months the dose was halved with no disease flare. A recent report of a case from India, also shows the favourable effect of colchicine in Epidermolysis bullosa acquisita (EBA) like disorders (Agrawal P et al).

Aram described a young woman with **linear IgA disease** who was given colchicine, 1.5 mg daily, after she failed to respond to dapsone. She improved significantly within 5 days and experienced complete resolution after 10 weeks. Silvers et al. described 3 patients with **dermatitis herpetiformis** who responded rapidly to colchicine 1.2–1.8 mg/day.

6. **Fibromatosis:** Dominguez-Malagon et al. described patients with musculoaponeurotic desmoid fibromatosis, Dupuytren's palmar fibromatosis, or Peyronie's disease who were given colchicine with good results. Microscopically, the abnormal long-spacing collagen present in rough endoplasmic reticulum is dissipated after treatment. Another patient with palmar fibromatosis responded well to a twice-weekly dose of 1.2 mg of colchicine.
7. **Sweet's syndrome:** Sweet's syndrome is characterized by pyrexia and a neutrophilic infiltrate. Beneficial responses to colchicine have been described. Suehisa et al described 4 patients with Sweet's syndrome who were given colchicine, 1.5 mg daily. All improved in 2–5 days.
8. **Amyloidosis:** Cutaneous lesions develop in up to 40% of patients with systemic amyloidosis, both primary and secondary. Colchicine alleviates amyloidosis associated with familial Mediterranean fever (Zemer D et al.).

   This drug prevents amyloid deposition and slows disease progression. Proteinuria secondary to ulcerative colitis–induced renal amyloidosis has also responded to colchicine. Treatment of primary amyloidosis has yielded mixed results.

Drug Interaction

1. Antibacterials: Increased risk of colchicine toxicity when given with clarithromycin or erythromycin, particularly in patients with pre-existing renal impairment.
2. P-glycoprotein or strong CYP3A4 inhibitors: Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-glycoprotein inhibitor (e.g. cyclosporin, verapamil or quinidine) or a strong CYP3A4

Table 17.1: Cyp3A4 inhibitors and p-glycoprotein inhibitors can increase plasma levels of colchicine and cause colchicine toxicity

CYP3A4 inhibitors	*P-Glycoprotein inhibitors*
Strong	
Atazanavir, nelfinavir, ritonavir, sequinavir, indinavir, clarithromycin, telithromycin, itraconazole, ketoconazole, nefazodone.	Cyclosporin, ranolazine, Digoxin (a PGP substrate)
Moderate	
Amprenavir, fosamprenavir, erythromycin, fluconazole, aprepitant, diltiazem, verapamil. grapefruit juice	

HMG CO-A Inhibitors: Rhabdomyolysis has been reported.

inhibitor (e.g. ritonavir, atazanavir, indinavir, clarithromycin, telithromycin, itraconazole or ketoconazole) (Table 17.1).

3. Cyclosporin: Colchicine should be used with caution with cyclosporin due to the possible increased risk of nephrotoxicity and myotoxicity.
4. Vitamins: The absorption of Vitamin B12 may be impaired by chronic administration or high doses of colchicine; requirement may be increased.
5 Statins: Acute myopathy has been reported in patients given colchicine with statins. Patients should be advised to report muscle pain or weakness.

Special Considerations

Use with great caution in elderly or debilitated patients, especially those with early manifestations of hepatic, renal, GI, or heart disease. Reduce dosage if weakness, anorexia, nausea, vomiting, stomach pain, or diarrhea occurs.

Reduce dose in patients with mild-to-moderate renal impairment.

A reduction in colchicine dosage or interruption of colchicine treatment is recommended in patients with normal renal and hepatic function if treatment with a P-glycoprotein or a strong CYP3A4 inhibitor is required.

Side Effects

Common

Abdominal cramps, watery diarrhea, nausea, vomiting:

- Seen in 80% cases receiving doses of 2–3 mg/day
- Infrequent at lower doses
- Leads to malabsorption of fats, fat soluble vitamins, vitamin K.

Rare

- Aplastic anemia, agranulocytosis, thrombocytopenia, (long-term administration), hepatotoxicity, myopathy, peripheral neuropathy
- Marrow suppression (agranulocytosis, thrombocytopenia, aplastic anemia)
  - Usually dose-dependent
  - Can be idiosyncratic as well
- Neuropathy (in pts. with renal impairment or on treatment lasting >6 months)
- Proximal myopathy (in pts. with renal impairment or on treatment lasting >6 months): presents with raised CPK, fibrillations, reversible.
- Azoospermia.

Monitoring

- CBC with differential and platelets, liver enzymes
- Signs of toxicity: Nausea, vomiting, diarrhea
- Signs of liver toxicity
- Signs of myopathy, peripheral neuropathy.

Laboratory tests	Baseline	Follow-up
CBC, KFT, LFT, Urinalysis	Yes	3 monthly

Special Groups

Pregnancy: Category C by oral route.

Lactation: Appears in breast milk. Considered compatible by American Academy of Pediatrics.

Liver Failure

Kidney Failure: Creatinine clearance <50 mL/minute: Creatinine clearance <10 mL/minute: decrease dose by 50% for acute attack.

Elderly: Reduce dosages if symptoms of toxicity appear, e.g. weakness, GI problems.

BIBLIOGRAPHY

1. Agrawal P, George R, Thomas M, Has C, Pas H, Schmidt E, et al. A childhood subepidermal autoimmune bullous disease resembling mechanobullous epidermolysis bullosa acquisita. Br J Dermatol. 2015. doi:10.1111/bjd.13833.
2. Aktulga E, Altac M, Muftuoglu A, et al. A double blind study of colchicine in Behcet's disease. Haematologia. 1980;65:399-402.
3. Altenburg A, El-Haj N, Micheli C, Puttkammer M, Abdel-Naser MB, Zouboulis CC. The treatment of chronic recurrent oral aphthous ulcers. Dtsch Arztebl Int. 2014;111(40):665-73.

4. Aram H. Linear IgA bullous dermatosis: successful treatment with colchicine. Arch Dermatol. 1984;120:960-1.
5. Barash J, Cooper M. Chronic cutaneous vasculitis in a C3-deficient patient treated with colchicine. Isr J Med Sci. 1993:29:310-1.
6. Belani H, Gensler L, Bajpai U, Meinhardt E, Graf J, Pincus L, et al. Neutrophilic urticaria with systemic inflammation: a case series. JAMA Dermatol. 2013;149(4):453-8.
7. Callen JP. Colchicine is effective in controlling chronic cutaneous leukocytoclastic vasculitis. J Am Acad Dermatol. 1985;13:193-200.
8. Dominguez-Malagon HR, Alfeiran-Ruiz A, Chavarria-Xircotencatl P, Duran-Hernandez MS. Clinical and cellular effects of colchicine in fibromatosis. Cancer. 1992;69:2478-83.
9. Goeser MR, Laniosz V, Wetter DA. A practical approach to the diagnosis, evaluation and management of cutaneous small-vessel vasculitis. Am J Clin Dermatol. 2014;15(4):299-306.
10. Katz J, Langevitz P, Shemer J, et al. Prevention of recurrent aphthous stomatitis with colchicine: an open trial. J Am Acad Dermatol. 1994;31:459-61.
11. Masuda K, Nakajima A, Urayama A, et al. Double masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behcet's disease. Lancet. 1989;1:1093-6.
12. Megahed M, Scharffetter-Kochanek K. Epidermolysis bullosa acquisita: successful treatment with colchicine. Arch Dermatol Res. 1994;286:35-46.
13. Mizushima Y, Matsumura N, Mori M, et al. Colchicine in Behcet's disease. Lancet. 1977;2:1037.
14. Mori S, Hino K, Izumi H, et al. Clinical manifestations and treatment of pustulosis palmaris et plantaris. J Dermatol. 1976;86:671.
15. Plotnick S, Hupert AS, Kantor G. Colchicine and leukocytoclastic vasculitis. Arthritis Rheum. 1989;32:1489-90.
16. Ruah CB, Stram JR, Chasin WD. Treatment of severe recurrent aphthous stomatitis with colchicine. Arch Otolaryngol Head Neck Surg. 1988;114:671-5.
17. Silvers DN, Juhlin EA, Berczeller PH, et al. Treatment of dermatitis herpetiformis with colchicine. Arch Dermatol. 1980;116:1373-4.
18. Suehisa S, Tagami H, Inoue F, et al. Colchicine in the treatment of acute febrile neutrophilic dermatosis (Sweet's syndrome). Br J Dermatol. 1983;108:99-101.
19. Tripathi SV, Leslie KS. Autoinflammatory diseases in dermatology: CAPS, TRAPS, HIDS, FMF, Blau, CANDLE. Dermatol Clin. 2013;31(3):387-404.
20. Zemer D, Pras M, Sohar E, et al. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. N Engl J Med. 1986;314:1001-5.

CLOFAZIMINE

Clofazimine (Lamprene or B663) is the most active antimycobacterial riminophenazine dye known and was developed in 1944.

Mechanism of Action

1. *In vitro*, clofazimine selectively binds to DNA guanine residues, which is seen in higher concentration in mycobacteria than in humans.
2. Inhibits the mitochondrial respiratory chains and inhibition of the increased production of free radicals within various cell lines.
3. It alters the functions of monocytes and neutrophils (PMN) by increasing the size and number of lysosomes and phagolysosomes. PMN motility and lymphocyte transformation are inhibited in a dose-dependent manner, and superoxide production is enhanced.
4. A study of clofazimine therapy showed, that the expression of intercellular adhesion molecule-1 and HLA-DR, as well as the mononuclear cell infiltrate in erythema dyschromicum perstans, were reduced on therapy.

Absorption and Distribution

The absorption of clofazimine after oral intake is variable but is increased if taken with food. The drug is highly lipophilic and concentrates in lipid-rich tissues, particularly within the reticuloendothelial system, but also in the breasts, intestines and liver. Because of this the drug is eliminated slowly, with a half-life of approximately 70 days.

There have been three proposed routes of hepatic metabolism, the clinical relevance of which is unknown. Only small amounts of the drug are found in urine. Minimal, but clinically significant, elimination occurs via the sebum, sputum, tears and sweat. Formal studies of fecal/biliary elimination have not been carried out.

Uses (Approved/Unapproved)

Dose: Usually 50–300 mg is given daily; doses as high as 400 mg daily have been reported by some authors. Larger doses are usually divided three to four times daily. Attempts to taper the drug to a maintenance dose should be made after clinical response occurs.

1. **Leprosy and other mycobacterial infections:** Clofazimine is approved for the treatment of lepromatous leprosy. It has also been used in the treatment of ENL. A study comparing Pentoxifylline and clofazamine with steroids in ENL showed that while the former effectively reduces initial severity; clofazimine provides sustained improvement but acts slowly.
2. The drug has been used for other multiple indications including pyoderma gangrenosum, cheilitis granulomatosa,

lichen planus pigmentosis, erythema dyschromicum perstans, though the results are variable.

Drug interaction

Concomitant use with either rifampin or isoniazid may affect the levels of the drug.

Side Effects

Common effects of less significance include abdominal cramping, nausea and diarrhea.

Cutaneous Effects

The most common adverse effect seen with its use is a reversible orange-brown discoloration of the skin beginning within 2–4 weeks of initiating use. The cause is not only direct drug deposition, but is also due to an induced hypermelanosis. This usually resolves spontaneously within 3–6 months of stopping therapy.

Approximately, 30% of patients experience a generalized xerosis, although progression to frank ichthyosis is not uncommon.

Systemic Effects

Visceral deposition of crystals may rarely cause a fatal enteropathy. Splenic infarction and eosinophilic enteritis have also been reported. There is one case report of cardiac dysrhythmia related to clofazimine use and a pre-existing electrolyte disturbance.

Monitoring

Patients with pre-existing gastrointestinal (GI) disease or individuals prone to electrolyte disturbances should be monitored .

In a dose >100 mg daily, liver function tests should be evaluated.

BIBLIOGRAPHY

1. Baranda L, Torres-Alvarez B, Cortes-Franco R, Moncada B, Portales-Perez DP, Gonzalez-Amaro R. Involvement of cell adhesion and activation molecules in the pathogenesis of erythema dyschromicum perstans (ashy dermatitis). The effect of clofazimine therapy. Arch Dermatol. 1997;133(3):325-9.
2. Roy K, Sil A, Das NK, Bandyopadhyay D. Effectiveness and safety of clofazimine and pentoxifylline in type 2 lepra reaction: a double-blind, randomized, controlled study. Int J Dermatol. 2015. doi: 0.1111/ijd.12793.

CHLOROQUINE AND HYDROXYCHLOROQUINE

Chemical Class

Antimalarial drugs are chemotherapy agents that are used in the treatment of malaria. These include drugs such as chloroquine, mefloquine and halofantrine.

The usefulness of antimalarials was not widely acknowledged until 1951 when a treatment series using quinacrine was published (17/18 of treated DLE patients improved). In dermatology in particular, antimalarial agents have been used successfully to treat a number of other diseases, and new uses continue to be found even today. The majority of studies on these drugs were performed decades ago, and thus current clinical studies using modern quality-based criteria are largely unavailable. The lack of interest in the evidence of their effectiveness is because of the meagre financial incentives for the pharmaceuticals majors, thus, it is unlikely that such studies will be performed any time soon.

As HCQS and CQ do not differ with regard to their mechanism of action, pharmacokinetics, toxicology, side effects, and indications, the following information applies to both drugs.

Mechanism of Action

The drugs' effects are better explained by various factors than by a single one alone (Table 17.2).

The major effects are *immunomodulatory*, *anti-inflammatory* and *antiproliferative* properties. They also help in reducing *UV-induced inflammation*, *inhibit thrombocyte aggregation*, enhance glucose tolerance and cause increased porphyrin excretion.

Immunomodulatory

An important effect results from the "lysosomotropic" properties of CQ/HCQ which will be discussed in greater detail.

CQ/HCQ are amphiphilic molecules (lipophilic ring structure, hydrophilic side chain). They thus tend to deposit in interphases, like phospholipid membranes. As weakly basic molecules, they can pass through the membranes and are protonated in the acidic milieu of the cytoplasm. They then loose their ability to pass through the membrane, and thus, accumulate there (factor 100–1000), primarily in macrophages and lysosomes. This leads to an increase in the vesicle pH from around 4.0–6.0, and consequently interfering with the acid-dependent subcellular functions. This *increased pH* has several postulated *immunoregulatory effects*, including stabilization of lysosomal membranes,

Table 17.2: Mode of action of antimalrial

Anti-infectious	Antimicrobial effects on HIV, SARS, coronavirus, influenza viruses
Anti-inflammatory effects	■ Inhibition of phospholipase A2 and C ■ Inhibition of formation of IL1 β, TNF α ■ Inhibition of mast cells ■ Inhibition of Toll-like receptor 9 signal pathway
Antiproliferative	Interaction with protein synthesis
Coagulation	Inhibition of thrombocyte aggregation
Immunogical Response	■ Inhibits autoantigen processing (MHCII) ■ Reduced stimulation of autoreactive CD4+ T cells ■ Reduced cytokine production: – CQ inhibits IL-1 and interferon- γ – CQ inhibits macrophage TNF- α mRNA transcription and endotoxin induced secretion of TNF- α, IL-1, and IL-6. ■ Binding to DNA and thus competitive inhibition of anti-DNA antibodies
Metabolic	■ Reduced cholesterol, triglyceride, LDL levels ■ Complex formation with porphyrins with increased excretion ■ Reduced hydroxylation vitamin D
UV absorption	■ Increased UV filtration? (Questionable relevance). It can cause spectral shift due to accumulation in melanin and increase in epidermal concentrations ■ Inhibition of UV-induced inflammatory reactions
Others	CQ, HCQ, and QE have all been shown to interfere with human immunodeficiency virus type 1 replication and function

attenuation of antigen processing and presentation, and inhibition of cell-mediated cytotoxicity.

In human leukocyte lysosomes, the accumulation of antigens (low-affinity peptides) on the "major histocompatibility complex" as well as stimulation of Toll-like receptor 9 is inhibited. The processing of autoantigens in particular is diminished and is, thus, also decreased in subsequent immunological effects. These indirect effects on T cells enable these agents to be well- combined with other immunomodulatory drugs. The *delayed* clinical effects may be explained by the fact that they primarily affect *antigen-presenting cells*.

Apoptosis or cell death plays an important role in the regulation of the immune system, and defects in apoptosis may allow for longevity and persistence of autoreactive lymphocyte clones and perpetuation of autoimmunity. CQ and HCQ have been shown to upregulate apoptosis and may downregulate autoimmunity by elimination of autoreactive lymphocytes.

Anti-inflammatory Properties

These include effects on the arachidonic acid cascade, by *downregulation* of *phospholipase A 2 and C*, which contribute to the production of proinflammatory prostaglandins and lipid peroxidation. Lipid peroxidation is thought to play a role in apoptosis, particularly in response to ultraviolet A and ultraviolet B irradiation (Ramakrishnan N et al.). Antimalarial agents also have antioxidant properties and may protect against tissue damage from free radicals (Miyachi Y et al.).

Dermatological Actions

The properties that are useful in dermatological and rheumatological disorders include, *photoprotective effect* which is likely via locally induced anti-inflammatory effects, inhibition of *platelet adhesion* and *aggregation* leading to an antithrombotic effect, favorable effect on *lipid profile* (reduced cholesterol, TG, VLDL, LDL) particularly in patients on concomitant corticosteroid therapy.

In the skin, CQ absorbs ultraviolet (UV) light in a concentration-dependent manner. It has been proposed that the beneficial effect of the HCQ and CQ in various photodermatoses may result from the ability of these drugs to enhance the protective early limb of the UV response. CQ and QE have been shown to bind cellular DNA by intercalation between base pairs, thus stabilizing the DNA. RNA transcription and subsequent translation are inhibited. These may be the mechanisms by which these molecules effect lupus.

Pharmacology

CQ/HCQ are water-soluble and are quickly and almost completely absorbed. Maximum plasma levels are reached within 3–4 hours (CQ) and in 8–12 hours (for HCQ). Plasma proteins binding: 50–70%. There is considerable variability in blood concentrations among patients treated with the same dose, but higher plasma levels do not correlate with a better therapeutic response.

The highest concentration occurs in melanin-containing cells, such as in the skin and retina. The skin can serve as a long-term reservoir whereby the drug can exert its effect, or toxicity, even after it has been stopped.

The half-life of HCQ and CQ is 40 to 50 days, and plasma levels increase gradually and equilibrate after 3 to 4 months. This may account for the slow appearance of therapeutic effect.

Absorption and Distribution

Because CQ/HCQ accumulate in thrombocytes, granulocytes, and erythrocytes, their concentration in whole blood is 3–10

times higher than in plasma. Due to the high affinity of chloroquine with melanin, the highest concentrations are found in the eyes and the skin where the concentration is 100–200 times higher than in plasma; in the epidermis it is 3–7 times higher than in the dermis. The greatest concentrations are found in the spleen, followed by the liver, kidneys, lungs, heart, muscles and brain.

Due to this accumulation in "deep compartments" the fictitious distribution volume is high: more than 100 l/kg. It takes at least 4 weeks for chloroquine and 6 months for hydroxychloroquine to reach plasma-tissue equilibrium.

Excretion

CQ/HCQ are very slowly eliminated. The plasma concentrations drop exponentially. In other words, the concentration decreases rapidly at first and then more gradually. To control compliance, plasma levels of HCQ or CQ concentrations in the hair may be measured.

Forty to seventy percent of CQ is eliminated unaltered in the urine. Renal impairment, thus, significantly prolongs the half-life of the drug. CQ itself, and in low levels, HCQ, can cause about a 10% reduction in creatinine clearance. Especially, in older patients, this can slow CQ excretion. 25–40% of CQ is metabolized by the cytochrome P450 in the liver into pharmacologically active metabolites. 5–10 % of CQ is excreted in stool.

HCQ forms an ether glucuronide that is excreted in bile. The low proportion (roughly 20%) of unchanged HCQ eliminated by the kidneys indicates that no dosage adjustment is necessary for patients with mild-to-moderate renal function impairment.

Clinical Use in Dermatology (Box 17.2)

Lupus Erythematosus

Chronic Cutaneous Lupus Erythematosus (DLE)

One study found that only 15 % of discoid skin lesions healed spontaneously; patients who were given antimalarial therapy had a healing rate of more than 85 %. The onset of action varies from *1 to 3 months*. In a double-blind study on patients with DLE, HCQ was more effective than placebo after 3 months and after 1 year.

Verrucous and hypertrophic plaques do *not* respond well to antimalarial therapy. Also patients who have SLE with prominent discoid LE lesions do not respond well. Significant scalp involvement with alopecia in addition to disseminated discoid, annular, or papulosquamous subacute cutaneous LE skin lesions also warrant antimalarials. In SLE, HCQS is useful for arthritis, pleuritis, pericarditis, and lethargy.

Box 17.2: Clinical use of antimalarial in dermatology

FDA approved	Lupus erythematosus Malaria Rheumatoid arthiritis
Off label	
Photosensitivity disorders	PCT, PMLE, solar urticaria
Granulomatosus Disorders	Sarcoidosis, granuloma annulare, LMDF
CT disorders	DM
Lymphocyctic disorders	Jessners infiltrate, lymphocyoma cutis
Panniculitis	Lupus paniculitis, erythema nodosum
Miscellaneous	Lichen planus Ulcerative stomatitis Atopic dermatitis Urticarial vasculitis Morphea Follicular mucinosis Psoriatic arthiritis

Because it takes a while to achieve consistent plasma concentrations, it is recommended that therapy be administered for at least two months before switching. Smokers have been shown to have a poorer response to treatment.

There is no evidence that the continuation of antimalarials after clearance prevents relapses. In a randomized double-blind study that lasted 8 weeks (cutaneous lupus), 400 mg HCQ was equally effective as 50 mg acitretin (response rate of about 50 %), but was associated with fewer side effects (Gunja N et al.). Hydroxychloroquine is less toxic, but also less effective than chloroquine phosphate, which is used in doses of 250–500 mg daily. Thus, patients who fail to respond fully to hydroxychloroquine may be switched to chloroquine, but the two should not be used together because of the concern that ophthalmologic toxicity may be enhanced (Feldmann R et al.).

Acute Cutaneous LE/Systemic Lupus Erythematosus (ACLE/SLE)

Compared with non-steroidal anti-inflammatory agents, antimalarial agents have the advantage that they carry a lower risk of cutaneous, liver or toxic kidney reactions.

Compared with immunosuppressants, there is neither the risk of bone marrow suppression nor opportunistic infection, with antimalarials. Based on the results of a systematic review, antimalarial drugs can inhibit the exacerbation of longstanding SLE and prolong patient survival (Ruiz-Irastorza G et al.).

In addition, the drug has a protective effect against irreversible organ damage, thrombosis, and loss of bone mass. Low evidence levels have been reported for favorable effects on blood lipids, protection against osteonecrosis, reduction in severe exacerbations, adjuvant effects on remission of lupus-related nephritis, delayed development of systemic lupus, and a protective effect against developing cancer (Ruiz-Irastorza G et al.). Additional symptoms such as fatigue, weakness, arthralgia, myalgia, serositis and mucous membrane ulcers have also shown improvement in SLE patients. It has also been seen that early hydroxychloroquine use is associated with delayed onset of SLE (James et al.).

Dermatomyositis

A retrospective study found that seven patients experienced near clearance of cutaneous symptoms with the use of antimalarials while four of them required combination therapy (hydroxychloroquine sulfate–quinacrine hydrochloride or chloroquine phosphate–quinacrine) (Ang GC et al.). It is a useful steroid sparing agent, though the potential for a drug eruption from HCQ in patients with dermatomyositis appears to be greater than for other patients with other diseases and is reported to be high (20%).

Jessner's Lymphocytic Infiltrate

Both chloroquine sulfate and hydroxychloroquine sulfate have been found to be useful but in different dosages as compared to DLE. Hydroxychloroquine 200 mg once or twice a day, or chloroquine 200 mg daily can be used (Toonstra et al.).

Pseudolymphoma

A dose of HCQ of 200 mg/day initially, increased to 400 mg/day has been noted to be effective

Porphyria Cutanea Tarda

Dose: Twice weekly 125 mg CQ or 100 mg HCQ. In patients with polyglobulia or elevated plasma iron levels, combination therapy, i.e. beginning with bloodletting—500 mL every 4 weeks—plus CQ 250 mg/weekly (HCQ 2 X100 mg/weekly) is recommended.

PMLE

Polymorphous light eruption is an inflammatory reaction seen on sun exposed skin. IL-1, -6, and -8 may play a role in the inflammatory process. Chloroquines decrease IL-1 and IL-6 and release and absorb UVA light. These drugs have been

used for polymorphous light eruption for several years. More recently, placebo-controlled trials have shown efficacy for this indication. HCQ at doses of 200 to 400 mg/day is effective. Topical sunscreens should also be used in conjunction with antimalarial therapy.

Chronic Ulcerative Stomatitis

This rare disease occurs at older ages in women. Clinically and histologically, chronic ulcerative stomatitis resembles lichen planus, but with certain immunological characteristics. The disease does not respond to topical or systemic corticosteroids, but it does respond to antimalarial agents. After long-term therapy, low-dose steroids are sometimes required.

Sarcoidosis

CQ, similar to corticosteroids, tends to suppress the disease rather than to cure it. Indications for administering CQ or HCQ in patients with sarcoidosis are chronic disfiguring skin lesions, progressive extracutaneous lesions in patients in whom steroid therapy is contraindicated, adjuvant therapy in steroid treatment, continued neurosarcoidosis with steroid failure. Hypercalcemia in sarcoidosis, but not in B-cell lymphoma, has shown improvement after hydroxychloroquine therapy.

Granuloma Annulare

HCQS has been tried in generalized granuloma annulare with a dose of 9 mg/kg/day for 2 months, tapered down to 6 mg/day for 1 month and 2 mg/kg/day for another 1 month.

Lichen Planus

Lichen Planus (Mucosal)

Oral lichen planus can improve on therapy and pain and redness improved after 1–2 months while it take 3–6 months for erosions to heal.

Actinic Lichen Planus

It appears that CQ/HCQ therapy is highly effective in this indication.

Panniculitis

There are reports of a response of nodular panniculitis (Weber–Christian variant), to CQ in a dose of CQ 250 mg/day.

Effects on Blood Lipids

Due to an increase in LDL receptors and inhibition of cholesterol synthesis in the liver, total cholesterol, LDL and triglyceride levels are decreased in SLE patients, especially in those who are on concomitant steroid therapy. Chloroquine reduces blood glucose levels, and thus, acts against the side effects of corticosteroids

Dosage

Hydroxychloroquine sulfate tablets contain 200 mg hydroxychloroquine sulfate, equivalent to 155 mg base, and are for oral administration. Each tablet of chloroquine phosphate, for oral administration, contains 250 mg of chloroquine phosphate, USP (equivalent to 150 mg base). Usual starting doses for HCQ are between 200 and 400 mg/day. Equivalent dosing for CQ is 250 to 500 mg/day

It is crucial to understand the special dosage employed for use of antimalarials as the feared complication of antimalarial drugs—irreversible retinopathy—depends *neither* on treatment *duration nor on* cumulative overall *dose*, but rather on whether the maximum ***daily dosage*** based on ideal body weight is exceeded.

The *maximum* daily dosage is 3.5 (–4) mg/kg of ***ideal*** body weight for chloroquine or 6 (–6.5) mg/kg ***ideal*** body weight for hydroxychloroquine. If the maximum dosages are observed, retinopathy is not a concern, even with for therapy lasting several years. Product information, advises that in "adults, cumulative dosages should not exceed 1 g chloroquine per kg of body weight (50–100 g total dose of chloroquine).

Dosage Calculation: For everyday clinical practice, given that CQ/HCQ are not stored in adipose tissue, dosages may be adjusted according to the patient's ideal body weight.

For men: (Height [in cm] – 100)–10%. For women: (Height [in cm] – 100) – 15% (See Tables 17.3 and 17.4). To avoid retinopathy, the maximum daily dosage of 3.5–(4) mg/kg of chloroquine or 6–(6.5) mg/kg hydroxychloroquine should not be exceeded for longer periods of time. Short-term administration of higher daily dosages is not a problem. This may be necessary, for instance, giving an initial higher dosage for a few days to rapidly reach therapeutic blood levels or if prescribing HCQ tablets that cannot be divided.

As given in the Table 17.4, a patient with an ideal body weight of 63 kg who is given 1 CQ tablet (250 mg)per day will still exceed the ideal dose and only at heavier weights is the administration of 1 tablet or more per day unproblematic (Tables 17.4 and 17.5). *Caution* should be exercised when treating patients with an actual or ideal body weight of less than **63** kg. This applies especially to smaller or lighter

Table 17.3: Dose for usage of HCQs

Weight (kg)	*Recommended dosages*
31–35	200 mg daily
36–39	400 mg once/week and 200 mg/d × 6 days
40–43	400 mg twice/week and 200 mg/d × 5 days
44–48	400 mg thrice/week and 200 mg/d × 4 days
49–52	200 mg thrice/week and 400 mg/d × 4 days
53–56	200 mg twice/week and 400 mg/d × 5 days
57–61	200 mg once/week and 400 mg/d × 6 days
> 61	400 mg/daily

Recommendations for maximum daily dosage of hydroxychloroquine (200 mg tablets): 6–6.5 mg/kg ***ideal*** body weight (height – 100) –10 % [men] or –15 % [women]; if this is less than actual weight, the actual weight is used). Lighter patients are given 6.5 mg/kg, and heavier ones 6 mg/kg.

For long-term therapy, lower daily dosages should be given if possible (weight = actual or ideal eight).

Table 17.4: Dose for usage of chloroquine

Ideal/Actual weight(kg)	*Recommended dosages chloroquine (250 mg)*
16–18	61.5 (¼)
20–23	81
31–35	125(½)
36–41	143.5
42–46	162
47–53	187.5 (¾)
54–58	206
58–64	224.5
63–72	250
78–89	312.5 (1 + ¼)
83–94	331
93–107	375 (1 + ½)

patients, in particular women or shorter but heavier patients. For these patients, even a single tablet at the usual dosage of 250 mg CQ or 400 mg HCQ (= equivalent dosages) given for a prolonged period of time is too much. If kidney or liver function is impaired, the dosage must be further decreased.

Usage Guidelines

If taken together with a *high-fat* and *protein-rich* meal, CQ/HCQ are better absorbed (Box 17.3).

Monitoring (Table 17.5)

Several studies have found that there are no relevant hematological or hepatotoxic effects of antimalarial drugs if

Box 17.3: Dosimetry of aminoquinolones in LE

Hydroxychloroquine initially at 200 mg twice daily, reducing to 200 mg/day once a response is achieved
Onset of action: **6 weeks (4 to 8 weeks)**
Duration: 6 months
Reduce by 25% every 3–6 months, maintain with 1–2 tablets/week
Efficacy: 60–75% of patients respond ;Subacute LE (60–75%): Tumid LE (90%)
Relapse: **50% relapse within 6 months**

Table 17.5: Monitoring

Laboratory tests	*Baseline*	*Follow-up*
	Fundoscopy , vision field testing, color vision testing , Amsler grid test	12 monthly*
	CBC, LFT,KFT	6 monthly (Renal/liver dysfunction or elderly)

*Because the risk of toxicity is low in the first 5 years, patients without risk factors, should follow American Academy of Ophthalmology guidelines based on age; however, most rheumatologists would favor annual screening or, at a minimum, every 2 years. For patients with risk factors, underlying ocular disease, or therapy duration more than 5 years, annual screening examinations are warranted (Marmor M et al.).
https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

the maximum daily dosage is not exceeded. Since 1999, the American College of Rheumatology has explicitly stated that no laboratory studies are needed before or during therapy.

The baseline examination is important for detecting central red scotomas which occur in up to 6% of the healthy population. Scotoma can also occur in patients with systemic lupus, as a result of vasculitis, or in patients with anti-phospholipid syndrome or corticosteroid-induced diabetes. Careful surveillance is essential if the suggested dosages are exceeded as well as in older patients and patients on long-term continuous therapy (>5 years). Self-testing with an Amsler grid test (once a month) is recommended for early detection (Easterbrook M).

According to British recommendations, ophthalmological examinations are *not* mandatory for HCQ if the maximum daily dosages are observed. Clinical controls during regular physician appointments (ask about scintillating scotomas, poor night vision and difficulty reading or recognizing faces) and annual vision testing are advised. Consultation of an ophthalmologist is only recommended for specific problems or for treatment exceeding five years (Jones SK et al.).

The recent guidelines of the AAO (Marmor M et al.) suggest that all patients have a 'baseline' examination within the first year of therapy. The baseline testing includes complete ophthalmologic examination including visual acuity and dilated examination of the cornea and retina, as well as a

baseline visual field testing. They contend that when HCQ is used at a dose of 400 mg/day and CQ at 250 mg/day, the risk of retinopathy in the first 5 years of therapy is negligible. In addition, at 5 years the risk begins to rise to roughly 1%. They suggest a baseline examination, and then the first annual evaluation should begin after 5 years of continuous therapy (the frequency is altered in patients at higher risk, primarily elderly patients).

Some authors recommend routine measurement of the enzyme, (G6-PD) while others believe it is unnecessary since the hemolytic effects of chloroquine are very minimal (Kalia S et al.).

Special Considerations

Drug Interactions

Drugs that decrease the effect of antimalarials	Antacids, kaolin, magnesium trisalicylate	
Drugs that increase the effect of antimlarials	Cyclosporine; digoxin, propafenone	
Additive effects with toxicity	QT prolongation, arrhythmias	Clarithromycin, pimozide, ephedra
	Seizures	Tramadol, bupropion
	Methemoglobinemia	Benzocaine, prilocaine
	GI side effects	Pyridostigmine;
	Decrease Botox activity	

Adverse Effects

In general, when individual daily doses (adjusted for ideal body weight) are observed (Tables 17.4 and 17.5), CQ/HCQ are well-tolerated. HCQ is said to have two-thirds of the effectiveness of CQ, but is only half as toxic (Table 17.6). HCQ has certain advantages because of its less side effects, but chloroquine is more effective.

Non-specific Effects

If the patient experiences unspecific symptoms (Table 17.6), treatment may be attempted again after a drug-free interval and dosage reduction.

Ocular Symptoms

Early eye symptoms can include defects in accommodation, conversion, or blurred vision, which resolve later. Other defects seen include corneal deposits, neuromuscular eye

Table 17.6: Overview of side effects of antimalarials

GIT	Nausea, abdominal cramps, bloating, diarrhea,acid reflux, difficulty concentrating, sleep disorders	CQ/HCQ: 1–10%
Ocular	Irreversible retinopathy (CQ/HCQ: 0.01–0.1%)	Central vision field loss; dependent on observing maximum daily dosage
	Corneal deposits (CQ: <1–10% HCQ: < 0.1–1%)	Reversible after discontinuing therapy
	Accommodation disorders (< 0.01–0.001%)	At higher dosages, reversible
Dermatological	Hyperpigmentation, exanthems, exfoliative reactions, phototoxic/allergic reactions pruritus	Gray discoloration on shins, palate, subungual; reversible
	Whitening, hair loss	Only in blond/red/light brown hair, reversible after stopping therapy rare <0.01–0.1%
CNS	Sleep disorders, confusion, dizziness, headache, paresthesia/dysesthesia drowsiness, fatigue, anxiety	<0.1–1%
Audiological	Hearing loss, tinnitus	CQ/HCQ: <0.1–0.01%
Locomotor system	Myopathies/neuromyopathies	CQ/HCQ: <0.01–0.1%, reversible
Cardiovascular system	Depression of T wave; possible chronic toxicity in conduction disorders	<0.1–1%; isolated reports of fatality
	Drop in blood pressure	CQ: <0.1–1%
	Cardiomyopathy	CQ: <0.001%
Hematological	Pancytopenia, agranulocytosis, thrombocytopenia	CQ/HCQ: <0.01–0.1%
	Exacerbation of porphyria	

toxicity and retinopathy. Only *retinopathy* is potentially *irreversible*. It has been divided into two forms, 'true' retinopathy and 'premaculopathy'. Premaculopathy is defined as changes on visual field or fundoscopic examination that are not associated with visual loss. It is believed that premaculopathy would progress if the antimalarial agent was continued, whereas it is potentially reversible with drug discontinuation.

Although retinal damage is highly unlikely when *ideal* body weight is used to determine the maximum daily dose (see above), an ophthalmological examination (fundoscopy, vision field testing, color vision testing, Amsler grid test) is advised before beginning treatment or within the first few months of therapy as are annual controls, or semi-annual controls for patients over 65 or with renal or liver insufficiency. CQ *deposits* in the cornea and anterior stroma (30–70%, only visible using a slit lamp) do *not* necessitate stopping treatment. They are less common in HCQ. Vision is not limited, but can be associated with halos around lights, though the condition is reversible after discontinuing the drug. In a small number of patients (especially those taking higher dosages >500 mg/day and adolescents), accommodation disorders can occur as a result of direct effects of chloroquine on the smooth muscle of the ciliary body. These symptoms also usually resolve spontaneously if therapy is continued at the same dosage.

Retinal toxicity is the most feared side effect, although it is rarely seen if proper dosage and monitoring protocols are followed. Less than 20 cases have been reported in the literature in more than 1 million patients prescribed the drug, and in a more recent review of six cases of retinal toxicity, all arose as a result of dosing above published guidelines. (Marmor M et al.). CQ has a higher risk of retinal toxicity than HCQ. In a retrospective study, Levy and associates demonstrated that HCQ was very safe if used in doses no greater than 6.5 mg/kg/day for up to 10 years.

Risk factors for retinopathy include high dosage, duration of use (>5 years), renal or liver disease, and age (>60 years old). HCQ or CQ retinopathy is described as bilateral **bull's eye maculopathy**, with retinal pigment epithelial cell depigmentation in the central macula with sparing of a small foveal island. Testing of the paracentral visual field usually can show toxicity before retinal pigment epithelial cell changes are visible. When advanced, visual loss may be irreversible and continue despite cessation of the drug owing to its long half-life in the retina, so early detection is essential.

Dermatological

Antimalarial can lead to hyperpigmentation, maculopapular/lichenoid/urticarial exanthems, exfoliative reactions, DRESS

syndrome, hypersensitivity to light. The pigmentation diminishes when the dose is reduced and disappears once therapy is stopped.

a. **Pigmentation:** A bluish-gray to black hyperpigmentation may occur in 10–30% of patients treated for 4 months or longer with any of the drugs. The pigmentation typically affects the shins (resembling ecchymoses), the face, the palate (with a sharp line demarcating the hard and soft palates), and the nailbeds (as transverse bands). The pigmentation may take months to fade after discontinuation of therapy.
b. Progressive **bleaching** of the hair roots of the scalp, the face, and the body is another unusual pigmentary disturbance that may appear in as many as 10% of patients taking CQ. This pigmentary phenomenon is also reversible. It has been suggested that taking CQ/HCQS for 3 weeks out of 4 weeks can help prevent this side effect.
c. The incidence of **pruritus** and various cutaneous eruptions associated with antimalarial use has been reported to be 10–20%. Pelle and Callen have reported that roughly 25% of all dermatomyositis patients experience hypersensitivity drug eruptions (mostly morbilliform) during antimalarial therapy.
d. Antimalarial drugs are known to occasionally exacerbate existing psoriasis. Psoriasis is not a contraindication for CQ therapy.

Hematological

Blood count changes such as aplastic anemia, leukopenia, agranulocytosis, and hemolysis are rare and almost always related to glucose-6-phophate-dehydrogenase deficiency and agranulocytosis caused by CQ. CQ and HCQ have been associated with hemolysis in patients with G6PD deficiency, but not in the usual dosage range. Hemolysis is considered more of a problem with the 8-aminoquinoline primaquine.

Neuromuscular Symptoms

Common neuromuscular symptoms include headache, insomnia, nightmares and irritability, which are mild and reversible with reduction of the daily dose. Tinnitus and deafness can occur. Neuromyotoxicity has been reported and manifests as insidious-onset proximal weakness with a normal creatine phosphokinase, which may be associated with a peripheral neuropathy and cardiac myotoxicity. Muscle biopsy specimens show curvilinear bodies and muscle fiber atrophy with vacuolar changes.

Cardiovascular

Rarely, conduction disturbances and cardiomyopathy have been reported.

Special Groups

Children

Antimalarials can be safely and successfully used in the treatment of children with LE, dermatomyositis, panniculitis, morphea and PCT. For young children, the issue of dosage form may be important. Neither HCQ nor CQ comes in a syrup. Ziering et al suggested that the capsules can be pulverized, weighed and put into packets or gelatin capsules containing the desired dosage. The powder can then be mixed with jam, jelly or apple sauce to mask the bitter taste.

Pregnancy

There are no reports of adverse effects on fertility. HCQ and CQ are considered FDA pregnancy category C. Because of the long half-life of HCQ, discontinuation of the drug at the time of pregnancy does not avoid fetal exposure. HCQ does cross the placenta, but there have been no reports of adverse outcomes or teratogenic effects in women who continue HCQ therapy during pregnancy. CQ also crosses the placenta and binds more tightly in tissue than HCQ, and there have been reports of fetal anomalies in women who took CQ during pregnancy.

Current recommendations are that HCQ may be continued throughout pregnancy, particularly in SLE, in which discontinuation could precipitate a flare, which would be more dangerous to the mother and the child.

Lactation

HCQ is found in low concentration in breast milk, but the American Academy of Pediatrics classifies it as compatible with breastfeeding.

BIBLIOGRAPHY

1. Ang GC, Werth VP. Combination antimalarial in the treatment of cutaneous dermatomyositis: a retrospective study. Arch Dermatol. 2005;141:855-9.
2. Burrows NP, Lovell CR. Disorders of connective tissue. Rook's Textbook of Dermatology, 8th edition. In: Burns DA, Breathnach SM, Cox NH, Griffiths CEM (Eds). 2010.
3. Cannella AM, O'Dell JR. Kelly's Textbook of Rheumatology. 9th edition. Elseiver. 2013;9.
4. Easterbrook M. Screening for antimalarial toxicity: current concepts. Can J Ophthalmol. 2002;37: 325-8,331-4.

5. Feldmann R, Salomon D, Saurat JH. The association of the two antimalarials chloroquine and quinacrine for treatment-resistent chronic and subacute cutaneous lupus erythematosus. Dermatol. 1994;189:425-7.
6. Gunja N, Roberts D, McCoubrie D, Lamberth P, Jan A, Simes DC, et al. Survival after massive hydroxychloroquine overdose. Anaesth Intensive Care. 2009;37:130-3.
7. James JA, Kim-Howard XR, Bruner BF, Jonsson MK, McClain MT, Arbuckle MR, et al. Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus Lupus. 2007;16:401-9.
8. Jones SK. Ocular toxicity and hydroxychloroquine: guidelines for screening. Br J Dermatol. 1999;140:3-7.
9. Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. Dermatol Ther. 2007;20:160-74.
10. Levy GD, Munz SJ, Paschal J, et al. Incidence of hydroxychloroquine retinopathy in 1207 patients in a large, multicenter outpatient practice. Arthritis Rheum. 1997;40:1482-6.
11. Marmor M, Carr R, Easterbrook M, et al. Information statement: Recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmol. 2002;109:1377-82.
12. Miyachi Y, Yoshioka A, Imamura S, et al. Antioxidant action of antimalarials. Ann Rheum Dis. 1986;45:244-8.
13. Ochsendorf FR. Use of antimalarials in dermatology. J Dtsch Dermatol Ges. 2010;8(10):829-44.
14. Pelle M, Callen JP. Adverse cutaneous reactions to hydroxychloroquine are more common in patients with dermatomyositis than in patients with cutaneous lupus erythematosus. Arch Dermatol. 2002;138(9):1231-3.
15. Ramakrishnan N, Kalinich J, McClain D. Ebselen inhibition of apoptosis by reduction of peroxides. Biochem Pharmacol. 1996;51:1443-51.
16. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann Rheum Dis. 2010;69:20-8.
17. Toonstra J, Wildschut A, Boer J, Smeenk G, Willemze R, van der Putte SC, et al: Jessner's lymphocytic infiltration of the skin. A clinical study of 100 patients. Arch Dermatol. 1989;125:1525-30.
18. Traditional DMARDs: Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine, and Combination Therapies.
19. Ziering CL, Rabinowitz LG, Esterly NB. Antimalarials for children: indications, toxicities, and guidelines. J Am Acad Dermatol. 1993;28(5 Pt 1):764-70.

DAPSONE

Because of its dual mechanism of action—antimicrobial and anti-inflammatory/immunomodulatory, effects—dapsone alone or in conjunction with other drugs is used worldwide for preventing and treating pathogen-caused diseases (e.g. leprosy, pneumocystis jiroveci pneumonia in individuals with HIV infection) or chronic inflammatory diseases, especially in the field of dermatology (e.g. autoimmune bullous eruptions).

Box 17.4: Chronology of dapsone use in dermatology

1908	Emil Fromm and Jakob Wittmann discovered the drug during their experiments in dye chemistry
1937	First *in vitro* use
1940s	Used in leprosy by Faget and coworkers
1950	Esteves and Brandao used it for dermatitis herpetiformis
1956	Sneddon and Wilkinson used it for subcorneal pustulosis

The drug has gone through various stages of development and today it has acquired the status of a remarkably safe drug (Box 17.4) in dermatology.

Mechanism of Action

Though a lot has to be understood about dapsone's mode of action, most of its action stems from the inhibition of the MPO enzyme system in *neutrophils*, *monocytes* and *eosinophils*. This explains its role in both neutrophilic and eosinophilic disorders. It is assumed that dapsone exerts a direct inhibition of MPO which leads to the formation of inactive intermediates of the enzyme. As hypochlorous acid is an integral part not only of the antibacterial/antiprotozoal armamentarium of PMN and eosinophils but can also cause tissue damage in noninfectious disease states, the inhibition of MPO by dapsone might account for the *anti-inflammatory* potential of the sulfone. Also its ability to scavenge free *oxygen radicals* explains most of its action in disorders like DH, linear IgA BD and LE.

It has an anti-inflammatory potential that—*cum grano salis*—equals that of classic NSAID's. It has been known to inhibit both the LOX and COX pathway. Some of its action is still experimental like its inhibition of leukocyte function antigen (LFA-1) (CD 11 a/CD 18), Mac-1 (CD 11b/CD 18) and p 150, 95 (CD 11 c/CD 18) which are important members of the β_2-integrin family of adhesion molecules. Its effect on lymphocytes likewise is controversial and it seems that it has an *immunostimulating* effect of dapsone in *lower* concentrations but an *immunosuppressive* in *higher* concentrations.

A list of its various actions is detailed (Table 17.7).

Absorption and Distribution

After oral administration, dapsone is almost completely absorbed from the gastrointestinal tract with bioavailability of more than 86%. Peak serum concentrations are generally attained within 2 to 8 hours. After ingestion of a single 50- to 300-mg dose of dapsone, maximal serum concentrations are reached between 0.63 and 4.82 mg/L. Under steady-state conditions, the most frequently used dosage of 100 mg/d

Table 17.7: Mode of action of dapsone

Antimicrobial activity	Streptococci, staphylococci, pneumococci and mycobacteria, and other strains. The mechanism of action of topical dapsone in the treatment of acne vulgaris may result from a combination of both antiinflammatory and antimicrobial effects
Anti-inflammatory mechanisms of action	Scavenger of **Reactive oxygen species** Reversible inhibition of **MPO** Inhibits Eosinophil **peroxidase**
	Adhesion molecules/cellular adhesion 1. Inhibits adherence of neutrophils to IgA and IgG (linear dermatosis and bullous pemphigoid) 2. Inhibition of adhesion of TNF-α- or platelet activating factor (PAF)-activated PMN of healthy donors by dapsone 3. Dapsone down regulates the expression of CD11b on activated neutrophils
	α-1-Protease inhibitor In vitro, dapsone possesses a protective effect on elastase inhibitor capacity of α-1-protease inhibitor (AIP), thereby showing similar properties as the physiologic antioxidant ceruloplasmine
	Membrane-associated-phospholipid metabolism (Fig. 17.1) *Prostaglandins* 1. Dose-dependent inhibition of the production of PGD_2 2. Direct inhibitory effect on COX 3. Inhibits PGE_2 *Leukotrienes* 1. Dapsone also inhibits enzymatic systems beyond 5-LOX 2. The inhibitory effect of dapsone on LTC_4 production could account for the observation that dapsone possesses corticosteroid-sparing effects in asthma patients **Interleukin 8:** Inhibition may explain its **a**ction on neutrophils

results in serum concentration of 3.26 (maximum) and 1.95 mg/L (after 24 hours).

After absorption, dapsone undergoes enterohepatic circulation. It is metabolized both by the liver and activated polymorphonuclear leucocytes (PMN) or mononuclear cells. In the liver, dapsone is metabolized primarily through *acetylation* by N-acetyltransferase to monoacetyldapsone (MADDS), and through *hydroxylation* by cytochrome P-450 enzymes, resulting in generation of dapsone hydroxylamine (DDS-NOH). (Fig 17.2).

Dapsone is distributed to all organs, crosses the blood–brain barrier and placenta, and is detectable in breast milk. Approximately, 20% of dapsone is excreted in urine as unchanged drug and 70% to 85% as water-soluble

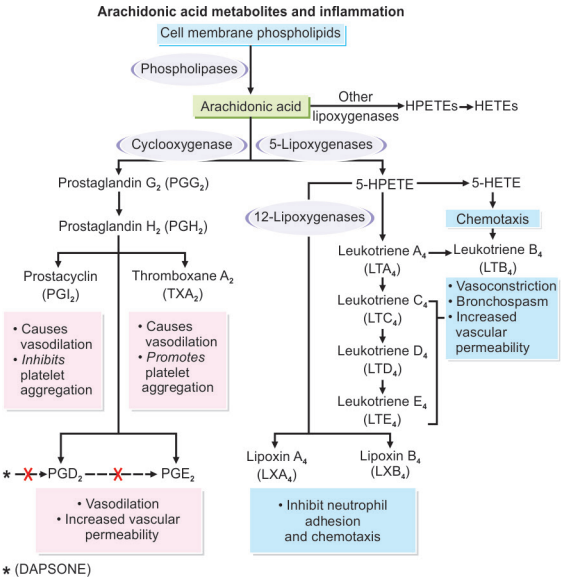


Fig. 17.1: An overview of the arachidonic acid metabolism and its action on dapsone*

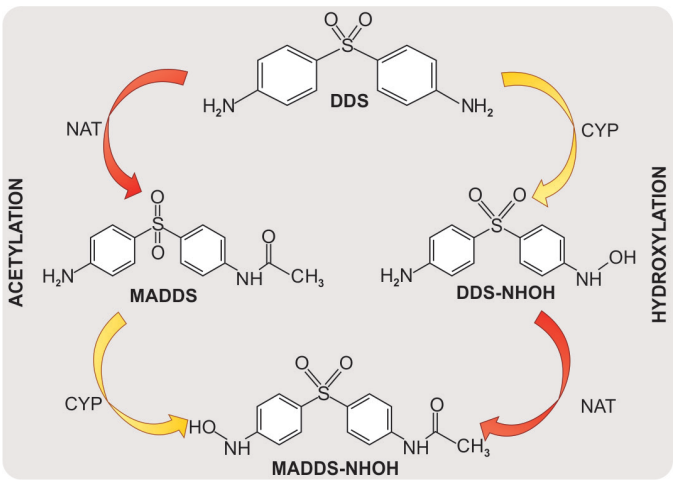


Fig. 17.2: Metabolism of dapsone via the acetylation and the hydroxylation pathway

Abbreviations: NAT, N-acetyl transferase; CYP, Cytochrome P450; DDS, 4,4′-diamino-diphenylsulfone; DDS-NHOH, dapsone hydroxylamine; MADDS, monoacetyl dapsone; MADDS-NHOH, monoacetyl dapsone hydroxylamine

metabolites. Additionally, a small amount may be excreted in feces.

Acetylation is genetically determined, resulting in significant variability in acetylation (rapid or slow acetylator). In fact, dapsone can be administered to determine the acetylation phenotype. In terms of both *efficacy* and induction of *adverse* effects, the most important factor is the generation of DDS-NOH; this occurs in lesional inflammatory processes in skin mediated by activated PMN.

Uses (Approved/Unapproved) (Table 17.8)

Apart from its role in leprosy it is also used in primary prophylaxis and prevention of recurrence in AIDS patients with *pneumocystis jiroveci* pneumonia and toxoplasmosis.

As anti-inflammatory agent, dapsone is employed primarily to treat chronic skin diseases characterized by an accumulation of neutrophils and/or eosinophils (Table 17.7), though some disorders like lichen planus are an exception where lymphocytes are abundant. In the literature, there are a large number of case reports, clinical studies and epidemiological analyzes representing beneficial effects of dapsone in such dermatological entities, collectively termed as sulfone-sensitives dermatoses. Despite a large body of evidence, the subsequent enumeration focused only a small number of relevant indications (Table 17.8).

If dapsone is going to be effective in the treatment of an inflammatory dermatosis, the patient will experience a relatively rapid response (within 24–48 hours) to dapsone therapy, with a similar relatively rapid recurrence of the disease after withdrawal of the medication.

In recent years, dapsone has been employed in a variety of *nondermatological* diseases including, *rheumatoid arthritis* (RA), *eosinophilic fasciitis*, *immune-thrombocytopenia* (*ITP*), *cortisone-dependent-asthma glioblastoma* and *seizures*.

Table 17.8: Dermatological uses of dapsone

FDA approved	Dermatitis herpetiformis Leprosy
Off Label (First choice)	■ Acropustulosis of infancy ■ Bullous eruption of systemic lupus erythematosus ■ Dermatitis herpetiformis ■ EED ■ Erythema elevatum diutinum ■ Linear IgA dermatosis (bullous dermatosis of childhood) ■ SCPD
(Adjuvant drug)	**Bullous dermatoses** : Bullous pemphigoid, Pemphigus vulgaris/foliaceus , cicatricial pemphigoid **Vasculitis** **Neutrophilic dermatoses**: Sweet syndrome, pyoderma gangrenosum, Behçet's syndrome **Miscellaneous** : Brown recluse spider bites Granuloma annulare Granuloma faciale Lichen planus Nodulocystic acne Panniculitis Pustular psoriasis Relapsing polychondritis Rosacea (granulomatous) Subacute cutaneous lupus erythematosus

Dosage

The dosage of dapsone in nearly all sulfone-sensitive disorders must be individually titrated to determine the minimum daily dose that effectively controls symptoms.

Initial dose: 50 to 100 mg/day. If the treatment goal is not achieved after 4–6 weeks, a higher dosage may be tried (150–300 mg/day). Administration of higher doses depends on tolerability and the results of laboratory monitoring. When a favorable response is attained, the dosage should then be reduced to the minimum that maintains a satisfactory clinical state.

Children

Dapsone can be crushed and dissolved, for example, in strawberry syrup. Studies evaluating bioavailability of dapsone after administration of this preparation have not been published. For some indications in childhood, such as infantile acropustulosis or eosinophilic folliculitis, a daily dosage of 2 mg per kilogram of body weight is recommended. Therapy with this dosage, or 4 mg/kg weekly, results in concentrations equivalent to those reached in adults receiving 100 mg/day. In the treatment of immune thrombocytopenia in children, dapsone was used in a similar dose of about 2 mg/kg body weight.

1. **Dermatitis herpetiformis**
   Dose: 100–200 mg of dapsone daily, though considerable variability exists in this response, with dosage ranges from 25 to 400 mg daily.
   Most patients will respond within 24–36 hours of initiating dapsone with a marked decrease in both itching and new blister formation. Similarly, withdrawal of dapsone results in a rapid (within 24–48 hours) initial recurrence of the signs and symptoms of DH.
2. **Linear IGA bullous dermatosis** and **chronic bullous dermatosis of childhood** 100–200 mg of dapsone daily.
3. **Bullous eruption of systemic lupus erythematosus:** Patients with the bullous eruption of systemic lupus erythematosus (SLE) have a vesicular eruption with a histologic picture similar to that seen in patients with DH. These patients often have a dramatic response to dapsone therapy in doses as low as 50 mg daily. The presence of neutrophils in a vesicular eruption in a patient with SLE suggests that dapsone will be effective, commonly reducing the need for systemic corticosteroids.
4. **Lichen planus:** The use of dapsone in LP defies its known mechanism of action as it has little effect on the immunological response. One unpublished observation

is that the drug might inhibit specific B cell clones causing a reduction of antigen-specific T-helper cell activity. This might explain its action in LP . In various studies dapsone, 200 mg/day for 16 weeks, has been used in various forms of LP and about 65% of patients achieve complete clearance while 19% have a partial response.

Drug Interaction

↓ Dapsone serum levels	Antibacterial – rifamycins Antacids- Anticonvulsants—Carbamazepine, phenobarbital, phenytoin Antifungal agents—Griseofulvin Bosentan Efavirenz, nevirapine
↑ Serum levels/↑ Hematologic risk of dapsone	Sulfonamide antibacterial agents, methotrexate, aprepitant, sulfonamide antibacterial agents
↑ Oxidative stress to RBC—result is hemolysis, methemoglobinemia	Antibacterial—sulfonamides, benzocaine, prilocaine, chloroquine, hyroxychloroquine

Special Considerations

Dapsone is *contraindicated* in patients who are allergic to the drug. It should not be administered to patients with severe anemia. Dapsone must be used *with caution* in the following conditions:

- Glucose-6-phosphate dehydrogenase deficiency
- Met-Hb-reductase deficiency
- Severe hepatopathy
- Cardiac insufficiency/heart failure
- Pulmonary diseases
- Co-medication with met-Hb-inducing drugs or compounds, respectively.

Side Effects

Table 17.9: An overview of side effect of dapsone

Hematologic	Hemolytic anemia, Methemoglobinemia, leukopenia, agranulocytosis
Hepatic	Hepatitis, infectious mononucleosis-like syndrome, cholestatic jaundice, hypoalbuminemia
Gastrointestinal	Nausea, vomiting
Neurologic and psychiatric	Motor neuropathy, mania
Cutaneous hypersensitivity reactions	Various skin exanthemata

Common

Hematologic

The hydroxylamines derivatives of dapsone, like DDS-NOH, are responsible for some of its major adverse effects including *met-Hb formation, hemolysis* and *agranulocytosis*. As this compound is bound to be formed during the metabolism of dapsone (Fig 17.2) , these effects are *obligatory* and vary only in intensity. Glucose-6-phosphate dehydrogenase (G6PD)-deficient patients are less susceptible to met-Hb production, but more susceptible to hemolysis.

Hemolysis

The older RBC are more susceptible to hemolysis and they get removed from the circulation. This may result in patients having an initial decrease in the hemoglobin (Hb), followed by a partial correction owing to increased production of new RBC from the bone marrow.

One result of the influx of new RBC into the circulation in response to dapsone-induced hemolysis is that it may result in falsely ***low*** levels of *HbA1c* in patients with poorly controlled diabetes mellitus. As the glycation of the HbA1c increases with the age of the erythrocytes, the increased relative proportion of young erythrocytes in the circulation of a patient with chronic hemolysis may result in a misleadingly low HbA1c value, which is not indicative of the overall glycemic control in the diabetic patient.

Methemoglobinemia

Cyanosis which is usually associated with mild methemoglobinemia may occur during dapsone treatment. This is also dose-related and small amounts of methemoglobin can be seen in individuals on low doses of dapsone. The methemoglobin formed is acted on by methemoglobin reductase in the RBC, leading to the regeneration of Hb.

It is not possible to accurately predict the amount of methemoglobin based on the degree of cyanosis of the patient, particularly in relatively darkly pigmented races. The effect of met-Hb is dependent on the Hb value, thus a patient with 10% methemoglobin but a total Hb of 15 g/dL will have a functional Hb of approximately 13.5 g/dL. The same percentage of methemoglobin (10%) in a patient with a total Hb of 10 g/dL will have a functional Hb concentration of 9g/dL, and will likely develop symptoms of anemia.

For treating patients with dapsone there is no threshold value of hemoglobin. The treatment initiation is based on a range of individual factors (e.g. age, profession, co-

medication, daily activities, pre-existing pulmonary and/or cardiac diseases). After initiation of dapsone therapy, evaluation of met-Hb levels should be carefully addressed. Different time points are of relevance as follows.

Met-Hb generation after a single dapsone dose reaches its maximum after approximately 6 hours and, therefore, undergoes a time-dependent process. In the early treatment phase, met-Hb should be determined 4–6 hours after ingestion of dapsone, because the maximum level of met-Hb in peripheral blood is indicative of real cardiopulmonary risk. For this reason, dapsone intake should be recommended in the *evening* in patients with activity during the day.

Approximately 14 days after initiation of treatment, determination of met-Hb will estimate the level *under steady-state conditions* and may also allow evaluation of patients adherence to therapy.

Other met-Hb determinations must be considered at any time if the patient`s condition has changed (e.g. increased dapsone dosage; clinical complaints, co-medication with other drugs, starting of smoking, use of pump water in agricultural regions with potential content of nitrites/anilines).

Acute methemoglobinemia occurs rarely, but may result in dyspnea, anemia, vascular collapse and in serious courses finally in death. Methemoglobin levels over 30%, however, should be treated by other, more rapid, means, such as methylene blue or plasma exchange. In patients who do ***not*** have G6PD deficiency, acute methemoglobinemia should be treated with intravenous methylene blue (1–2 mg/kg given by slow injection). The effect is generally complete within 30 minutes, but the procedure may need to be readministered if met-Hb reaccumulates.

Rare

Agranulocytosis is the most serious but *rare* idiosyncratic reaction to dapsone and is probably due to the hydroxylamine metabolites . The median duration of therapy with dapsone before the development of agranulocytosis is *7 weeks*, with an average dosage of 100 mg daily, though it can occur as early as 3 weeks after beginning therapy.

The clinical features are fever, pharyngitis, and occasionally signs of sepsis. In addition, patients should be instructed to discontinue the medication if they develop persistent fevers or flu-like symptoms.

Dermatological

Various skin eruptions have been described,including exfoliative dermatitis, erythema multiforme, urticaria, erythema nodosum, morbilliform and scarlatiniform exanthema and toxic epidermal necrolysis. Dapsone-induced

photosensitivity is quite rare, not dose-dependent and might be caused not only by the parent compound dapsone but also by its metabolites.

Nervous system

Rarely, peripheral neuropathy with primarily *motor* function loss has been reported in patients receiving dapsone. Electrophysiologic studies have revealed findings consistent with an axonal degeneration predominantly affecting motor nerves. The mechanism of dapsone neuropathy is unknown. In some cases, it is clearly a dose-related phenomenon, occurring in close approximation to acute, high-dose exposure to dapsone. In other cases, the neuropathy has occurred after relatively short-term, low-dose therapy. There has been speculation that the acetylator phenotype of patients may play a role, but this has not been clearly established.

The dose that can lead to this ranges from a high-dose, short-term exposure (1.2 g daily for 7 days) or chronic relatively low-dose therapy (approximately 150 mg daily for 5 years). Daily doses of dapsone have ranged from 75 to 600 mg. Most patients recover completely with discontinuation of the dapsone, which can take from several weeks to up to 2 years.

Tragic cases of patients who had ingested dapsone with suicidal intention confirm the ability of the drug to damage the peripheral nervous system, including the optic nerve resulting in blindness . It has been proposed that the retinal damage is secondary to severe hypoxia and the associated RBC fragments found in patients with dapsone overdosage.

Gastrointestinal Effects/Hepatic Reactions

Adverse gastrointestinal (GI) effects including anorexia, abdominal pain, nausea and vomiting can be encountered in patients receiving dapsone.

Due to their potential severity, hepatic adverse effects deserve special attention. There are three types of reactions:

Isolated abnormalities of liver function tests (e.g. increased bilirubin and/or liver enzymes) ***without*** evidence of hepatitis or hepatosis. If any abnormality is detected, the dosage of dapsone should be decreased or the drug should be discontinued until the source is established.

Prehepatic jaundice induced by hemolytic anemia. Hyperbilirubinemia may occur more often in patients with G6PD-deficiency. All affected patients should be monitored periodically after reduction of dapsone dosage/ discontinuation of treatment.

Toxic or cholestatic hepatitis in conjunction with hypersensitivity syndrome (HS). Hepatic coma is indeed the most frequent cause of death in the hypersensitivity syndrome.

Other rare adverse events associated with dapsone include severe hypoalbuminemia, gallbladder perforation, and pancreatitis.

Hypersensitivity Syndrome (HS)

The prevalence is 1.4%. Latency of HS after initiation of dapsone treatment is ≤20 days with a maximum latency of 20 weeks.

Nearly all patients present with a rash (91.1%) and fever (96.9%) and about 73.7 % showed lymphadenopathy. Hepatic dysfunction is seen in the majority of cases, its severity ranging from abnormal liver tests overt hepatosplenomegaly and jaundice to hepatic coma. About half of the patient demonstrate hematologic changes (leukocytosis 56.6%, eosinophilia 43.8%). Following withdrawal of dapsone (and in most cases therapy with steroids), majority of patients (82.3%) recover. Mucosal involvement, hepatitis, older age and concomitant diseases which occurred predominantly in third-world countries, all associated with a higher risk of fatal outcome.

Monitoring

A few important facts are discussed below. Table 17.10 elucidates the monitoring protocol.

1. A G6PD level should be obtained as its deficiency most often occurs in African-Americans and patients of Middle Eastern or Far Eastern ancestry. A a screening test for G6PD deficiency may be falsely normal if the patient has an elevated reticulocyte count or has a variant of the enzyme that is less capable of handling oxidative stresses in the RBC. G6PD deficiency means that individuals with similar G6PD levels may respond markedly differently to the same dose of dapsone, making close monitoring of Hb in the early periods of dapsone therapy of critical importance in all patients.
2. After *12 weeks* of therapy on stable doses of dapsone, changes in Hb rarely occur and agranulocytosis has rarely been reported.

Table 17.10: Monitoring of dapsone

Laboratory tests	*Baseline*	*Follow-up*
Complete-blood-count with-differential WBC count	Yes	2 weekly for 3–6 months 2 monthly after that
LFT(SGOT/SGPT)	Yes	3–4 monthly
KFT and urinalysis	Yes	3–4 monthly
Glucose-6-phosphate dehydrogenase level	Yes	No

3. Methemoglobin levels need *not* be measured unless the patient is experiencing symptoms such as excessive fatigue, headaches, or increasing cardiac or pulmonary symptoms.
4. All patients on dapsone will show some degree of increase in their reticulocyte count owing to the expected low-grade hemolysis. When patients on dapsone fail to show some increase in reticulocyte count despite a persistent anemia, the possibility of an associated iron, folate, or B 12 deficiency should be considered.

Strategies to Reduce Hematologic Adverse Effects

N-hydroxylation of dapsone via the 3A-family of isoenzymes or CYP 2E1 of the hepatic cytochrome P-450 system leads to the production of DDS-NOH, which has been made responsible for hematologic side effects. Though one approach is to suppress its production but it has to be borne in mind, however, that DDS-NOH possesses anti-inflammatory effects on its own right. An option is to give antioxidants like ascorbic acid and vitamin E. For daily practice, in cases of pronounced hematologic adverse effects, co-administration of cimetidine during the first weeks of treatment can be recommended if there are no alternative treatment modalities.

LEFLUNOMIDE

Classification

Disease-modifying antirheumatic drug (DMARD).

Mechanism of Action

- Leflunomide undergoes rapid conversion, both in the intestine and in the plasma, to its active metabolite, A77-1726. This metabolite inhibits dihydroorotate dehydrogenase, leading to a decrease in ribonucleotide synthesis and the arrest of stimulated cells in the G1 phase of cell growth
- Inhibits *T* and *B* lymphocytes and production of autoantibodies by B cells
- Increases of *interleukin-10* receptor mRNA
- Decreased interleukin-8 receptor type A mRNA, decreased TNF-dependent nuclear factor kappa B (NF-kB) activation
- At higher concentrations, A77 1726 also inhibits tyrosine kinases, interfering with cell signal transduction
- *Ex vivo* and *in vitro* studies in humans have shown that both leflunomide and MTX inhibit *neutrophil* chemotaxis, which may decrease the recruitment of inflammatory cells into the joints

- Leflunomide has also been shown to decrease the ratio of MMP-1 to TIMP-1
- Leflunomide alters the synthesis of cytokines by *augmenting* the immunosuppressive cytokine-transforming growth factor-β1 and *suppressing* the immunostimulatory cytokine IL-2.

Pharmacokinetics

Bioavailability: 80%; T1/2: 15 to 18 days

It undergoes extensive enterohepatic recirculation with predominantly renal excretion.

Usage Guidelines

A loading dose of **100 mg** per day for **3 days** followed by **20 mg** daily is the recommended dosing schedule. As the loading dose, causes gastrointestinal intolerance in clinical practice is often omitted.

Daily administration of 10 mg is an option in some patients often resulting in reduced side effects. Maintenance dose is 10 to 20 mg once daily for rheumatoid arthritis and 20 mg once daily for psoriatic arthritis. The therapeutic effect usually starts after 4 to 6 weeks of therapy. Because of its long half-life, some clinicians give leflunomide less often (three to five times per week).

Clinical Use

Leflunomide is indicated for the treatment of adult patients with:

- Active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD)
- Active psoriatic arthritis.

Recent or concurrent treatment with hepatotoxic or hematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered with these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without following the washout procedure may also increase the risk of serious adverse reactions even for a long time after the switching.

Rheumatoid Arthiritis

In rheumatoid arthritis leflunomide therapy is usually started with a loading dose of 100 mg once daily for 3 days. Omission of the loading dose may decrease the risk of adverse events. The recommended maintenance dose is leflunomide 10 mg to 20 mg once daily depending on the severity (activity) of the disease.

Psoriasis and Psoriatic Arthritis

Leflunomide therapy is started with a loading dose of 100 mg once daily for 3 days. The recommended maintenance dose is leflunomide 20 mg once daily.

The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months. There is no dose adjustment recommended in patients with mild renal insufficiency. No dosage adjustment is required in patients above 65 years of age.

The results are variable with some noting a dramatic improvement while others being less enthusiastic about its use.

Others

Atopic dermatitis, sarcoidosis, SLE/Sjogren's disease, refractory multicentric reticulohistiocytosis and alopecia areata.

Monitoring

- CBC and LFT: Alanine aminotransferase (ALT) or serum glutamopyruvate transferase (SGPT) and a complete blood cell count, including a differential white blood cell count and a platelet count, must be checked simultaneously and with the same frequency:
  - Before initiation of leflunomide
  - Every two weeks during the first 6 months of treatment
  - Every 8 weeks thereafter.

  If ALT increases, X2 normal values stop the medicine
- Mantoux test
- Blood pressure should be monitored regularly during therapy.

Special Considerations

- The GIT symptoms are often transient in nature and may respond to dose reduction
- Leflunomide is contraindicated in patients with abnormal liver function values, hepatitis infection, or heavy alcohol intake
- A high risk is there in patients of ILD if previous have been treated with methotrexate
- Washout procedure. If serious adverse effects occur during leflunomide therapy, licensed product information recommends that a drug washout procedure is performed. This may also be considered if a patient becomes pregnant while taking leflunomide, or if it is necessary to swap to another disease-modifying antirheumatic drug such as methotrexate.

For the washout procedure, either 8 g of colestyramine is given orally 3 times daily or 50 g of activated charcoal is given orally or via a nasogastric tube 4 times daily. Therapy is normally continued for 11 days, but should be repeated until plasma concentrations of the primary metabolite A-771726 are below 20 ng/mL, verified by two separate tests at least 14 days.

Adverse Effects

Common

Diarrhea dyspepsia, abdominal pain, nausea, and oral ulcerations, weight loss (20%), headache, dizziness, leucopenia, asthenia, paresthesia and increased transaminase levels in 2 to 4% of patients. Reversible alopecia is the commonest dermatological problem.

Gastrointestinal and Hepatic Side Effects

The most common side effect that limits the use of leflunomide is *diarrhea*, which responds to dose reduction and may be less common if the loading dose is not used. Abdominal pain, dyspepsia, and nausea from leflunomide appear to be slightly increased over placebo rates. Liver toxicity can occur in association with leflunomide administration. Leflunomide given in combination with MTX resulted in ALT/AST elevations greater than 1 × ULN in 31% and greater than 2 × ULN in 5% of patients. Furthermore, this change in transaminases was more commonly seen in prostate-specific antigen (PSA) patients.

Rare

- Pancytopenia and peripheral neuropathy
- Interstitial lung disease
- Other skin manifestations: Sjogren syndrome, ankylosing spondylitis, erythema multiforme, toxic epidermal necrolysis, lichen planus like eruption, photodistributed lichenoid drug reaction, Reiter syndrome, leukocytoclastic vasculitis, leg ulcers, alopecia areata and syringotropic hypersensitivity reaction.
- Weight loss: Significant weight loss has also been reported to occur in patients taking leflunomide.

Special Groups

Pregnancy

Women wishing to become pregnant should wait for **2 years** after stopping therapy, or if this is not feasible, a **washout**

procedure should be performed and a waiting period of 6 weeks be observed from the time plasma concentrations of the metabolite fall below 20 ng/mL before attempting conception.

A washout procedure with a waiting period of at least **3 months** is recommended in men who wish to father children. Women who become pregnant during therapy should also undergo a washout.

Washout Procedure

After stopping treatment with leflunomide:

- Cholestyramine 8 g is administered 3 times daily for a period of 11 days
- Alternatively, 50 g of activated powdered charcoal is administered 4 times daily for a period of 11 days.

However, also following either of the washout procedures, verification by two separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/L and fertilization is required.

Women of childbearing potential should be told that a waiting period of 2 years after treatment discontinuation is required before they may become pregnant. If a waiting period of up to approximately 2 years under reliable contraception is considered impractical, prophylactic institution of a washout procedure may be advisable.

Both colestyramine and activated powdered charcoal may influence the absorption of estrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with colestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended:

- **Children X**
- **Lactation X**
- **Renal:** To be avoided.

Hepatic

Leflunomide is contraindicated in patients with hepatic impairment. Patients who develop moderate elevations of liver enzyme values (defined as transaminase levels 2 to 3 times the normal upper limit) while receiving leflunomide treatment should have their dose reduced to 10 mg daily. If moderate elevations persist or if severe elevations occur, leflunomide should be stopped and washout procedures started.

LEUCOVORIN: CALCIUM FOLINATE (CALCIUM LEUCOVORIN)

Classification

Folic acid-derived antidote for folic acid antagonists.

Absorption and Metabolism

- Oral 20–30 min/3–6 h
- IV < 5 min/3–6 h
- IM 10–20 min/3–6 h.

Mechanism of Action

Drug acts as a cofactor in the biosynthesis of purines and pyrimidines which is blocked by folic acid antagonists such as methotrexate, trimethoprim, and pyrimethamine.

Pharmacology

The L isoform is useful as it is rapidly metabolized to folates and can bypass the methotrexate inhibition of folate metabolism.

Clinical Use in Dermatology

- Tablets, scored, folinic acid (as calcium salt) 15 mg (NA in India)
- Injection, folinic acid (as calcium salt) 3 mg/mL, 15 mg/mL, 50 mg/mL
- As an adjuvant with methotrexate, leucovorin **5 mg** PO **weekly** (begin 24 h after dosing methotrexate) can be given as an alternative to folic acid
- If a high dosage therapy is given to prevent methotrexate-induced adverse effects, usually start 12–24 hours after start of methotrexate infusion, by intramuscular injection, or by intravenous injection, or by intravenous infusion, **15 mg, repeated every 6 hours** for **24 hours** (may be continued by mouth) for 10 doses
- Suspected methotrexate overdosage, by intravenous injection or by intravenous infusion (at a maximum rate of 160 mg/minute), initial dose equal to or exceeding dose of methotrexate.

Monitoring

- Serum creatinine and methotrexat levels (daily)

- Hydration and urinary alkalinization should be continued till the methotrexate levels is below 5×10^{-8} mol/L.

Special Considerations

- Urinary pH every 6 hours. pH should be maintained > 7 to decrease the nephrotoxic effects of methotrexate. Alkalinizeurine with acetazolamide or sodium bicarbonate
- Leucovorin should be administered as soon as possible after it is determined that the folic acid antagonists have caused toxicity. Doses should be given within 24 hours of last dose of methotrexate. Most effective if given within 1 hour of overdose
- Use with caution in children treated for seizures
- Methotrexate rescue: Hydrate patient and alkalinize urine with sodium bicarbonate or acetazolamide
- Folic acid deficiency: Advise diet high in meat, dried beans, and green leafy vegetables
- Advice to patient: Drink 3 L of fluid per day.

Drug Interactions

- Leucovorin decreases effects/toxicity of trimethoprim–sulfa-methoxazole, barbiturates, phenytoin, primidone
- Leucovorin increases effects/toxicity of 5-fluorouracil, other fluoropyrimidines.

Adverse Effects

Anaphylactoid reaction, thrombocytosis.

Special Groups

Pregnancy: C.

METFORMIN

500 mg, 850 mg,1,000 mg, SR tablet.

Metformin is a biguanide antihyperglycemic agent used in the management of type 2 diabetes mellitus. It does not affect insulin secretion; rather, it reduces hepatic glucose production and enhances glucose utilization by muscle. Reported increases in glucose utilization in muscle are 7–35%. In addition to blood glucose reductions (mean 53 mg/dL), metformin may have beneficial effects on serum lipids.

Absorption and Distribution

Pharmacokinetics

Absorption half-life is 0.9–2.6 hours for immediate-release tablets; peak levels occur at 4–8 hours (median 7 hours) with

the SR formulation. Absolute bioavailability is 50–60% for both products. With immediate-release tablets, peak serum levels are 1–2 mg/L, with the SR formulation, peak levels are 20% lower. Plasma protein binding is negligible. Metformin is excreted in the urine unchanged.

$t\frac{1}{2}$ (Immediate-release) 1.7–4.5 hours with normal renal function.

Dosage

Dose PO for type 2 diabetes (immediate-release) initiate 500 mg tablets with a dosage of 1 tablet bid with morning and evening meals. Increase dosage in 500 mg/day increments at weekly intervals, to a maximum of 2.5 g/day. To switch from the immediate-release to the SR formulation, give the same daily dosage of SR as a single dose with the evening meal.

In dermatology the most common dose is 500 mg twice a day.

Patient instructions: Take metformin just *before* meals to reduce gastrointestinal side effects (diarrhea, nausea, and heartburn).

Do not take metformin if you develop a serious medical condition such as myocardial infarction, stroke, or serious infection; require surgery; consume excessive amounts of alcohol; or require X-ray procedures with contrast dyes.

Discontinue metformin and contact your healthcare provider immediately if hyperventilation, muscle pain, malaise, unexplained drowsiness, or other unusual symptoms occur that might indicate the development of lactic acidosis.

Uses (Approved/Unapproved)

Approved

Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycemic control.

If a patient does not respond to metformin monotherapy, combination therapy with a sulfonylurea or a thiazolidinedione might be effective. Weight loss has been associated with metformin therapy (mean 0.8 kg); weight gain (mean 2.8 kg) has been found in patients treated with sulfonylureas. Reductions in total cholesterol, LDL cholesterol, and triglycerides of 5%, 8%, and 16%, respectively, and an increase of 2% in HDL cholesterol has been observed.

Unapproved

A list of indications are given in Table 17.11 and a few of these conditions will be discussed.

Acne: A recent study has looked at the possibility of using metformin in patients who were *recalcitrant* to therapy and

Table 17.11: Uses of metformin in dermatology

Reduction of hyperinsulinemia	■ In obese diabetics ■ Acanthosis nigricans
Reducing hyperandrogenism	■ Hirsutism ■ PCOD ■ Acne ■ HS (hidradenitis suppurativa)
Lipid-lowering action	■ Eruptive xanthomas
Tumor-suppressant effect	■ Cutaneous SCC ■ Melanoma

found a significant improvement in acne (G Fabbrocini et al.). Notably, the treatment was with concomitant topical agents and it took 6 months for an appreciable response. Also the study did not mention the kind of therapies used before, as in my experience in isotretinoin is supremely effective in most cases, and the study did not mention what therapy the patients were taken before starting metformin.

Patients who *might benefit* from metformin are those with PCOS, associated diabetes or impaired glucose tolerance.In alarge study on 188 women (Bergstrom KG et al.) with PCOS (subdivided by BMI into lean, overweight and obese groups) treated with a weight-adjusted dose of metformin between 500 and 1,000 mg twice daily for a 6-month period, noted an improvement in acne severity, testosterone level, insulin resistance and menstrual irregularities in all three groups.

In a randomized open-labelled trial on 34 adolescents (Ibanez L et al.) with hyperinsulinemic androgen excess compared the effect of ethinyl estradiol-cyproterone acetate (EE-CA) vs a low-dose combination of pioglitazone, flutamide and metformin (PioFluMet) over a period of 6 months on multiple outcomes including acne and hirsutism scores, androgen excess, fasting insulin, lipid profile, among others. Although EE-CA and PioFluMet attenuated the androgen excess comparably, low-dose PioFluMet had a more significant effect on other parameters including insulinemia, cholesterol, triglycerides and acne scores, among others. Within the pathophysiological cascade of PCOS, Flu-Met seems to counter upstream anomalies like hyperinsulinemia or hyperandrogenism, thereby preventing or reversing downstream effects. In contrast, an OC essentially masks downstream symptoms like hirsutism, acne or irregular menses, whereas the upstream aberrations remain unaltered or may even be worsened.

Hirsutism

In approximately 90% of women with hirsutism, the underlying disorder is either PCOS or idiopathic. In addition

to hirsutism, acne, seborrhea and alopecia represent other manifestations of hyperandrogenism. Most of the evidence on the efficacy of metformin in hirsutism is derived from studies on PCOS where it improves the insulin resistance. This can be used as an adjunct to other therapies.

Hidradenitis Suppurativa

The use of metformin in the treatment of hidradenitis suppurativa (HS) was first documented in the case of a 50-year-old woman who had long-standing HS and type 2 diabetes for which she was maintained on metformin 500 mg three times daily for more than 5 years. While on metformin, her HS was stable without the need for repeated antibiotic courses. However, after discontinuing metformin due to good glycemic control, she noticed a flare of her HS. The drug is used as an adjuvant to other therapies in HS.

Acanthosis Nigricans

Metformin has been used with some success in selected cases to correcting hyperinsulinemia associated acanthosis nigricans (AN). In insulin-dependent juvenile acanthosis nigricans associated with obesity metformin can reverse the finding of AN with diet control. In severe cases, it can be combine with isotretinoin. Prolonged metformin treatment resulted in complete improvement of acanthosis nigricans in an adolescent with normal weight.

Side Effects

Acute side effects occur in as many as 30% of patients treated with metformin. Side effects include primarily gastrointestinal (GI) complaints, such as diarrhea, abdominal discomfort, nausea, anorexia, and metallic taste. GI side effects are usually transient and dose related and can be mitigated by giving the drug just before meals, initiating therapy with small doses and slowly increasing the dosage.

Metformin reduces serum vitamin B_{12} levels in approximately 7% of patients but is rarely associated with anemia. Vitamin B_{12} deficiency anemia can be treated with vitamin B_{12} supplementation or by discontinuing metformin. Diminished vitamin B_{12} absorption and transport can be improved with oral calcium supplementation.

Lactic acidosis has been reported; however, almost all cases occur in patients in whom metformin was contraindicated or in patients who attempted suicide by overdose.

Drug Interactions

Furosemide and nifedipine increase serum levels of metformin, the clinical relevance of which is unknown.

Cimetidine reduces the tubular secretion of metformin and can increase peak serum concentrations by as much as 60%.

Monitoring

Monitor renal function, hepatic function, and CBC before initiation of therapy and at least annually thereafter. Monitor renal function more closely in the elderly because of the age-related changes in renal function and greater risk for acute renal failure. The goal of therapy is to reduce fasting blood glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dosage of the drug.

Special Populations

Pediatric dosage: Safety and efficacy not established.
Geriatric dosage: Initial and maintenance dosages should be lower in the elderly. Avoid usual maximum adult dosage. Do not start metformin in patients ≥80 years unless renal function is normal.

BIBLIOGRAPHY

1. Badr D, Kurban M, Abbas O. Metformin in dermatology: an overview. J Eur Acad Dermatol Venereol. 2013;27(11):1329-35.
2. Bergstrom KG. Everything old is new again: spironolactone and metformin in the treatment of acne. J Drugs Dermatol. 2010;9:569-71.
3. Ibanez L, Diaz M, Sebastiani G, et al. Treatment of androgen excess in adolescent girls: ethinylestradiol-cyproterone acetate versus low-dose pioglitazone-flutamide-metformin. J Clin Endocrinol Metab. 2011;96:3361-6.
4. Fabbrocini G, Izzo R, Faggiano A, Del Prete M, Donnarumma M, Marasca C, et al. Low glycaemic diet and metformin therapy: a new approach in male subjects with acne resistant to common treatments. Clin Exp Dermatol. 2015 Jun 6. doi: 10.1111/ced.12673.
5. van Zuuren EJ, Fedorowicz Z, Carter B, Pandis N. Interventions for hirsutism (excluding laser and photoepilation therapy alone). Cochrane Database Syst Rev. 2015;4:CD010334.

OXYBUTYNIN HYDROCHLORIDE

Mechanism of Action

Oxybutynin is an anticholinergic medication able to antagonize the M1, M2, and M3 subtypes of the muscarinic acetylcholine receptor. It is generally used to relieve urinary and bladder difficulties, including frequent urination and the inability to control urination (urge incontinence), by decreasing muscle spasms of the bladder. In dermatology, it also acts on the receptors (M1) that cause increased sweat secretion.

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. It exhibits one fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle but 4–10 times the antispasmodic activity.

Absorption and Distribution

Pharmacodynamic Properties

Oxybutynin has both direct antispasmodic action on the smooth muscle of the bladder detrusor muscle as well as an anticholinergic action in blocking the muscarinic effects of acetylcholine on smooth muscle. These properties cause relaxation of the detrusor muscle of the bladder in patients with an unstable bladder.

Pharmacokinetic Properties

Oxybutynin is poorly absorbed from the gastrointestinal tract. It is highly bound to plasma proteins, the peak plasma level is reached between 0.5–1 hour after administration.

The half life is *biexponential*, the first phase being about 40 minutes and the second about 2-3 hours. The elimination half life may be increased in the elderly, particularly if they are frail.

Oxybutynin and its metabolites are excreted in the feces and urine. There is no evidence of accumulation.

Uses (Approved/Unapproved)

FDA approved	Urinary incontinence, urgency and frequency in the unstable bladder, whether due to neurogenic bladder disorders (detrusor hyperreflexia) in conditions such as multiple sclerosis and spina bifida, or to idiopathic detrusor instability (motor urge incontinence). **Pediatric population** Oxybutynin hydrochloride is indicated in children *over* 5 years of age for:
	■ Urinary incontinence, urgency and frequency in unstable bladder conditions due to idiopathic overactive bladder or neurogenic bladder disorders (detrusor overactivity) ■ Nocturnal enuresis associated with detrusor overactivity, in conjunction with non-drug therapy, when other treatment has failed
Off label	Hyperhidrosis

Dosage

1. FDA approved indications
   Adults: The usual dose is **5 mg two or three times a day**. This may be increased to a maximum of 5 mg four times

a day to obtain a clinical response provided that the side effects are tolerated.

Elderly (including frail elderly): The elimination half-life is increased in the elderly. Therefore, a dose of **2.5 mg twice a day**, particularly if the patient is frail, is likely to be adequate. This dose may be titrated upwards to 5 mg two times a day to obtain a clinical response provided the side effects are well tolerated.

Children (under 5 years of age): Not recommended.

Children (over 5 years of age): *Neurogenic bladder instability*—the usual dose is **2.5 mg twice a day**. This dose may be titrated upwards to 5 mg two or three times a day to obtain a clinical response provided the side effects are well tolerated. *Nocturnal enuresis*: the usual dose is 2.5 mg twice a day. This dose may be titrated upwards to 5 mg two or three times a day to obtain a clinical response provided the side effects are tolerated. The last dose should be given before bedtime.

2. **Hyperhidrosis:** A simple dosage regimen is as follows *2.5 mg daily for the first week,* then *2.5 mg* **twice daily** from *day 8 to day 21*, and then *5 mg twice daily* starting at *day 22*.
   a. Generalized hyperhidrois: Oxybutynin was started at a dose of 2.5 mg per day and increased gradually to 7.5 mg per day. In cases of generalized hyperhidrosis, oxybutynin was superior to (60%) placebo (27%) with dry mouth being the most common side effect (Schollhammer M et al).
   b. Palmo/plantar hyperhidrosis: A good initial response to oxybutynin was seen in more than 82% of cases.

Drug Interaction

The anticholinergic activity of oxybutynin is increased by concurrent use of other anticholinergics or medicinal products with anticholinergic activity, such as amantadine and other anticholinergic antiparkinsonian medicinal products (e.g. biperiden, levodopa), antihistamines, antipsychotics (e.g. phenothiazines, butyrophenones, clozapine), quinidine, digitalis, tricyclic antidepressants, atropine and related compounds like atropinic antispasmodics and dipyridamole.

By reducing gastric motility, oxybutynin may affect the absorption of other drugs. Oxybutynin is metabolized by cytochrome P450 isoenzyme CYP 3A4. Concomitant administration with a CYP3A4 inhibitor can inhibit oxybutynin metabolism and increase oxybutynin exposure. Oxybutynin may antagonize prokinetic therapies.

Concomitant use with cholinesterase inhibitors may result in reduced cholinesterase inhibitor efficacy.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Special Considerations

Contraindications

- Hypersensitivity to oxybutynin or any component
- Myasthenia gravis
- Narrow-angle glaucoma or shallow anterior chamber
- Gastrointestinal obstructive disorders including paralytic ileus, intestinal atony
- Patients with toxic megacolon
- Patients with severe ulcerative colitis
- Patients with bladder outflow obstruction where urinary retention may be precipitated.

Special Advise

- Anticholinergics should be used with caution in elderly patients due to the risk of cognitive impairment
- Gastrointestinal disorders: Anticholinergic medicinal products may decrease gastrointestinal motility and should be used with caution in patients with gastrointestinal obstructive disorders, intestinal atony and ulcerative colitis
- Oxybutynin may aggravate tachycardia (and thus be cautious in case of hyperthyroidism, congestive heart failure, cardiac arrhythmia, coronary heart disease, hypertension), cognitive disorders and symptoms of prostatic hypertrophy
- Anticholinergic CNS effects (e.g. hallucinations, agitation, confusion, somnolence) have been reported; monitoring recommended especially in first few months after initiating therapy or increasing the dose; consider discontinuing therapy or reducing the dose if anticholinergic central nervous system effects develop
- Since oxybutynin can cause narrow-angle glaucoma, patients should be advised to contact a physician immediately if they are aware of a sudden loss of visual acuity or ocular pain
- Oxybutynin may reduce salivary secretions which could result in dental caries, parodontosis or oral candidiasis
- Anticholinergic medicinal products should be used with caution in patients who have hiatus hernia/gastro-esophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate esophagitis

- When oxybutynin is used in high environmental temperatures, this can cause heat prostration due to decreased sweating.

Side Effects

1. Gastrointestinal disorders
   - Very common—constipation, nausea, dry mouth
   - Common—diarrhea, vomiting
   - Nervous system disorders
2. Common: confusional state
   - Very common—dizziness, headache, somnolence
3. Eye disorders
   - Very common—vision blurred
   - Common—dry eyes
4. Renal and urinary disorders
   - Common—urinary retention
5. Vascular disorders
   - Common—flushing which may be more marked in children
6. Skin and subcutaneous tissue disorders
   - Very common—dry skin.

Special Groups

Children

Primary hyperhidrosis is mainly considered an adult burden; however, 1.6% of adolescents and 0.6% of prepubertal children are affected. The efficacy of oxybutynin in children with palmar hyperhidrosis found that after 6 weeks of treatment with oxybutynin, improved hyperhidrosis in 85% of the children. More than half experienced adverse effects (most commonly, dry mouth), although treatment discontinuation was not necessary (Wolosker N).

Obese

Overweight and obese patients have greater difficulty in maintaining normal body temperature levels and, therefore, produce excessive perspiration as a compensatory mechanism. The oxybutynin dose protocol is the same regardless of body weight, with 2.5 mg of oxybutynin administered once a day for the first week, 2.5 mg twice a day for the next 5 weeks, and 5 mg twice a day to the end of the 12th week.

Women

Oxybutynin has also been successfully administered in postmenopausal women reporting associated secondary

generalized hyperhidrosis. Most of the 21 women enrolled in a recent study were treated with 5 mg of oxybutynin per day for 3 months.

According to its teratogenic effects, oxybutynin is ascribed to category B.

BIBLIOGRAPHY

1. Schollhammer M, Brenaut E, Menard-Andivot N, Pillette-Delarue M, Zagnoli A, Chassain-Le Lay M, et al. Oxybutynin as a treatment for generalized hyperhidrosis: a randomized, placebo-controlled trial. Br J Dermatol. 2015 Jun 26. doi: 10.1111/bjd.13973.
2. Wolosker N, Teivelis MP, Krutman M, de Paula RP, Kauffman P, de Campos JR, et al. Long-term results of the use of oxybutynin for the treatment of plantar hyperhidrosis. Int J Dermatol. 2015;54(5):605-11.
3. Wolosker N, Teivelis MP, Krutman M, de Paula RP, Schvartsman C, Kauffman P, et al. Long-term efficacy of oxybutynin for palmar and plantar hyperhidrosis in children younger than 14 years. Pediatr Dermatol. 2015;32(5):663-7.

PENICILLAMINE

Mechanism of Action

It is primarily a metal chelator but in dermatology it interferes with collagen maturation, which is the reason for its use in progressive systemic sclerosis (PSS).

Absorption and Distribution

Penicillamine is a thiol-group drug containing chelating agent, variably absorbed from the gastrointestinal tract. The drug undergoes a rapid distribution phase, followed by a slower elimination phase. The peak plasma concentration of the parent compound occurs within 1–3 hours after a dose; its half-life is approximates 1–3 hours.

Penicillamine is strongly plasma-protein bound. Most penicillamine is bound to albumin but some is bound to globulins or ceruloplasmin.

Penicillamine is not extensively metabolized in man.

About 80% of the absorbed dose is excreted rapidly in the urine, mostly as mixed disulphides. Some of the dose is excreted as a penicillamine copper complex and some as the S-methyl derivative.

Uses (Approved/Unapproved)

FDA approved	a. Severe active rheumatoid arthritis, including juvenile forms b. Wilson's disease (hepatolenticular degeneration) in adults and children (0–18 years)

Contd...

Contd...

	c. Cystinuria—dissolution and prevention of cystine stones in adults and children (0–18 years) d. Lead poisoning in adults and children (0–18 years) e. Chronic active hepatitis in adults

Rheumatoid Arthritis

125 to 250 mg daily for the first month. Increase by the same amount every four to 12 weeks until remission occurs. The minimum maintenance dose to achieve suppression of symptoms should be used and treatment should be discontinued if no benefit is obtained within 12 months. Improvement may not occur for some months.

The usual maintenance dose is 500–750 mg daily. Up to 1500 mg daily may be required.

If remission is established and has been sustained for 6 months, gradual reduction by 125–250 mg amounts every 12 weeks may be attempted.

Progressive Systemic Sclerosis

Dermatologists have been historically used penicillamine primarily for the treatment of various forms of PSS, though now it is restricted for localized PSS. Importantly the drug has been found to be *no better than a placebo* in PSS and does *not* find place in standard textbooks of rheumatology, but as some dermatologists still prescribe this drug details are given below.

In most cases of PSS adult dosing is initiated at 125–250 mg daily, with increases of 125–250 mg daily occurring incrementally every 1–3 months until satisfactory remission or toxicity occurs (usually at levels between 750 and 1500 mg daily). Therapy is commonly required for several months, with time to response and remission varying widely. The dose should be gradually reduced while maintaining remission. Using such a regimen, Jimenez and Sigal reported a cutaneous response rate of over 90% in a 15-year prospective study of the use of penicillamine in PSS. But in rheumatology practice the drug is rarely used for PSS (Harding S).

Periocular Pigmentation

Pigmentationn due to deposition of lead in "kohl" has been shown to be mitigated by the use of D-PCN in a low divided dose (750 mg/day) (El Safoury OS et al.).

Drug Interaction

- Concomitant use of iron or antacids: Oral absorption of penicillamine may be reduced by concomitant administration of iron or antacids

- Concomitant use of digoxin: Oral absorption of digoxin may be reduced by concomitant administration of penicillamine
- Concomitant use of NSAIDs and other nephrotoxic drugs may increase the risk of renal damage
- Concomitant use of clozapine: Penicillamine may potentiate the blood dyscrasias seen with clozapine Concomitant use of zinc: Oral absorption of penicillamine may be reduced by concomitant administration of zinc; absorption of zinc may also reduced by penicillamine
- Pyridoxine daily may be given to patients on long-term therapy, especially if they are on a restricted diet, since penicillamine increases the requirement for this vitamin.

Special Considerations

Contraindications

- Hypersensitivity to penicillamine or any of the ingredients
- Agranulocytosis, aplastic anemia or severe thrombocytopenia due to penicillamine
- Lupus erythematosus
- Moderate or severe renal impairment.

Side Effects

The most common of all side-effects is thrombocytopenia and proteinuria.

- Thrombocytopenia occurs commonly. The reaction may occur at any time during treatment and is usually reversible
- Proteinuria occurs in up to 30% of patients and is partially dose-related
- Skin.

The adverse cutaneous effects include the bullous dermatoses (including several forms of pemphigus, cicatricial and bullous pemphigoid, and epidermolysis bullosa acquisita), a lupus-like syndrome, lichen planus, elastosis perforans serpiginosa, and pseudoxanthoma elasticum. More rarely described adverse effects with penicillamine use include characteristic nail changes, a unique dermatopathy, and a Goodpasture-like syndrome.

Skin and subcutaneous tissue disorders	
Rare:	Alopecia, pseudoxanthoma elasticum, elastosis perforans, skin laxity
	Rash, urticarial reactions, dermatomyositis, pemphigus, Stevens-Johnson syndrome, acquired epidermolysis bullosa, penicillamine dermopathy

Monitoring

1. Full blood and platelet counts should be performed and renal function should be assessed prior to treatment with penicillamine. Monitoring of blood and platelet counts should be carried out at appropriate intervals.
   During the first **eight** weeks of therapy full blood counts should be carried out **weekly or fortnightly** and also in the week after any increase in dose, otherwise monthly thereafter.
   Withdrawal of treatment should be considered if platelets fall below **120,000/mm^3** or white blood cells below **2,500/mm^3**, or if three successive falls are noted within the normal range. Treatment may be restarted at a reduced dose when counts return to normal, but should be permanently withdrawn on recurrence of leucopenia or thrombocytopenia.
2. Urinalysis for detection of hematuria and proteinuria. Urinalysis should be carried out weekly at first, and following each increase in dose, then monthly, although longer intervals may be adequate. Increasing or persistent proteinuria may necessitate withdrawal of therapy.
   Especially careful monitoring is necessary in the elderly since increased toxicity has been observed in this patient population regardless of renal function.

BIBLIOGRAPHY

1. El Safoury OS, El Fatah DS, Ibrahim M. Treatment of periocular hyperpigmentation due to lead of kohl (surma) by penicillamine: a single group non-randomized clinical trial. Indian J Dermatol. 2009;54(4):361-3. doi:10.4103/0019-5154.57614.
2. Ingen-Housz-Oro S, Grootenboer-Mignot S, Ortonne N, et al. Epidermolysis bullosa acquisita-like eruption with anticollagen VII autoantibodies induced by D-penicillamine in Wilson disease. Br J Dermatol. 201;171(6):1574-6.
3. Jimenez SA, Sigal SH. A 15-year prospective study of treatment of rapidly progressive systemic sclerosis with d-penicillamine. J Rheumatol. 1991;18:1496-503.
4. Harding S, Khimdas S, Bonner A, Baron M, Pope J. Canadian Scleroderma Research Group. Best practices in scleroderma: an analysis of practice variability in SSc centres within the Canadian Scleroderma Research Group (CSRG). Clin Exp Rheumatol. 2012;30(2 Suppl 71):S38-43.

PENTOXIFYLLINE[2]

Classification

Methyl-xanthine derivative

The drug has properties similar to theobromine, caffeine and theophylline (except fewer cardiac side effects).

Absorption and Distribution

Metabolism of pentoxifylline is given Figure 17.3.

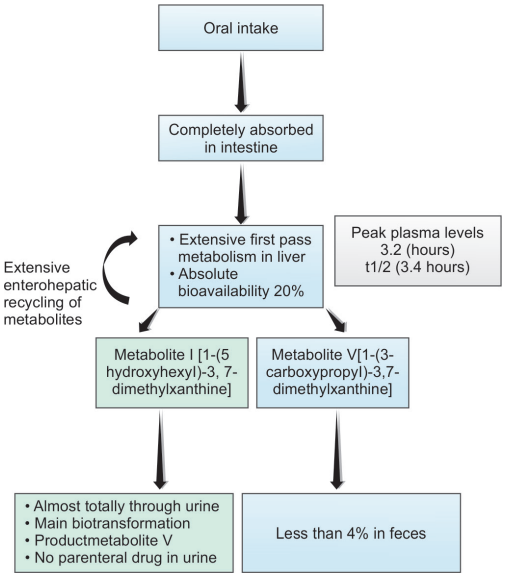


Fig. 17.3: Metabolism of pentoxifylline

Mechanism of Action

- It lowers blood viscosity and improves erythrocyte flexibility
- It increases leukocyte deformability and inhibits neutrophil adhesion and activation
- It improves tissue oxygenation
- It inhibits tumor necrosis factor alpha synthesis
- There is evidence to suggest that it affects T-cell adherence to endothelial cells and keratinocytes.

Immune Modulation

Increase	*Decrease*
Leukocyte deformability	Neutrophil degranulation
Chemotaxis	Leukocyte adhesion and aggregation
	Production of monocyte-derived TNF
	Leukocyte responsiveness to IL-1 and TNF
	Natural killer cell activity
	Anti-TNF-α effects

Hemorheological Effects

Almost complete hemorheological effect:

Increases	*Decreases*
Red blood cell deformability	Blood cell aggregation

Contd...

Contd...

Erythrocyte adenosine triphosphate and other cyclic nucleotide levels	Inhibition of thromboxane
Prostacyclin synthesis	Platelet aggregation and adhesion
Plasminogen activator, plasmin and antithrombin III	Fbrinogen, alpha 2-antiplasmin, alpha-1 antitrypsin and alpha-2 macroglobulin
Leukocyte deformability	Vasoconstriction

Wound Healing and Connective Tissue

Increases	*Decreases*
Fibroblast collagenases	Fibroblast collagen
	Fibroblast fibronectin
	Fibroblast glycosaminoglycans
	Fibroblast response to TNF-α

Nonselective Inhibitor of Cyclic-3', 5'-phosphodiesterase (PDE)

Increase I/C levels of cAMP and cGMP and augments signal transduction effects inflammation.

Others

Reduces expression of adhesion molecules ICAM-I on keratinocytes and E-selectin expression on endothelial cells.

Pharmacology

Dose

Oral: 400 mg tds (controlled release tab) with food or milk. Doses as high as 2200 mg daily have been well tolerated in severe peripheral vascular disease.

The recommended initial dose is 1 tablet (400 mg) three times daily; two tablets daily may prove sufficient in some patients, particularly for maintenance therapy. Tablets should be taken with or immediately after meals, and swallowed whole with plenty of water.

Elderly:	No special dosage requirements.
Children:	Trental 400 is not suitable for use in children.

Special cases: In patients with impairment of renal function (creatinine clearance below 30 mL/min) a dose reduction by approximately 30–50% may be necessary guided by individual tolerance.

Intravenous: Slow IV infusion begin with 100 mg/day with daily increments of 50 mg to maximum. 300 mg/day (but doses as high as 600 mg twice a day have been used successfully.

Clinical Use in Dermatology

FDA approved	Intermittent claudication: Approved in 1984
Off label	■ Vascular – Venous leg ulcers – Raynaud's phenomenon – Livedoid vasculopathy (*atrophie blanche)* – Pigmented purpuric dermatoses ■ Infections – Leprosy—ENL – Cutaneous leishmaniasis ■ Connective tissue disorders – Aphthosis and Behçet disease ■ Radiation injury – Oral submucous fibrosis ■ Necrobiosis lipoidica diabeticorum ■ Granuloma annulare ■ Actinic granuloma ■ Pretibial myxedema ■ Kasabach-Meritt syndrome ■ Kimura's disease ■ Toxic epidermal necrolysis/Stevens-Johnson syndrome ■ Malignant atrophic papulosis ■ Cryofibrinogenemia ■ Pruritic papular eruption of HIV-infected patients **Nondermatological uses** ■ Prevention of thromboembolic strokes ■ Septic shock ■ Sickle cell disease ■ Nausea and headaches in high altitude mountain sickness ■ Acute alcoholic and non-alcoholic steatohepatitis and alcoholic liver disease

The dosages vary with variable effects and can be divided into either its effect on vascular pathology or on T cell and TNF alpha. A summary of the various indications is given above though venous ulcers and intermittent claudication probably have the best evidence for its use.

In dermatology, they have been used in various indications though the initial enthusiasm in PPD has given way to pragmatic realism. Thus, probably the drug is best used as a adjuvant or in mild cases.

Aphthous stomatitis: A RCT has found that it is useful as a adjunct but not as a first line therapy.

Degos disease: The use of the drug is based on its role in vasculitis.

Diabetic ulcers: Pentoxifylline 800 mg/d was found to be effective in improving the symptoms in patients with noninsulin-dependent diabetes mellitus. Studies show that pentoxifylline is an alternative to vascular surgery in the management of peripheral vascular disease in diabetic patients, particularly in those with chronic ulceration of the lower extremities that does not heal despite other optimal treatment regimens.

Erythema nodosum leprosum: It is probably not as effective as thalidomide but a useful adjunct.

Febrile ulceronecrotic Mucha-Habermann disease (FUMHD): These agents may be of therapeutic benefit in the treatment of FUMHD, in part by suppressing tumor necrosis factor-alpha, which we believe may mediate the disease process.

Granuloma annulare: A few reports describe its use but larger studies are awaited.

Claudication: The three drugs useful for this indication are cilostazol, naftidrofuryl oxalate and pentoxifylline.

Perniosis: Pentoxyfylline was shown to be an effective and safe drug for treatment of perniosis, and superior to oral plus topical glucocorticoids. The dosage used is 400 mg TDS for 2 weeks.

PPD: A study has found it to have a efficacy in generalized PPD in a BD dosage though it works only in the early stage.

Psoriasis (with sulfasalazine): The logic of combining the two is the concomitant action on TNF alpha. This therapy cannot be a replacement for standard therapy.

Pemphigus: It has been used an adjuvant primarily inhibiting TNF alpha but probably it is not as useful as the other immunosuppressive adjuvants used.

Sarcoidosis: The logic of using the drug is that modulate cytokines is relevant in conditions where TNF-α plays a role. The efficacy as compared to steroids is not marked.

Special Considerations

Before prescribing pentoxifylline, following parameters should be specifically considered:

- Allergic to caffeine containing products (coffee, tea, colas), pentoxifylline, theobromine, theophylline or any other drugs
- Prior medications, especially anticoagulants such as warfarin (Coumadin) and vitamins
- Kidney disease
- Pregnant, planning pregnancy or lactating
- Any surgery in the near future
- Advice to avoid driving a car or operating machinery

- Rule out recent cerebral and/or retinal hemorrhage, peptic ulcer disease.

Drug Interactions

- Previous hypersensitivity reactions to xanthine related products—caffeine, theophylline and theobromine
- High doses of trental injection have been shown, in rare cases, to intensify the hypoglycemic action of insulin and oral hypoglycemic agents
- Post-marketing cases of increased anticoagulant activity have been reported in patients concomitantly treated with pentoxifylline and anti-vitamin K. Monitoring of anti-coagulant activity in these patients is recommended when pentoxifylline is introduced or the dose is changed
- Trental 400 may potentiate the effect of antihypertensive agents and the dosage of the latter may need to be reduced
- Trental 400 should not be given concomitantly with ketorolac as there is increased risk of bleeding and/or prolongation of prothrombin time
- Concomitant administration of pentoxifylline and theophylline may increase theophylline levels in some patients. Therefore, there may be an increase in and intensification of adverse effects of theophylline
- Concomitant administration with ciprofloxacin may increase the serum concentration of pentoxifylline in some patients. Therefore, there may be an increase in and intensification of adverse reactions associated with coadministration.

Adverse Effects

Side-effects include gastrointestinal disturbances, dizziness, agitation, sleep disturbances, headache; rarely flushing, tachycardia, angina, hypotension, thrombocytopenia, intrahepatic cholestasis, hypersensitivity reactions including rash, pruritus and bronchospasm.

An overview of the side effect is given in Box 17.5 and Table 17.12.

Box 17.5: Common side effects of pentoxifylline

Digestive
- Dyspepsia, nausea and/or vomiting—<3%
- Bloating, flatus and belching—<1%

Neurologic
- Dizziness and headache—<2%
- Tremor, anxiety, and confusion—<0.3%

Cardiovascular
- Angina and chest pain—0.3%
- Mild hypotension—0.1%
- Cardiac arrhythmia and tachycardia—rarely

Table 17.12: Rare side effect of pentoxifylline

Rare	*Potentially fatal*
Jaundice, hepatitis, aplastic anemia, purpura, leukemia, thrombocytopenia, pancytopenia, urticaria, pruritus, epistaxis, laryngitis, xerostomia paresthesias, blurred vision, scotoma and conjunctivitis	Fatal hemorrhage (cerebral and gastrointestinal tract) Anaphylactoid reaction

Special Groups

- **Pregnancy:** Category C drug
- **Lactation:** Excreted in breast milk; may cause adverse effects in infant
- **Liver failure:** Dose should be reduced
- **Kidney failure:** Dose reduced in significant renal impairment
- **Children:** Safety and efficacy not established
- **Geriatric:** Use with caution, usually starting at the lower dosage range, because of the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.

FURTHER READING

1. Delanian S, Porcher R, Balla-Mekias S, Lefaix JL. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. J Clin Oncol. 2003;21(13):2545-50.
2. Inflammation and Allergy—Drug Targets, Pentoxifylline Use in Dermatology. 2012;11:422-32.
3. Jull AB, Waters J, Arroll B. Pentoxifylline for treating venous leg ulcers. Cochrane Database Syst Rev. 2002;(1):CD001733. Review.
4. Mehrotra R, Singh HP, Gupta SC, Singh M, Jain S. Pentoxifylline therapy in the management of oral submucous fibrosis. Asian Pac J Cancer Prev. 2011;12(4):971-4.
5. Sales AM, et al. Double-blind trial of the efficacy of pentoxifylline vs thalidomide for the treatment of type II reaction in leprosy. 2007;40(2):243-8.
6. Samlaska CP, Winfield EA. Pentoxifylline. J Am Acad Dermatol. 1994;30:603-21.
7. Smith RV, Waller ES, Doluisio JT, Bauza MT, Puri SK, Ho I, et al. Pharmacokinetics of orally administered pentoxifylline in humans. J Pharm Sci. 1986;75:47-52.
8. Thornhill MH, et al. Randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. Arch Dermatol. 2007;143(4):463-70.
9. Ward A, Clissold SP. Pentoxifylline: a review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. Drugs. 1987;34:50-97.

POTASSIUM IODIDE

Classification

Cation, mineral.

Mechanism of Action

- It is known to inhibit *neutrophil* chemotaxis
- It is unclear whether KI works against fungi by a fungicidal mechanism or by enhancing the body's immunologic and nonimmunologic defense mechanisms. It is used widely for *sporotrichosis* although how it acts as unclear since antifungal activity was not found in vitro against *Sporothrix schenkii*. It has also been shown to be effective in the treatment of *phycomycosis* caused by *Basidiobolus haptosporus* but again the mode of action is unclear.

Absorption and Distribution

Iodide is well absorbed throughout the gastrointestinal tract and concentrated in the thyroid, stomach, salivary glands, and breast milk. Almost 90% of the orally administered dose is excreted in the urine. Sweat, breast milk, and feces account for the remainder of the excretion. Renal clearance is 1.8 L/h/kg; approximately 100 μg of iodine is excreted in urine daily. Onset of action 24–48 h; peak level: 14 days.

Dosage

Mode of administartion: Dilute solution in a glass (8 fluid ounces) of liquid before taking; it may be taken with food, milk, or an antacid to minimize stomach upset. Do not use if solution turns brownish-yellow. If crystals form in the solution, they can be dissolved by warming the closed container in warm water.

Dose

The solution (SSKI) has about *30 mg/drop* iodide (1 g/mL). If droppers are calibrated then, **0.3 mL is equal to 300 mg and 0.6 mL is equal to 600 mg** (0.3 mL = 10 drops).

Adult dosage: 300 mg TDS.

Children: 150 mg TDS.

For treatment of *inflammatory dermatoses* an oral dose of 300 mg (approximately 10 drops of SSKI) 3 times daily, followed by weekly increase till it is tolerated is recommended.

The dose used for *mycoses* is often higher, beginning at 600 mg orally 3 times daily and often increased to 6 g (approximately 127 drops of SSKI) daily if tolerated. Progress

is slow and treatment should be continued until 4 weeks after apparent cure.

Uses

SSKI is not FDA-approved for any cutaneous disease. The off label uses are listed below:

- **Erythema nodosum:** 360–900 mg daily (Duration: 2 days to 2 weeks)
- Behçet's syndrome, erythema multiforme, and Sweet's syndrome: 300 mg 3 times daily
- **Pyoderma gangrenosum:** 300 mg 3 times daily. (2–4 months)
- **Wegener's granulomatosis:** Steroids with 800 mg of KI daily
- **Sporotrichosis:** 500–1500 mg daily divided into three doses gradually increase to 4,000–6,000 mg daily and then continue for approximately 6–10 weeks. In children a single daily dosage (150–160 mg/kg) is used. Yamada K et al. have found SSKI to be effective in sporotrichosis with a cure rate of 94.7%
- **Entomophthoromycosis:** The starting dose is 1 mL three times daily, and this is increased up to 4–6 mL three times daily as tolerated. Treatment must be continued for at least 1 month after the lesions have disappeared. Ramesh et al. in a study used the drug in combination with itraconazole to hasten the response, with gratifying results
- **Chromoblastomycosis:** Though not the first line therapy it can be used though a longer period is required for a response. The therapeutic response to itraconazole and terbinafine is thought to be better if the causative agent is *C. carrionii*. While in case of *F. pedrosoi*, potassium iodide alone can be effective (Chandran V et al.).

Drug Interaction

Potassium iodide increases effects/toxicity of antithyroid drugs (methimazole, propylthiouracil), potassium-sparing diuretics, ACE inhibitors, potassium supplements.

Special Considerations

Contraindication

- Hypersensitivity to iodine, hyperkalemia, tuberculosis, active bronchitis, pulmonary edema, GI obstruction, renal failure.
- Discontinue use and report if fever, skin rash, epigastric pain, or joint swelling occur.
- May contain sulfite. Warn patient if allergic.

- May downregulate thyroid hormone production, leading to hypothyroidism (Appendix).
- Use iodides with caution in patients with untreated Hashimoto's thyroiditis, in iodide-deficient patients, in children with cystic fibrosis, and in euthyroid patients with a history postpartum thyroiditis, subacute thyroiditis, amiodarone or lithium-induced thyroid disease, or previously treated Graves' disease because they can be particularly sensitive to iodide-induced hypothyroidism. In all patients one should look for symptoms of hypothyroidism: weight gain, lethargy, hair loss, hirsuitism.
- Look for signs and symptoms of iodism: Metallic taste, skin lesions, GI upset.
- Monitor serum potassium level periodically.

Side Effects

Common: GI upset, acne, iodism (metallic taste, GI upset, soreness of teeth and gums, coryza, frontal headaches, painful swelling of salivary glands, diarrhea, acneiform skin eruptions, and erythema of face and chest).

Rare: Urticaria, angioedema, hypothyroidism with goiter.

Poisoning: It causes corrosive effects on the gastrointestinal tract; a disagreeable metallic taste, vomiting, abdominal pain, and bloody diarrhea occur. Systemic toxicity may lead to shock, tachycardia, hypotension, fever, metabolic acidosis and renal impairment. Death may be due to circulatory failure, edema of the epiglottis resulting in asphyxia, aspiration pneumonia, or pulmonary edema. Esophageal stricture may occur if the patient survives the acute stage.

Victims of acute poisoning have been given copious draughts of milk or starch mucilage; lavage should probably not be attempted, and certainly not unless the ingested iodine was in sufficiently dilute form not to produce gastrointestinal corrosion. Other possible oral treatments include activated charcoal or sodium thiosulfate solution (usually as a 1% solution) to reduce iodine to the less toxic iodides.

Monitoring

- Signs and symptoms of **iodism**: Metallic taste, skin lesions, GI upset.
- Symptoms of **hypothyroidism**: Weight gain, lethargy, hair loss, hirsuitism.
- Monitor serum potassium level periodically.
- Monitor thyroid function tests every 6–12 months during long-term use in patients with family history of thyroid disease or goiter.
- Monitor serum potassium frequently in patients who are taking other drugs that might affect serum potassium (e.g. diuretics).

Special Groups

- **Kidney disease:** Decrease dose.
- **Liver disease:** None.
- **Elderly:** None.
- **Pediatric:** See above.
- **Pregnancy:** Category D.
- **Lactation:** Appears in breast milk. The BNFC considers treatment with iodine or iodides to be a contraindication to breastfeeding. As considered compatible by American Academy of Pediatrics.

Appendix

The normal daily requirement of iodine ranges from 100 to 300 micrograms. When the daily dose exceeds 2 mg there is an initial rise in thyroid hormone production, but at still higher doses, production decreases (the **Wolff-Chaikoff effect**). It is normally transient, adaptation occurring on repeated dosage. In certain individuals a lack of adaptation produces a chronic inhibition of thyroid hormone synthesis leading to goiter and *hypothyroidism*.

Excess iodine may also induce *hyperthyroidism* (the **Iod-Basedow or Jod-Basedow phenomenon**). Iodine-induced hyperthyroidism has been associated and occurs after 1 to 3 years after supplementation begins, with the incidence returning to normal within 3 to 10 years despite continued iodine exposure.

BIBLIOGRAPHY

1. Arthur JR, Beckett GJ. Thyroid function. Br Med Bull. 1999;55:658-68.
2. Chandran V, Sadanandan SM, Sobhanakumari K. Chromoblastomycosis in Kerala, India. Indian J Dermatol Venereol Leprol. 2012;78(6):728-33.
3. Kamalam A, Thambiah AS. Muscle invasion by Basidiobolus haptosporus. Sabouraudia. 1984;22:273-7.
4. Kelly S, et al. Subcutaneous phycomycosis in Sierra Leone. Trans R Soc Trop Med Hyg. 1980;74:396-7.
5. Ramesh V, Ramam M, Capoor MR, Sugandhan S, Dhawan J, Khanna G. Subcutaneous zygomycosis: report of 10 cases from two institutions in North India. J Eur Acad Dermatol Venereol. 2010;24(10):1220-5.
6. WHO. Iodine. In trace elements in human nutrition and health. Geneva: WHO; 1996. pp. 49-71.
7. WHO. WHO model formulary. Geneva: WHO; 2004.
8. Yamada K, Zaitz C, Framil VM, Muramatu LH. Cutaneous sporotrichosis treatment with potassium iodide: a 24-year experience in São Paulo State, Brazil. Rev Inst Med Trop Sao Paulo. 2011;53(2):89-93. PubMed PMID: 21537756.
9. Yangco BG, et al. In vitro susceptibilities of human and wildtype isolates of Basidiobolus and Conidiobolus species. Antimicrob Agents Chemother. 1984;25:413-6.

SULFASALAZINE (AZO COMPOUNDS)

Drugs that contain 5-aminosalicylic acid (5-ASA) have been used successfully for decades in the treatment of inflammatory bowel diseases. 5-ASA differs from salicylic acid only by the addition of an amino group at the 5 (meta) position. Aminosalicylates are believed to work topically (not systemically) in areas of diseased gastrointestinal mucosa. Up to 80% of unformulated, aqueous 5-ASA is absorbed from the small intestine and does not reach the distal small bowel or colon in appreciable quantities. To overcome the rapid absorption of 5-ASA from the proximal small intestine, a number of formulations have been designed to deliver 5-ASA to various distal segments of the small bowel or the colon. These include *sulfasalazine, olsalazine, balsalazide*, and various forms of mesalamine.

Sulfasalazine, balsalazide, and olsalazine contain 5-ASA bound by an azo (N=N) bond to an inert compound or to another 5-ASA molecule. In sulfasalazine, 5-ASA is bound to sulfapyridine; in balsalazide, 5-ASA is bound to 4-aminobenzoyl-alanine; and in olsalazine, two 5-ASA molecules are bound together. The azo structure markedly reduces absorption of the parent drug from the small intestine. In the terminal ileum and colon, resident bacteria cleave the azo bond by means of an azoreductase enzyme, releasing the active 5-ASA. Consequently, high concentrations of active drug are made available in the terminal ileum or colon.

SULFASALAZINE (SAAZ DS 100 mg SAAZ 500 mg)

Sulfasalazine (SSZ) was the first agent to be synthesized specifically for rheumatoid arthritis in 1938, by Professor Nanna Svartz of Stockholm, in collaboration with the Swedish pharmaceutical company Pharmacia. The prevailing notion at that time was that RA was caused by infection, and SSZ was designed with both anti-inflammatory and antibacterial properties.

Classification

Anti-inflammatory agent/immunomodulator.

Mechanism of Action

The active moiety of SSZ is controversial. The parent compound, SSZ, seems to have the most biologic activity compared with sulfapyridine and 5-ASA. But some studies (Taggart A) have shown that both SSZ and sulfapyridine both seem to have a role in the therapeutic efficacy seen in RA. Others claim that the active moiety is 5-ASA. In essence the original compound SSZ works better than ASA.

There are three main mechanisms of this drug:

1. Antinflammatory action
2. Immunomodulatory action
3. Inhibition of endothelial cell function.

a. SSZ has a significant **immunomodulatory** effect and acts on T and B lymphocytes, granulocytes, macrophages, endothelial cells, and a number of mediators produced by these cells. SSZ also has been shown to possess multiple immunomodulatory properties. In vitro, SSZ inhibits T cell proliferation, natural killer cell activity, and B cell activation, with resultant decline in immunoglobulin synthesis and RF production. In all of these systems, sulfapyridine and 5-ASA are ***less*** active than SSZ. Cytokine profiles are also altered by SSZ, resulting in inhibition of the T cell cytokines IL-2 and γ-interferon, and the monocyte/macrophage cytokines IL-1, TNF, and IL-6.

b. SSZ has been demonstrated in vitro to possess multiple **anti-inflammatory** properties. First, SSZ weakly inhibits the proinflammatory effects of the *arachidonic acid* cascade, with a slight inhibitory effect on prostaglandin E_2 synthetase activity, as well as lipoxygenase products. SSZ also downregulates neutrophil chemotaxis, migration, and proteolytic enzyme production and degranulation, and has been shown to inhibit *neutrophil* activation by decreasing the flux of second messengers involved in intracellular signal transduction.

   SSZ inhibits *folate-dependent enzymes*, including ATIC and dihydrofolate reductase, resulting in increased adenosine release. This action is *similar to MTX* and thus it modulates inflammation via increased adenosine release (Cronstein B). This effect seems to be due solely to **SSZ** because sulfapyridine and 5-ASA are inactive. SSZ is a more potent inhibitor of ATIC than MTX (Weinblatt M). The immunomodulatory effect of SSZ is more than sulfapyridine and 5-ASA.

   Other potential mechanisms of action of the 5-ASA drugs relate to their ability to interfere with the production of *inflammatory cytokines*. 5-ASA inhibits the activity of nuclear factor-KB (NF-KB), an important transcription factor for proinflammatory cytokines. 5-ASA may also inhibit cellular functions of natural killer cells, mucosal lymphocytes, and macrophages, and it may scavenge reactive oxygen metabolites.

c. One potential site of action for SSZ that may explain its systemic action despite its low serum levels is the mucosa-associated lymphoid tissue (MALT) in the small bowel (Smedegard G). In the gut lumen, the therapeutic concentration of SSZ is at least two times greater than in

the serum, and drug concentration in the surrounding mucosal tissue is likely also high. The gut immune system is extensive, and active communication with the rest of the body occurs via migration and recirculation of activated lymphocytes. It has been shown that treatment with SSZ has been shown to decrease circulating IgA-producing cells and serum levels of IgA, correlating with disease improvement.

Pharmacology

Sulfasalazine is a conjugate of sulfapyridine linked to mesalamine by an azo bond. This bond is cleaved by colonic bacteria to sulfapyridine and mesalamine, the active moiety. In dermatological indications, probably the sulfonamide moiety may also play a role in its effect in conditions like lichen planus and dermatitis herpetiformis.

Absorption and Distribution

Onset and duration: Maximum effect is in 1–2 weeks; duration is 10 ± 2 hours after an oral dose. The steady-state serum concentration of SSZ is 5 μg/mL after an oral dose of 2 g/day.

The bioavailability of standard SSZ is similar to that of enteric-coated SSZ. Administration of SSZ with food decreases the blood concentration of both SSZ and sulfapyridine.

Anti-inflammatory action	*Reduced* ■ TNF-α expression in macrophages IL-1-α production and activity IL-2 production IL-6 production ■ Arachidonic acid metabolism: Leukotriene B 4 ,5-HETE, thromboxane B 2, and secretory phospholipase A ■ TNF-alpha expression in macrophages ■ Granulocyte activation, phagocytosis, superoxide production, motility, chemotaxis, and endothelial cell damage ■ Histamine and TNF-alpha release from mast cells
Immunomodulatory effect	■ T-cell proliferation and mitogen-induced transformation ■ Presentation of processed antigen to T cells ■ T-cell and natural killer cell cytotoxic activity ■ B-cell activity and immunoglobulin production and secretion

Fate: Sulfasalazine is 25–30% absorbed from the small intestine, but the absorbed drug is almost completely secreted unchanged in the bile. It is then metabolized in the large bowel by intestinal bacteria to *sulfapyridine* and *mesalamine*. Most of the sulfapyridine is *absorbed* from the bowel. Sulfapyridine is metabolized by acetylation to acetylsulfapyridine. Acetylsulfapyridine concentration depends on acetylator phenotype: slow acetylators have higher serum sulfapyridine concentrations, fast acetylators have lower serum sulfapyridine concentrations.

After an oral dose of sulfasalazine, about 91% of sulfapyridine is recovered in the urine in 3 days as sulfapyridine, its metabolites, and small amounts of sulfasalazine. Most of the 5-ASA (80% to 90%) remains in the bowel and is is eliminated primarily in the feces; only a small portion is absorbed, metabolized, and excreted in the urine as N-acetylmesalamine.

The half-life of SSZ is 6–17 hours with upper range values reflecting older patients, and the half-life of sulfapyridine is 8–21 hours with upper range values reflecting slow acetylators.

Usage Guidelines

Initial: 1–2 g daily. Increase to 3–4 g daily if needed. Maintenance: 2 g/d.

To minimize side effects, most clinicians will prescribe 500 mg daily and will escalate the dose by 500 mg/d every week to the standard dose of 1,500–3,000 mg divided daily.

The only obvious advantage of mesalamine over sulfasalazine is that the former has less adverse effects. However, sulfasalazine may be some-what more potent and is much less costly than the newer mesalamine compounds.

Clinical Use in Dermatology

Clinical uses of sulfasalazine are given in Box 17.6.

Box 17.6: Uses of sulfasalazine

FDA approved	■ Ulcerative colitis ■ Rheumatoid arthritis
Off label	■ Alopecia areata ■ DH ■ Eosinophilic fasciitis ■ Lichen planus ■ Linear IgA disease ■ Neutrophilic disorders ■ Pemphigus ■ Psoriasis ■ Subcorneal pustulat dermatoses ■ Urticaria

Alopecia Areata

The use of an adjuvant drug in alopecia areata as a disease-modifying agent is based largely on its immunomodulatory

effect, but as most studies are uncontrolled without a placebo arm a definite conclusion is difficult to draw. Rashidi T et al. used the drug in 39 patients with persistent alopecia areata in a dose of 3 g for 6 months, and found a good response in 10 of the 39 patients (25.6%). Ellis CN et al. found a good response in 23% of cases with severe alopecia areata. The agent can be used with steroids and is a good option for maintenance.

Based on the authors' experience, a starting doses of 500 mg/day were suggested, increasing the dose steadily to achieve a dose of 3 g/day for at least 4 months. For an adequate trial, non-responding patients should receive 4 g/day for at least 3 additional months. Bakar et al. used sulfasalazine in combination with oral corticosteroids for 2 to 6 months followed by sulfasalazine alone for 4–12 months while steroids were tapered.

Discoid Lupus Erythematosus

Though a few discoid lupus erythematosus (DLE) patients have been treated with the drug sometimes successfully, the potentially photosensitizing nature of the drug makes its uses limited to patients with resistant disease that has not responded to more conventional therapy.

Lichen Planus (Omidian M)

A total of 52 patients with generalized lichen planus (LP) were analyzed in a double-blind, randomized, placebo-controlled, prospective study. Sulfasalazine was given in a maximum dose of 2.5 g/day. After 6 weeks of treatment, 82.6% of patients improved in the treatment group. Apart from minor GIT side effects it was found to be a safe drug.

Bauzá A et al. used sulfasalazine in an initial doses of 1.5 g/day, increasing by 0.5 g/week to 3 g/day for 4–16 weeks. Complete responses were observed in 13 patients and partial responses in seven patients.

The varied imunomodulatory and inflammatory action of SSZ may explain the favorable results though we feel that the efficacy may be comparable to dapsone, consequent to the sulfapyridine moiety.

Pemphigus

A study (el-Darouti M) used a combination of both sulfasalazine (SSZ) and pentoxifylline (PTX) (low-cost anti-TNF drugs) as an adjuvant therapy for pemphigus vulgaris (PV). This was found to induce a faster and more significant decrease in the serum level of TNF-alpha, and this decrease was associated with rapid clinical improvement. In our opinion with the major role of B cells in pemphigus, the effect of SSZ is marginal.

Psoriasis

Based on its anti-TNF action it has been used in psoriasis but the effect is delayed and probably methotrexate is a better option. A study found (Gupta AK) a marked improvement in 41% of cases but the side effects are an issue with the drug.

Urticaria

McGirt LY et al. reported a study on 19 patients with antihistamine-unresponsive CIU who were treated with sulfasalazine between 2002 and 2005. Of these 14 patients (74%) reported significant improvement. Of the 13 patients who required systemic steroids to control their urticaria, all were able to reduce or discontinue steroid use during sulfasalazine therapy.

Dermatitis Herpetiformis (Willsteed E)

Dermatitis herpetiformis that is not controlled using dapsone and a gluten-free diet presents a therapeutic challenge where sulfasalazine can be used. This is based on the fact that sulfasalazine is metabolized variably to sulfapyridine, a sulfonamide known to be an effective therapy for dermatitis herpetiformis.

Monitoring

CBC with differential, liver function tests: These should be carried out before starting therapy and periodically during the first 3 months. These tests are recommended monthly during the next 3 months and afterward every 3 months.

	Baseline	*Follow Up*
CBC, LFT, KFT	Yes	<3 months of drug therapy (every 2–4 week) 3–6 months of therapy (every 8–12 week)

- Periodic serum BUN and creatinine, urinalysis with microscopic examination
- Signs of hemolytic anemia in patients with G6PD deficiency
- Serum sulfapyridine levels. Level of this metabolite >50 μg/mL is associated with an increase in adverse reactions.

Special Considerations

- Hypersensitivity to sulfasalazine, sulfonamides (sulfa drugs, thiazides, oral hypoglycemic drugs), salicylates; intestinal or urinary obstruction, porphyria

- Drink large amounts of fluid (2.5–3 L) per day and maintain adequate fluid intake after discontinuing the drug
- To minimize possible photosensitivity reaction, apply adequate sunscreen and use proper covering when exposed to strong sunlight
- Report to treating physician if you experience the following symptoms: sore throat, fever, jaundice
- Do not take antacids with sulfasalazine
- Be aware that your urine and skin may turn orange-yellow and that soft contact lenses may be permanently stained
- Decreased folate absorption can came anemia, so folic acid supplementation is recommended
- In men, sulfasalazine frequently leads to a reversible decrease in sperm count and abnormal sperm morphology

Drug Interactions

- Sulfasalazine decreases effects/toxicity of digoxin, folic acid
- Ferrous sulfate decreases absorption of sulfasalazine
- It should not be combined with methotrexate, sulfonylureas and warfarin.

Adverse Effects

The most common side effects include gastrointestinal effects, headache, dizziness, and rash.

Gastrointestinal and Hepatic

Nausea and upper abdominal discomfort are the most common adverse effects with SSZ. Nausea frequently occurs with central nervous system (CNS) effects, including dizziness and headache. Nausea is more common in patients who achieve higher sulfapyridine levels and in slow acetylators. Diarrhea can occur, usually in the first several months. Gastrointestinal effects may be decreased by administration of enteric-coated preparations.

Elevations in liver transaminases may occur and are usually transient. However, they may be accompanied by fever, rash, hepatomegaly, and possibly eosinophilia.

Hematologic

Hematologic disturbances are rare, occurring in less than 3% of patients; they usually occur within the first **3 months**. The most common abnormalities include leukopenia that usually reverses upon cessation of the drug, although some cases of fatal agranulocytosis have been reported, warranting continued surveillance. Macrocytosis and hemolysis have

been reported with SSZ; its use should be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Folic acid supplementation may be reasonable because of SSZ effects on folate metabolism. Thrombocytopenia is rare.

Dermatologic

Rashes occur in less than 5% of patients, usually in the first 3 months of therapy. Rarely erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome have been reported.

Patients who develop a rash while on SSZ should be cautioned to avoid other sulfonamide-containing agents, such as thiazide diuretics, celecoxib, and antibiotics.

Pulmonary

Pulmonary toxicity from SSZ is rare and manifests as reversible infiltrates with peripheral eosinophilia, cough, dyspnea, fever, and weight loss. Pathology reveals an eosinophilic pneumonia with interstitial infiltrates with or without fibrosis. Most cases resolve with discontinuation of SSZ with or without corticosteroids.

Miscellaneous

Minor reactions, such as irritability, anxiety, headache, and difficulty sleeping, may occur. Rare cases of drug-induced lupus, hypogammaglobulinemia, and aseptic meningitis have been reported. Advise patients that they may develop orange discoloration of their urine, sweat, and tears.

Special Groups

- **Pregnancy:** FDA category B, C
- **Children:** In pediatric patients, SSZ is dosed initially at 10 to 12.5 mg/kg/day, with a weekly dose increase of 50 mg/kg/day in two divided doses, until a maintenance dose of 2 g/day is achieved. This can be escalated to 3 g/day if no response is seen with lower doses
- **Lactation:** Use with caution
- **Renal:** Minor modifications may be needed
- **Hepatic:** Safe
- **Elderly:** Dosing recommendations for SSZ in geriatric patients are the same as for the general adult population. Studies of pharmacokinetics in the elderly have shown that although the elimination half-life is longer, it is primarily dependent on acetylator phenotype; however, the dose should be reduced for renal insufficiency.

MESALAMINE [(5-AMINOSALICYLIC ACID (5-ASA)]

This is thought to be the active moiety of sulfasalazine. The mechanism of action of mesalamine in inflammatory bowel disease is unknown, but mesalamine seems to inhibit cyclooxygenase and 5-lipoxygenase, thereby downregulating the production of inflammatory prostaglandins in the colon. An immunomodulatory response also might occur because mesalamine inhibits and prevents the secretion of antibodies and lymphocytes during active disease. Mesalamine inhibits macrophage and neutrophil chemotaxis, reduces intestinal mononuclear cell production of immunoglobulin A and G antibodies, and is a scavenger of oxygen-derived free radicals, which are increased during active inflammatory bowel disease.

These appears to be no clinically important advantage of one oral mesalamine product over the other.

A mesalamine preparation might be beneficial in the sulfasalazine-sensitive patient and men who wish to have children because mesalamine does not alter sperm count, morphology, or motility.

BIBLIOGRAPHY

Books

1. Cannella AC, O'Dell JR. Methotrexate, Leflunomide, Sulfasalazine, Hydroxychloroquine, and Combination Therapies. Kelly's Textbook of Rheumatology, 8th edn, Philadelphia: Saunders Elsevier; 2008. pp.2052-110.
2. Katzung BG. Basic and Clinical Pharmacology. In: Katzung BG, Masters SB, Trevor AJ (Eds). Chapter 62. 11th edn. Drugs Used in the Treatment of Gastrointestinal Diseases. Anesth Prog. 2012;59(4):159-69.

Journals

1. Bakar O, Gurbuz O. Is there a role for sulfasalazine in the treatment of alopecia areata? J Am Acad Dermatol. 2007;57(4):703-6. Epub 2007 Jul 3.
2. Bauzá A, España A, Gil P, Lloret P, Vázquez-Doval FJ. Successful treatment of lichen planus with sulfasalazine in 20 patients. Int J Dermatol. 2005;44(2):158-62.
3. Cronstein B. The antirheumatic agents sulphasalazine and methotrexate share an anti-inflammatory mechanism of action. Br J Rheumatol. 1995;34(Suppl 2):30-32.
4. Delaporte E, Catteau B, Sabbagh N, Gosselin P, Breuillard F, Doutre MS, et al. Treatment of discoid lupus erythematosus with sulfasalazine: 11 cases. Ann Dermatol Venereol. 1997;124:151-6.
5. el-Darouti M, Marzouk S, Abdel Hay R, el-Tawdy A, Fawzy M, Leheta T, et al. The use of sulfasalazine and pentoxifylline (low-cost antitumour necrosis factor drugs) as adjuvant therapy for the treatment of pemphigus vulgaris: a comparative study. Br J Dermatol. 2009;161(2):313-9.

6. Ellis CN, Brown MF, Voorhees JJ. Sulfasalazine for alopecia areata. J Am Acad Dermatol. 2002;46(4):541-4.
7. Gupta AK, Ellis CN, Siegel MT, Duell EA, Griffiths CE, Hamilton TA, et al. Sulfasalzine improves psoriasis. A double-blind analysis. Arch Dermatol. 1990;126:487-93.
8. McGirt LY, Vasagar K, Gober LM, Saini SS, Beck LA. Successful treatment of recalcitrant chronic idiopathic urticaria with sulfasalazine. Arch Dermatol. 2006;142(10):1337-42.
9. Omidian M, Ayoobi A, Mapar MA, Feily A, Cheraghian B. Efficacy of sulfasalazine in the treatment of generalized lichen planus: randomized double-blinded clinical trial on 52 patients. J Eur Acad Dermatol Venereol. 2010;24(9):1051-4.
10. Rashidi T, Mahd AA. Treatment of persistent alopecia areata with sulfasalazine. Int J Dermatol. 2008;47(8):850-2.
11. Smedegard G, Bjork J. Sulphasalazine: Mechanism of action in rheumatoid arthritis. Br J Rheumatol. 1995;34(Suppl 2):7-15.
12. Taggart A, Gardiner P, McEvoy F, Hopkins R, Bird H. Which is the active moiety of sulfasalazine in ankylosing spondylitis? A randomized-controlled study. Arthritis Rheum. 1996;39(8):1400-5.

TRANEXAMIC ACID

Trans-4-aminomethyl cyclohexane carboxylic acid.

Mechanism of Action

We will largely focus on the mode of action in melasma:

1. This drug is one of the plasmin inhibitors and can prevent *UV-induced plasmin activity* in keratinocytes by preventing the binding of plasminogen to the keratinocytes, which ultimately results in less free arachidonic acids and diminished ability to produce prostaglandins, and decreases melanocyte tyrosinase activity.
2. It is well known that plasmin plays an important role in angiogenesis. Plasmin converts extracellular matrix-bound VEGF into freely diffusible forms. Tranexamic acid (TXA), a plasmin inhibitor, suppresses angiogenesis, and also inhibits neovascularization induced by basic fibroblast growth factor (bFGF). Thus, *reduced erythema* and *vessel numbers* might be the results of TXA antiangiogenic action.
3. Pigmentation of melasma is confined to the epidermis,but dermal factors are suspected to be the main culprits behind the recurrent and refractory nature of this disorder. TXA has been shown to reverse melasma-related dermal changes, such as vessel proliferation and increased mast cell numbers. Although it remains unknown which dermal factors are the main causes of melasma, TXA may act by reducing dermal factors related to melasma and this might explain the differential effects of TXA on lesional skin.

Absorption and Distribution

Pharmacodynamic Properties

Tranexamic acid is an antifibrinolytic compound which is a potent competitive inhibitor of the activation of plasminogen to plasmin. At much higher concentrations it is a non-competitive inhibitor of plasmin. The inhibitory effect of tranexamic acid in plasminogen activation by urokinase has been reported to be 6–100 times and by streptokinase 6–40 times greater than that of aminocaproic acid. The antifibrinolytic activity of tranexamic acid is approximately ten times greater than that of aminocaproic acid.

Pharmacokinetic Properties

Following oral administration, 1.13% and 39% of the administered dose were recovered after 3 and 24 hours respectively. Tranexamic acid administered parenterally is distributed in a two compartment model. Tranexamic acid crosses the placenta, and may reach one hundredth of the serum peak concentration in the milk of lactating women. Tranexamic acid crosses the blood–brain barrier.

Following intravenous administration, the biological half-life of tranexamic acid has been determined to be 1.9 hours and 2.7 hours.

Uses (Approved/Unapproved)

FDA Approved

Reduction of heavy menstrual bleeding over several cycles in women with regular, 21–35 day cycles with no more than 3 days individual variability in cycle duration.

The recommended dosage is 2 tablets 3 times daily for as long as needed, but for a maximum of 4 days. If there is very heavy menstrual bleeding, the dosage may be increased. A total dose of 4 g daily (8 tablets) should not be exceeded.

Unapproved

Melasma: This is a off label use and the dose varies from **250 mg TDS to 500 mg TDS**.

Drug Interaction

Contraindications

Mild-to-moderate renal insufficiency:

- Hypersensitivity to tranexamic acid or any of the excipients
- Active thromboembolic disease
- A previous thromboembolic event and a family history of thrombophilia
- Hematuria
- Irregular menstrual bleeding

- Patients being administered warfarin or other anticoagulants
- Patients taking oral contraceptives.

Special Considerations

The following patients should consult their doctor prior to initiating treatment:

- If menstrual bleeding is not reduced after three menstrual cycles
- Women over the age of 45 years
- Patients who are obese and diabetic
- Those with polycystic ovary syndrome or a history of endometrial cancer in a first-degree relative
- Women receiving unopposed estrogen or tamoxifen
- Patients who experience visual disturbance should be withdrawn from treatment.

Side Effects

Common

Gastrointestinal discomfort is the most common undesirable effect that may occur but disappear when the dosage is reduced.

Frequency of undesirable effects at a dose of 4 g/day.

Gastrointestinal disorders	
Common (≥1/100 to <1/10):	Nausea, vomiting diarrhea
Skin and subcutaneous tissue disorders	
Uncommon (≥1/1,000 to <1/100)	Allergic skin reactions

Other adverse events have been reported with the use of tranexamic acid but the frequency of the reports cannot be estimated from the available data: thromboembolic events, retinal/artery occlusion and impaired color vision or other visual disturbances.

THALIDOMIDE (Redemide, Thalix)[3]

Classification

Its a lipophilic, non-polar piperidinedione, two-ring structure: left-sided phthalimide, right-sided glutarimide.

Metabolism

Peak plasma levels are attained 2–6 hours after ingestion and absorption is not affected by food intake. The half-life

of thalidomide is 9 hours. Although the major degradative pathway is non-enzymatic hydrolysis, the drug is also metabolized by the cytochrone P450 (CYP) enzymes. The precise method of excretion is not known, but it is non-renal.

Mechanism of Action

- *Immunomodulatory:* Decreases the T-helper (CD4) to T-suppressor (CD8) cell ratio in patients with erythema nodosum leprosum by decreasing the number of T-helper cells and increasing the number of T-suppressor cells.
- Thalidomide, in vitro, converts lymphocyte response from *Th1 to Th2*.
- Specific inhibition of *TNF-α release*.

Pharmacology

Dosage Principles

Thalidomide is available in 50, 100, 150 and 200 mg capsules. Thalidomide should be taken until signs and symptoms of active disease have decreased, usually by 2–8 weeks. The dose should be tapered by **50 mg every 2–4 weeks**. If maintenance of the therapy is necessary, the minimal effective dose should be given and a further taper should be attempted every 3–6 months thereafter. As there is a definite risk of neuropathy the drug should be tapered down as soon as possible.

Drug Interactions

Drugs that cause sedation, neuropathy, or decrease the efficacy of oral contraceptives should be used carefully if thalidomide is added to the patient's regimen. It enhances activity of alcohol, barbiturates, chlorpromazine and reserpine; raises serum levels of acetaminophen and increases its toxicity. It antagonizes acetylcholine, histamine, prostaglandins and serotonin *in vitro*.

Clinical Use in Dermatology

Thalidomide should be used only in severe disabling conditions and only after other treatment options have failed.

1. **Erythema nodosum leprosum (ENL):** 100 to 400 mg. The optimal initial effective dosage is 300–400 mg/day, with a maintenance dosage of 50–100 mg/day. Almost 50% of patients require treatment for 6 years or more
2. **Recurrent aphthous stomatitis:** Two dosage regimens have been tried 100 mg/day or 400 mg daily tapered to 200 mg daily. In about 44% of cases with severe aphthosis, a complete remission can be achieved. But as the disease is recurrent permanent cure is difficult to achieve.

3. **HIV-associated oral aphthae and neutrophilic dermatoses**:100 mg/d.
4. **Discoid lupus erythematosus (DLE):** 50–100 mg/day is subsequently tapered to 25–50 mg/day.
5. **Prurigo nodularis (PN):** 50–300 mg daily.
6. **Lichen planus (LP):** Thalidomide can be a valuable treatment of LP; however, it is reserved only for severe, unresponsive disease. Dosages of 100 mg daily initially have been effective, and clinical response frequently occurs after 3–4 months or more of treatment.
7. **Sarcoidosis:** The dose has ranged from 50 mg to more than 400 mg daily, and dosages for long-term maintenance have ranged from 50 mg every 15 days to 100 mg every other day.

Monitoring

Pregnancy test 2 weeks prior to starting, along with appropriate contraceptive advice. Baseline *nerve conduction studies* (NCS) are recommended to monitor for the subclinical development of peripheral neuropathy. Sensory nerve action potential amplitudes need to be measured in at least three peripheral nerves, usually the median, radial, or sural. A fall from baseline values of more than 40% on repeat testing should lead to discontinuation of the treatment, and a decrease of 30–40% should lead to a review of its use. Follow-up testing should be done every 6 months or 10 g cumulative dose.

Special Considerations

Thalidomide distributes extensively in the body and has been found in semen, making it necessary for male patients taking the medication to wear condoms even if they have had a vasectomy; their female partners are also advised to use an additional form of birth control.

Drug Interactions

Thalidomide may amplify the sedative effects of alcohol, barbiturates, chlorpromazine and reserpine.

Any drug that significantly induces the CYP3A4 enzymes may decrease the effectiveness of hormonal contraception, increasing the potential of pregnancy and, thus, teratogenicity.

Adverse Effects

Common: Sedation, Constipation, Teratogenecity (phocomelia, Amelia)

Nerve damage (primarily sensory neuropathy) can develop and is more common with long-term therapy. A significant

correlation between neuropathy and cumulative doses for patients receiving more than **20 g** of thalidomide has been noted. They also found that the symptoms were rapidly reversible if use of the drug was discontinued at the first sign of a problem.

Dose modifications due to peripheral neuropathy are described in Table 17.13.

Table 17.13: Recommended dose modifications for thalidomide Celgene-related neuropathy

Severity of neuropathy	*Modification of dose and regimen*
Grade 1 (paresthesia, weakness and/or loss of reflexes) with no loss of function	Continue to monitor the patient with clinical examination. Consider reducing dose if symptoms worsen. However, dose reduction is not necessarily followed by improvement of symptoms
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose or interrupt treatment and continue to monitor the patient with clinical and neurological examination. If no improvement or continued worsening of the neuropathy, discontinue treatment. If the neuropathy resolves to grade 1 or better, the treatment may be restarted, if the benefit/risk is favorable
Grade 3 (interfering with activities of daily living)	Discontinue treatment
Grade 4 (neuropathy which is disabling)	Discontinue treatment

Amenorrhea and primary ovarian failure may occur.

Rare: Myocardial infarction, severe leukopenia, exfoliative erythroderma and TEN Peripheral edema can develop occasionally. Vascular thromboses is unusual unless the patient is receiving concomitant corticosteroids.

Other side effects: Brittle fingernails, xerosis, pruritus and red palms, urticaria and skin rash.

Special Groups

Females

Teratogenic Effects

Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects. Thalidomide must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Thalidomide Celgene Pregnancy Prevention Program are met. The conditions of the Thalidomide Celgene

Pregnancy Prevention Program must be fulfilled for **all male and female patients**.

Criteria for Women of Non-childbearing Potential

A female patient or a female partner of a male patient is considered to have child-bearing potential unless she meets at least one of the following criteria:

- Age ≥50 years and naturally amenorrheic for ≥1 year
- Premature ovarian failure confirmed by a specialist gynecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner's syndrome, uterine agenesis.

Counseling

For women of childbearing potential, thalidomide is contraindicated unless all of the following conditions are met:

- She understands the teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence the treatment as soon as thalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks
- She acknowledges that she understands the hazards and necessary precautions associated with the use of thalidomide.

As thalidomide is found in *semen, male* patients taking thalidomide must meet the following conditions:

- Understand the teratogenic risk if engaged in sexual activity with a pregnant woman
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception.

The prescriber must ensure that:

- The patient complies with the conditions of the Thalidomide Celgene Pregnancy Prevention Program

- The patient confirms that he (she) understand the aforementioned conditions.

Contraception

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and during 4 weeks after thalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred preferably to an appropriately trained healthcare professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of effective methods of contraception:

- Subcutaneous hormonal implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilization
- Sexual intercourse with a vasectomized male partner only; vasectomy must be confirmed by two negative semen analyzes
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel).

Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence.

Prior to Starting Treatment

A medically supervised pregnancy test should be performed during the consultation, when thalidomide is prescribed or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with thalidomide.

Follow-up and End of Treatment

A medically supervised pregnancy test should be repeated every *4 weeks*, including *4 weeks* after the end of treatment. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men

As thalidomide is found in semen, male patients must use *condoms* during treatment and for **1 week** *after* dose inter-

ruption and/or cessation of treatment if their partner is pregnant or is of childbearing potential not using effective contraception.

Elderly Population

No specific dose adjustments are recommended for the elderly.

Patients with Renal or Hepatic Impairment

Thalidomide has not formally been studied in patients with impaired renal or hepatic function. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions.

Thalidomide Analogs

The exploration of the antiangiogenic and immunomodulatory activities of thalidomide has led to the study and creation of thalidomide analogs. Two groups that exhibit distinctive spectra of biological activity, termed SelCIDs and immunomodulatory drugs (IMiDs), respectively, with enhanced TNF-inhibitory activity compared with thalidomide

In 2005, Celgene received FDA approval for lenalidomide (Revlimid) for MDS as the first commercially useful derivative. Other derivatives include pomalidomide (Actimid) and ENMD-0095.

ZINC SALTS

Zinc is an essential trace element, with catalytic, structural, and regulatory function used in more than 200 metalloenzymes involved in many biochemical pathways. It is found in most animal products, legumes, whole grains, and dairy products, although phytate, found in cereal grains and legumes, binds zinc and inhibits its absorption. Although the concentration of zinc in bovine milk is greater than that in breast milk, zinc absorption is greater from breast milk than bovine milk. The reason for this difference is still unknown but is thought to be related to a high-molecular weight protein associated with bovine milk zinc compared with a low-molecular-weight protein associated with human milk.

Age and gender determine the recommended daily intake, which ranges from 2 to 13 mg.

Absorption and Distribution

Approximately 20 to 30% of dietary zinc is absorbed primarily from the duodenum and ileum. The amount absorbed depends on the bioavailability of the food. Zinc is the most bioavailable from red meat and oysters. After absorption zinc is bound in the intestine to the protein metallothionine. Zinc is primarily eliminated (approximately 40%) in the feces and to lesser extent in the urine aand in perspiration.

Dosage

Different salt forms provide different amounts of elemental zinc. **Zinc sulfate** contains **23%** elemental zinc; 220 mg zinc sulfate contains 50 mg zinc. **Zinc gluconate** contains **14.3%** elemental zinc; 10 mg zinc gluconate contains 1.43 mg zinc. The **Zn-methionine complex** (100 mg) contains 20 mg of zinc. The doses mentioned in (mg/kg) unless specified are for the elemental Zn.

Dosage schedule: Take one hour before or two hours after food. Consumption of fibre-containing foods inhibit absorption of zinc. Take the tablets an hour before, or two hours after, food high in fiber.

Route of administration: Oral.

Adults, children over 12 years and the elderly: One capsule to be taken three times a day an hour before food or two hours after meals.

Children under 12 years: Not recommended.

Uses (Approved/Unapproved)

For the treatment of zinc deficiency which can occur in individuals on an inadequate diet, in malabsorption, with increased tissue loss due to trauma, burns, and protein-losing conditions and during intravenous feeding.

In dermatology though a long list of conditions have been prescribed zinc therapy, but most of them, except acne or warts, do not have sufficient evidence to merit their use.

FDA approved	*Acrodermatitis enteropathica*
Off Label	**Acne vulgaris**: Oral zinc salts, (sulfate, gluconate and methionine based) have been useful in moderate to severe acne **Alopecia areata**: 5 mg/kg/day of oral zinc sulfate induced significant hair growth after 6 months of therapy **Behcet's disease and oral aphthae**: Oral zinc sulfate 100 mg/day was an effective in oral aphthosis and Behcet's disease **Cutaneous leishmaniasis** : Oral zinc sulfate in doses of 2.5, 5, and 10 mg/kg/day for 45 days was an effective and safe treatment option **Hidradenitis suppurativa**: Oral zinc gluconate 90 mg/day showed significant clinical improvement
	Rosacea: Oral zinc sulfate 100 mg thrice a day was effective in rosacea after 3 months of therapy **Vitiligo:** Oral zinc sulfate showed moderate efficacy when given as an adjuvant with topical steroids. **Warts**: 10 mg/kg/day oral zinc sulfate for 2 months

Acquired Zinc Deficiency

Acquired zinc deficiency is more common than acrodematitis enteropathica and results from decreased dietary intake, decreased absorption, or increased elimination. Individuals

who are alcoholic, anorexia nervosa, vegetarians, and those who depend on total parenteral nutrition are at increased risk for zinc deficiency because of decreased intake. Diets high in cereal grains and low in meats, as in Southeast Asia, sub-Saharan Africa, and rural areas of the middle east, predispose individuals to zinc deficiency because of phytate binding of dietary zinc.

Premature infants are also at risk because of high metabolic demand from rapid growth, inadequate stores, poor absorption, and increased losses. Zinc stores in premature infants are inadequate because maternal transfer of zinc occurs primarily in the last 10 weeks of gestation. Inefficient zinc absorption by premature gut epithelium and higher urinary, fecal, and cutaneous zinc loss than full-term infants further contributes to this deficiency. Low levels of zinc in breast milk, despite normal maternal plasma zinc levels, can contribute to zinc deficiency in preterm and full-term infants. Conditions that interfere with zinc absorption in the gut also predispose to zinc deficiency. Zinc deficiency can be one of the presenting signs of cystic fibrosis and should be considered in the differential diagnosis of an eruption resembling acrodermatitis enteropathica. Gastrointestinal disorders, including gastric bypass surgery, inflammatory bowel disease, celiac disease, short bowel syndrome, and chronic diarrhea, can cause chronic disruption in zinc absorption from the gut. Increased elimination from alcoholism, malignancy, burns, infections, pregnancy, renal disease, and stress also predispose individuals to zinc deficiency.

Medications such as penicillamine, diuretics, antimetabolites, and valproate can decrease serum zinc levels.

Mildly deficient individuals (40–60 μg/dL; normal reference range, 70–250 μg/dL) may show signs of subacute or chronic zinc deficiency. Children and adolescents present with growth retardation, hypogonadism in males, dysgeusia, and abnormal dark adaptation. Psoriasiform dermatitis may be present on the hands, feet, and occasionally knees.

Doses of elemental zinc should be 0.5–1.0 mg/kg/d in children with acquired zinc deficiency and 15–30 mg/d in adults.

Acrodermatitis Enteropathica

Acrodermatitis enteropathica is a rare disease with an onset of symptoms around **4–6 weeks** after weaning or even earlier in infant not on breast milk. It is an autosomal recessive disorder associated with defective zinc absorption in the small intestine. The causative mutation has been identified as SLC39A4 on chromosome 8q24.3, 72 which encodes the ZIP4-transporter

on enterocytes. The infant becomes irritable and withdrawn and develops photophobia. Anorexia, pica, growth impairment, hypogonadism, impaired taste and smell, night blindness, and neuropsychiatric symptoms (mood changes, tremors, dysarthria, and jitteriness) eventuate in untreated cases.

Cutaneous changes include periorificial and acral dermatitis (some lesions are burn like, oozy, or psoriasiform) localized around mouth, cheeks, ears, nostrils, buttocks, anus, dorsal skin of hands, feet, fingers, toes, and heels, paronychia, nail dystrophy, and hair loss. Delayed wound healing, angular stomatitis, conjunctivitis, blepharitis, increased susceptibility to infection, and growth retardation may also be seen. Low serum alkaline phosphatase and zinc levels (<50 μg%) are diagnostic and will improve after zinc therapy but hypoalbuminemia does not necessarily indicate zinc deficiency.

Treatment with oral zinc (2–3 mg/kg/day) will cure all clinical manifestations within 1–2 weeks and needs to be continued up to adulthood.

Acne Vulgaris

The use of zinc in acne is based on two observations, one is its safety in pregnancy, children and second its efficacy based on its antinflammatory and antindrogen action (Sardana K, 2014). Recent studies have shown it to be effective against resistant *P. acnes* (Iinuma K). In fact it was found to have an additive action with topical clindamycin (Iinuma K).

In vivo studies have shown that oral zinc sulfate is more effective in the treatment of severe acne than for the treatment of mild-to-moderate acne but nausea, vomiting, and diarrhea occur frequently. Similarly, oral zinc gluconate has been found useful in managing inflammatory acne. They have been found to be either as effective as tetracyclines or inferior to minocycline. Recently a methionine bound zinc complex with antioxidants has been tried and found useful in managing mild-to-moderate acne vulgaris (Sardana K, 2010).

In clinical practice different Zn salts have varying *bioavailability* and methionine based Zn has the best amongst the salts. Though slow to act the results in acne are comparable to antibiotics and in patients who are not willing to take other systemic agents it is a ideal choice.

Behcet's Disease and Oral Aphthosis

Behcet's disease is a vasculopathic condition characterized by recurrent episodes of oral and genital ulcerations with positive pathergy test. Oral aphthae are another troublesome condition of obscure etiology characterized by recurrent painful oral ulcerations particularly in adolescents. Several treatment modalities including corticosteroids and immunosuppressants have been used with variable results.

Sharquie et al. in a randomized, controlled, double-blind crossover trial comprising 30 subjects found oral zinc sulfate, 100 mg given thrice daily for three months, to be an effective treatment modality for Behcet's disease without any major adverse effects. They also found oral zinc sulfate (100 mg thrice daily) useful in the treatment of recurrent oral aphthae. Zinc sulfate had both therapeutic and prophylactic action as it also reduced the relapse rate in recurrent aphthae.

Verruca Vulgaris

Oral zinc sulfate (10 mg/kg/day) given for 2 months in common warts resulted in complete clearance in 61% patients in one month and 87% after two months of therapy in a placebo-controlled trial by Al-Gurairi et al., whereas clearance rate was 50% with the same dose of oral zinc sulfate after 2 months in an open-label clinical study by Mun et al.

Oral zinc (10 mg/kg/day) has been reported to clear recalcitrant warts in a patient with epidermodysplasia verruciformis in 12 weeks.

In clinical practice, the drug is useful for verruca plana and multiple warts. For localized warts topical therapies are useful.

Cutaneous Leishmaniasis

Sharquie et al. used oral zinc sulfate in doses of 2.5, 5, and 10 mg/kg/day for 45 days among 104 patients with cutaneous leishmaniasis and observed cure rates of 83.9%, 93.1%, and 96.9% for the 2.5 mg/kg, 5 mg/kg, and 10 mg/kg treatment groups, respectively, without significant adverse effects. Although low cost and better safety profile of oral zinc sulfate as compared to antimonials appears advantageous, inconsistent outcome remains a limiting factor.

Leprosy

Zinc is found to stimulate production of IL-2 and induces a *shift* from **Th2 toTh1** response. It has also been demonstrated to decrease the serum levels of TNF-α and inhibit the TNF-induced apoptosis of peripheral blood mononuclear cells that helps in controlling the disease activity and reactional states (A. Gupta).

In a study comprising patients of recurrent erythema nodosum leprosum additionally receiving zinc, the steroids could be tapered off completely and the duration and severity of reaction were also reduced (NK Mathur). It could be used as a useful adjuvant drug in reactions.

Drug Interaction

Concurrent administration of zinc salts may diminish the effect of penicillamine and the absorption of tetracycline and iron. Large doses inhibit copper absorption.

Copper: Large doses of zinc inhibit the absorption of copper in the intestine.

Tetracycline antibacterials: Zinc decreases the absorption of tetracyclines by the formation of an insoluble chelate. The absorption of zinc may be reduced by tetracyclines; when both are being given an interval of at least three hours should be allowed.

Quinolone antibacterials: Zinc may reduce the absorption of quinolones—ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin.

Penicillamine: The absorption of zinc may be reduced by penicillamine, also the absorption of penicillamine may be reduced by zinc.

Calcium salts: The absorption of zinc may be reduced by calcium salts.

Food: The absorption of zinc is reduced when it is taken concurrently with phytates (found in bran, whole grain breads), fiber containing foods or phosphorus containing medication and foods (milk or poultry).

Iron: The absorption of zinc may be reduced by oral iron, also the absorption of oral iron may be reduced by zinc.

Side Effects

Most common side effects of zinc salts are abdominal pain and dyspepsia.

Gastrointestinal disturbances such as dyspepsia, epigastric pain, gastric irritation, gastritis, nausea, vomiting, diarrhea, leukopenia (fever, chills or sore throat) and neutropenia (continuing ulcers and sores in mouths), headache, lethargy, irritation.

Special Groups

Pregnancy: No problems have been reported but as with all drugs, caution is recommended if the tablets are to be taken in the first three months of pregnancy.

BIBLIOGRAPHY

1. Al-Gurairi FT, Al-Waiz M, Sharquie KE. Oral zinc sulphate in the treatment of recalcitrant viral warts: randomized placebo-controlled clinical trial. British Journal of Dermatology. 2002;146(3):423-31.
2. Gupta A, Sharma VK, Vohra H, Ganguly NK. Inhibition of apoptosis by ionomycin and zinc in peripheral blood mononuclear cells (PBMC) of leprosy patients. FEMS Immunology and Medical Microbiology. 1999;24:49-55.
3. Iinuma K, Noguchi N, Nakaminami H, Sasatsu M, Nishijima S, Tsuboi I, et al. Oral zinc sulfate treatment for viral warts: an open-label study. Journal of Dermatology. 2011;38:541-45.

4. Iinuma K, Noguchi N, Nikaminami H, Sasatsu M, Nishijima S, Tsuboi I, et al. Susceptibility of Propionibacterium acnes isolated from patients with acne vulgaris to zinc ascorbate and antibiotics. Clin Cosmet Investig Dermatol. 2011;4:161-5.
5. Mathur NK, Bumb RA, Mangal HN. Oral zinc in recurrent erythema odosum leprosum reaction. Leprosy in India. 1983;55(3):547-52.
6. Sardana K, Chugh S, Garg VK. The role of zinc in acne and prevention of resistance: have we missed the "base" effect? Int J Dermatol. 2014;53(1):125-7. doi: 10.1111/ijd.12264. PubMed PMID: 24350859.
7. Sardana K, Garg VK. An observational study of methionine-bound zinc with antioxidants for mild-to-moderate acne vulgaris. Dermatol Ther. 2010;23(4):411-8. doi: 10.1111/j.1529-8019.2010.01342.x. PubMed PMID: 20666829.
8. Sardana K, Garg VK. Antibiotic resistance in acne: is it time to look beyond antibiotics and Propionobacterium acnes? Int J Dermatol. 2014;53(7):917-9.
9. Sharquie KE, Najim RA, Al-Dori WS, Al-Hayani RK. Oral zinc sulfate in the treatment of Behcet's disease: a double blind cross-over study. Journal of Dermatology. 2006;33(8):541-6.
10. Sharquie KE, Najim RA, Farjou IB, Al-Timimi DJ. Oral zinc sulphate in the treatment of acute cutaneous leishmaniasis. Clinical and Experimental Dermatology. 2001;26(1):21-6.

Index

Page numbers followed by f and t refer to figure and table, respectively. Diseases are in bold font

A

Acanthosis nigricans 726
Acitretin 506, 512
  serum levels of 512
Acne 38, 49, 178, 215, 399, 588, 724
  conglobata 492
  fulminans 492
  variants 492
  vulgaris 489, 659, 766
  hormonal 181*t*
Acrodermatitis enteropathica 765
Acyclovir 254, 261, 262
  resistance 253
  toxicity of 259
Adalimumab 270, 288, 289
Adrenal hirsutism 196
Alanine aminotransferase 343
Albendazole 247
  dosage of 248
Alcohol 445, 512
Alefacept 267
Alitretinoin 516
Alkylamines 122
Allergic rhinitis 160
Allylamine 111
Alopecia 178, 571
  areata 403, 465, 749
  female pattern 196, 201
  male pattern 195*t*, 201
Alpha lipoic acid 641
Alprazolam 567
American Academy of Dermatology 588
American College of Rheumatology 342
Aminoimidazole-carboxamide ribonucleotide 328
Aminopenicillins 16
Aminoquinolones, dosimetry of 700
Amitriptyline 559, 560
Amphotericin B 85, 238
  lipid complex 238
Amyloidosis 685
Anal fissures, chronic 519
Analgesics 663, 664
  classification of 664*t*
Anaphylaxis 72
Anidulafungin 119
Animal bites 19
Anthrax 77
Antibacterial agents, classification of 5*t*
Antibiotics 1
Anticoagulants 208, 443
Anticonvulsants 101, 667
Antidepressant 548, 549*t*, 553, 664
  receptor specificity of 555*t*
Antidrug antibodies 288
Antifungal 105, 111
  antibiotics 83
  classification of 82
  drugs 82, 83, 84*f*
  drugs, systemic 83
  medications 82
Antigen presenting cells 305, 692
Antihistamines 136, 139, 142, 143
  action of 126
  anti-inflammatory effects of 125*f*
  drugs 145
  functional classification of 121*f*
Antimalarials, side effects of 702*t*
Antimetabolites 70
Antioxidant 578, 633, 634
  synergy 636
Antiphospholipid antibody syndrome 442
Antiprotozoal drugs, uses of 225*t*
Antipsychotics 539
  classification of 540*t*
  monitoring of 546*t*
Antiviral 101
  agents, classification of 251*t*
  drugs 255*f*
Anxiety disorder 536, 566, 568
  generalized 551

Anxiolytic drugs 569*t*
Aphthous stomatitis 684, 738, 758
Apoptosis 692
Arachidonic acid 438
  metabolism 438*f*, 709*f*
Aripiprazole 543
Aspartate aminotransferase 342
Aspergillosis 100, 116
Aspirin 439, 441
  indications of 442*t*
Atherosclerosis 427
Atopic dermatitis 125*f*, 143, 301, 332, 367, 404, 462, 579, 656
Atrophie blanche 442
Atrophoderma vermiculatum 492
Autoimmune connective tissue disorders 682
Autosomal recessive congenital ichthyosis 605
Azathioprine 314, 317, 349, 349*f*, 357
  uses of 352
Azoles 95

B

Bacteria 4*t*
Bacterial cell
  typical structure of 1
  wall 2*f*
Bartonella infections 64
Behçet's disease 332, 404, 766
Behçet's syndrome 683
Benzodiazepines 567
Benzylamine 85*f*
Beta-lactamase inhibitor combinations 17
Bexarotene 514, 515
  drug levels of 515
Bilastine 160
Biotin 623
Blastomycosis 100
Bleaching 704
Blood
  cell count 343
  dyscrasias 336
  glucose 502
  lipids 698
  pressure 520
  tests 342
Body dysmorphic disorder 551, 562
Bone 511
  loss 495
  marrow suppression 378
Bowel perforation 426
Brachioradial pruritus 669
Bradycardia 524
Breastfeeding 155
British National Formulary 513
Brodalumab 273
Bronchospasm 524
Bulimia and post-traumatic stress disorder 548
Bull's eye maculopathy 703
Bullous congenital ichthyosiform erythroderma 510
Bullous dermatosis, chronic 684, 711
Bullous disease 684
Bullous disorders 586, 682
Bullous pemphigoid 332, 406, 586
Bullous urticaria 301
Buspirone 568

C

Calcinosis cutis 519
Calcipotriol 509
Calcium
  channel blockers 517
  folinate 722
  leucovorin 722
  salts 768
Cancer
  chemoprevention 441
  prevention 609
  prostate 198
  skin 284, 495, 616, 639, 659
Candida albicans 239
Carbapenams 4, 30
Carboxypenicillins 17
Cardiac toxicity 378
Cardiovascular inflammation reduction trial 334
Carotene, uses of 614
Carotenoids 610, 611*f*
  biodistribution 612
Caspofungin 118, 118*f*, 119
Cataract 429
Cell
  membrane 3
  surface-associated molecules 448
  walls 3

Central nervous system 431, 440, 501, 525, 570
depression 109
Cephalosporins 4, 9, 12, 13, 21, 27, 28
classification of 23*t*
spectrum of activity of 24*t*
Cerebrovascular disease 213
Certolizumab pegol 275
Cetirizine 128, 145
Cheilitis granulomatosa 39
Chickenpox 258, 265
Chloroquine 691, 699*t*
Chlorpheniramine maleate 162
Chromoblastomycosis 743
Chromomycosis 100
Cicatricial pemphigoid 406
Clavulanic acid 8
Clindamycin 4, 40
Clofazimine 688
Coccidiodomycosis 100
Codeine 672
Coenzyme
A 626
Q10 637
Colchicine 681
Combination therapy 139, 52, 508
Combined oral contraceptives 221
Community acquired pneumonia 37
Community associated methicillin-resistant staphylococcus aureus 12*f*
Complete blood count 260, 514
Condylomata acuminata 492
Congenital ichthyosiform erythroderma 510
Congestive heart failure 285
Connective tissue disease 289
Contact dermatitis, air borne 353
Contraception 762
Copper 768
Corticosteroids 387
systemic 444
Corticotropin-releasing hormone 394
Cosmetic antioxidants 635
Coumarin 443
Curcumin 638, 639
Cutaneous leishmaniasis 228, 234, 240, 767
Cutaneous lupus erythematosus, acute 695
chronic 694
Cyclic guanosine monophosphate 526
Cyclo-oxygenase 437
Cyclophosphamide 314, 317, 373*f*, 377-379
levels of 378
uses of 375
Cyclosporine 44*f*, 315, 360, 368*f*, 456
A 533
induced hypertension 520
Cytokine 145, 309
production 267
Cytosolic retinoic acid-binding protein 482
Cytostatic drugs 306*f*, 309
classification of 305*t*

D

Dalbavancin 12
Danazol 202
Dapsone 706, 708*t*, 709*f*
dermatological uses of 710*t*
monitoring of 716*t*
side effects of 712*t*
Darier's disease 494, 510
Decubitus ulcers 660
Degos disease 738
Dehydroepiandrosterone sulfate 214
Dendritic cells 305
Deoxyguanosine triphosphate 254
Depression 537
Depressive disorders 547
Dermatitis
artefacta 544
herpetiformis 587, 685, 587, 711, 751
Dermatomyositis 407, 696
Dermatophyte infection 100
Dermatoses 535
Dermis 448*f*
Desloratadine 155
Diabetes mellitus 429
Diabetic peripheral neuropathy 667
Diabetic ulcers 739
Diazepam 567
Dibenzoxepin tricyclics 122
Dietary carotenoids 610

Digoxin 443
Dihydrolipoic acid 641
Dihydrotestosterone 207
Diltiazem 517
Discoid lupus erythematosus 494, 750, 759
Disseminated atypical infection 64
Diuretics 444
DNA-RNA inhibitors 83
Doripenem 30
Doxepin 134, 558
  indications of 558
Doxycyline 47, 48, 48*t*
Drospirenone 218
Drug
  hypersensitivity syndrome 56
  interaction 150, 159, 163, 164
  monitoring 230
Dry skin 495
Dual-energy X-ray absorptiometry 421
Dutasteride 200
Dysplastic nevi 617

E

Ebastine 150
Echinocandins 117
Eczema
  acute 409
  subacute 409
Eicosapentaenoic acid 578
Electrolyte imbalance 370
Empiric therapy 12*f*
Endogenous antioxidant systems 635
Endothrix 94
Endotoxin 3
Enicillamine 732
Enterobacteriaceae 9
Enterobiasis 248
Entomophthoromycosis 743
Epicutaneous tests 20
Epidermis 448*f*
Epidermolytic ichthyosis 605
Epidermophyton 92
Ergosterol synthesis inhibitors 83
Erythema nodosum 19, 443, 743
  leprosum 739, 758
Escitalopram 561
Estrogen 211
Etanercept 270, 281
Ethanolamines 122
Ethinyl estradiol 214, 218

F

Famciclovir 264
Fasting blood lipids 502
Fat soluble
  antioxidants 637, 641
  vitamins 597
Fatty acids
  essential 574, 588, 574, 644
  polyunsaturated 577, 644
Febrile neutropenia 88
Febrile neutrophilic dermatosis, acute 403
Febrile ulceronecrotic Mucha-Habermann disease 739
Fexofenadine 139, 152
Fibromatosis 685
Finasteride 200
Flavin
  adenine dinucleotide 619
  mononucleotide 619
Flu like syndrome 67
Fluconazole 105, 109, 533
  dosimetry of 107*t*
  levels of 109
Fluoroquinolones 4
Fluoxetine 561, 562
Folic acid 328*f*, 335
Follicle stimulating hormone 209
Food dependent, exercise-induced anaphylaxis 583
Fosfomycins 12

G

Gabapentin 668
  toxicity of 669, 670
Gastrointestinal disorders 757
Gastrointestinal tract 500
Gelatin 573
Geriatric dosage 164
Glaucoma 429
Glibenclamide 533
Glucocorticoid
  sensitivity and resistance 416
  therapy 423*f*
  withdrawal regimens 413
Glucose intolerance 429
Glutathione 633, 639
Gluten 587
  free diet 578
Glycopeptides 12
  spectrum of activity of 32

Graft-versus-host disease 463
Gram-negative
bacteria 14*f*, 32*f*, 37*f*, 70
cell structure 3
folliculitis 77, 492
organism, structure of 3*f*
Gram-positive
bacteria 1, 9, 37*f*, 70
organism, structure of 2*f*
Granuloma annulare 66, 697, 739
Granulomatous dermatoses 51, 289
Griseofulvin 92, 94
Guselkumab 274

H

Hair 99, 106, 112, 594, 631
loss 511, 572
Hand eczema, chronic 514
Headache 217, 241
Heart rate 520
Hemangioma 404, 521
infantile 520
Hematologic toxicity 72, 285, 336
Hemolysis 713
Hemorrhagic cystitis 381
Heparin 5443
Hepatic damage 336
Hepatitis
B 283
C 283
Hepatotoxicity 512
Herpes
genitalis 250
labialis 258, 265
simplex virus
infection 260
primary 259
recurrent 259, 263, 265
suppressive 259, 263, 265
thymidine kinase 254
zoster 259, 262, 265, 404
Herpetic infections 251
Hidradenitis suppurativa 66, 494, 726
Hirsutism 180, 196, 725
types of 182*t*
Histamine 123, 557
receptors, types of 124
Hormonal contraception, serum concentration of 220
Hormone
adrenocorticotropic 394
replacement therapy 422
Human
bites 19
immunodeficiency virus 508
associated oral aphthae 759
Hydroxychloroquine 318, 691
Hydroxyzine hydrochloride 163
Hyperglycemia 109
Hyperhidrosis 729
Hyperkalemia 525
Hyperkeratotic palmoplantar dermatitis 510
Hyperlipidemia 370
Hyperparathyroidism 603
Hypersensitivity syndrome 716
Hypertension 370
Hypertriglyceridemia 656
Hypnotics 568
Hypoglycemia 523, 524
Hypotension 109, 524
Hypothalamic-pituitary-adrenal 393, 411
axis 393, 411, 431
Hypoxanthine-guanine phosphoribosyltransferase 349

I

Ibuprofen 444
Ichthyosis 510, 605
Idebenone 638
Imidazoles 85*f*
Immunobullous dermatoses 51
Immunoglobulin 657
Immunopharmacological drugs 313
targets of 309
Immunosuppressive drugs 304
Indian Council of Medical Research 602
Induction 544
Inflammatory linear verrucous epidermal nevus 605
Infliximab 286, 287
Inhibit thrombocyte aggregation 691
Injectable glucocorticoids 411
Inosine triphosphate pyrophosphohydrolase 350
Intercellular adhesion molecule-1 660

International Union against Tuberculosis and Lung Disease 64
Intracranial hypertension, benign 55
Intradermal test 20
Intramuscular steroids 412
Iron 572, 594, 595, 768
  absorption 592
  deficiency 593, 594
    stages of 593
  storage 593
  transport and usage 592
Isotretinoin 484, 484*t*, 495, 503
  levels of 495
  side effects of 497*t*
Itolizumab 289
  uses of 291
Itraconazole 97, 98
  dosimetry of 100*t*
  plasma concentrations 101*t*
  systemic 96*t*
Ivermectin 243
Ixekizumab 270, 273

J

Janus kinase 270
Jarisch-Herxheimer reaction 29
Jessner's lymphocytic infiltrate 696

K

Keloids 519
Keratoderma 510
Kerion 405
Ketoconazole 110
Ketolides 36, 134
Khellin 457
Kidney 68, 148
  disease 95, 153, 155, 163, 669, 745
  failure 149, 236, 249, 261, 263, 265, 298, 345, 385, 503, 687, 741

L

Lactation 68, 153, 155, 163, 199, 230, 246, 298, 345, 358, 372, 434, 470, 503, 513, 669, 687, 705, 741, 745, 753
Latent tuberculosis infection 283
Leflunomide 317, 717
Legionella neumophila 63
Leishmania donovani 232, 233
Leishmaniasis 239
Leprosy 64, 689, 767
  drug therapy of 65*t*
Leucovorin 722
Leukocyte function 681
Leukocytoclastic vasculitis 684
Leukotrienes 652
Levocetirizine 147
Lichen
  planus 353, 368, 405, 463, 494, 510, 697, 711, 750, 759
  sclerosus et atrophicus 510
  simplex chronicus 544
Lincosamides 36
Linear IgA
  bullous dermatosis 33, 711
  disease 586, 685
Linezolid 4, 59
Linoleic acid 648, 654
Lipids 511
Lipodystrophy 429
Lipoglycopeptide 12, 32
Lipopolysaccharide 3
Lipoxins 652
Lithium 443
Livedoid vasculopathy 442
Liver 68, 236, 500, 511
  biopsy 339, 343
  disease 95, 153, 155, 163, 670, 745
  dysfunction 82
  failure 249, 298, 345, 384, 502, 503, 533, 687, 741
  function 511, 514
    tests 384
  toxicity 67
Lopinavir 533
Loratidine 153
Low density lipoprotein 428
Lupus erythematosus 407, 494, 694
  cutaneous 510
Lupus nephritis 377
Lycopene 638
Lymphocyte 312
  targeting pharmaceuticals 314*t*
Lymphogranuloma venereum 51
Lymphomatoid papulosis 332, 466

M

Macrolide 4, 36
Malignancy, chemoprevention of 509
Mastocytosis, systemic 301
Mastodynia 217
Melasma 609, 630, 756
Membrane function, inhibitors of 80
Menstrual cycle 217
Menstrual disturbances 433
Mesalamine 754
Metformin 723
  uses of 725*t*
Methemoglobinemia 713
Methicillin-resistant coagulase-negative staphylococci 33
  S. aureus 11, 16
Methotrexate 316, 326, 327, 336, 341, 343, 443, 444, 456
  toxicity 344
  uses of 330
Methoxypsoralen 460
Micafungin 119
Microsize 94
Miltefosine 231
Minimal erythema dose 460, 630
Minocycline 46, 48, 48*t*
Minoxidil 200
Mirtazapine 134, 564
Mizolastine 158
Monoamine oxidase 61
  inhibitor 549, 560
Monobactams 31
Monotherapy 52, 508
Morphea 19, 465
Mucocutaneous leishmaniasis 229, 234, 240
Mucous membrane pemphigoid 406
Mupirocin 4
Mycobacterial infections 52, 64, 689
Mycophenolate mofetil 317, 319
Mycophenolic acid metabolism 321*f*
Mycosis fungoides 514
Myocardial infarction 213, 334, 441
Myositis 408*t*

N

Nail 98, 106, 595
  changes 29
  pharmacokinetics 112
  psoriasis 508
Naltrexone 673
Natural penicillins, antimicrobial activity of 16*t*
Nervous system 715
Neutrophilic dermatoses 289, 682, 759
Neutrophilic disorders 681
Niacin 621
Nicotinamide adenine dinucleotide 621
  phosphate 621
Nifedipine 517
Nitric oxide 526
Nocturnal pruritus 562
Nonbenzodiazepines 568
Noninvasive tests 340
Non-melanoma skin cancer 284, 509
Nonsteroidal anti-inflammatory drugs 437, 439, 444, 653
  classification of 437*t*
Noradrenergic selective serotoninergic antidepressant 565
Nortriptyline 559, 560
Nucleic acid 4
  inhibition 62

O

Obesity 578
Obsessive-compulsive disorder 539, 548, 551, 561
Ofatumumab 279
Olanzapine 543
Olopatadine 128, 156
Omalizumab 299
  associated anaphylaxis 302
Onychomycosis 100
Opioids 671
Opportunistic infections 341, 356, 383
Oral aphthosis 766
Oral contraceptive 53, 209, 216*t*
  pill 218
Oral iron 592
Oral minipulse
  steroid 408
  therapy 411

Oral steroid therapy 409
Oritavancin 12
Osteonecrosis 422
Osteoporosis 371, 417
  prevention of 424*t*
Ovarian hirsutism 196
Oxybutynin hydrochloride 727

P

Pain
  classification 663
  disorders 552
  neuropathic 664, 668, 669, 676*t*, 677*t*
  relief 665*t*, 666*t*
Palmoplantar dermatoses 466
Palmoplantar pustulosis 683
Panic disorder 548, 566
Panniculitis 697
Panton-valentine leukocidin 10
Papulosquamous disorders 682
Paracetamol 439
Paraneoplastic pemphigus 586
Parasitic infections 224*t*
Parasitosis, delusion of 541, 543
Paroxetine 561
Partial thromboplastin time, activated 619
Pemphigus 324, 405, 586, 739, 750
  vulgaris 586
Penicillamine 768
Penicillin 4, 13
  action of 12
  allergy testing 19
  antistaphylococcal 11*f*, 16
  binding proteins 2, 11*f*, 14
  classification of 8*t*, 15*t*
Penicillinase resistant penicillins 4
Penicillium griseofulvum 92
Pentamidine 224
Pentoxifylline 735, 741*t*
  metabolism of 736*t*
  side effects of 740
Peptic ulcer disease 426
Periocular pigmentation 733
Perioral dermatitis 50
Perniosis 739
Peroxisome proliferator-activated receptors 648
Phace syndrome 521
Phaeohyphomycosis 100
Phenylalanine 457
Phenytoin 445
Phosphodiesterases 270
Phospholipids 3
Photochemotherapy 447*t*
  uses of 453
Photodermatoses 352, 464
Photoprotection 614
Photosensitivity 54
  reactions 21, 29, 55, 79,356
Phytoestrogens 576
Pigmentation 79, 704
Pimozide 543
Pioglitazone 509
Piperazine 145, 147
Piperidine 153
Pityriasis lichenoides 466
Pityriasis rosea 39, 466
Pityriasis rubra pilaris 332, 494, 510
Plantar pustulosis 466
Plant-derived antioxidants 636
Plasma protein binding 395
Poisoning 744
Polyene antibiotic 86
Polymorphic light eruption 464
Polymorphonuclear lymphocytes 681
Polymyxin 80
Porphyria cutanea tarda 696
Post-herpetic neuralgia 404, 544, 555, 667, 669
Potassium iodide 742
Prednisolone, oral minipulse of 472-474
Pregabalin 670
  toxicity of 670
Pregnancy 68, 82, 114, 153, 155, 156, 163, 199, 230, 236, 246, 253, 260, 263, 265, 298, 302, 345, 358, 372, 433, 470, 503, 512, 669, 687, 705, 720, 741, 745, 753, 768
  category 286, 302
  test 501, 762
Premenstrual dysphoric disorder 552
Premenstrual syndrome 552
Premenstrual tension 217
Procollagen 681
Progressive systemic sclerosis 733
Propranolol 520
  monitoring of 525
Prostaglandin 652
  biosynthesis, inhibition of 438

Prostatic hyperplasia, benign 207
Protein 3
synthesis 35*f*
inhibitors of 34
pathway 35*f*
Prothrombin time 619
Prurigo 466
nodularis 759
Pruritus 66, 142, 157, 562, 565, 594, 669, 704
drug induced 562
Pseudoallergens 583
Pseudolymphoma 696
Pseudotumor cerebri 495
Psoralen 446, 449
plus ultraviolet A
erythema 450
therapy 469
ultraviolet B 460
Psoriasis 266, 275, 276, 291, 330, 362, 453, 455, 476, 507, 577, 604, 658, 719, 739, 751
Psoriatic arthritis 719
Psychosis 538
Psychotropic drugs 535
Pulse
steroids 412
therapy 397, 405
Pustular psoriasis 508
generalized 508
Pyoderma 18, 39, 42, 64, 69, 76
gangrenosum 409, 743

Q

Quetiapine 542
Quinolone 73
antibacterials 768
classification of 74

R

Raynaud's phenomenon 519, 562
Reiter's disease 333
Renal
damage 336
dysfunction 82
function 514
toxicity 241
Reproductive toxicity 341, 382
Respiratory system 501
Retinoic acid 588
metabolism blocking agents 516
receptor 482
response element 482
Retinoid 456, 481
classification of 483*t*
systemic 481
X receptor 482
Rheumatoid arthritis 387, 718, 733
Riboflavin 619
Rickettsial diseases 51
Rifampicin 533
Rifamycins 62
antimicrobial activity of 62*t*
Risperidone 542
Ritonavir 533
Rituximab 279, 294
Rosacea 50, 494
fulminans 492

S

Sarcoidosis 66, 333, 406, 697, 739, 759
Scalp, dissecting cellulitis of 494
Scleroderma 333, 467, 605
Sclerosis, systemic 333, 519
Seborrheic dermatitis 100, 466
Secukinumab 269, 272
Selective serotonin receptor inhibitors 549, 560, 565, 673
Serenoa repens 206
Serotonin-noradrenalin reuptake inhibitor 565
Serotonin-norepinephrine reuptake inhibitors 666, 673
Sertraline 561
Serum
blood urea nitrogen 260
creatinine, monitoring of 368*f*
Sézary syndrome 514
Sildenafil 526, 533
Skeletal survey 502
Skin 98, 102, 106, 112, 371, 591, 598, 631, 734, 757
antioxidant systems in 633
barrier 654
diseases 605, 656
disorders 548
infections 12*f*
Small molecular weight inhibitors 270

Society of Obstetricians and Gynaecologists of Canada 260
Sodium stibogluconate 224, 227, 233
Sperm 198
Spontaneous urticarial, chronic 136
Sporotrichosis 100, 743
Stasis dermatitis 660
Steroid 313
  dosimetry 414*f*
  myopathy 408*t*
  psychosis 432
  systemic 389*t*
Stevens-Johnson syndrome 297, 406
Streptococcus pneumoniae 22
Streptogramins 36, 69
Streptomyces 69
Subcutaneous tissue disorders 734, 757
Sulbactam 9
Sulfasalazine 319, 746
  uses of 749
Sulfobutyl ether β-cyclodextrin 114
Sulphonylureas 443
Sunlight exposure 480
Superoxide dismutase 633
Suppressive therapy 258
Sweet's syndrome 403, 685
Syndrome of inappropriate antidiuretic hormone 384
Synthetic antifungal drugs 83
Syphilis 19, 51
Systemic lupus erythematosus 304, 333, 377, 440, 659, 695
  bullous eruption of 711
Systemic psoralen plus ultraviolet A
  protocol 476
  treatment 477

T

Tachyphylaxis 134
Tacrolimus 316, 444
Tapentadol 673
Tazobactam 9
T-cell receptor 305
Telithromycin 36
Telogen effluvium, chronic 572
Tendon or joint disorders 80
Terbinafine 94, 111, 113, 113*t*
  levels of 113
Testosterone production 214
Tetracycline 4, 43, 48
  antibacterials 768
Tetrahydrofolate 70
Thalidomide 317, 757
  analogs 763
Thiopurine methyltransferase 349
Thromboxanes 652
Thyroid stimulating hormone 514
Thyroxine 514
Tigecycline 58
Tildrakizumab 274
Tinea versicolor 100
Tofacitinib 270
Topical antifungal drugs 83
Topical psoralen plus ultraviolet A 452, 454, 459, 460
Toxic epidermal necrolysis 33, 406
Tramadol 672
Tranexamic acid 755
Transglutaminase 583
Transrepression 390
Triazoles 85*f*
Trichotillomania 563
Tricyclic antidepressant 134, 549, 555, 565, 665, 673
Trimethoprim-sulfamethoxazole 70
Tropical parasitic infections 224
Tuberculin skin test 284
Tuberculosis 283
  treatment of 63
Tumor necrosis factor 160, 275, 448

U

Ubiquinone 637
Ulcerative stomatitis, chronic 697
Ultramicrosize 94
Ultraviolet protection 608
Ureidopenicillins 17
Uricosuric agents 443
Urticaria 136, 136*f*, 160, 367, 582, 751
  pigmentosa 463
Urticarial
  chronic 160, 332
  treatment of 137, 137*f*
  vasculitis 684
Ustekinumab 269

V

Valacyclovir 262
Vancomycin resistant
  enterococci 11
  S. aureus 11
Varicella 261
  infection, treatment of 257
  zoster infections 256
Vascular cell adhesion
    molecule-1 278, 660
Vascular disorders 213
Vascular endothelial growth
    factor 281
Vasculitis 56, 289, 333, 353, 376,
    408, 682
Vasodilator drugs 517, 517*f*
Venlafaxine 565
Verruca vulgaris 767
Visceral leishmaniasis 228,
    233, 234, 240
Vision 529
Vitamin 575
  A 588, 610
    deficiency 613*t*
  B_{12} 625, 626
  B_2 619
  B_3 621
  B_6 622
  B_7 623
  B_9 625
  C 627, 640
  D 579, 597, 605
    deficiency 601, 603, 604*t*
    synthesis 598*f*
  E 607, 637
  K 618
    deficiency bleeding 618
Vitiligo 52, 353, 408, 456, 477,
    605
Voriconazole 114

W

Water-soluble
  antioxidants 639, 641
  vitamins 619
Wegener's granulomatosis 743
Weinstein and Frost regimen
    331
Wheat-dependent exercise-
    induced anaphylaxis 583
Withdrawal syndrome 564
Wound healing 519, 639, 737

Z

Zinc
  deficiency, acquired 764
  salts 763
Zycolchin 681