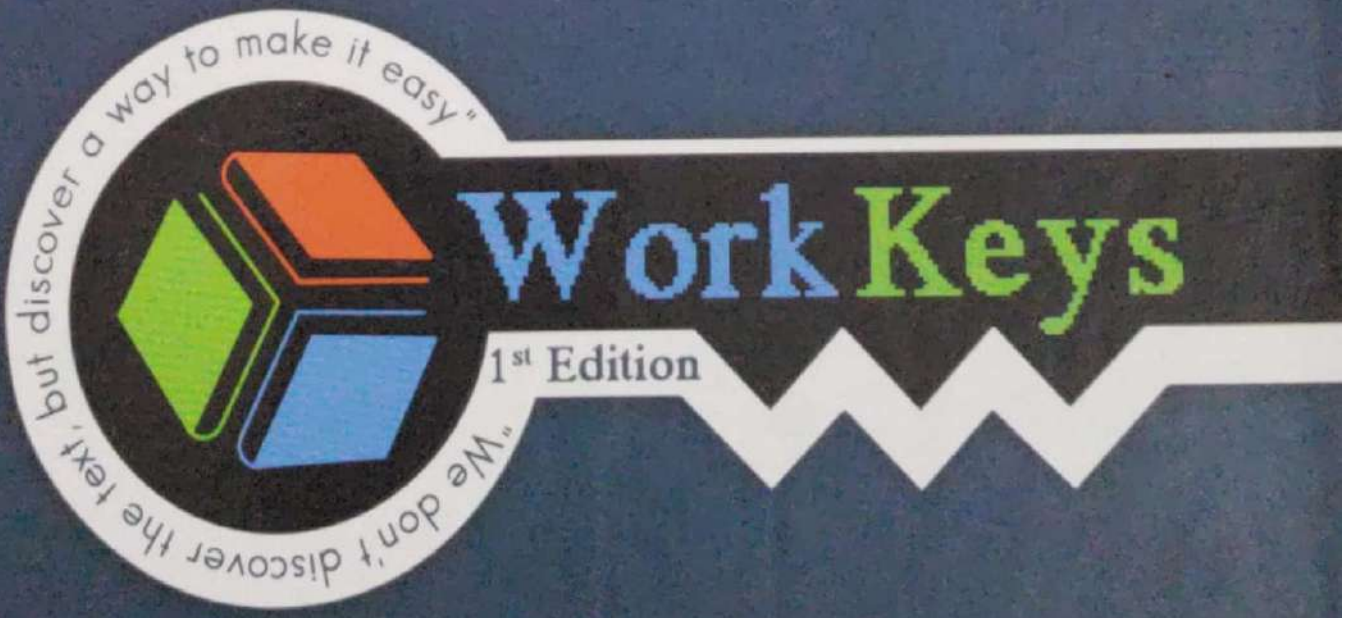
Pharma Guide®

Basic and Clinical Pharmacology

Just Open it.

Pre-Work 1st Edition

Pharmacy Practice for Postgraduate



Dhshan Hassan Dhshan

45 Days of Study

Ph M.F

Pharma Guide®

Pre-Work 1st Edition

Pharmacy Practice for Postgraduate

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عزيزي: الخريج/الصيدلي/الطبيب :

تشكرك على اقتناء هذا الكتاب، الذى بُذل فيه جهدٌ كبير، كي يخرج فى هذه الصورة المتواضعة، فنحاول جاهدين إخراج الكتاب بنهج دقيق متقن، و مراجعته قبل الطباعة مراجعة دقيقة، لأن النقص يعتري أعمال البشر، والكمال لله وحده ..

أخي العزيز: إن ظهر لك خطأ طباعي أثناء قراءتك للكتاب فأرسله لنا عبر البريد الخاص بالمؤلف

Dr.Dhshan@Gmail.com

أو تواصل معنا عبر الهاتف عن طريق الرقم الخاص بالمؤلف

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حتى نتداركه فى الطباعات اللاحقة، وبهذا تكون قد شاركت معنا بجهد مشكور يتضافر مع جهدنا جميعا فى سيرنا نحو الأفضل والأكمل ..

هل كتاب Pharma Guide Pre-Work المخصص للخريجين .. مفيد لي؟

- عزيزي المقبل على شراء هذا الكتاب: إن هذا الكتاب صمم بعناية **للخريجين** المقبلين على سوق العمل ليساعدهم من خلال **تذكيرهم** بالمجموعات الدوائية، والأسماء التجارية، والفروقات الهامة بين كل مجموعة وآخرى، أو دواء وآخر بنفس المجموعة، والوصف الأولي لكل دواء، وأهم الأعراض الجانبية، والتداخلات الدوائية، والجرعات، وأهم ما يميز الكتاب هو شرح كيفية تقديم المشورة الصيدلانية للمجموعات الدوائية لوصف الدواء **Patient Counselling**.

- صمم الكتاب ليسهل للخريج خلال فترة زمنية وجيزة (**45 يوم**) سرعة الانخرط في مجال العمل الدوائي.

- لا يُنصح إطلاقاً بإقتناء هذا الكتاب **للطلاب** دارسى علم الفارماكولوجى كعلم أكاديمي .. اقتناؤك لهذا الكتاب فى مرحلة الدراسة بالجامعة يبعدك عن تعليم أساسيات علم الفارماكولوجى ولا ينصح بهذا، لأن تعلم الأساسيات بشكل سليم داخل المرحلة الجامعية يجعلك تكمل تعليمك بعد التخرج بكل سهولة.

- كتاب **Pharma Guide Pre-Work** مصمم بعناية فائقة فيصعب علينا أن نختصر المحتوى العلمى أكثر من ذلك حتى لا يختل المفهوم العلمى، ولا يمكن أن نقوم بزيادة المحتوى أكثر من ذلك فيختل هدف الكتاب فى سرعة الانخراط بالعمل.

- يتوفر شرح الفارماكولوجى كعلم **أكاديمى أساسي وسريري وفارماكوثيراپى** فى مجموعة كتب أخرى مقدمة من فارما جايد.

- **تحذير:** تعريب المحتوى العلمي للكتاب أو اختصاره بواسطة الآخرين لإنشاء محتوى مشابه .. من المحتمل أن يؤدى الى خلل فى إيصال المعلومة للمتلقى، فقد تصل ناقصة غير مكتملة الفهم أو تفهم بطريقة خاطئة، عوضاً على احتمالية إساءة استخدام المحتوى المعرب بواسطة غير المختصين "الدخلاء".

حقوق الطبع محفوظة

رقم الإيداع	2017/15123	Deposit Number
الترقيم الدولى	978-977-203-324-9	International Standard Book Number (ISBN)

الآن:

- يمكنك متابعة فيديوهات فارما تيوب الموسم الجديد (2015-2017) مجاناً، والتى تتضمن شرح علم الفارماكولوجي الأساسي والسريري والفارماكوثيرابى من خلال هاتفك الأندرويد عبر تحميل تطبيق "فارما تيوب" او "Pharma Tube" من جوجل بلاى.

- يمكنك تحميل تطبيق "Pharma Guide MCQs" مجاناً من جوجل بلاى واختبر نفسك فى أكثر من 1000 سؤال تطبيقي مقدم من فارما جايد.

فارما تيوب:

- فارما تيوب هى أول فيديوهات شرح باللغة العربية قدمت على اليوتيوب منذ عام 2011 وقدمت أكثر من موسم، وأخر موسم تم إصدارة عام 2015 "الموسم الرابع" بإجمالى عدد ساعات 220 ساعة حتى عام 2017.
- شاهد الفيديوهات "منذ الإنشاء" أكثر من 3 مليون مشاهد مع أكثر من 40 ألف مشترك بالقناة حتى عام 2017.

فارما جايد :

- فى عام 2011 تم إصدار كتاب Pharma Guide الإصدار الأول الذى تطور سريعاً، وأصدر منه الإصدار الثانى فى عام 2012 وبعدها الإصدار الثالث عام 2014، نجح الإصدار الثالث وحقق نجاحا كبيراً وجعل اسم فارما جايد منافس قوى وسط الكتب الطبية.
- هذا النجاح يعطينا الإصرار على المزيد من التطور والنجاح ونعدكم بالعديد من المفاجآت التى تهدف إلى تسهيل علم الفارماكولوجي على كل المختصين بالمجال الطبى وجارى العمل على سلسلة Pharma Guide مع بداية عام 2015، حيث إن كتاب Pre-Work هو أحد كتب هذة السلسلة.

الفكرة الرئيسة لفارما جايد :

Pharma Guide®
Basic and Clinical Pharmacology
Just Open it.

"لا نبتكر المعلومة، ولكننا نبتكر طريقة لجعلها سهلة"

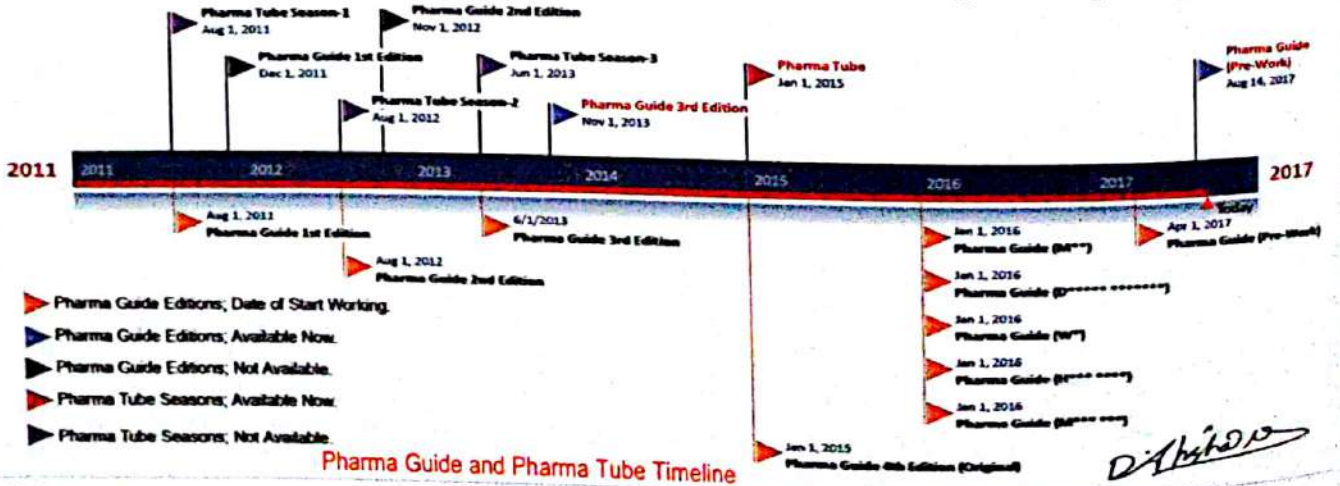
"We don't discover the text, but discover a way to make it easy"

المؤلف:

- هو الصيدلي دهشان حسن دهشان خريج صيدلة الأزهر- القاهرة عام 2013 وبدأ العمل على فارما تيوب و فارما جايد منذ عام 2011.

المطورون:

- المطورون هم محبون ومتابعو لفارما تيوب وفارما جايد على مستوى العالم نتجمع سوياً من خلال جروب "المطورون" على الفيس بوك Pharma Guide Developers ويتم وضع الاقتراحات والأفكار لتنفيذها، سوف نكون سعداء بإنضمامك إلينا ☺ www.facebook.com/groups/Pharma.Guide.Developers ☺



Pharma Guide and Pharma Tube Timeline

Contents

Book Symbol Guide

#	Important	##	Very Important
####	Very-very Important	> or <	Higher or lower
>>	Very higher or more details		
CAPITAL	Very-very Important, *like*; ***Aminoglycosides***; **OTOTOXICITY**		
3rd Generation Cephalosporins			Drug Class Shading Colour
Parenteral			Sub-Class Shading Colour
Ceftriaxone (Rocephin®)#			Generic/Brand Shading Colour
Ceftriaxone			Generic Name Colour
Rocephin®			Brand Name Colour
Ex.☞ **Typhoid fever** and **meningitis**			Therapeutic Uses colour

Study Timeline Table

* Steps to Complete Pre-Work Study;

1) *Open* Pharma Guide Pre-Work book and *study* topics in Day 1 in this table.
2) *Open* Check Yourself *chapter* in the end of *your day* and evaluate yourself.
3) *If* your correct answers are; ≥ 3 questions *from* 5 "*mark* in this table; Good).
4) *If* your correct answers are; < 3 questions *from* 5 "*mark* in this table; Need Revision).
5) In pharmacy practice *column* in this table; you need to work in the Pharmacy to *complete* it by *yourself*.

Day	Topics	Pre-Work Questions	Pharmacy Practice
1	Antibiotics Introduction β-lactam Antibiotics	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
2	Non-β-lactam Antibiotics Antibiotics Disrupt Cell Membrane Functions Antibiotics Inhibits Protein Synthesis	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
3	Quinolones and Fluoroquinolones Sulfonamides Anti-Mycobacterial	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
4	Antifungal Drugs Antiviral Drugs Antiparasitic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
5	Revision	❑ Good (≥ 3/5)	
6	Drugs for Peptic Ulcer Disease Promotility (Prokinetic) Agents	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
7	Antiemetic Agents Antidiarrheal Agents Laxatives	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
8	Drugs for IBS Drugs for IBD Pancrelipase and Drugs for Gallstones	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
9	Revision	❑ Good (≥ 3/5)	
10	Antihistamines	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
11	Drugs for Asthma and COPD	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved

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12	Allergic Rhinitis Medications Cough Medications	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
13	Revision	❑ Good (≥ 3/5)	.....
14	Drugs for Sexual Dysfunction Sexual Transmitted Disease Regimens	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
15	Drugs for Kidney Stones Drugs for Benign Prostatic Hyperplasia Drugs for Urinary Incontinence	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
16	Revision	❑ Good (≥ 3/5)	.....
17	NSAIDs Paracetamol	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
18	Opioid Analgesics Skeletal Muscles Relaxants	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
19	Drugs for Gout and Hyperuricemia Disease Modifying Antirheumatic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
20	Drugs for Osteoarthritis Drugs for Osteoporosis	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
21	Revision	❑ Good (≥ 3/5)	.....
22	Diuretics Antihypertensive Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
23	Antihypotensive Drugs Antianginal Drugs Drugs for Heart Failure (HF)	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
24	Antiarrhythmic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
25	Antithrombotic & Antihemorrhagic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
26	Antihyperlipidemic Agents Drugs for Varicose Veins & Haemorrhoids	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
27	Revision	❑ Good (≥ 3/5)	.....
28	Sedative-Hypnotic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
29	Antidepressant Drugs and Lithium Therapy	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved

30	Psychostimulant Drugs Antipsychotic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
31	Drugs for Neurodegenerative Diseases	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
32	Antiepileptic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
33	Headache Managements General Anesthetics and Local Anesthetics	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
34	Revision	❑ Good (≥ 3/5)	.....
35	Pituitary Hormones Thyroid and Antithyroid Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
36	Adrenocortical Hormones Insulin and Antidiabetic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
37	Gonadal Hormones Contraceptive Methods	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
38	Revision	❑ Good (≥ 3/5)	.....
39	Cancer Chemotherapy	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
40	Immunosuppressants	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
41	Hematopoietic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
42	Revision	❑ Good (≥ 3/5)	.....
43	Acne Skin Aging and Wrinkles Sun Damage (Sunburn and Suntan)	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
44	Cold Sores, Shingles and Warts Cellulitis, Erysipelas, Psoriasis and Vitiligo Skin Tag, Freckle and Moles	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
45	Dermatitis, Eczema, Scabies and Lice Tinea Infections and Pityriasis Rosea Hair loss (Alopecia)	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved

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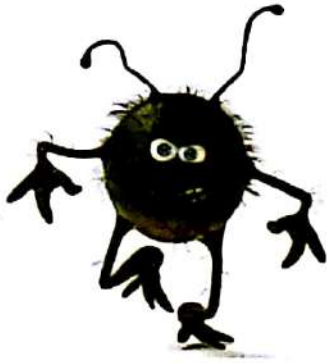
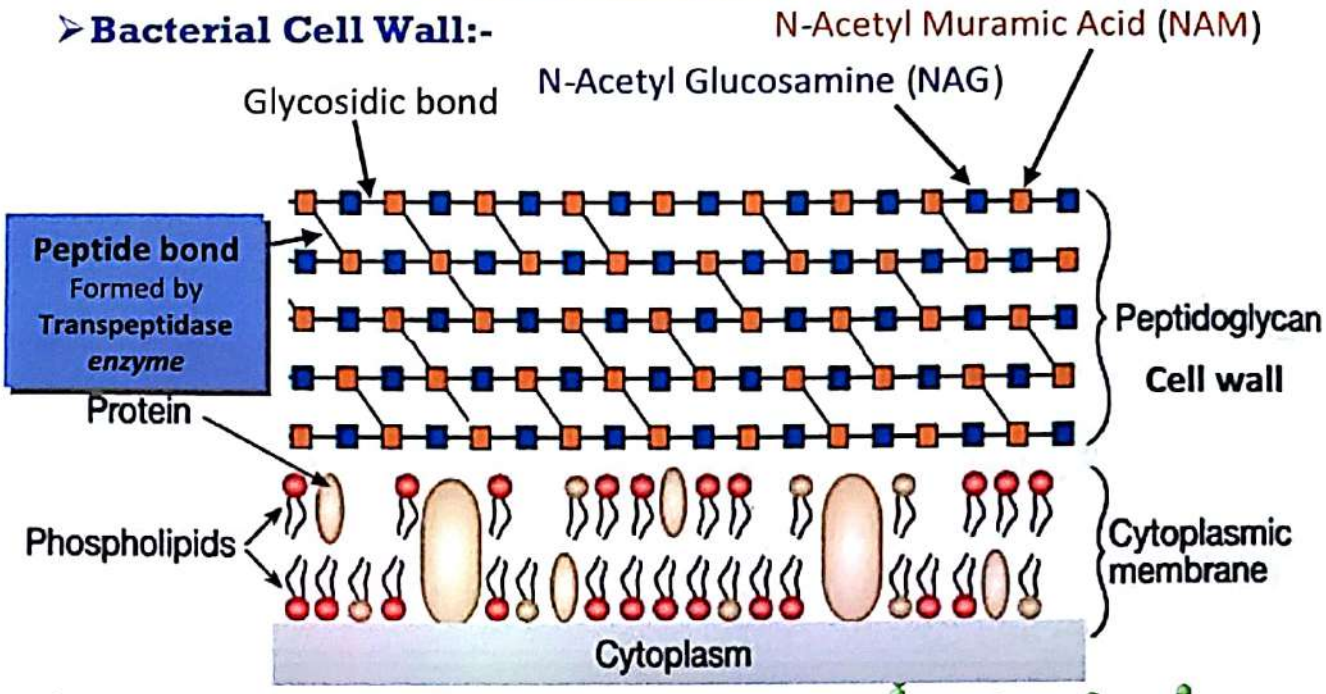
Antimicrobial Agents



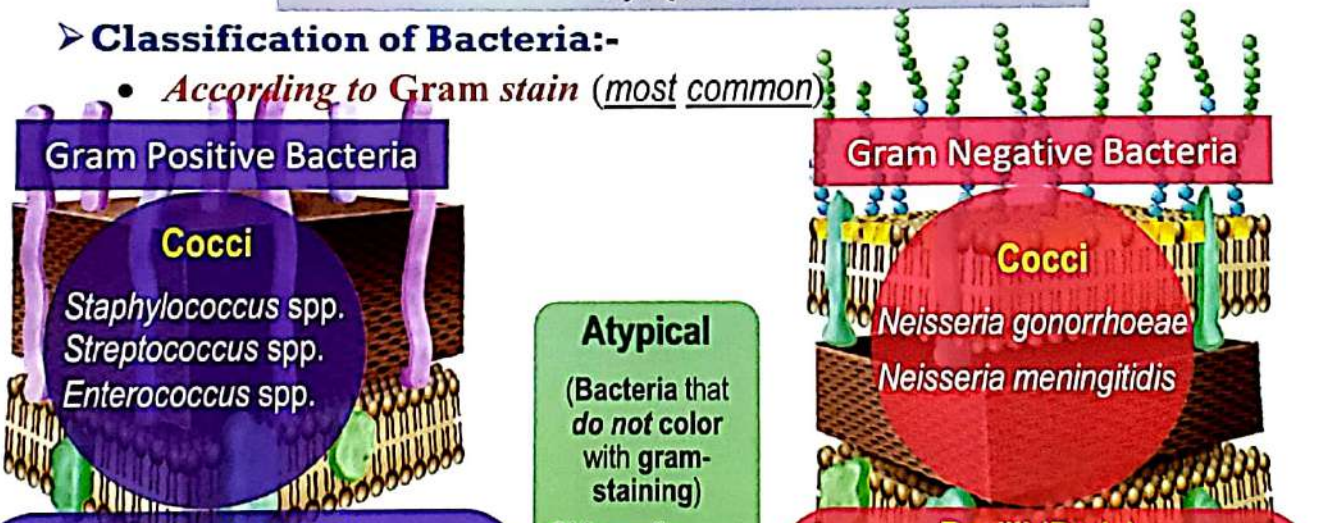
Introduction

➢ Bacterial Cell Wall:-



➢ Classification of Bacteria:-

- *According to* Gram *stain* (most common)



Bacilli (Rods)

Non-Spore Forming (Aerobic)

Propionibacterium spp.
Actinomyces spp.
Corynebacterium spp.
Erysipelothrix spp.
Listeria spp.
Nocardia spp.

Non-Spore Forming (Anaerobic)

Lactobacillus spp.
Peptostreptococcus spp.
Bifidobacterium spp.
Mobiluncus spp.

Spore-forming (Aerobic)

Bacillus spp.

Spore forming (Anaerobic)

Clostridium spp.

Atypical

(Bacteria that *do not* color with gram-staining)

Chlamydia
Mycoplasma
Rickettsia

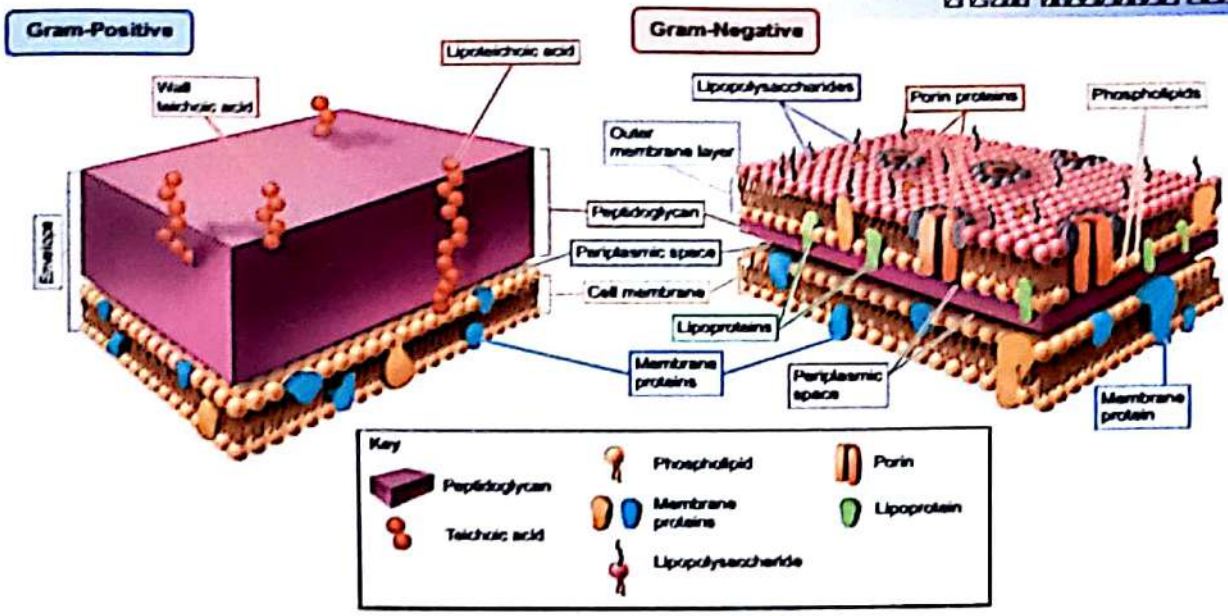
Mycobacteria

(*Mycobacteria* a genus of *rod-shaped* acid-fast bacteria having *two significant* pathogenic species)

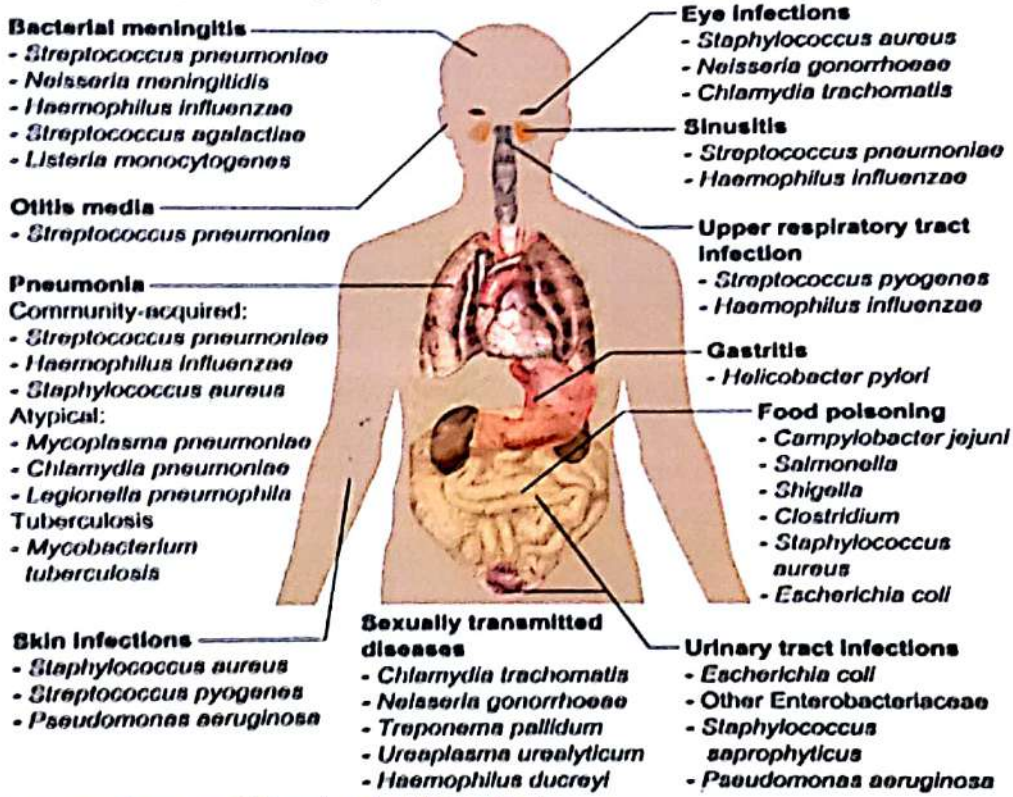
- *Mycobacterium leprae*; leprosy.
- *Mycobacterium tuberculosis*; tuberculosis.

Bacilli (Rods)

Escherichia coli
Vibrio cholerae
Klebsiella spp.
Salmonella spp.
Shigella spp.
Proteus spp.
Pseudomonas aeruginosa
Helicobacter pylori
Legionella pneumophila
Haemophilus influenza
Brucella spp.
Bordetella pertussis



- *According to site of infection*;



➢ Mechanism of Bacterial Resistance:-

- **Enzymatic inactivation**; e.g. β-lactamase enzyme (Penicillinase) which *inactivate* Penicillin by *hydrolysis* of β-lactam ring.
- **Impermeability to antibiotic**; *Many* antibiotics *enter* the cell *through* protein channels called "**Porin**" *absence* or *mutation* or *loss* of a porins channel can *slow* the rate of drug *entry into a* cell or *prevent* entry.
- **Efflux**; Bacteria also have **efflux pumps** that can *transport* drugs *out* of the cell (*common in* Gram -ve).
- **Mutation**; is a *change* in the DNA that can *sometimes cause*;
  - *Decrease* affinity of target enzyme.
  - *Alteration of* target site.
  - *Over production* of target site or metabolite.

Classification of Antibiotics:-

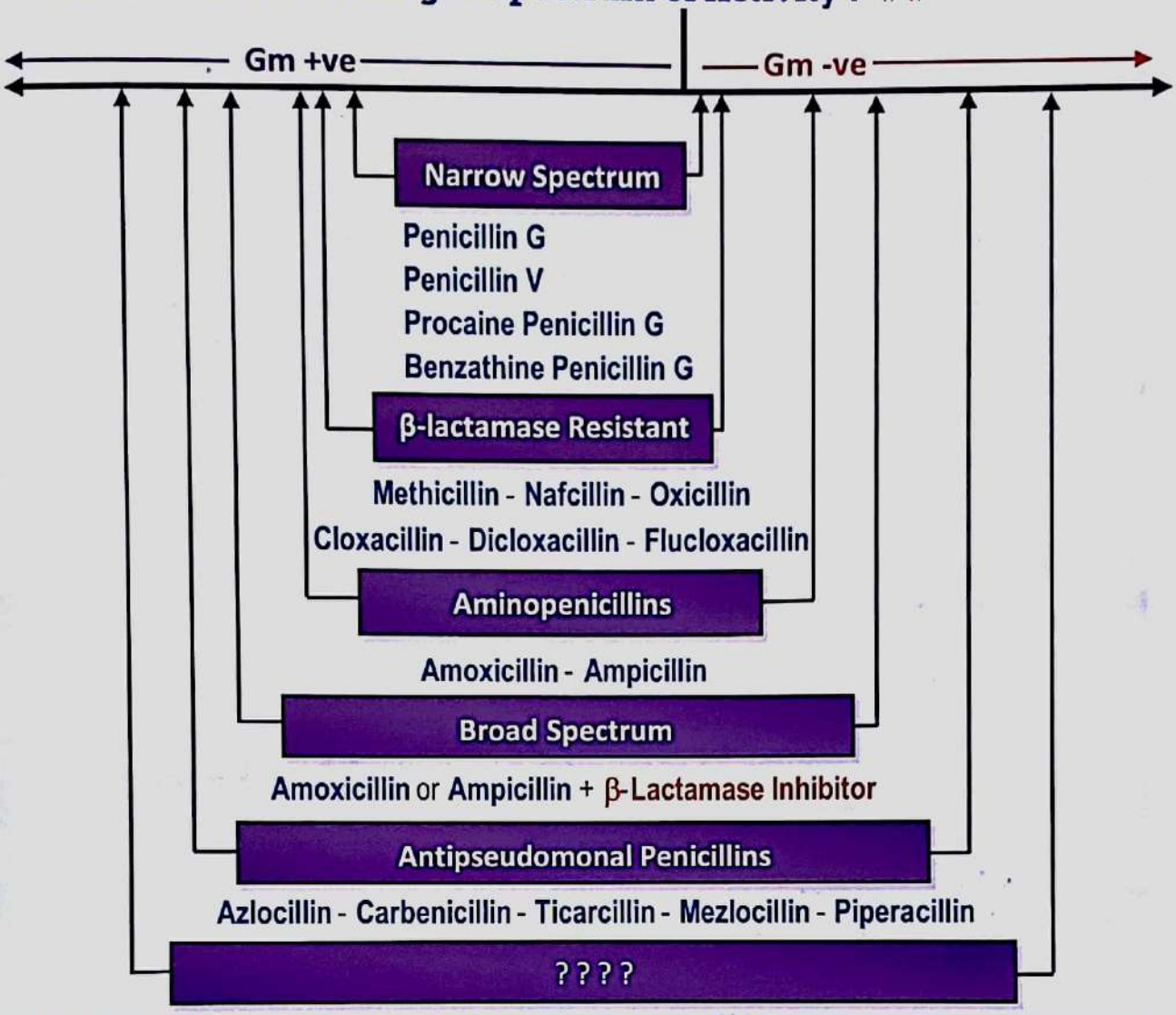
Inhibit	Classification		Antibiotics
Cell Wall Synthesis	Beta Laclams	Penicillins	Natural Penicillins: Penicillin G; Penicillin V; Procaine Penicillin G; Benzathine Penicillin G
			Antistaphylococcal Penicillins: Methicillin; Nafcillin; Oxacillin; Cloxacillin; Dicloxacillin; Flucloxacillin
			Aminopenicillins: Ampicillin; Amoxicillin
			Broad Spectrum Penicillins: Ampicillin/Sulbactam; Sultamicillin; Co-Amoxiclav (Amoxicillin/Clavulanate)
			Anti-Pseudomonal Penicillins: Carboxypenicillins: Ticarcillin; Carbenicillin; Ureidopenicillins: Piperacillin; Mezlocillin; Azlocillin; Combination: Ticarcillin/Clavulanate; Piperacillin/Tazobactam
		Cephalosporins	1st Generation: Cefadroxil; Cephalaxin; Cephradine; Cefazolin
			2nd Generation: Cefaclor; Cefuroxime; Cefprozil; Cefoxitin
			3rd Generation: Ceftriaxone; Cefotaxime; Cefoperazone; Ceftazidime; Ceftazidime/Avibactam; Cefixime; Cefdinir; Cefpodoxime; Cefditoren
			4th Generation: Cefepime; Cefpirome
			5th Generation: Ceftobiprole; Ceftaroline; Ceftolozane/Tazobactam
		Monobactams	Aztreonam
		Carbapenems	Imipenem/Cilastatin; Meropenem; Doripenem; Ertapenem
	Non-β-lactams	Glycopeptide Antibiotics	Vancomycin; Teicoplanin; Telavancin; Dalbavancin; Oritavancin
		Others	Fosfomycin; Bacitracin; Cycloserine
Cell Membrane			Colistin; Daptomycin
Protein Synthesis	30S	Tetracyclines	Tetracycline; Oxytetracycline; Doxycycline; Minocycline
		Glycylcyclines	Tigecycline
		Aminoglycosides	Streptomycin; Neomycin; Amikacin; Gentamicin; Tobramycin
	50S	Macrolides	Erythromycin; Clarithromycin; Azithromycin; Spiramycin; Josamycin
		Ketolides	Telithromycin
		Macrocyclic	Fidaxomicin
		Chloramphenicol	Chloramphenicol
		Oxazolidinones	Linezolid; Tedizolid
		Lincosamides	Clindamycin
		Streptogramins	Quinupristin/Dalfopristin; Pristinamycin
	Others		Fusidic Acid; Rifaximin; Retapamulin; Plazomicin; Mupirocin
Nucleic Acid Synthesis	DNA Topoisomerases	Quinolones	Nalidixic acid; Cinoxacin
		Fluoro quinolones	Second: Ciprofloxacin; Norfloxacin; Ofloxacin; Enoxacin; Lomefloxacin; Pefloxacin
			Third: Levofloxacin; Sparfloxacin; Grepafloxacin
			Fourth: Trovafloxacin; Moxifloxacin; Gatifloxacin; Gemifloxacin
	Antifolates	Sulfonamides	Sulfamethoxazole; Sulfadiazine; Silver Sulfadiazine; Sulfadoxine; Mafenide; Sulfacetamide
		DHFR inhibitor	Trimethoprim; Pyrimethamine
		CO	Co-Trimoxazole; Sulfadoxine/Pyrimethamine

Cell Wall Inhibitors

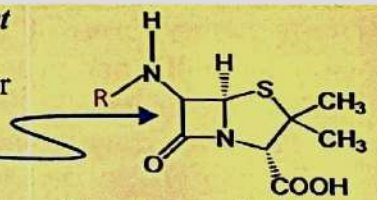
A) β-Lactam Antibiotics

I) Penicillins

➢ **Penicillins According to Spectrum of Activity :- # #**



- **Penicillins** *was* **discovered** in **1928** by *Scottish scientist* **Alexander Fleming.**
- **Penicillin** *was* *isolated* *naturally* *from* ***Penicillium notatum*** (or ***penicillium chrysogenum***).
- **Penicillins** are *derivatives* *of* **6-AminoPenicillanic Acid (6APA).**
- *Distribution*; **distribute** *well throughout the body*;
  - *Pass easily* **placental barrier ☞ Not Teratogenic.**
  - ***Not*** **penetrate CSF ☞ Pass** *easily* **in** ***inflamed*** **meninges.**
- *Excretion*; ***Active*** **renal excretion (*Inhibited by* Probenecid).**

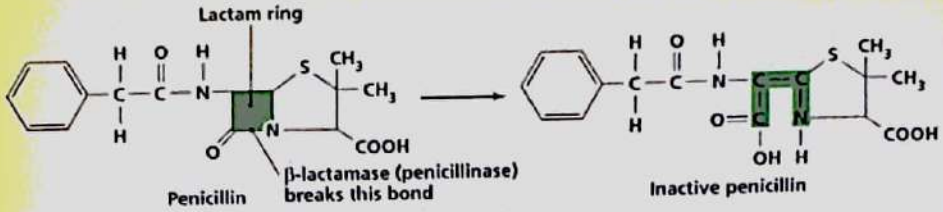


Penicillins are differ from one another in the **R** substituent attached to the **6APA** residue

\# *Mechanism*; **Penicillins** (and ***other*** **β-lactams**) *act by* ***binding with*** **Penicillin Binding Proteins (PBPs)** on **transpeptidase enzymes ☞** ***Inactivation*** of **transpeptidase enzymes** which is *responsible for* ***formation*** of **peptide bond** (***cross-linkage***) during ***formation*** or ***repair*** of **peptidoglycan ☞** ***Decrease*** **rigidity** of **cell wall ☞ cell wall** ***can't*** able to ***protect*** **bacterial cell** from ***high internal*** **osmotic pressure ☞** ***cytolysis*** **☞ death (Bactericidal).**

Bacterial Resistance;

1) **Enzymatic inactivation**; by **β-lactamase enzyme (Penicillinase)**.



2) ***Impermeability*** to **antibiotic** (*loss of* **Porin**). 3) **Efflux.**

4) ***Modification of target*** **Penicillin Binding Proteins (PBPs).**

Most Common Adverse Reactions;

1) **Hypersensitivity Reaction; # # #**

- *About* **5%** of ***patients*** will ***develop*** a **hypersensitivity reaction.**
- **Hypersensitivity test *must be*** applied at **all time** of ***injection.***
- **Hypersensitivity test** may give ***false*** **negative result** (rare).
- **Anaphylactic shock** (***very rare***); is a ***life-threatening allergic reaction include*** those of an **allergic reaction,** as well as **bronchospasm** & ***severe*** **hypotension.**
  - ***Anaphylaxis Treatments***; ***Triple Therapy*** # #
    1) **Epinephrine; Physiologic specific antidote.**
       - One ampoule of epinephrine = 1:1000 (1mg in 1 ml).
       - If one ampoule is diluted to 10ml = 1:10,000 (0.1 mg/1ml).
       - **Dose in allergic reaction;**
         - IM: 0.1 to 0.5 mg (0.1 to 0.5 mL of 1:1000 solution).
         - May be repeated every 10 to 15 minutes.

    2) **Solu-Cortef® (Hydrocortisone);** ***faster.*** 3) **Antihistamine *injection.***

Cross-allergic reactions *occur among* **the β-lactam antibiotics # #**

2) **Super-infection;** (Kill good bacteria in mouth and colon) # # #

- **Diarrhea☞ Pseudomembranous colitis** (***clostridium difficile***); ***Treated by*** (**Vancomycin## or Metronidazole#**)
- **Candidiasis** (oral and/or vaginal); ***Treated by*** **Nystatin# or Miconazole#.**

Narrow Spectrum Penicillins

Ultra-short Acting

Penicillin G (Benzyl-penicillin)

- **Penicillin G** is ***not effective*** **orally** (destroyed by gastric acidity), it is ***administrated*** **IV** or **IM** (**IV** is ***preferred*** because of irritation and local pain from IM injection of large doses),
- **Penicillin G** has ***ultra-short*** **duration of action** (half-life; about 30 minutes).

2 long acting forms of **Penicillin G** are *available* for **IM injection; Benzathine benzylpenicillin** and **procaine benzylpenicillin.**

Uses and *spectrum*;

- **Penicillin *remains*** the ***drug of choice***; **Gas Gangrene** (*Clostridium perfringens*), **Syphilis** (*Treponema pallidum*) and **Meningitis** (*Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae*).
- **Bacterial Endocarditis** (*Staphylococcus aureus, Streptococcus viridans* and *Enterococci*)
- **Cellulitis** (*Streptococcus* and *Staphylococcus aureus*) and **Erysipelas** (*Streptococcus*).
- **Diphtheria** (*Corynebacterium diphtheriae*) and **Anthrax** (*Bacillus anthracis*).
- **Actinomycosis** (*Actinomyces israelii*) (painful abscesses in the mouth, lungs, breast, or GIT).
- **Tetanus** (*Clostridium tetani*); Combined with anti-toxins.

- ***Dose***; - ***Adult***; 5-24 million *units/day* IV/IM in *divided doses* every 4-6 hours.
  - ***Pediatric***; 50,000–400,000 units/kg/day in *divided doses* every 4-6 hours.

Short Acting

Penicillin V (Phenoxy-methyl-penicillin) (Ospen®)# (Pen-Vee® K)

- **Penicillin V**, the ***oral form*** of **penicillin** (**Orally Penicillin**); ***more acid stable than*** **Penicillin G.**

Uses and ***spectrum***; **Penicillin V** has a ***similar spectrum*** to that of **Penicillin G**, ***but*** is ***indicate only*** in **minor infections** ***because*** of its *relatively* ***poor*** **bioavailability** (***not used*** for **bacteremia**).

- ***Dose***; - ***Adult***; 125-500 mg every 6-8 hours.
  - ***Children***; **< 12 years**; 25-50 mg/kg/day in *divided doses* every 6-8 hours.

Intermediate Acting

Procaine Penicillin (Procaine Benzylpenicillin) or Penicillin G Procaine

- **Procaine** (***local anaesthetic***) makes the **Benzylpenicillin** ***intermediate acting***, ***following*** deep **IM injection**, it is ***slowly absorbed*** into the **circulation** and ***hydrolysed to*** **Benzylpenicillin**, can ***last*** for ***up to*** **24 hours**.
- ***Dose***; - ***Adult***; 600,000 units to 1 million units/day IM in 1 or 2 *divided* doses.
  - ***Pediatric***; 25,000 to 50,000 units/kg/day IM in 1 or 2 *divided* doses.

Long Acting

Benzathine Penicillin (Benzathine Benzylpenicillin) (Retarpen®)# (Durapen®)# (Bicillin® L-A)

- **Benzathine Penicillin** can ***last*** for ***up to*** **3-4 weeks** ***after*** a ***single*** **IM dose**.
- ***Dose***; - ***Adult***; 1.2-2.4 million unit IM as a *single dose*, in *secondary prevention every* 3-4 weeks or 600,000 units IM *every* 2 weeks.
  - ***Pediatric***; 50,000 units/kg/day IM as a *single dose* (*maximum*: 2.4 million units).

Indications; **Upper Respiratory Tract Infections, Rheumatic Fever *Prophylaxis*** and **Syphilis** # #.

Penicillinase-Resistant (Antistaphylococcal) Penicillins

Methicillin	Oxacillin	Cloxacillin	Dicloxacillin	Flucloxacillin

Antistaphylococcal penicillins are ***semisynthetic*** **penicillins** with **β-lactamase (penicillinase)-resistant**; their use is ***restricted*** to the **treatment** *of* ***infections*** caused by **Methicillin Sensitive** ***Staphylococcus aureus*** **(MSSA)**.

In ***recent years*** the **empirical use** of these drugs has ***decreased substantially because*** of ***increasing*** **rates** of **Methicillin-Resistance** ***Staphylococcus aureus*** **(MRSA)**.

MRSA is ***currently*** a ***source of*** **serious infections** and is ***resistant*** to ***most commercially*** *available* **β-lactam antibiotics**.

- **Methicillin** is ***not*** **absorbed** ***orally***, ***only*** **given** by **IV route** and has a ***higher*** **frequency** of **interstitial nephritis**.
- **Nafcillin** has ***poor*** **oral absorption** and is **given** by **IV** or **IM routes**, it is ***used for staphylococcal*** **endocarditis**.
- **Oxacillin, Cloxacillin, Dicloxacillin** and **Flucloxacillin** can be ***administered*** **orally**.
- ***Common combinations with*** **Aminopenicillins**;
  - **Cloxacillin** 250 mg + **Ampicillin** 250 mg; **Ampiclox®** 500 mg
  - **Dicloxacillin** 250 mg + **Ampicillin** 250 mg; **Cloxapen®** 500 mg
  - **Flucloxacillin** 125/250/500 mg + **Amoxicillin** 125/250/500 mg; **Flumox®** 250/500/1000 mg

Aminopenicillins

Ampicillin # | Amoxicillin

- *Unlike* the *natural* penicillins, *these agents* exhibit *increased* stability in gastric acid.
Ampicillin and Amoxicillin have an antibacterial spectrum *similar* to that of Penicillin G but are *more effective against* Gram -ve bacilli (↑ penetrate the gm -ve outer membrane).
- *Bioavailability* of Amoxicillin is *greater than* Ampicillin (*oral* Ampicillin has been *favored for* treatment of a localized *Shigella* infection).
Absorption of Ampicillin is *impaired* by food, and the drugs *should be* administered *at least* 1 hour *before* or 2 hours *after* a meal.
- Bacampicillin is a *prodrug* of Ampicillin to *increase* absorption.
- Ampicillin (*with* or *without* Gentamicin); *drug of choice* for *Listeria monocytogenes.*
Ampicillin and Amoxicillin are *excreted* unchanged in the urine.
Doses; - *Adult*; 250-500 mg *orally* (Ampicillin *every* 6 hours - Amoxicillin *every* 8 hrs).
- Ampicillin; 500 mg to 2 g IM/IV *every* 6 hours.
- *Pediatric*; 25-50 mg /kg/day in; Amoxicillin 3 *divided* doses, Ampicillin 4 *divided* doses.
Most common side effects; Diarrhea☞ Pseudomembranous colitis.

Broad Spectrum Penicillins (Aminopenicillins + β-lactamase Enzyme Inhibitors)

Ampicillin/Sulbactam (Unasyn®)# | Sultamicillin (Unasyn® Oral)#

Co-Amoxiclav (Amoxicillin/Clavulanate) (Augmentin®)#

- Sulbactam, Clavulanate (Clavulanic acid), Tazobactam and Avibactam are β-lactamase enzyme *inhibitors* that are *similar* in chemical structure to β-lactam antibiotics *allows* to *interact with* the β-lactamase enzyme & *irreversible inhibits* β-lactamase enzyme.
Sultamicillin; is a *prodrug oral form* of the Ampicillin/Sulbactam *results in* 2.5 times *greater concentration* of Ampicillin and Sulbactam *than* when *given* alone.
Indications; Otitis Media, Sinusitis, Respiratory Tract Infections, Skin *and* Skin Structure Infections & Urinary Tract Infections.
A) Amoxicillin/Clavulanate; (Augmentin®) (Curam®) (Hibiotic®) >>>;
- *Adult*; 500 mg (Augmentin® 625) *orally every* 8 hours
OR; 875 mg (Augmentin® 1 gm) *orally every* 12 hours.
- *Children* < 40 kg; 30 mg/kg/day *divided doses every* 12 hours.
Augmentin® ES-600; 600 mg Amoxicillin /42.9 Clavulanic acid in *5 mL*;
- 90 mg/kg/day for 10 days in *recurrent* or *persistent acute* otitis media.
Augmentin XR; 1000 mg Amoxicillin /62.5 Clavulanic acid in 1 *tablet*;
- ≤ 16 years; 2 tabs *every* 12 hrs in community acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis; 7-10 days.
B) Ampicillin/Sulbactam (Unasyn® - Unictam®); 250, 375, 750, 1000, 3000 mg;
- *Adult*; 1.5-3 g IV or IM *every* 6 hours (Sulbactam *not exceed* 4 g *per* day).
- *Children* < 40 kg; 300 mg/kg/day *divided doses every* 6 hours (300 mg *represents* the *total* Ampicillin + Sulbactam).
After reconstitution, use *within* 2 hours if *stored* at room temperature, or *within* 4 hours if *stored under* refrigeration.
C) Sultamicillin (Unasyn® - Unictam®); *Adults*; is 375-750 mg *orally* twice daily.

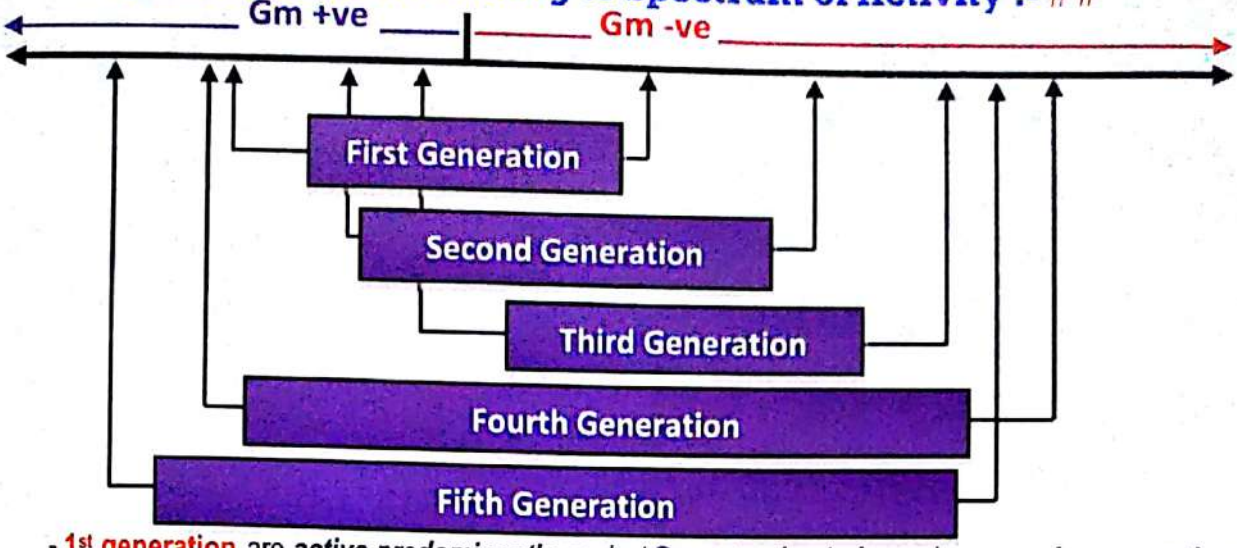
Anti-Pseudomonal Penicillins

Carboxypenicillin Group	Ticarcillin (Ticar®) - Carbenicillin (Geocillin®)
Ureidopenicillins Group	Piperacillin (Pipril®) Mezlocillin (Mezlin®) Azlocillin (Azlin®)

Developed to further increase activity against Gm -ve resistant aerobes, *especially Pseudomonas aeruginosa* ##. Piperacillin; *most potent*. Carbenicillin; *only* orally *available*.
Formulation are *available* and *widely* used.
Ticarcillin + Clavulanic acid (Timentin®); - *Adult*; ≥ 60 kg; 3.1 g IV *every* 4-6 hours.
- *Children* < 60 kg and > 3 months; 200-300 mg/kg/day IV *divided doses every* 4-6 hrs.
Piperacillin + Tazobactam (Tazocin®) (Piprataz®); - *Adult*; 3.375 g IV *every* 4-6 hours.
- *Children* < 40 kg; 80-100 mg/kg IV *every* 4-6 hours.

II) Cephalosporins

➢ **Cephalosporins According to Spectrum of Activity :-** # #



- 1st generation are ***active predominantly*** *against* Gram +ve bacteria, and ***successive generations*** >>>>>> ***increased activity*** *against* Gram -ve bacteria.
- 2nd generation; *has* ***effect*** on Gram +ve (***less than*** 1st generation) and ***some*** of Gram -ve.
- 3rd generation; *has* high ***effect*** on Gram -ve.
- 4th generation; *has* ***high*** effect on Gram -ve and Gram +ve.

Cephalosporins are **β-lactam antibiotics** that are ***closely related*** both ***structurally*** and ***functionally*** to the **Penicillins**; have the ***same*** **mode of action** as **Penicillins**, and they are affected by the ***same*** **resistance mechanisms.**

- **Cephalosporins** ***was isolated naturally*** *from* ***Cephalosporium acremonium*** in **1945.**
- **Cephalosporins** are ***derivatives*** *of* **7-Amino-Cephalosporanic Acid (7-ACA).**

Common Side effect ***of*** **Cephalosporins;**

Allergic reactions (cross-sensitivity);

- *About* **5-10%** of *patients* with a *history of* **Penicillin *allergy*** will have an ***allergic reaction*** if given a **Cephalosporin (*especially* first-generation cephalosporins).**

Mild **stomach cramps or upset nausea, vomiting and diarrhea.**

Superinfection (*as* Penicillins). - **Interstitial Nephritis.**

First Generation Cephalosporins

Cefadroxil (Biodroxil®)= (Ibidroxil®)= (Duricef®)= (Curisafe®)= (Longicef®)

Cephalexin (Ceporex®)= (Keflex®)= (Cephalex®)

Cephradine (Velosef®)= (Cefadrin®) | **Cefazolin** (Zinol®)=

Good **activity *against* Gram +ve**	***Staphylococcus*** spp. ***Streptococcus*** spp. ***Anaerobic streptococci***	★★
Some **activity *against* Gram -ve**	***Escherichia coli*** ***Klebsiella pneumoniae*** ***Proteus mirabilis***	★

Cefazolin is ***available only*** in ***parenteral*** **formulation.**

This group *not* cross the blood-brain barrier (BBB) ⇨ *Not effective* in Meningitis.

Agent	Usual Adult Dose	Usual Children Dose
Cefadroxil	500-1000 mg orally every 12 hours	30 mg/kg/day orally divided every 12 hours
Cephalaxin	250-1000 mg orally every 6 hours	25-50 mg/kg/day orally divided every 6-8 hours
Cephradine	250-500 mg orally every 6 hours 500-1000 mg orally every 12 hours	25-50 mg/kg/day divided every 6-12 hours
Cefazolin	500-1000 mg IV every 6-8 hours	25-100 mg/kg/day IV/IM divided every 6-8 hrs

Second Generation Cephalosporins

Cefaclor (Ceclor®)# (Bacticlor®) (Cefaclor®) (Tabiclor®)

Cefuroxime (Zinnat®)# (Zinacef®) (Zenax®)

Cefprozil (Cefzil®)# | **Cefoxitin** (Mefoxin®)# (Primafoxin®)

Less activity *against* Gram +ve	*Staphylococcus aureus* *Streptococcus pyogenes* *Streptococcus pneumoniae* Anaerobic streptococci	★
Good activity *against* Gram -ve	Same as 1st generation *Haemophilus influenza* *Enterobacter aerogenes* *Neisseria* spp.	★★

This group *not* cross the BBB *except* Cefuroxime (*less effective than* Ceftriaxone or Cefotaxime).
Orally Cefuroxime is *not* acceptable taste *need to* shaking for long time to decrease *it*.
Cefotetan, Cefoxitin and Cefmetazole are *only* second generation cephalosporins have *moderate* activity *against* anaerobes.

Agent	Usual Adult Dose	Usual Children Dose
Cefaclor	250-500 mg orally every 8 hours	20-40 mg/kg/day orally divided every 8 hours
Cefuroxime	250-500mg orally every 12 hours 500-750 mg IV every 8 hours	30 mg/kg/day orally divided every 12 hours 75-150 mg/kg/day IV/IM divided every 8 hours
Cefprozil	250-500 mg orally every 12 hours	15-30 mg/kg/day divided every 12 hours
Cefoxitin	1-2 g IV every 6-8 hours	80-160 mg/kg/day IV divided every 4-6 hours

Third Generation Cephalosporins

Parenteral

Ceftriaxone (Rocephin®)# (Ceftriaxone®)# (Wintriaxone®)# (Triaxone®)# (Cefaxone®)# (Epicephin®)# (Oframax®)# (Xoraxon®)# (Cefotrix®)# (Enoxirt®) >>>

Cefotaxime (Claforan®)# (Cefotax®)# (Rametax®)# (Xorin®)# (Foxime®)

Cefoperazone (Cefobid)# (Cefazone®)# | **Ceftazidime** (Fortum®)# (Cefidime®)#

Oral

Cefixime (Suprax®)# (Ximacef®)# | **Cefdinir** (Omnicef®)# (Cefdin®)# (Dinar®)#

Cefpodoxime (Orelox®)# (Cefodox®)# (Cefoprox®) | **Cefditoren** (Meiact®)#

Less activity *against* Gram +ve	*Streptococcus pneumoniae* *Streptococcus pyogenes* Anaerobic streptococci	
Excellent activity *against* Gram -ve	Same as 2nd generation *Pseudomonas aeruginosa* *Serratia marcescens*	★★★

3rd generation cephalosporins and are able to *cross* the BBB.
This group *have* a broad spectrum of *activity* & *further increased* activity *against* gram -ve.
Ceftazidime and Cefoperazone are the *only* two drugs *have* antipseudomonal activity.
Cefoperazone 1000 mg are *available* in *combination with* Sulbactam 500 mg; Sulperazon®
Cefoperazone may *cause* testicular atrophy in animals, *not* widely *used* in children.
Ceftriaxone are soluble in Lidocaine and *available* in IM *parenteral* formulations (IM ONLY; to *avoid* systemic toxicity of Lidocaine).
DON'T MIX Ceftriaxone with a Calcium-containing product (Ringer's solution).
Ceftriaxone NOT used in premature neonates & hyperbilirubinemic neonates; *displace* Bilirubin.
The *excretion* of Cefoperazone and Ceftriaxone is *mainly* through the biliary tract, and NO *dosage* adjustment is *required* in renal insufficiency.

Common indications; Otitis Media, Skin and Skin Structure Infections, Pharyngitis, Tonsillitis, Respiratory Tract Infections, Urinary Tract Infections, Bacterial Septicemia, Bone and Joint Infections, Intra-abdominal Infections and Surgical Prophylaxis.

Agent	Usual Adult Dose	Usual Children Dose
Ceftriaxone	1-2 g/day IV/IM in single daily dose OR divided every 12 hours	50-75 mg/kg IV/IM in single daily dose OR divided every 12 hours
Cefotaxime	1-2 g IV every 8 hours	50-200 mg/kg/day IV/IM divided every 8 hours
Cefoperazone	2-4 g/day IV/IM divided every 12 h	100-150mg/kg/day IV/IM divided every 8-12h
Ceftazidime	500 mg-2 g IV/IM every 8-12 hours	30-50 mg/kg IV every 8-12 hours
Cefixime	400 mg/day orally in single daily dose OR divided every 12 hours	8 mg/kg/day orally in single daily dose OR divided every 12 hours (weight X 0.4 = mL)
Cefdinir	600 mg/day orally in single daily dose OR divided every 12 hours	14 mg/kg/day orally in single daily dose OR divided every 12 hours
Cefpodoxime	100-400 mg orally every 12 hours	5 mg/kg (max. 200 mg) orally every 12 hours
Cefditoren	*Approved only* for; ≥ 12 years; 200-400 mg orally every 12 hours	

Ceftazidime/Avibactam (Avycaz®); It was *approved* in 2015 for ***Complicated* Intra-Abdominal Infections (cIAIs)** and ***Complicated* Urinary Tract Infections (cUTIs)**. **Avibactam** is a *novel* **non-β-lactam β-lactamase inhibitor**.

Fourth Generation Cephalosporins

Cefepime (Maxipime®)# (Forcetex®)# (Wincef®)# | **Cefpirome** (Cefrom®)#

- **This group** *have* an ***excellent* activity** ***against* Gram -ve** and **Gram +ve**.
- **This group** *have* **good activity** ***against* *Pseudomonas aeruginosa***, ***Staphylococcus aureus***, and ***multiple drug-resistant Streptococcus pneumoniae***.

- **Cefepime** (**Maxipime®**); ***used*** in;
  - **Pneumonia**.
  - ***Empiric* treatment of febrile neutropenic patients**.
  - ***Uncomplicated* and *Complicated* Urinary Tract Infections**.
  - ***Uncomplicated* Skin** and **Skin Structure Infections (uSSSIs)**.
  - ***Complicated* Intra-abdominal Infections** (***in combination*** with **Metronidazole**).
  - **Brain abscess**.
- ***Doses***; **Cefepime**;- ***Adult***; 1-2 g IV every 8-12 hours. - ***Children***; 50 mg/kg IV every 12 hours.
  Cefpirome;- ***Adult***; 1-4 g IV every 12 hours. - ***Children***; Not recommended.

- Febrile neutropenia is the development of fever, often with other signs of infection, in a patient with neutropenia.

Fifth Generation Cephalosporins

Ceftobiprole (Zevtera®) | **Ceftaroline** (Teflaro®) | **Ceftolozane** (Zerbaxa®)

- **This group** are ***developed for*** the **treatment** of ***infections*** with **gram -ve** and **gram +ve** **bacteria** that have ***become*** **resistant** to ***conventional*** **antibiotics**.

- **They are *active against***; - **Methicillin-resistant *Staphylococcus aureus* (MRSA)**.
  - **Vancomycin-resistant *Staphylococcus aureus* (VRSA)**.
- **Ceftobiprole** and **Ceftaroline** are the ***active moiety*** of the ***prodrug*** **Ceftobiprole medocaril** and **Ceftaroline fosamil**.
- **Ceftolozane** is ***combined with*** the **β-lactamase inhibitor Tazobactam**.
- ***Indications***;
  - **Ceftobiprole** (**Zevtera®**); - ***Hospital*-Acquired Pneumonia (HAP)**.
    - ***Community*-Acquired Pneumonia (CAP)**.
  - **Ceftaroline fosamil** (**Teflaro®**); - ***Community*-Acquired Pneumonia (CAP)**.
    - ***Complicated* Skin and Skin Structure Infections (cSSSIs)**.
  - **Ceftolozane/Tazobactam** (**Zerbaxa®**); - ***Complicated* Urinary Tract Infections (cUTIs)**.
    - ***Complicated* Intra-Abdominal Infections (cIAIs)**.

III) Monobactams

Monobactams are *β-lactam antibiotics* wherein the **β-lactam ring** is ***alone*** (*monocyclic* β-lactam) and ***not fused*** to ***another*** **ring**, in *contrast to* **most** *other* β-lactams.

Aztreonam (Azactam®)#

Aztreonam, is the *only* ***commercially available*** monobactam.
Antimicrobial activity; **primarily** ***against*** Gram -ve, *including* *Enterobacteriaceae* and *Pseudomonas aeruginosa* (***similar to*** 3rd **generation cephalosporins**).
It *lacks activity* ***against*** Gram +ve or anaerobes.
Administration; **IV** or **IM** and can ***accumulate*** in **patients** with **renal dysfunction**.
- It ***penetrates*** **well** ***into*** the **cerebrospinal fluid**
Uses; *Serious infections* (**pneumonia**, **meningitis**, & **sepsis**) caused by ***susceptible*** Gm -ve in ***patients with*** **hypersensitivity to penicillins** (**NO cross-hypersensitivity**).
- *Dose*; - *Adult*; 1-2 g IV/IM *every* 8-12 hours. - *Children*; 30 mg/kg IV *every* 8 hours.
Nebulized forms of Aztreonam (Cayston®) is ***approved*** for **cystic fibrosis**.

IV) Carbapenems

Carbapenems are *one* ***of the*** MOST broad spectrum antibiotics
Carbapenems in ***general*** have **seizure risk** in ***high*** **doses**. → Nausea, Vomiting & Diarrhea
Most common side effects (***more common*** with Imipenem); NVD, skin rashes & infusion reactions.
Renal failure; **Doses** *must* be *adjusted* (***may lead*** to seizures); Meropenem, Doripenem, and Ertapenem are ***much less*** **likely** to *cause* **seizures** *than* Imipenem.

Imipenem/Cilastatin (Tienam®)#

- Imipenem is the *first drug* of this **class**, *discovered by* **Merck** in the *mid*-**1970s**.
Imipenem is *compounded with* Cilastatin [SYE-la-STAT-in] to *protect it* from **metabolism** by **renal dehydropeptidase**;
  # Imipenem is *rapidly* ***degraded by*** the Dehydropeptidase (Dipeptides) ***renal enzyme*** when **administered** ***alone*** (Nephrotoxic Metabolite).
  # *Co-administered* with Cilastatin (Dehydropeptidase *enzyme inhibitors*) ⇨ ***Prevent*** this ***inactivation*** (***prevents*** **formation** of **toxic metabolite** and ***increase*** **urinary concentration**).
It is ***administered*** IV & ***penetrate well*** into **body tissues fluids** & **CSF** in ***inflamed*** **meninges**.
Spectrum of activity; **aerobic**, **anaerobic**, **Gram +ve** and **Gram -ve** *including* *Pseudomonas*.
Uses **Pneumonia**, **sepsis**, **endocarditis**, **joint infections**, **intra-abdominal infections** & **UTIs**
Dose; - *Adult* (≥70 kg); IV; 250-1000 mg *every* 6-8 hours.
  - *Pediatric* (*for non-CNS infections*); 25 mg/kg IV; *every* 12 hours in age less than 7 days.
  every 8 hours in age 1 to 4 weeks.
  every 6 hours in age 4 weeks to 3 months.
  15-25 mg/kg IV; *every* 6 hours in age 3 months or older.

Meropenem (Meronem®)# (Merrem®) | Ertapenem (Invanz®)#
Doripenem (Doribax®) | Tebipenem (Orapenem®)

UN-LIKE Imipenem; NOT ***metabolized by*** dehydropeptidase.
LIKE Imipenem; SAME *spectrum of* activity (*Except* Ertapenem is *not* active ***against***; *Pseudomonas*, *Acinetobacter* and enterococci) #
- Tebipenem; is the *first* **oral carbapenem** whose *prodrug* ***only*** *marketed* in **Japan**.
Uses; - ***Complicated*** **Skin and Skin Structure Infections (cSSSIs)**.
  - ***Complicated*** **Intra-Abdominal Infections (cIAIs)**.
  - ***Community***-**Acquired Pneumonia (CAP)**.
  - ***Complicated*** **Urinary Tract Infections (cUTIs)**.
  - **Febrile Neutropenia**.
  - **Acute Pelvic Infections**

Agent	Usual Adult Dose	Usual Children Dose
Meropenem	500-1000 mg IV *every* 8 hours	≥ 3 months; 10-40 mg/kg IV *every* 8 hours
Ertapenem	> 13 years; 1 g IV/IM *per* day	3 months-13 years; 15 mg/kg IV/IM *twice* daily.
Doripenem	Only for ≥18 years; 500 mg IV infusion *over* 1 hour *every* 8 hours	

- Meropenem 1g/Vaborbactam 1g (Vabomere®) is **FDA approved** in **Aug, 2017** for **adults** *with* **cUTIs**.

B) Non-β-Lactam Antibiotics

Glycopeptide Antibiotics

Vancomycin

Vancomycin is *active only against* Gram +ve bacteria; NOT effective *against* Gram -ve; *poorly* penetrate phospholipid membrane, it is *not absorbed* after oral *administration*.

FIRST-LINE; 1) IV; *complicated* skin infections, bacteraemia, endocarditis, bone and joint infections, and meningitis *caused by* Methicillin-resistant *Staphylococcus aureus* (MRSA) and Methicillin-resistant *Staphylococcus epidermidis* (MRSE).

2) Oral; Pseudomembranous colitis *caused by Clostridium difficile* (Oral capsules; *not absorbed* and Vancomycin *act* locally).

Vancomycin *inhibits* cell wall synthesis by *binding* firmly to the D-alanyl-D-alanine (D-Ala-D-Ala) in *peptidoglycan*, *preventing further* elongation of *peptidoglycan*.

Vancomycin-resistant *Staphylococcus aureus* (VRSA); are a *strains* of enterococci *resist* Vancomycin by *modification of* the D-Ala-D-Ala *binding* site;

Dose; - IV Infusion; 15-20 mg/kg/*every* 8-12 hr (In a dilute solution #slowly#, over at least 60 min.).
- Dosage is reduced in patients with renal insufficiency.
- Oral; 125 mg orally *every* 6 hours for10 day {Powder for injection can be used to prepare oral capsules or solution for oral administration if not available or expensive}.
- Inhalation (*off-label*); via nebulizer; 250 mg (5 mL diluted vials) twice daily by nebulization.

Side Effects; # Red Man Syndrome (RMS) # # # or Red Neck; *infusion reaction*
* *Usually* appearing *rapidly after* infusion.
* *Non-specific* mast cell degranulation → ↑ Histamine → *Redness* & *hotness* in face & neck.
* *Treatments*; ↓ infusion rate, use emollients, topical steroids, antihistamines & antibiotics.
* *Prophylaxis*; *prolonging* infusion period to 1–2 hours and *pre-treatment* with antihistamine.

Nephrotoxicity & Ototoxicity; *increases* the toxicity of *other* nephrotoxins or ototoxins such as Aminoglycosides. Vancomycin is FDA pregnancy *category* B.

Teicoplanin (Targocid®)#

Teicoplanin is a *semi-synthetic derivative* of Vancomycin, *Unlike* Vancomycin, it can be given IM or IV and has a *long* half-life (45–70 hrs); *once-daily* dosing.

Telavancin (Vibativ®)#

Telavancin is *semi-synthetic* lipoglycopeptide *derivative* of Vancomycin, it is *active against* Gram +ve bacteria, *including* strains with *reduced* susceptibility to Vancomycin.

Mechanism; *Like* Vancomycin, *In addition*, it *disrupts* bacterial *cell membranes*.

Half-life; *about* 8 hours, *which* supports once-daily IV dosing *for complicated* Skin and Skin Structure Infections (cSSSIs) and *for hospital-acquired* pneumonia *by S. aureus*.

Monitoring; *Unlike* Vancomycin *therapy*, *monitoring* of serum Telavancin is *not required*.

Pregnancy; Telavancin is *potentially* teratogenic, and pregnancy test *must be* confirmed.

Dalbavancin (Dalvance®) (Xydalba®) | Oritavancin (Orbactiv®)

Dalbavancin and Oritavancin are a *novel* 2nd generation *semisynthetic* lipoglycopeptide.

Spectrum; *Improved* activity *against* many Gram +ve. - *Mechanism*; *Like* Vancomycin.

Half-life; *about* 6-11 days, *which* supports once-weekly IV dosing (*single dose*).

Dalbavancin and Oritavancin was *approved* in 2014 for *acute* bacterial skin and skin structure infections (ABSSSIs) in *adults*. - Oritavancin *inhibits* Warfarin *metabolism*.

Fosfomycin

Fosfomycin (Monuril®)# (Monurol®)#

Fosfomycin (Phosphomycin or Phosphonomycin) is a *broad-spectrum antibiotic* (*against many* Gram +ve and Gram –ve), it is *indicated* in the *treatment* of urinary tract infections.

Dose; - *Single* 3 g dose *for uncomplicated* lower urinary tract infections.
- 3 g *every* 2 to 3 days *for* 3 doses *for complicated* urinary tract infections (*off-label*).
- 3 g *every* 3 days *for* 21 days *for* prostatitis (*off-label*).

Pregnancy; *FDA category* B. - Parenteral *formulation* may *available* in *some* countries.

Cycloserine

Cycloserine (Seromycin®)

Cycloserine *inhibits many* Gram +ve and Gram -ve bacteria, *but* it is *used* ONLY as a *second line* in treat **tuberculosis**.
Side Effects; *serious* dose-related CNS toxicity; headaches, tremors, psychosis & convulsions.

Polypeptide

Bacitracin

- Bacitracin is a *cyclic peptide* mixture (polypeptide) *first* obtained in 1943.
- *Spectrum*; *active against* Gram +ve bacteria (*high* molecular weight; *poorly* penetrate Gram -ve *phospholipid* membrane and *poorly* absorbed).
- Bacitracin is *highly* nephrotoxic when *administered* systemically and is ONLY *used* topically. It is often *combined with* Polymyxin or Neomycin and *may cause* allergy.

Cell Membrane Disruption Antibiotics

Polypeptide

Polymyxin B | Polymyxin E (Colistin)

Polymyxins *inhibit many* important Gram -ve bacteria including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter* species, and *Enterobacter* species.
Polymyxins are *relatively* neurotoxic and nephrotoxic, so are usually *used* ONLY as a *last* resort in *treating* infections *caused by* multiple drug-resistant bacteria.
Only 2 forms of Polymyxins are *available* in *clinical used*;
  # Polymyxin B; *available as* parenteral, ophthalmic and topical *preparations*.
  # Polymyxin E (Colistin); *available as* a prodrug, Colistimethate sodium, which is *administered* IV or inhaled via a nebulizer.

Lipopeptide

Daptomycin (Cubicin®)#

Daptomycin is a *novel* cyclic lipopeptide, *used* in the *treatment of systemic* and *life-threatening* infections caused by Gram +ve bacteria.
Spectrum; *Similar to* Vancomycin, *but more rapidly* bactericidal and *active against* Vancomycin-resistant strains of *enterococci* (VRE) and *Streptococcus aureus* (VRSA).
It is *indicated for*; for *systemic* and *life-threatening* infections *caused by* Gram +ve;
  - *Complicated* Skin and Skin Structure Infections (cSSSIs).
  - *Staphylococcus aureus* Bacteraemia.
  - *Staphylococcus aureus* Endocarditis.

- *Dose*; 4-6 mg/kg IV *every* 24 hours.

Protein Synthesis Inhibitors

Tetracyclines	Aminoglycosides	Macrolides	Chloramphenicol
Tetracycline	Streptomycin	Erythromycin	Oxazolidinones
Oxytetracycline	Neomycin	Clarithromycin	Lincosamides
Demeclocycline	Gentamicin	Azithromycin	Streptogramins
Minocycline	Amikacin	Roxithromycin	
Doxycycline	Tobramycin	Spiramycin	
Glycylcyclines		Ketolides	Others

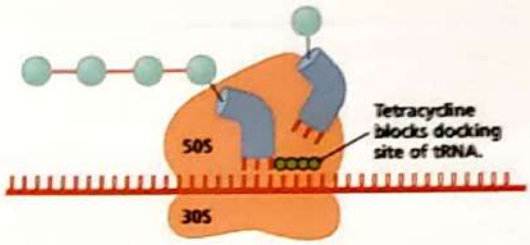
Tetracyclines

Low Lipid Solubility (Short-Acting)	High Lipid Solubility (Long-Acting)
Tetracycline (Sumycin®)	**Doxycycline** (Vibramycin®)# (Tabocin®)#
Oxytetracycline (Terramycin®)	**Minocycline** (Minocin®)
- *Rarely* used *now*. - *Affected* by food; chelation *with* metals e.g. Ca, Mg, Fe and Al (tooth bleaching). - Fanconi Syndrome; *nephrotoxic metabolite*.	- *Common* Tetracyclines used *now*. - *Less* chelation. - *Not cause* tooth bleaching. - *Absence* of nephrotoxic *metabolite*.

Only Doxycycline and Minocycline *achieve* therapeutic levels in the CSF.
Minocycline *reaches very high* concentrations in tears and saliva, *makes* it useful for *eradication of* meningococcal *carrier state*.
Tetracycline is *eliminated* renally and *should not* be used in renal insufficiency.
Doxycycline *doesn't* need dose adjustment in renal or hepatic dysfunction.
Mechanism; *reversibly* bind to 30S ribosomal *subunit*, *block* tRNA binding Bacteriostatic.

High effective against (*Drug of choice*);
- Rickettsia infection.
- Lyme disease.
- Mycoplasma pneumonia.
- Brucellosis.
- Chlamydial infections.
- Cholera.

Also effective against;
- Acne vulgaris.
- Acne rosacea.
- Anthrax.
- Plague.
- *Helicobacter pylori*.
- Malaria & Filariasis.
- Syphilis (*If* Penicillin is *contraindicated*).



Doxycycline; * Oral or IV infusion;
- Adult; - *Initial*; *Oral*; 200 mg in 2 divided doses in the first day.
  IV Infusion; 200 mg in 1 or 2 divided doses in the first day.
- *Maintenance*; *Oral*; 100 mg orally once a day OR 50 mg orally every 12 hrs.
  IV Infusion; 100 to 200 mg/day IV infusion.
- Children; - *Initial*; > 8 years; 4.4 mg/kg *orally*/*IV* on the first day, in 2 divided doses.
- *Maintenance*; > 8 years; 2.2 mg/kg *orally*/*IV* once a day OR 1.1 mg/kg twice.

Minocycline; * Oral or IV infusion; - Adult; 200 mg initially followed by 100 mg every 12 hours.
Side Effects; - Children; >8 years: 4 mg/kg initially followed by 2mg/kg every 12hrs
GIT discomfort (*local irritation*); Esophageal irritation, anorexia, NVD (may be *minimized* by *coadministration* with food [*except* Tetracycline] or fluids with *standing up* & *use* capsule.
Calcified tissues; Discoloration and hypoplasia of teeth and *effect* on bone growth in *children less than* 8 years and fetus *during* pregnancy (Teratogenic; Category D).
Vestibular disturbance; Dizziness, vertigo and tinnitus *particularly* with Minocycline.
Photosensitivity; *Severe* sunburn *may occur* and *more frequently* with Tetracycline.
Hepatotoxicity; *rare*, *but* fatal; may occur *with* high IV doses, *particularly* in pregnancy or patients hepatic or renal *dysfunction*.
Renal Toxicity (*except* Doxycycline); Acidosis and azotaemia.
Fanconi syndrome; Results by *ingesting expired* Tetracyclines; *converted to* 4-Epitetracycline and Anhydrotetracycline which *damage* proximal tubule.

CONTRAINDICATIONS; Children *less than* 8 year and Pregnancy (Category D).

PATIENT COUNSELLING

1) *Taken with* food (*except* Tetracycline), *with large* amount of water and *remain* upright *if possible*, and *choose* capsule products.
2) *Don't take* with calcium-rich foods as; milk & milk products.
3) *Don't take* with *other drugs specially*; Ca, Iron and Antacids.
4) *Don't used* for children *less than* 8 years and pregnancy.
5) *Avoid* sun exposure OR *Use* sun screen.
6) *Need* dose adjustment in kidney/liver failure (*except* Doxycycline).
7) Check *for* expiry date.

Glycylcyclines

Tigecycline (Tygacil®)#

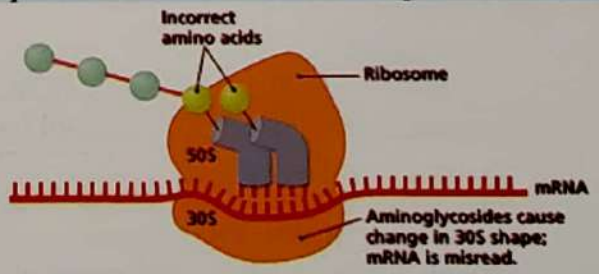
- Tigecycline is the *first* and *only* glycylcycline, *more* effectively *than* the Tetracyclines.
Spectrum; Broad-spectrum activity *including* those of multi-drug resistance; MRSA, VRE, β-lactamase-*producing* Gram -ve bacteria and *many* anaerobic.
- *Not* active against; *Proteus*, *Providencia* or *Pseudomonas* species (PPP).
Indications; - *Complicated* Skin and Skin Structure Infections (cSSSIs).
- *Complicated* Intra-Abdominal Infections (cIAIs).
- *Community*-Acquired Pneumonia (CAP).
- *Dose*; - *Adult*; > 17 years; 100 mg IV infusion *initial dose, followed by* 50 mg IV *every* 12 hours.
- *Pediatric*; - 8 *to* 11 years; 1.2 mg/kg IV infusion *every* 12 hours.
- 12 *to* 17 years; 50 mg IV infusion *every* 12 hours.
Tigecycline *primary* excreted *via* biliary/faecal (*No* dose adjustments in *patients with* renal impairment), *However*, a *dose reduction* is *recommended* in *severe* hepatic dysfunction.
- *Black box warning*; Tigecycline *should be* reserved *for* use in situations *when* alternative treatments are *not* suitable; *increased* mortality.
- Tigecycline may also *have potential* for use in acute myeloid leukemia.
- *Side effects*; LIKE Tetracyclines.
- Tigecycline may *decrease* the clearance of Warfarin and *increase* prothrombin time.

Aminoglycosides

Streptomycin | **Neomycin** | **Amikacin** (Amikin®)
Gentamicin (Garamycin®) | **Tobramycin** (Tobrex®)

All Aminoglycosides (*except* Neomycin; *due to severe* nephrotoxicity) *must be given* parenterally (IM or IV *infusion*); *absorbed very* poorly *from* GIT.
Oral Aminoglycosides such as Neomycin can be *used for* preoperative bowel preparation and for hepatic encephalopathy or hepatic coma (act *locally* in *ammonia-producing* bacteria).
Once-daily dosing; *more* effective, *more* convenient, and *safer* dosing regimen *than* 2 or 3 *equally divided* doses but, *generally avoided* in *patients with severe* renal impairment.

Mechanism; irreversibly bind to the 30S subunit, *cause misreading* of mRNA; Bactericidal.
Aminoglycosides are *effective against* majority of aerobic Gram -ve bacilli *including* those that may be *multidrug resistant*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* & *Enterobacter* spp.



In *combination with* a β-lactam or Glycopeptide (Vancomycin): Aminoglycosides are *effective against staphylococci* (*including*; MRSA), *streptococci* and *enterococci* (*Enterococcal* endocarditis) (Gentamicin and Streptomycin are the *best*); β-lactams and Aminoglycosides are *administered* in 2 separate syringe *due to* acid/base *interaction*.
Gentamicin and Streptomycin is also *useful against Francisella tularensis* (Tularemia; is a pneumonia *acquired* during rabbit hunting season by *hunters* skinning *infected* animals), *Yersinia pestis* (Plague) and *Mycobacterium* (Tuberculosis).
Streptomycin (Streptoquin®) and Neomycin used in *combination* or *alone* with antidiarrheal/antiseptic; locally *killing* bacteria *that cause* diarrhea.
- Tobramycin (TOBI®); a *new formula* of Tobramycin used as *inhalation* for Cystic Fibrosis.
Side Effects; OTOTOXICITY, NEPHROTOXICITY, Neuromuscular paralysis.
- *Risk* of nephrotoxicity are *increased by*; *Concurrent use* of NSAIDs, Diuretics, Cisplatin, Cyclosporine, Cephalosporins, Amphotericin and Vancomycin.

Agent	Usual Adult Dose	Usual Children Dose
Streptomycin	15-30 mg/kg/day OR 1-2 g IM only	20-40 mg/kg/day IM only
Gentamicin Tobramycin	*Conventional*; 1-2.5 mg/kg/dose IV/IM every 8-12 h *Once-Daily*; 4-7 mg/kg/dose IV once daily	≥ 5 years: 2-2.5 mg/kg/dose IV/IM every 8 hrs < 5 years: 2.5 mg/kg/dose IV/IM every 8 hrs
Amikacin	5-7.5 mg/kg/dose IV/IM every 8 hours (R; Lexicomp®)	
Neomycin	*Bowel Preparation*; 1 g orally every 1 hr for 4 doses *followed by* 1 g every 4 hrs for 5 doses *Hepatic Encephalopathy* (or *Coma*); 4-12 g/day orally divided every 4-6 hours for 5-6 days	*Bowel Preparation*; 90 mg/kg/day orally divided every 4 hours for 2-3 days *Hepatic Encephalopathy* (or *Coma*); 50-100 mg/kg/day orally divided every 6-8 hrs for 5-6 d
Tobramycin	(TOBI®); ≥ 6 years; 300 mg every 12 hours for 28 days and followed by 28 days off drug	

Macrolides

Erythromycin (Erythrocin®)# | **Clarithromycin** (Klacid®)# (Klacid® XL)#

Azithromycin (Zithromax®)# (Zisrocin®)# (Xithrone®)# (Azimak®)#

Spiramycin (Rovamycin®)# (Rovac®)#

Roxithromycin (Roxicin®) | **Josamycin** (Josaxin®)#

Erythromycin base is ***destroyed by*** **gastric acid** and ***must be*** **given** as *either* **enteric-coated** or ***more-stable*** **salts** or **esters**. **Clarithromycin** & **Azithromycin** are ***stable*** in **stomach acid**.

Food ***interferes*** with the **absorption** of **Erythromycin** and **Azithromycin** (**Azithromycin capsules** and **extended release suspension** ***should*** be ***administered*** **1 hour** ***before*** or **2 hours** ***after*** **meals**, ***while*** **Azithromycin tablets** and **immediate release suspension** can be ***taken with*** or ***without*** **food**). **Food** *slightly* ***delays*** the **onset** of **Clarithromycin** **absorption**, but ***increases*** the ***peak*** **plasma concentration** by *about* **24%**.

Azithromycin ***have*** *relatively* ***low*** **serum concentrations** and ***penetrates*** into **most tissues** (*except* **CSF**); with **tissue concentrations** ***exceeding*** **serum concentrations** by **10-100-fold** (**tissue** ***half-life*** of **2–4 days**) to ***produce*** an ***elimination*** **half-life** *approaching* **3 days** (**For example**, a ***single*** **1-g dose** of **Azithromycin** is ***as effective as*** a **7-day** ***course*** of **Doxycycline** for **chlamydial cervicitis** and **urethritis**).

Spiramycin ***crosses*** the **placenta** and ***reaches*** **concentrations** in the **placenta** ***up to*** **5 times** ***higher than*** **serum**; ***used*** to treat **toxoplasmosis** ***during*** **pregnancy**.

Erythromycin (***potent*** **liver microsomal enzyme inhibitor**; **CYP1A2**, **CYP3A4**) is ***extensively*** **metabolized** ***by*** **CYP450** ***system***; **Interference** with the ***metabolism*** of **drugs**, such as **Theophylline**, **Statins** and ***numerous*** **Antiepileptics**.

Clarithromycin is ***partially*** **metabolized** by **CYP3A4**.

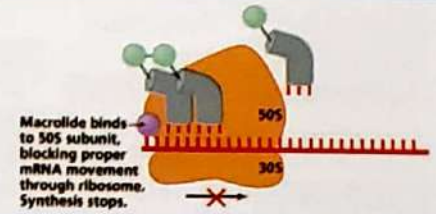
Azithromycin ***does not*** **inactivate** **CYP450 enzymes**; ***because*** it has a **15-*member*** ***not*** **14-*member*** **lactone ring** like **Erythromycin** and **Clarithromycin**; ***not*** **CYP450 substrate**.

Erythromycin and **Azithromycin** are ***primarily*** **excreted** in the **bile** *via* **feces**.

Clarithromycin and ***its*** **metabolites** are ***eliminated by*** the **kidney**; **Dose** ***should be*** **adjusted** in ***patients with*** **renal impairment**.

Mechanism; ***irreversibly*** **bind** to **50S ribosomal subunit**, ***inhibit*** **translocation**; **Bacteriostatic** in *general*.

Clarithromycin and **Erythromycin** are ***similar*** **antibacterial activity** ***except*** that **Clarithromycin** is ***more active against*** ***Mycobacterium avium*** **complex**, ***Chlamydia***, ***Legionella***, ***Moraxella***, ***Ureaplasma*** **species** & ***Helicobacter pylori***.



Clarithromycin also ***active against*** ***Mycobacterium***, ***Toxoplasma gondii*** & ***Haemophilus influenzae***.

Azithromycin is ***slightly*** ***less*** **active** than **Erythromycin** and **Clarithromycin** ***against*** ***streptococci*** and ***staphylococci*** and ***slightly*** ***more*** **active** ***against*** ***Haemophilus influenzae***.

Azithromycin is ***active against*** ***Mycobacterium avium*** **complex** (**MAC**) and ***Toxoplasma gondii***.

Azithromycin is ***highly*** ***active against*** ***Chlamydia*** **species**.

Indications;
- # *Mycoplasma pneumoniae*.
- # **Pertussis** (**whooping cough**) (***Bordetella pertussis***).
- # **Otitis media**, **sinusitis** and **bronchitis** (***Moraxella***, ***Streptococcus pneumoniae*** and ***Haemophilus influenzae***).
- # **Pharyngitis** and **tonsillitis** (***Streptococcus pyogenes***).
- # **Pyogenic skin infection** (***Staph. aureus*** or ***Streptococcus pyogenes***).
- # **Acne vulgaris** (***Propionibacterium acnes***).
- # ***Chlamydia* Infections**; **Azithromycin**.
- # ***Campylobacter* gastroenteritis**; **Erythromycin - Azithromycin**.
- # ***Helicobacter pylori***; **Clarithromycin**.
- # **Diphtheria** (***Corynebacterium diphtheriae***) **Erythromycin**.
- # **Toxoplasmosis *during* Pregnancy** (***Toxoplasma gondii***); **Spiramycin**.
- # **Macrolides** may also be ***used*** to ***prevent*** **bacterial endocarditis** (**rheumatic fever *prophylaxis***) in **patients** who ***cannot*** take **Penicillins**.
- # **Erythromycin** is the ***most potent*** **prokinetic drug** *when given* **IV** and *may be* **used** to ***improve*** **delayed stomach emptying** in ***patients*** *with* **severe gastroparesis**.

Agent	Usual Adult Dose	Usual Children Dose
Erythromycin	250-500 mg (Base, Estolate, Stearate) OR 400 to 800 mg (Ethylsuccinate) orally *every* 6 hours	40-50 mg/kg/day orally in divided doses *every* 6 hours.
Clarithromycin	*Immediate-release*; 250-500 mg orally every 12 hours OR *Extended-release* (Klacid® XL); 1000 mg (two 500 mg extended release tablets) orally every 24 hours	7.5 mg/kg orally every 12 hrs
Spiramycin	**Mild-Moderate infections**; 6-9 million IU (4-6 cap. of 500mg)/day in 2 divided doses **Severe infections**; 12-15 million IU (8-10 cap. of 500 mg)/day in 2 divided doses **Gonorrhoea**: 12-13.5 million IU (8-9 capsules of 500 mg) as a single dose.	

Doses of **Azithromycin**;
- # # **Azithromycin capsules** and **extended release suspension** ***should*** be ***administered*** **1 hour *before*** or **2 hours *after* meals**, ***while*** **Azithromycin tablets** and **immediate release suspension** can be ***taken with*** or ***without*** **food**.
- # **1 g *orally once*** as a **single dose**; **Chancroid** (**genital ulcer disease**), **gonococcal infection** {***gonorrhea***} (or; **2 g *orally*** **once**), **non-gonococcal urethritis** (*such as*; **chlamydia infection**) and **sexual transmitted disease *prophylaxis***.

Concn.	Dosage Form	Description
250 mg	6 tab/cap	2 tab/cap once *daily* for *consecutive* 3 days/week OR 2 tab/cap once *in the* first day and 1 capsule in day 2 to day 5
	4 tab/cap	4 tab/cap once; 1 g orally once as a single dose
500 mg	3 tab/cap	1 tab/cap once *daily* for *consecutive* 3 days/week
	5 tab/cap	1 tab/cap once *daily* for *consecutive* 5 days/week
600 mg	3 tab/cap	1 tab/cap once *daily* for *consecutive* 3 days/week
100mg/5mL 10 mg/kg	Suspension *Dose*; Weight/2= mL	15 mL — 10 kg; 5 ml/day *for consecutive* 3 days/week
		22.5 mL — 15 kg; 7.5 ml/day *for consecutive* 3 days/week
		30 mL — 20 kg; 10 ml/day *for consecutive* 3 days/week
		60 mL — 40 kg; 20 ml/day *for consecutive* 3 days/week
200mg/5mL 10 mg/kg (Zithromax®)	Suspension *Dose*; Weight/4= mL	15 mL (600 mg) — 20 kg; 5 ml/day *for consecutive* 3 days/week
		22.5 mL (900 mg) — 30 kg; 7.5 ml/day *for consecutive* 3 days/week
		30 mL (1200 mg) — 40 kg; 10 ml/day *for consecutive* 3 days/week
2 g	Suspension (Zmax®)	Adult; *Should be* taken as a *single* 2 g dose Pediatric; *Should be* taken as a *single* dose of 60 mg/kg
500 mg	Vial	**Infusion rate**; should be either 1 mg/mL over 3 hrs or 2 mg/mL over 1 hr

Side Effects; # **GIT discomfort** (***especially*** with **Erythromycin** is a **prokinetic agent**).
- # **Cholestatic hepatitis** (***impaired* liver function**); *especially* **Erythromycin Estolate**
- # **QT interval *prolongation***; **Macrolides** may ***prolong*** **QT interval**.
- # **Ototoxicity**; ***especially*** **Erythromycin** at ***high dosages***.
- # **Others**; **Azithromycin** *may cause* **taste/smell perversion *and/or* loss**.

Ketolides

Telithromycin (Ketek®)#

Telithromycin is a *first* ketolide antibiotic, *semi-synthetic* Erythromycin *derivative* by *substituting* the cladinose sugar with a keto-group and *attaching* a *cyclic* carbamate group in the 14-*membered* lactone ring; *inhibits* CYP450 (*like* Erythromycin & Clarithromycin).
Telithromycin have *similar* antimicrobial coverage of Macrolides, *However*, the Ketolides are *active against many* Macrolide-*resistant* Gram + ve strains.
Telithromycin is *stable* in stomach acid and *widely* distributed in the tissues.
It is *used for* Community-acquired pneumonia. *Dose*; 800 mg (2 tab.) *orally once daily*.
FDA WARNINIG; *fatal* breathing problems may *occurred* in *patients with* myasthenia gravis.
Side effects; *like* Macrolides; GIT discomfort, prolonged QT interval and hepatitis (*rare*).

Macrocyclic Antibiotics

Fidaxomicin (Dificid®)#

Fidaxomicin is a macrocyclic antibiotic (*new class*), with *very narrow* spectrum of activity *limited to* Gram +ve *only* and has bactericidal *activity against Clostridium difficile*.
#*Absorption*; *minimal* systemic absorption and *act* locally in GIT (*ideal for Clostridium difficile*).
Use; *Clostridium difficile*-associated diarrhea (CDAD).
Dose: *Oral*: 200 mg *twice* daily for 10 days.
- *Side effects*; Nausea, Gastrointestinal hemorrhage, abdominal pain, vomiting, anemia, neutropenia and hypersensitivity reaction.

Chloramphenicol

Chloramphenicol

- Chloramphenicol was *isolated* from the soil organism *Streptomyces venezuelae* in 1947. *Because* of potential toxicity, *bacterial* resistance; Chloramphenicol is *rarely* used in the United States (oral Chloramphenicol in the US *stopped* in 1991).
- Chloramphenicol *binds reversibly* to the 50S *subunit* of the bacterial ribosome and *inhibits* peptide bond *formation* (*inhibit* peptidyl transferase); Bacteriostatic.
- *Formulations* and *uses*;
  - Eye ointment or drops; for eye *infections*.
  - Oral (*was removed from the US market*).
  - IV injection; *only as* alternative.
    - Typhoid fever (*3rd generation* Cephalosporins & Fluoroquinolones are *drug of choice*).
    - Meningitis (*3rd generation* Cephalosporins are *drug of choice*).
    - Rickettsial infection (Tetracyclines are *drug of choice*).

It is *metabolized by* the liver to Chloramphenicol glucuronate by glucuronidation.
Side Effects;
  # # Bone marrow suppression; rare, idiosyncratic reaction; *aplastic anemia*, *thrombocytopenia* and *increased risk* of childhood leukemia.
  # # Hemolytic anemia; in patients *with* glucose-6-phosphate dehydrogenase *deficiency*.
  # # Gray baby syndrome; Neonates have a *low capacity* to glucuronidation, and they have *underdeveloped* renal function; which *accumulates active* Chloramphenicol *levels* that *interfere with* the function of mitochondrial ribosomes. This *leads to poor* feeding, *depressed* breathing, cardiovascular collapse, cyanosis (gray baby) and death.
- Chloramphenicol is a *liver microsomal enzyme inhibitor*, thus *decrease* metabolism of *other* drug *such as*; Antiepileptics and Anticoagulants.

Oxazolidinones

Linezolid (Zyvox®)# (Averozolid®)# (Bactizolid®)# (Voxazoldin ®)# >>>

Linezolid is a *synthetic* oxazolidinone *developed* to combat *resistant* Gram + ve *strains*, *such as*; - Methicillin-resistant *Staphylococcus aureus* (MRSA).
- Vancomycin-resistant *Streptococcus aureus* (VRSA).
- Vancomycin-resistant *enterococci* (VRE). - Penicillin-resistant *streptococci*.

Advantage of Linezolid *over* Tigecycline, Daptomycin and Vancomycin;
Oral *formulation* is *completely absorbed* (Bioavailability: 100%); IV is also available.
Widely distributed *throughout* the body.
No dose adjustments are *required* for renal or hepatic dysfunction.
Used in children and pregnancy (*category* C).
Local brands are *less expensive*.

Indications; - *Complicated* Skin & Skin Structure Infections (cSSSIs).
- *Uncomplicated* Skin & Skin Structure Infections (uSSSIs).
- Vancomycin-*Resistant Enterococcal* (VRE) Infections.
- Pneumonia.

- *Dose*; - *Adult* (≥12 years); 600 mg IV or oral *every* 12 hours; 10-14 (or 14-28 days *in VRE infections*).
- *Pediatric* (<12 years); 10 mg/kg IV or oral *every* 8 hours; 10-14 (or 14-28 days *in VRE infections*).

Side effects; # *Most common*; GI upset, nausea, diarrhea, headache and rash.
Hematologic (*reversible* and *generally* mild); *due to* bone marrow suppression (*related to* Linezolid-*induced* *inhibition* of mitochondrial protein *synthesis*);
- *Most common*; Thrombocytopenia (*mainly* occur if *used* *longer than* 10 days).
- Anemia and neutropenia *may also occur*.

Others; # # SEROTONIN SYNDROME # # (Linezolid *possesses* *non-selective* MAOI)
Optic and peripheral neuropathy (irreversible and *mainly* occur if *used* *longer than* 28 days) and lactic acidosis (*due to* mitochondrial toxicity and *mainly* occur if *used* *longer than* several months).

Drug interactions; Monoamine Oxidase Inhibitors (MAOIs) and *other* Serotonergic Drugs.
Monitoring; # *Weekly* complete blood counts (CBC) *during* Linezolid therapy.
Treatment last *no more than* 28 days.

Tedizolid (Sivextro®)

Tedizolid is a *second-generation* oxazolidinone *derivative* that is 4-to-16-fold *more potent* *against* *staphylococci* and *enterococci* compared to Linezolid.
Tedizolid has been *approved by* US FDA in 2014, for the *treatment* of Acute Bacterial Skin and Skin Structure Infections (ABSSSI).
Differences *between* Linezolid & Tedizolid are *minor*; dose interval & *duration* of therapy.
- *Dose*; ≥ 18 years; Oral or IV: 200 mg *once daily* for 6 days.

Lincosamides

Clindamycin (Dalacin®-C)# (Clindam®)# >>

Clindamycin *like* Erythromycin, *inhibits* protein synthesis by *inhibit* translocation.
Resistance to Clindamycin, which *generally* *confers* cross-resistance to Macrolides.
Clindamycin used *primarily* in *many* Gram + ve anaerobes & *some* of Gram -ve anaerobes.
High concentrations in bone, teeth and urine *but poor* entry into the CSF *even* with *inflamed*.
Preparations; Capsules, Ampoules, Solution/Lotion/Gel/Foam 1% and Vaginal Cream/Suppository 2% (Oral suspension is not favored; extremely foul taste and odour).
Indications; Otitis media, sinusitis, bone or joint infections, dental infections, pelvic inflammatory disease, bacterial vaginosis, intra-abdominal anaerobic infections, pneumonia, endocarditis prophylaxis, bite wounds, inhalational/gastrointestinal anthrax, CNS toxoplasmosis, acne and malaria.
Usual Adult dose; 150-300 mg orally *every* 6 hrs OR 600-1200 mg/day IV/IM divided *every* 12-6 hrs.
- *Side effects*; Diarrhea (pseudomembranous colitis) nausea and skin rashes.

Streptogramins

Streptogramins are a *new class* of antibiotics, *developed against* multidrug-resistant organisms.
Streptogramins A (Dalfopristin) and B (Quinupristin), they are bacteriostatic, but in *combination* they are *synergistically* bactericidal (Synercid®) ☺

Quinupristin/Dalfopristin (Synercid®)#

Quinupristin/Dalfopristin are *both* Streptogramin *antibiotics*, are *combined in* a weight-*to*-weight *ratio* of 30% Quinupristin to 70% Dalfopristin.
Spectrum; Primarily *against* Gram + ve *cocci*, including those *resistant* to *other* antibiotics; *Enterococcus faecium* (*including* VRE *strains*, but *not active against Enterococcus faecalis*), *penicillin-resistant* strains of *Streptococcus pneumoniae*, Methicillin *susceptible* and -*resistant* strains of *staphylococci* (MSSA and MRSA); cSSSIs, bacteremia, infective endocarditis and intravascular catheter-associated bacteremia.
Dose; IV; 7.5 mg/kg every 8-12 hours.
Side effects; - Phlebitis (*ideally should be* administered via a central line).
- *High incidence* of myalgias (muscle pain) and arthralgias (Joint pain).
- Hyperbilirubinemia.
Drug interactions; Quinupristin/Dalfopristin also *inhibits* CYP3A4.
Precautions; Quinupristin/Dalfopristin *must* be *mixed* and *administered with* 5% Dextrose *in* water (D5W) solutions *only* (*insoluble* and can *crystallize* in normal saline).

Others

Fusidic Acid (Fucidin®)#

Fusidic acid is a *steroid* antibiotic that *derived from* the fungus *Fusidium coccineum* and was *developed by* Leo Pharma and *released for* clinical use in the 1960s.
Fusidic acid is *often* used topically but *may* also be given *orally* or *parenterally*.
Spectrum; Primarily *against* Gram + ve; *such as Staphylococcus* species, *Streptococcus* species and *Corynebacterium* species.
Fusidic acid *should not* be used with Quinolones, with which they are *antagonistic*. When *combined* with Rifampicin, the action is *additive* or *synergistic*.
Systemic Fusidic acid *should not* be given with Statins *because* of a *risk* of *serious* and *potentially fatal* rhabdomyolysis.

Rifaximin (Xifaxan®)# (Gastrobiotic®)#

Rifaximin is a *new* GI antibiotic, was *approved by* US FDA in 2004 *for* traveler's diarrhea, irritable bowel syndrome and hepatic encephalopathy; *poor* oral absorption (act *locally*).
Rifaximin may use *with* Vancomycin in *treating* patients *with* relapsing *Clostridium difficile*
Dose; - Traveler's Diarrhea; 200 mg orally *every* 8 hours for 3 days.
- Irritable Bowel Syndrome; 550 mg orally *every* 8 hours.
- Hepatic Encephalopathy; 550 mg orally *every* 12 hours.
Side effects; Flatulence, headache, abdominal pain, bowel urgency, nausea & rectal tenesmus.

Retapamulin (Altabax®)# (Altargo®)

Retapamulin is the *first* drug in the *new class* of Pleuromutilin antibiotics *developed by* GlaxoSmithKline, used *topically* for skin infections *such as* impetigo, *approved* in 2007.

Mupirocin (Bactroban®)#

Mupirocin (Pseudomonic acid) is *rapidly* inactivated *after* absorption, and systemic *levels* are *undetectable*, so it is used *only* as topical preparations (3 times daily).
Mupirocin is a protein synthesis inhibitor that is *useful* in impetigo & *other* Gm +ve *including* MRSA; *should not* be *applied for longer than* 10 days to *avoid* bacterial resistance.

Nucleic Acid Inhibitors

Quinolones and Fluoroquinolones

Classification According to Generation

First — Quinolones

Nalidixic acid
Cinoxacin

- First generation ⇨ Quinolones.
- Second, Third and Fourth ⇨ Fluoroquinolones.
- First generation less used today.
- Moderate activity against Gram - ve.
- Nalidixic acid is the first quinolone drug (was introduced in 1962) during the manufacture of Quinine.

Second — Fluoroquinolones

Ciprofloxacin
Norfloxacin
Ofloxacin
Enoxacin
Pefloxacin
Lomefloxacin

- Expanded activity against Gram - ve (including *Pseudomonas* species)
- Some activity against Gram + ve.
- Some activity against atypical bacteria such as Mycoplasma and Chlamydia.

Third — Fluoroquinolones

Levofloxacin
Sparfloxacin
Grepafloxacin

- Retain expanded Gram - ve activity
- Improve activity against gram +ve and atypical bacteria.

Fourth — Fluoroquinolones

Trovafloxacin
Moxifloxacin
Gatifloxacin
Gemifloxacin

- They are also called respiratory Fluoroquinolones.
- Improve activity against Gram +ve.
- Gains anaerobic coverage.

There is another classification (1997) includes only Trovafloxacin in fourth generation

Antifolates

A) Sulfonamides

B) Dihydrofolate Reductase (DHFR) inhibitor (**Trimethoprim** and **Pyrimethamine**)

First Generation

Nalidixic acid (NegGram®)# (Nalidram®)#

Second Generation

Ciprofloxacin (Cipro®)# (Ciprofar®)# (Ciprobay®)# (Rancif®)# (Serviflox®)#

Norfloxacin (Noroxin®)# (Noracin®)#

Ofloxacin (Tarivid®)# (Kiroll®)

Enoxacin (Penetrex®)# (Enroxil®)

Lomefloxacin (Lomax®)# (Lomeflox®)#

Third Generation

Levofloxacin (Tavanic®)# (Tavacin®)# (Levoxin®)# >>>

Sparfloxacin (Parox®) (Spara®) (Zagam®)

Fourth Generation

Moxifloxacin (Avalox®)# (Moxiflox®)#

Gatifloxacin (Tequin®) (Floxin®)

Gemifloxacin (Flobiotic®)# (Factive®)# (Quinabiotic®)# (Gemique®)

- ***Over* 10,000 Fluoroquinolone analogs** have been **synthesized**, including ***several*** with *wide* **clinical applications**

Fluoroquinolones available for ***systemic*** **use** in the **US** include; **Ciprofloxacin**, **Levofloxacin**, **Ofloxacin**, **Gemifloxacin** and **Moxifloxacin**.

All **Fluoroquinolones** are ***rapidly*** **absorbed**; **bioavailability**; **80-95%**, **Norfloxacin**, **Gemifloxacin** and **Ciprofloxacin** are ***lower*** **bioavailability**; **Calcium**, **Iron**, **Zinc**, **Sucralfate** and **Antacids** ***reduce*** the **absorption**; ***oral*** **Fluoroquinolones** ***should be*** **taken** **2 hours** ***before*** or **4 hours** ***after*** ***any*** **products** ***containing these*** **cations**.

Ophthalmic preparations; **Ciprofloxacin** (**Ciloxan**®), **Levofloxacin** (**Quixin**®), **Gatifloxacin** (**Zymar**®) & **Moxifloxacin** (**Vigamox**®); **IV** ***preparations*** of ***this drugs*** are ***available***.

Concentrations of **Fluoroquinolones** are ***above*** *those* in **serum** in **bone**, **urine**, **kidney**, **prostatic** and **lungs**;

- ***Lowest*** **urine concentrations** are **Moxifloxacin** and **Gemifloxacin** (***not used*** in **UTIs**).
- ***Highest*** **urine concentrations** are **Gatifloxacin** and **Levofloxacin** (***excreted*** by the **kidney** completely **unchanged**).

Ciprofloxacin and **Ofloxacin** have ***good penetration*** into **CSF** in **inflamed meninges**.

Most **Fluoroquinolones** are ***excreted*** **renally** (**dosage adjustments** are ***needed*** in **renal dysfunction**); **Moxifloxacin** is ***excreted*** **primarily** by the **liver** (***no dose*** **adjustment** is ***required for*** **renal impairment**); **dosage adjustments** are ***needed*** in **liver dysfunction**.

Levofloxacin, **Gemifloxacin**, **Gatifloxacin** and **Moxifloxacin** has ***relatively*** **long half-lives**, ***permit*** ***once***-**daily dosing**.

Mechanism; **Bactericidal**; **Fluoroquinolones** ***block*** **bacterial DNA** ***synthesis*** by ***inhibiting*** bacterial **Topoisomerase II** (**DNA Gyrase**) and **Topoisomerase IV**.

- ***Inhibition*** of **DNA Gyrase**; ***more significant*** in **Gram -ve**;
  - **Agents** with ***higher*** **affinity** for **Topoisomerase II** (*such as* **Ciprofloxacin** and **Levofloxacin**) ***more potent*** **activity** ***against*** ***Pseudomonas aeruginosa***.
- ***Inhibition*** of **Topoisomerase IV**; ***more significant*** in **Gram +ve**.
  - **Agents** with ***higher*** **affinity** for **Topoisomerase IV** (*such as* **Moxifloxacin**, **Gemifloxacin** and **Gatifloxacin**) ***more potent*** **activity** against ***Streptococcus pneumoniae***.

Spectrum of activity;

- **Quinolones** such as **Nalidixic acid** did ***not achieve*** **systemic antibacterial** ***levels*** and were **useful** ***only*** in the **treatment** of ***lower*** **Urinary Tract Infections** (**UTIs**).
- **Fluorinated** ***derivatives*** (**Fluoroquinolones**) ***achieve*** **bactericidal** ***levels*** in **blood** & **tissues**.
- **Fluoroquinolones** were ***originally*** **developed** ***because excellent*** **activity** ***against*** **Gram -ve** **aerobic**; ***E. coli***, ***Pseudomonas aeruginosa***, ***Haemophilus influenzae***, ***Klebsiella pneumoniae***, ***Legionella pneumophila***, ***Proteus mirabilis***, ***Shigella*** and ***Enterobacter*** **spp**.
- ***Several*** **newer agents** have ***improved*** **activity** ***against*** **Gram +ve** ***cocci***.
- **Norfloxacin** is the ***least*** **active** of **Fluoroquinolones** ***against*** *both* **Gram -ve** & **Gram +ve**.
- **Ciprofloxacin**, **Enoxacin**, **Lomefloxacin**, **Ofloxacin**, **Levofloxacin** and **Pefloxacin** ***possessing*** ***excellent*** **Gram -ve** ***activity*** and ***moderate*** to ***good*** **activity** ***against*** **Gram +ve**.
- **Ciprofloxacin** (**THE BEST**) & **Levofloxacin** are ***most potent*** **activity** ***against*** ***P. aeruginosa***.
- **Levofloxacin** has ***superior*** **activity** ***against*** **Gram +ve** ***organisms***, including ***S. pneumoniae***.
- **Moxifloxacin** (**THE BEST**), **Gatifloxacin** & **Gemifloxacin** ***improved*** **activity** ***against*** **Gm +ve** ***organisms***, ***particularly*** ***Streptococcus pneumoniae*** and ***some staphylococci***.
- **Moxifloxacin** is the ***only approved*** has ***modest*** **activity** ***against*** **anaerobic** ***bacteria***.

Indications;

Ciprofloxacin (**Cipro**®), (**Ciprofar**®),(**Ciprobay**®), (**Rancif**®),(**Serviflox**®), >>>

* **Urinary Tract Infections**; *Adult and Children*
* **Urethral** & **Cervical Gonococcal Infections**.
* **Anthrax** & **Plague** (*prophylaxis* & *ttt*); *Adult & Children*
- **Intra-abdominal Infections**.
- **Skin/Skin Structure Infections**.
- ***Lower*** **Respiratory Tract Infections**.
- **Empirical Therapy** in **Febrile Neutropenic Patients**.
- ***Non-cystic*** **Fibrosis Bronchiectasis**; *Dry powder for inhalation*.
* ***Chronic*** **Bacterial Prostatitis**.
* **Infectious Diarrhea**.
* **Typhoid Fever**.
- **Bone** & **Joint Infections**.
- ***Acute*** **Sinusitis**.
- ***Nosocomial*** **Pneumonia**.

Levofloxacin (Tavanic®)# (Tavacin®)# (Levoxin®)# >>>
* *Uncomplicated* & *Complicated* Urinary Tract Infections. * *Chronic* Bacterial Prostatitis
* Anthrax & Plague (*prophylaxis* & *ttt*); *Adult & Children* * Acute Pyelonephritis.
- *Acute* Bacterial Sinusitis & *Community*-Acquired Pneumonia; *Adult (and Children off-label)*
- *Acute* Bacterial Exacerbation of Chronic Bronchitis. - *Nosocomial* Pneumonia.
- Skin/Skin Structure Infections. - Epididymitis & Acne (*Off-label*).
- *Pseudomonas aeruginosa* Pulmonary Infections (Quinsair®); Inhalation.

Moxifloxacin (Avalox®)# (Moxiflox®);
* *Acute* Bacterial Sinusitis. * *Community*-Acquired Pneumonia.
* *Acute* Exacerbation of Chronic Bronchitis. * Skin & Skin Structure Infections.
- Intra-abdominal Infections. - Pneumonic & Septicemic Plague.

- Fluoroquinolones has also *activity against M. tuberculosis*.
- Ofloxacin and Levofloxacin are *second line therapy* for *Chlamydia* Infection *after* Azithromycin 1 g *single dose* or Doxycycline 100 mg *twice* daily *for* 7 days.
- *Doses*; Ciprofloxacin and Levofloxacin are *available as* oral suspensions in *many* countries.

Agent	Usual Adult Dose	Usual Children Dose
Ciprofloxacin	500-750 mg orally every 12 hours OR 400 mg IV every 12 hours	10 mg/kg orally or IV every 12 hours (Ciprofloxacin and Levofloxacin are the *only* Fluoroquinolones *used* in pediatrics and children)
Norfloxacin	400-800 mg orally every 12 hours	<18 years: Safety and efficacy not established
Ofloxacin	200-400 mg orally every 12 hours	<18 years: Safety and efficacy not established
Levofloxacin	500-750 mg orally/IV every 24 hrs	8 mg/kg orally/IV every 12 hours
Moxifloxacin	400 mg orally/IV every 24 hours	<18 years: Safety and efficacy not established
Gatifloxacin	200-400 mg orally/IV every 24 hrs	<18 years: Safety and efficacy not established
Gemifloxacin	320 mg orally every 24 hours	<18 years: Safety and efficacy not established

Side Effects; *In general*; Fluoroquinolones are *generally* well tolerated. Like *most* antibiotics, *most common* side effects are nausea, vomiting and diarrhea.

CNS; *Common*; Headache, dizziness & insomnia. *Less common*; Hallucinations & depression. *Rare*; Neurotoxicity (Seizures) *inhibit* GABA; [*especially with* Norfloxacin and Ciprofloxacin]; *Only* in patients *underlying* neurologic diseases (epilepsy), *renal* insufficiency or *concomitant* use of neurotoxic drug.

Cardiovascular; QT interval *prolongation* [*especially with* Levofloxacin, Gatifloxacin, Gemifloxacin and Moxifloxacin].Moxifloxacin *carries* the *greatest* risk, *while* Ciprofloxacin *appears to* be *associated with* the *lowest* risk.

Dermatologic; Photosensitivity; *Severe* sunburns *may occur*; can be *avoided* or *prevented* by *avoiding* *exposure* to sunlight or *should be* *advised to* use sunscreen.

Musculoskeletal; Articular Cartilage Erosion (Arthropathy) has *been observed*. *Thus*, these drugs are *not routinely* *recommended for* patients *under* 18 years *of* age (*Except*; Ciprofloxacin and Levofloxacin in *some* indications).
- Tendon rupture; a *rare* complication that has been *reported in* elderly, *patients with* renal dysfunction and *those* taking Corticosteroids.

Glucose Metabolism; Gatifloxacin has been *associated with* hyperglycemia in diabetic patients and *with* hypoglycemia in patients also *receiving* oral hypoglycemic *agents* (*was withdrawn in US in* 2006).

In 2016; FDA *required* the *addition* of a warning for all systemic Fluoroquinolones that *their* risks *outweigh* *their* benefits for *most cases* of sinusitis, bronchitis, and *uncomplicated* UTIs *unless* other options are *not* available.

PATIENT COUNSELLING

1) *Don't take* with calcium-rich foods as; milk & milk products.
2) *Don't take* with *other drugs specially*; Ca, Iron and Antacids.
3) *Don't take* with Corticosteroids *especially* in elderly and patients *with* renal dysfunction.
4) *Don't used* for children *less than* 18 years and pregnancy.
5) *Used cautiously* in epileptic patients.
6) *Avoid* sun exposure OR *Use* sun screen.
7) *Need* dose adjustment in kidney failure (*except* Moxifloxacin).

Antifolate Antibiotics

Co-Trimoxazole (Trimethoprim/Sulfamethoxazole) (Septrin-D.S.®)#

Combining the Sulfonamide (Sulfamethoxazole; SMX) with Dihydrofolate Reductase (DHFR) *inhibitor* (Trimethoprim; TMP); the **generic name** for the ***combination*** is Cotrimoxazole; ***provides*** a synergistic combination.

Cotrimoxazole OR Sulfamethoxazole (SMX)/Trimethoprim (TMP) is the ***most widely*** used antifolate; ***broad-spectrum*** **against** *both* **Gram +ve & Gram -ve** ***bacteria*** and ***some*** **protozoa**.

Mechanism; Cotrimoxazole ***blocks*** **2 consecutive** ***steps*** in the ***biosynthesis*** of **nucleic acids** in ***many*** **bacteria**.

1) ***Due to*** **structural similarity** *between* Sulfonamides &P-Amino-benzoic acid (PABA) ⇨ ***Compete*** with PABA ⇨ ***Inhibition of*** Dihydropteroate synthase.
2) Trimethoprim ***inhibits*** Dihydrofolate reductase.
* From 1 and 2 ⇨ ***Inhibit of*** Folic acid ***synthesis*** which is ***essential for*** *synthesis of* **DNA**.

Advantage of combination (SMX/TMP);

- **Synergistic effect**.
- ***Decrease*** the **bacterial resistance**.
- **Bactericidal action**.
- ***Decrease*** the **dose** of **each one**.
- ***Increase*** the **spectrum of activity**.

Spectrum of activity; ***Staphylococcus aureus*** (*including* many **MRSA strains**), ***Streptococcus pneumoniae***, ***Streptococcus pyogenes*** ***Haemophilus influenzae***, ***Escherichia coli***, ***Salmonella***, ***Shigella***, ***Klebsiella pneumoniae***, ***Nocardia***, ***Stenotrophomonas maltophilia***, ***Listeria monocytogenes*** & ***Pneumocystis jirovecii***.

Indications; **Urinary tract infections**, **respiratory tract infections** and **gastrointestinal tract infections** and ***other*** **infections** caused by ***sensitive*** **organisms**.

Dose; TMP/SMX *comes* in a ***fixed*** **1:5 ratio** of the ***two*** **components**.

- **Tablets**; - ***Single***-**strength**; Septrin® (80:400 mg TMP:SMX).
  - ***Double***-**strength**; Septrin-D.S.® (160:800 mg TMP:SMX); 1-2 tab. orally every 12-24hr.
- **Oral Suspension**; **>2 months**; 8-10 mg TMP/kg/day PO divided every 12hr.
- **IV**; 8-20 mg TMP/kg/day IV *every* 6-12hr.

Side Effects;

Dermatologic: - **Rash** (***much*** **more common** in **AIDS patients** and ***severe*** in **elderly**).
- **Stevens-Johnson syndrome** *also occur* *but* **rare**.

GIT; **Nausea**, **vomiting** and **diarrhea**.

Hematologic; - **Bone-marrow suppression** (dose-dependent).
- **Hemolytic anemia**; *may occur* in **patients** *with* **G6PD** ***deficiency***.

Renal; **Crystalluria** (blood urea and creatinine elevations), **acute interstitial nephritis** and can ***lead to*** **acute renal failure** (*very rare*).

Electrolytes; **Hyperkalemia**.

Newborns; **Kernicterus** (Bilirubin-induced brain dysfunction; Neurotoxic hyperbilirubinemia).

Contraindications; **hypersensitivity** to **sulfa**, **Age <2 months**, **CrCl <15 mL/min**, **G6PD deficiency** (**Favism**), **hepatic impairment**, **pregnancy** and **nursing mothers**.

Drug interactions; - ***Increase*** **concentration** of Phenytoin and Warfarin (inhibit metabolism).
- ***Increase*** **concentration** of Methotrexate (displacement from plasma proteins).

N.B.; Trimethoprim is ***about*** **50,000 times** ***less efficient*** in ***inhibition*** of **mammalian Dihydrofolic acid reductase**. Trimethoprim is **20- to 50-fold** ***more*** **potent** ***than*** the Sulfonamides.

Sulfadiazine/Pyrimethamine

Sulfadiazine/Pyrimethamine is used ***for*** **Toxoplasmosis**.

Sulfadoxine/Pyrimethamine (Fansidar®)

Sulfadoxine/Pyrimethamine is used as **antimalarial drug**.

Urinary Tract Antiseptics

- Urinary tract infections (UTIs) are *prevalent* in women *of* child-bearing age and in the elderly.
- *E. coli* is the *most common* pathogen, causing *about* 80% of *uncomplicated upper* and *lower* UTIs.
- *Staphylococcus saprophyticus* is the *second* most common bacterial pathogen causing UTIs.
- *In addition to* Fluoroquinolones, Cotrimoxazole and Fosfomycin UTIs may be *treated with* any one of a group of agents *called* urinary tract antiseptics.
- Urinary tract antiseptics *do not* achieve antibacterial levels in the circulation, but because they are *concentrated* in the urine, microorganisms at that site can be *effectively* eradicated.

Nitrofurantoin (Uvamin® retard)# (Macrodantin®)# (Macrobid®)#

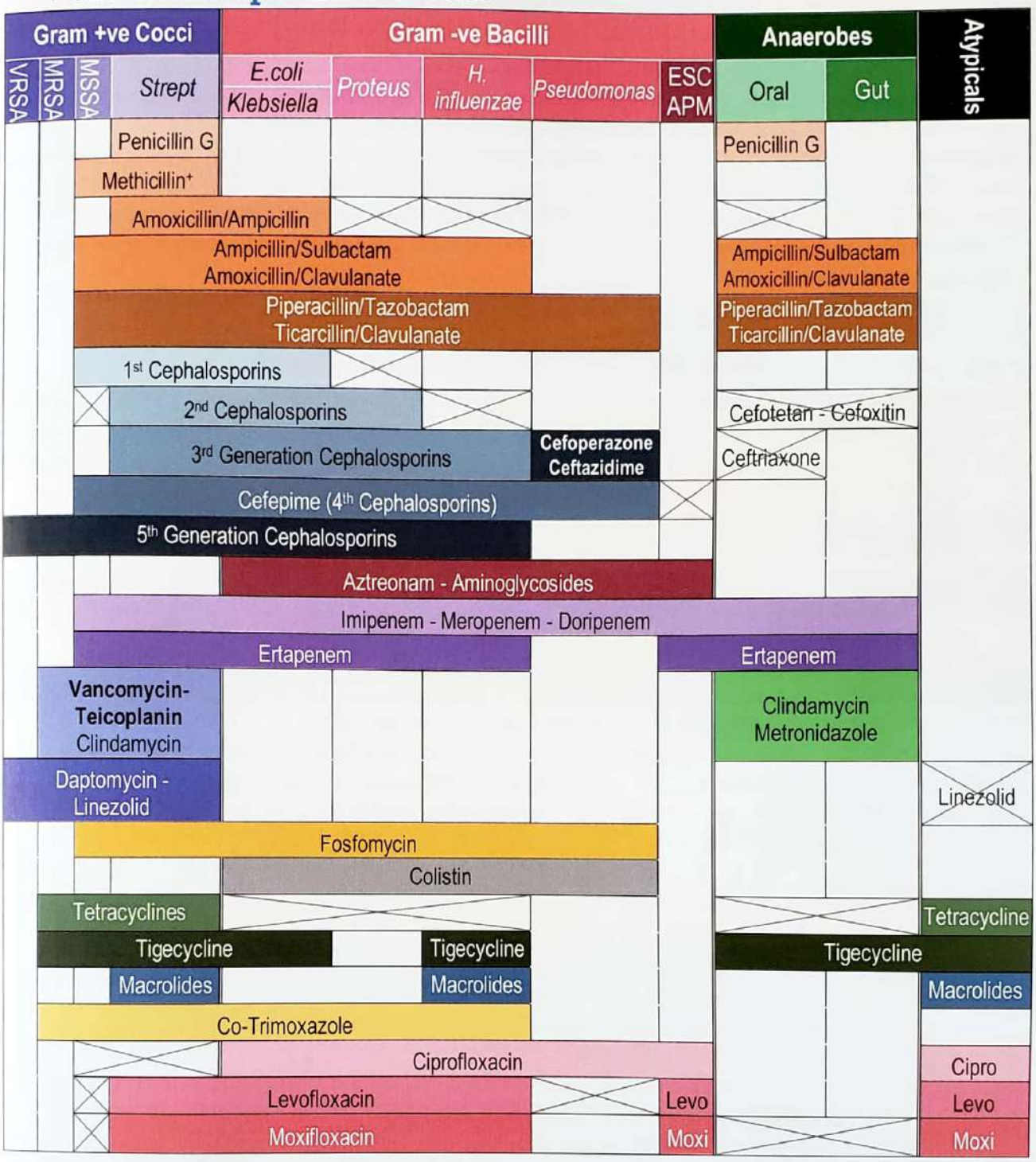
Nitrofurantoin is the *most common* urinary tract antiseptic.
Formulations and *absorption*;
  # Nitrofurantoin Monohydrate; *well* absorbed (*higher* dissolution); *more* GI distress.
  # Nitrofurantoin Macrocrystals (Uvamin® retard & Macrodantin®) absorbed *more* slowly (*slower* dissolution); *less* GI distress; 4 *times* daily.
  # 75 mg Monohydrate + 25 mg Macrocrystal *formulation* (Macrobid® 100); *twice* daily.
Nitrofurantoin is metabolized and excreted *rapidly* (*no systemic* antibacterial action).
Nitrofurantoin is bactericidal for *many* Gram +ve and Gram -ve *bacteria*; such as *Escherichia coli*, *Staphylococcus saprophyticus*, *Enterobacter* species, *Klebsiella* species and *Staphylococcus aureus*.
Pseudomonas aeruginosa and *many strains* of *Proteus* and *some* of *Klebsiella* are *inherently* resistant to Nitrofurantoin.
Doses; *Take* with food or milk to *improve* absorption and *decrease* GI distress.
- Macrocrystals; 50-100 mg orally every 6 hours for 7 days or for 3 days after obtaining sterile urine.
- Monohydrate/Macrocrystals; 100 mg orally every 12hr for 7 days or for 3 days after obtaining sterile urine.
- *Children*; >1 month-12 years (Macrocrystals *only*); 5-7 mg/kg/day orally divided every 6 hors for 7 days.

Pregnancy; US FDA category B.
Contraindications & *precautions*; ###### PATIENT COUNSELLING
  # *Significant* renal insufficiency (Creatinine Clearance < 60 mL/min).
  # Hepatic dysfunction or cholestatic jaundice.
  # Pregnancy at term (38-42 weeks of *gestation*).
  # Neonates (<1 month).
  # *Caution* in patients with G6PD deficiency (risk for hemolytic anemia).
  # *Avoid* long-term use in the elderly (risk for pulmonary toxicity).
#*Side effects*;- *Most common*; GI disturbances (Nausea and vomiting); *Take* with food or milk.
- *Rare*; pulmonary toxicity and neurologic problems.

Methenamine

Methenamine or Hexamethylenetetramine is a urinary tract antiseptic, it is *decomposes* at an acidic pH of 5.5 or *less* in the urine, thus *producing* Formaldehyde, which *acts* locally and is toxic to most bacteria.
Bacteria *do not* develop *resistance* to Formaldehyde, which is an *advantage* of this drug.
Dose;
  - *Adult*; Methenamine mandelate; 1 g 4 *times* daily - Methenamine hippurate; 1 g *twice* daily.
  - *Children*; Methenamine mandelate; 50 mg/kg/d - Methenamine hippurate; 30 mg/kg/d.
Acidifying agents (*such as* Ascorbic acid; 4–12 g/d) may be given to *lower* urinary pH *below* 5.5.
Sulfonamides *should not* be given at the *same time* *because* they *may* form an *insoluble* compound with the Formaldehyde.
Side effects; *Most common*; GI disturbances.

➢ Antibiotic Spectrum Guide:-



Coloured	***Good*** to ***excellent*** activity
	Moderate activity
	Little to ***no*** activity
Methicillin+	**Methicillin Group (Nafcillin - Oxicillin - Cloxacillin - Dicloxacillin - Flucloxacillin)**
ESCAPM*	*Enterobacter* spp., *Serratia* spp., *Citrobacter freundii*, *Aeromonas* spp., *Providencia* spp. and *Morganella morganii*.

➢ Topical Antibacterial Agents:-

Bacitracin	Polymyxin	Fusidic Acid	Mupirocin
Erythromycin	Clindamycin	Neomycin	Gentamicin
	Retapamulin	Dapsone	

Anti-Mycobacterial

- **Mycobacteria** are ***resistant*** to ***most*** **antibiotics**; *because* they **grow** ***more*** **slowly** *than* ***other*** **bacteria**, **antibiotics** that are ***most active*** *against* ***rapidly*** **growing cells** are ***relatively*** **ineffective**.
- **Mycobacteria cell walls** contain **mycolic acids**.
- **Antimycobacterial drugs** are used for the ***treatment*** of **mycobacterial infections**, ***including*** **tuberculosis** (*Mycobacterium tuberculosis*), **leprosy** (*Mycobacterium leprae*) and ***non*****tuberculous mycobacteria** (These species include; *Mycobacterium avium* **complex** (MAC) [*Mycobacterium avium-intracellulare*], *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium kansasii*, and *Mycobacterium fortuitum*).

Anti-Tubercular Drugs

- **Tuberculosis** (TB) is an **infectious disease** *caused by* the **bacterium** *Mycobacterium tuberculosis*.
- **TB** is a *multi-systemic* **disease** affects ***mainly*** the **lungs**, ***but*** can also ***affect*** *other* **parts** of the **body**.
- The **classic symptoms** of ***active*** **TB** are a *chronic* **cough** with *blood-containing* **sputum**, **fever**, **night sweats** & **weight loss**. **TB treatment** ***generally*** includes **4** *first-line* **drugs**.
- **Second-line drugs** are *typically* ***less*** **effective**, ***more*** **toxic**, and ***less*** **extensively studied** and used for **patients** who ***cannot*** **tolerate** the ***first-line*** **drugs** or **who** are ***infected*** with ***resistant*** **TB**.

First-line

1) Rifamycins (RIF)

Rifampicin or Rifampin (RIF) (Rimactane®)#

- **Rifampicin** ***inhibits*** **bacterial DNA-*dependent* RNA polymerase**.

Rifampin is ***used*** in ***combination*** with **other anti-tuberculous drug** (**Isoniazid**, **Pyrazinamide** and **Ethambutol**); **Rimactazide®**; **Rifampin 300 mg + Isoniazid 150 mg**.

Rifampicin is **potent** **CYP450 inducer**, ***leading*** to ***numerous*** **drug interactions**.

Uses; - **Mycobacterial Infections**; **10 mg/kg/day** ***orally*** OR **10 mg/kg** ***orally*** **twice weekly** (*usually* 600 mg/d; not to exceed 600 mg/day), ***must be*** **administered** *with* **Isoniazid** or ***other*** **antituberculous drugs** to **patients** with **active tuberculosis** to ***prevent*** **emergence** of **drug-resistant mycobacteria**.

- **Neisseria Meningitidis Carrier**; 600 mg twice daily for 2 days.
- **Haemophilus Influenzae *Type B* Infection Prophylaxis**; 600 mg/day orally/IV for 4 days.

Side Effects; # **Nausea**, **vomiting** and **rash** are the ***most common***.

Orange-red ***discoloration*** *of* **urine**.

Hepatotoxicity (transient abnormalities in liver function tests) & **Jaundice**; ***incidence*** of **hepatic dysfunction** ***increased*** when **Rifampicin** is co-administered with **Isoniazid**.

Flu-like symptoms, **acute renal failure**, **hemolytic anemia**, **thrombocytopenia** and **shock** *may occur* in ***high*** **doses**.

Rifabutin (Mycobutin®)

Rifabutin is ***preferred for*** **Mycobacterium avium complex** (**MAC**).

- **MAC** *infections* are ***most*** **common** in **patients** ***with*** **human immunodeficiency virus** (**HIV**), who are often taking **antiretroviral therapy** that is ***metabolized by*** **CYP450**. ***Because*** **Rifabutin** **less-potent** **CYP450 inducer** ***than*** **Rifampicin**; **Rifabutin** is usually ***preferred*** in **MAC**.

Side effects; ***Like*** **Rifampicin** **but** can also ***cause*** **neutropenia**.

Rifapentine (Priftin®)

Rifapentine has **activity** ***greater than*** **Rifampicin**, and it also has a ***longer*** **half-life**, *may be* ***used*** **once** ***weekly***.

Side effects; ***Like*** ***other*** **Rifamycins** **but** can also ***cause*** **hyperuricemia**.

2) Isoniazid (INH)

Isoniazid (INH)

Isoniazid, *also known as* **Iso-Nicotinyl-Hydrazide (INH)**, *along with* **Rifampicin**, is **one** of the **two *most important* TB drugs**. # The **structural *similarity*** to **pyridoxine (Vitamin B6)**.
It is ***never*** **given** as a ***single*** **agent** in the *treatment of* **active tuberculosis**.
Isoniazid is a ***drug of choice*** for the **treatment** of **latent tuberculosis**; It can be given as **monotherapy** for **latent** (**NOT** Active) **disease**.
Elimination Half-life; ***Pharmacogenomic metabolism***; - ***Fast*** **acetylators**: **30-100 min**. - ***Slow*** **acetylators**: **2-5 hrs**.
Isoniazid is **active *only*** **against** ***Mycobacterium tuberculosis*** & ***Mycobacterium kansasii***.
Mechanism; **Isoniazid *prevents*** the **synthesis** of **mycolic acids** in the **cell wall**.
- ***Doses***; - **5 mg/kg/d** (300 mg orally once daily); Typical dose.
- **10 mg/kg/d** (600 mg orally once daily); For serious infections or in malabsorption.
- **15 mg/kg dose** (900 mg orally) once or twice-weekly.

Side effects; # **Peripheral neuropathy (*dose-related*)**; **25–50 mg/d** of **Pyridoxine (Vitamin B6)**.
Hepatotoxicity (*Mild* ***increase*** **liver function tests**); ***Like other*** **Rifamycins**.
GI reactions; **Nausea**, **vomiting**, **stomach pain** & **Hypersensitivity reactions**.
Drug Interactions; **Isoniazid** can ***reduce*** the **metabolism** of **Phenytoin** (**CYP450 *inhibitor***).

3) Pyrazinamide (PZA)

Pyrazinamide (PZA) (P.T.B®)

Pyrazinamide (PZA) is a ***synthetic*** **relative** of **Nicotinamide**, **only** **used** in ***combination*** with **Isoniazid**, **Rifampin** and **Ethambutol**.
It is ***generally*** **used *only*** in the ***first*** **2 months** of **tuberculosis therapy**.
Pyrazinamide is ***well*** **absorbed orally**, ***widely*** **distributed** in **body tissues**, *including* **inflamed meninges** (100%); **effective** *with* **Rifampin** & **Isoniazid** in **tuberculous meningitis**.
Pyrazinamide is **active *only*** **against** ***Mycobacterium tuberculosis***.
- ***Doses*** (# *usually discontinued after* ***2 months*** *of a 6-month regimen* #);
- **Daily therapy**; (Non-HIV); 15-30 mg/kg orally once daily; maximum: 2 g/day.
- OR; **Twice weekly Directly Observed Therapy (DOT)**; 50 mg/kg orally twice weekly; maximum: 2 g/day.
- **HIV-exposed/infected**; 20-40 mg/kg/dose once daily; maximum: 2 g/day.
- **Renal Dose**; (CrCl < 30 mL/min or hemodialysis); 25-35 mg/kg per dose three times per week.

Side effects; **Hyperuricemi**, **Hepatotoxicity** and **Arthralgias** (joint pain).
- N.B.; If **hyperuricemia** is ***accompanied by*** **acute gouty arthritis**, **Pyrazinamide** ***should be*** **discontinued**.

4) Ethambutol (EMB)

Ethambutol (EMB) (Etibi®)

Ethambutol is a ***first-line*** **drug** for the **treatment** of ***both*** **active tuberculosis** and **MAC infections** (***along with*** **Macrolides** and **Rifabutin** *for* **MAC infections**).
Ethambutol ***like*** **others**, it's **used** **only** in ***combination*** in the *treatment of* **active tuberculosis**.
Ethambutol can be **used** as a ***substitute*** for **Rifampin** in **patients** who are ***unable*** to take **Rifampin** ***during*** the **Continuation Phase** (***after*** **2 months**) of **active tuberculosis *therapy***.
Spectrum; ***Mycobacterium tuberculosis***, ***Mycobacterium avium*** & ***Mycobacterium kansasii***.
- ***Doses***; - **Daily therapy**; 15–25 mg/kg orally once daily.
- **Directly Observed Therapy (DOT)**; 40 mg/kg orally twice a week or 30 mg/kg orally 3 times a week.

Ethambutol is ***very*** **well** ***tolerated***, ***unlike*** **others** (**Rifampin**, **Isoniazid** and **Pyrazinamide**) it's ***not*** ***associated*** with **hepatotoxicity**.
Side effects; **Optic Neuritis** *OR* **Retrobulbar Neuritis**; **Ethambutol = Eyes**;
- ***Diminished*** **visual acuity**.
- ***Loss*** of **ability** to **discriminate** ***between*** **red** & **green** (**Red-green *color* blindness**).
- ***Not recommended*** in **children < 5 years** old; difficult to monitor visual acuity.
- **Vision tests** *needed for* **monitoring**.

- ***Other side effects***; **Peripheral neuropathy** and **hyperuricemia**.

Drug Regimen Example (2HREZ/4HR3)

Rifampicin; **RIF** or **R** - **Isoniazid**; **INH** or **H** - **Pyrazinamide**; **PZA** or **Z** - **Ethambutol**; **EMB** or **E**
- **2HREZ/4HR3**; *means*; **Isoniazid**, **Rifampicin**, **Ethambutol**, **Pyrazinamide** ***daily*** for **2 months**, *followed by* **4 months** of **Isoniazid** and **Rifampicin** given **3 *times*** a **week**.

Second-line

- **Second-line drugs** are ***only*** **used** to **treat disease** that is ***resistant*** to **first-line therapy** (**Multi-Drug Resistant TB**; **MDR-TB**).
- **Second-line drugs** (WHO Tuberculosis Guidelines 4th edition);
  - ***Aminoglycosides***; **Streptomycin**, **Amikacin** and **Kanamycin**.
  - ***Fluoroquinolones***; **Ofloxacin**, **Levofloxacin** and **Moxifloxacin**.
  - ***Polypeptides***; **Capreomycin**.
  - ***Thioamides***; **Ethionamide** and **Prothionamide**.
  - ***Others***; ***p*-aminosalicylic acid**, **Cycloserine** and **Terizidone**.

Third-line

Third-line drugs are drugs that ***may be*** **useful**, ***but*** have **doubtful** or **unproven** ***efficacy***:
Third-line drugs (WHO Tuberculosis Guidelines 4th edition); **Clofazimine**, **Linezolid**, **Co-Amoxiclav**, **Thioacetazone**, **Imipenem/cilastatin**, *high-dose* **Isoniazid** & **Clarithromycin**.

Anti-Lepral Drugs

- **Leprosy** (**Hansen's disease**) is a ***chronic*** **infectious disease** caused by ***Mycobacterium leprae***.
- ***M. leprae*** **multiplies** ***slowly*** and ***incubation*** **period** of the **disease**, on ***average***, is **5 years**. *In some cases*; **symptoms** may *occur* ***within*** **1 year** but can also take as ***long as*** **20 years** to ***occur***.
- **Leprosy** ***mainly*** **affects**; **skin**, **peripheral nerves**, **mucosa** of **upper respiratory tract**, and *also* **eyes**.
- ***Prevalence***; **< 1 case** ***per*** **10,000** ***persons*** was achieved globally in the **year 2000**.
- **Leprosy** can be **treated** ***effectively*** with **Dapsone**, **Rifampicin** and **Clofazimine**.

A 24-year-old man with leprosy (1886)

Dapsone

Dapsone (**Di-amino di-phenyl sulfone**) is **structurally** ***related to*** the **sulfonamides** and **similarly** ***inhibits*** **dihydropteroate synthetase** in the **folate synthesis** ***pathway***.
Dapsone used in ***combination*** *with* **Rifampicin** and **Clofazimine** for the ***treatment of*** **leprosy**.
- It may also be **used** to ***prevent*** and ***treat*** ***Pneumocystis jiroveci*** **pneumonia** *in* **AIDS patients**.
- ***Other Uses***; **Dermatitis Herpetiformis** and **Toxoplasmosis**.
Usual adult **dosage** in **leprosy**; **100 mg** ***daily*** in ***combination with*** other **antileprosy drugs**.
Common side effects; **Hemolysis** (with **favism**) and **Methemoglobinemia**.

Rifampicin

Rifampicin (*see previous topic*) is **only** ***given*** in ***combination*** in a **single** **monthly** ***dose*** of **600 mg** in **adult** ***with*** **Dapsone** and **Clofazimine**.

Clofazimine (Lamprene®)

Clofazimine is a ***phenazine dye***, *works by* ***inhibiting*** **bacterial DNA synthesis**.
It is **used** ***for***; - **Dapsone-sensitive leprosy**; **50 mg orally daily** in ***combination*** *with* **Dapsone** and **Rifampicin**.
  - **Dapsone-resistant leprosy** or when patients are ***intolerant*** to **sulfones**; **100 mg** ***orally*** **daily** in ***combination*** *with* **1** or ***more*** other **antileprosy drugs**.
Clofazimine has some **anti-inflammatory** and **anti-immune** ***activities***, thus, **erythema nodosum leprosum** *may* ***not develop*** in **patients** ***treated*** *with* ***this*** **drug**.
Common side effects; #**Skin discoloration** *ranging from* **red-brown** to ***nearly*** **black** (75-100%).
  # **GI intolerance**; **Nausea**, **vomiting** and **stomach pain** (40-50%).
  #**Ichthyosis** and **dry skin** (8-28%).

Drug Regimen Example

MDT-Combi® packs; *donated by* **Novartis** for **WHO Multi-Drug Therapy** (**MDT**) ***regimens*** for **Leprosy**. *Each* **blister** of **MDT-Combi® pack** ***contains*** *treatment for* **4 weeks**.

Antifungal Drugs

Infectious diseases *caused by* fungi (**fungal infections** or **mycotic infections** or **mycoses**); are *often* **chronic** in **nature** and **many** of **mycoses** are **superficial** (*involve only* **outer layers** of the **skin** and **hair** , such as **Tinea versicolor**), while **others** ***may*** ***penetrate*** the **skin**, causing;
Cutaneous (**epidermis** and **nail**); *such as* **Tinea** (**ringworm**).
Subcutaneous (**dermis, subcutaneous tissues, muscle** and **fascia**); *such as* Debridement.
Systemic infections (*primarily* **lungs** and *may* other **organ systems**); *such as* Aspergillosis.
Serious systemic fungal infections ***less common*** **but** ***more serious*** and *increased* **incidence** in ***patients with chronic*** **immune suppression** ***due to*** **organ transplantation, cancer chemotherapy** or infection with **human immunodeficiency virus** (**HIV**); such as **aspergillosis, fungal endocarditis** and **fungal meningitis** (**cryptococcal meningitis**).

- *Unlike Bacteria*;
Fungi are **eukaryotic**, with ***rigid*** **cell walls** *composed largely* of **Chitin** ***rather than*** **peptidoglycan**.
Fungal cell membrane *contains* **Ergosterol** *rather than* the **cholesterol** *found in* **mammalian membranes**.
Cytochrome P450 (**CYP450**) enzyme (***C-14 α-demethylase***) in **fungal cell** *responsible for* ***demethylation*** of **Lanosterol** *to* **Ergosterol**.
Fungal infections are *generally* ***resistant to*** **antibiotics**, and *conversely*, **bacteria** are ***resistant to*** **antifungal agents**.

Antifungal agents or **Antimycotic agents** are **fungicide** or **fungistatic** ***used to treat*** & ***prevent*** **mycoses** such as; **athlete's foot, ringworm, candidiasis** (***thrush***), **serious systemic infections**

Systemic Antifungal for Systemic Infections

Polyene Antifungals

Amphotericin B (Fungizone®)# (AmBisome®)#

Amphotericin B ***remains*** the **drug of choice** for the *treatment of* ***several*** **life-threatening mycoses** (***broad*** **antifungal** ***spectrum*** and a **lack** of *available* **alternatives**).

Mechanism; ***Bind to*** **Ergosterol** in **cell membrane** → ***forming*** **pores** → **electrolytes** (*particularly* **potassium**) and **cell constituents** ***leak from*** the **cell** → **cell death**.

Amphotericin B is *nearly* ***insoluble*** in **water** and it *have* **renal** & **infusion toxicity**, therefore ***prepared*** in a ***several*** **formulations**; to ***improve*** **tolerability** and ***decrease*** **toxicity**, *but* may *show* ***different*** **pharmacokinetic characteristics** *compared to* **Conventional Amphotericin B**;
- **Amphotericin B Sodium Deoxycholate** (**ABD**). - **Amphotericin B Colloidal Dispersion** (**ABCD**).
- **Amphotericin B Lipid Complex** (**ABLC**). - **Liposomal Amphotericin B** (**LAmB**); ***high*** **cost**.
- *Recently* (2011); **AmbiOnp**; a ***novel*** **solid lipid nanoparticles** of **Amphotericin B** were ***formulated*** for **oral administration** for ***systemic*** **infections**.

- ***Uses***; - ***Antifungal***; **Life-threatening mycoses**, such as **Mucormycosis, Cryptococcal meningitis** and *certain* **aspergillus** and **Candidal infections**.
- ***Antiprotozoal***; **Visceral Leishmaniasis** and **Amoebic Meningoencephalitis**.

- ***Dose*** (*Usual Adult*); "Double-check that dose of amphotericin B; which formulation are using"
- **Conventional Amphotericin B**; 0.25-1 mg/kg IV infusion (***Should not exceed*** 1.5 mg/kg/d).
- **Liposomal Amphotericin B** (**LAmB**); 3-6 mg/kg/day IV.

- **Amphotericin B** in ***diluted*** **solutions** it is ***sensitive*** to **light** and is ***inactivated*** at ***low*** **pH** (***should be protected from*** **light** *during* **administration**).

Side effects; ######## **Amphotericin B PRECAUTIONS**

A) Infusion-Reactions; **Fever, chills, muscle spasms, vomiting, headache & hypotension.**
Can be attenuated by; # ***Slowing*** the **infusion rate**.
Using **initial dosing** ***regimen***.
Pre-medicating with **Acetaminophen**, **Hydrocortisone** and **Antihistamine**
Liposomal Amphotericin B has the ***lowest*** **incidence** of ***infusion-related*** **reactions**, while **Amphotericin B Colloidal Dispersion** has the ***greatest***.

B) Nephrotoxicity; **Renal tubular acidosis** and ***severe*** **hypokalemia** and **hypomagnesemia** (***Caution*** when **coadministration** with other drugs that cause **hypokalemia**; e.g., **corticosteroids**, **digoxin**).

C) Others; **Hepatotoxicity, Anemia & Thrombophlebitis** (decreased by adding heparin to infusion).

Antimetabolite Antifungals

Flucytosine or 5-Fluorocytosine (Ancobon®)#

Flucytosine or 5-Fluorocytosine (5-FC) was *discovered* in 1957 *during* a search for *novel* antineoplastic agents, but it was *without* anticancer properties, and *became* apparent that it was a *potent* antifungal agent. # # It is *specifically* used, *together with* Amphotericin B. #

Mechanism; Flucytosine *enters* the fungal cell *via* a cytosine permease *enzyme* (not found in mammalian cells), Flucytosine is *converted* intracellularly *first* to 5-fluorouracil (5-FU) and *then* to 5-fluorodeoxyuridine monophosphate (FdUMP) and Fluorouridine triphosphate (FUTP), which *inhibit* DNA, RNA and protein *synthesis*.

Amphotericin B *increases* cell permeability, *allowing* *more* Flucytosine to *penetrate* the cell and *leading to* synergistic effects.

Metabolism; *About* 10% by intestinal bacteria to 5-fluorouracil (5-FU).

Uses; Flucytosine is *not* used *as* a single agent *because* of;

It has synergistic effect with *other* agents.

To *avoid* the development of *secondary* resistance.

Flucytosine is used in *combination* *with*;

A) Amphotericin B for *treating* Candidiasis and Cryptococcosis.

B) Itraconazole (or Fluconazole) for *treating* Chromoblastomycosis.

Dose; 50-150 mg/kg/day orally *divided* *every* 6 hours.

Side effects;

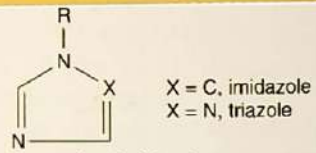
GI disturbances (nausea, vomiting, and diarrhea); are *common*.

Bone marrow suppression (anemia, leukopenia and thrombocytopenia); *result from* *metabolism* of Flucytosine to 5-fluorouracil by *intestinal* flora.

Reversible hepatic dysfunction (*elevation* of serum transaminases and alkaline phosphatase).

Azole (Triazole) Antifungals

- Azoles are a class of *five-membered* heterocyclic compounds *containing* a nitrogen *atom* and at *least* one other *non-carbon* atom (i.e. nitrogen, sulfur or oxygen) as *part* of the ring.
- Azoles that are *available for* clinical use are *classified as* either Imidazoles or Triazoles *according* to *number of* nitrogen *atoms*.



Azole Nucleus

Imidazoles (Ketoconazole, Miconazole & Clotrimazole); *now* used *only* topically.

Triazoles (Fluconazole, Itraconazole, Posaconazole & Voriconazole); used systemically.

Although these drugs *have* *similar* mechanisms of action and spectra of *activity*, their pharmacokinetics and therapeutic uses *vary* significantly.

Ketoconazole is the *first* azole-*based* oral treatment of *systemic* fungal infections, in the *early* 1980s, but *now* has *largely* been *replaced* due to *risk of* severe liver injury, antiandrogenic (Ketoconazole *shampoo may be beneficial* alopecia) and antiglucocorticoid and *adverse* drug interactions. *Later*, Triazoles such as Fluconazole and Itraconazole, with *improved* safety *profile* were developed.

Mechanism; Azoles in *general* are fungistatic.

- Azoles are *inhibit* C-14 α-demethylase (*a* cytochrome P450 enzyme), *thereby* *blocking* the *demethylation* of Lanosterol *to* Ergosterol, the *principal* sterol of fungal membranes.
- The *inhibition* of Ergosterol *biosynthesis* *disrupts* membrane *structure* and *function*, which, in turn, *inhibits* fungal cell *growth*.
- The *selective* toxicity of Azoles *results* *from* their *greater* affinity for fungal *than* for human cytochrome P450 *enzymes*.

Imidazoles *exhibit* a *lesser* degree of *selectivity* *than* the Triazoles, *accounting* for their *higher* incidence of drug interactions and adverse effects.

All Azoles *inhibit* the hepatic CYP450 isoenzymes (*especially* CYP450 3A4) to *varying* degrees; *decrease* metabolism of other drugs, *leading* to *numerous* drug interactions.

Fluconazole (Diflucan®)# (Fungican®)#

Fluconazole was the *first* member of the Triazole class of *antifungal agents*, was *patented by* Pfizer in 1981, and in *early* 1990s Fluconazole was a *breakthrough* in antifungal pharmacotherapy.
Fluconazole is *highly* bioavailable (*available* in *both* oral and IV *formulations*), with *fewer* hepatic enzyme *interactions* (*least* CYP450 *effect*), with *better* GI *tolerance* and *widest* therapeutic index of *all* Azoles.
Antifungal spectrum; *least* spectrum of *all* Triazoles (*least* CYP450 *effect* of *all* the Azoles);
  # *Highly* active *against most Candida* species (*but* NOT *Candida krusei* or *Candida glabrata*)
  # *Good* activity *against Cryptococcus neoformans* (e.g.; Cryptococcal meningitis).
  # *Also* active *against some* dimorphic *fungi*.
  # *No* activity *against Aspergillus* species.
Uses; Dose is *same* in IV and oral administration; *highly* bioavailable.
  # Vulvovaginal Candidiasis; 150 mg orally as a *single* dose (May repeated if complicated or recurrent)
  # Oropharyngeal *and* Esophageal Candidiasis; 200 mg IV or orally on the *first* day *followed by* 100 mg IV or orally *once* a day.
  # *Systemic* Candidiasis *and* Cryptococcal Meningitis; 400 mg IV or orally on the *first* day *followed by* 200 mg IV or orally *once* a day.
  # Dermatomycosis (*such as*; tinea); 150 mg *once weekly* OR 50 mg *once* daily; 2-4 weeks, tinea pedis (athlete's foot); *may require* up to 6 weeks.
  # Onychomycosis (fungal nail infections); 150 to 300 mg orally *once* a week (3 to 6 months).
  # *Prophylaxis* of Candidiasis with Bone Marrow Transplantation (BMT); 400 mg/day IV/*orally*.
Usual children dose; 6-12 mg/kg on the *first* day *followed by* 3-12 mg/kg/day; Duration and dosage depend on severity of infection.
Side effects;
  - ***Most common***; headache, nausea, vomiting and skin rashes.
  - Hepatotoxicity *can also* occur (*should be* used with caution in *patients with* liver dysfunction).
  - QT interval *prolongation* is *also possible*.

Itraconazole (Sporanox®)#

Itraconazole is a *second* member of the Triazole class, it was *invented* in 1984.
Itraconazole has a *broader* spectrum of activity *than* Fluconazole (BUT *not as broad as* Voriconazole or Posaconazole); It is active *against Aspergillus*, which Fluconazole is *not*.
Itraconazole is the *drug of choice* for; Blastomycosis, Sporotrichosis, Histoplasmosis, and Onychomycosis. It is *rarely used* for *Candida* and *Aspergillus* species *because* of the *availability* of *newer* and *more* effective agents (Voriconazole or Posaconazole).
- Itraconazole is *available* in oral and IV *formulations* (IV *has been discontinued*).
Oral dosage forms (capsules have *lower* bioavailability than oral solution)
  # Oral solution; *should be* taken on an empty stomach, as food *decreases* the absorption.
  # Capsules; *should be* taken *with* food, and *ideally* an acidic beverage (orange juice or cola) to *increase* absorption; acid suppression *therapy* like PPIs; *decrease* absorption;
    # Sporanox® capsules *contain tiny* 1.5 mm pellets *with complex* three-layer structure to *increase* absorption and bioavailability (Korean Patent Laid-open No. 10-2001-2590);
      1) Inner layer; Itraconazole 1 part by weight.
      2) Mid-layer; Citric acid 0.25 part by weight.
      3) Outer layer; Hydroxypropylmethylcellulose 0.25 part by weight.

- It is > 99% *protein-bound* and penetrates *poorly* into CSF (*NOT* preferred in meningitis)
Antifungal spectrum;
  # *Highly* active *against most* of *Candida* and *Aspergillus* species, *Cryptococcus neoformans*, and *many* dimorphic fungi (Itraconazole is the *azole of choice* for dimorphic infections).
  # *Good* activity *against Candida krusei* and *Candida glabrata*.
Uses; Blastomycosis, Sporotrichosis, Histoplasmosis and Onychomycosis.
Usual dose; - *Adult*; 100-200 mg twice a day. - *Children*; ≥3 years: 3-5 mg/kg/day.
Side effects; - ***Most common***; nausea, vomiting and rash.
  - Hypokalemia, hypertension, edema and headache are *common*.
  - Hepatotoxicity *can* also occur.
Negative inotropic effect *can* also occur (*should be* avoided in patients *with* heart failure).

Voriconazole (Vfend®)#

Voriconazole is *similar* to Itraconazole in its *spectrum*, having *excellent* activity *against* *Candida* (*including* Fluconazole *resistant* species such as *Candida krusei*), *Cryptococcus neoformans*, *Aspergillus*, *Scedosporium* and *Fusarium* species (Voriconazole is the drug of choice for invasive aspergillosis; *less toxic* than Amphotericin B), and *many* dimorphic *fungi*.
Unlike Itraconazole, Voriconazole is *well* absorbed and *available* in *both highly* bioavailable oral *formulation* and IV admixture (*exceeding* 95%).
Voriconazole IV admixture with Sulfobutylether β-Cyclodextrin (SBECD) is *restricted* in patients with renal insufficiency (CCL <50 mL/min); SBECD *accumulate* in renal dysfunction.
Uses; Invasive Aspergillosis, Candidemia, Esophageal Candidiasis & *Serious* Mycoses.
- *Usual dose*; 6 mg/kg IV *every* 12 hours on day 1, then 4 mg/kg IV *every* 12 hours (IV therapy should continue for at least 7 days), oral dose 100 mg (< 40 kg) to 200 mg (> 40 kg) *every* 12 hrs
Side effects; - *Most common*; Visual disturbances (up to 28%).
- *Very common*; Skin rashes, phototoxicity, headaches, peripheral edema, fever, *trouble* breathing, nausea, vomiting and diarrhea.

Posaconazole (Noxafil®)

Posaconazole is a *broad-spectrum* triazole antifungal, *structurally* *similar* to Itraconazole, that is *more* active *against* *many* fungi.
Posaconazole is available as an oral suspension, oral tablet or IV formulation; *absorption* is *improved* when taken *with* *high* fat meals (*increases* concentration by 4 times *compared to* fasting *state*); acidic beverage (orange juice or cola) *increase* absorption; PPIs *decrease* absorption.
Posaconazole is the *broadest* spectrum *member* of the azole family, with *activity* *against* *most* species of *Candida*, *Aspergillus* and *Zygomycetes*.
Uses; - Invasive aspergillosis and candidiasis.
- Oropharyngeal candidiasis (OPC); *including* *refractory* to Itraconazole and/or Fluconazole.
- *Usual dose*; 300 mg orally *twice* a day on the *first* day, *then* 300 mg orally *once* a day.
Side effects; *Most common* (> 10%); Headache, fever, nausea, diarrhea, anemia, hypokalemia and hypomagnesemia.

Isavuconazole (Cresemba®)

- Isavuconazonium sulfate is a *prodrug* for Isavuconazole.
Isavuconazole is the *newest* triazole antifungal; FDA approval in March 2015.
It is *used* to treat invasive aspergillosis & invasive mucormycosis (Zygomycosis).
- *Dose*; - *Loading*; 1 vial (372 mg) IV or 2 capsules (372 mg) orally, every 8 hours for 6 doses (48 hours).
- *Maintenance*; 1 vial (372 mg) IV or 2 capsules (372 mg) once daily.

Echinocandins

- Echinocandins are the *newest* class, Caspofungin was the *first* drug; approved in 2001.
Echinocandins are *large* cyclic peptides, So they are *available* *only* in IV *formulations*.
Echinocandins have *potent* activity *against* *Aspergillus* and *most* *Candida* species.
Echinocandins cause *mild* Histamine-*mediated* infusion-*related* reactions (flushing).

Caspofungin (Cancidas®)#

Uses; - Invasive Candidiasis, *including* Candidemia; *first line*.
- Invasive Aspergillosis in patients *refractory to* or *intolerant* of *other* therapies (e.g., Amphotericin B or Itraconazole); *second line*.
- *Dose*; 70 mg IV infused over 1 hr in day first day, then 50 mg IV infused over 1 hr per day.
Warning; - Hypersensitivity and Anaphylaxis.
- *Do not* use Dextrose *diluents* (Caspofungin is not stable).
- *Do not* use *with* Cyclosporine (unless benefits outweigh risks).
- *Not* for bolus administration.

Micafungin (Mycamine®) | Anidulafungin (Eraxis®)

Uses; Invasive Candidiasis, *including* Candidemia.
- *Dose*; - Micafungin; 100-150 mg/day IV infusion (*only* echinocandin *not require* a loading dose).
- Anidulafungin; 200 mg IV infusion in first day, then 100 mg/day IV.
N.B.; Anidulafungin is *not* metabolized by liver *can be* *used* in severe hepatic dysfunction.
N.B.; Micafungin *not* used *with* Sirolimus and Nifedipine.

Systemic Antifungal for Cutaneous Mycotic Infections

Griseofulvin (Ultragriseofulvin®)# (Grifulvin V®)

NOW Griseofulvin has been *largely replaced by* **oral** Terbinafine for the ***treatment of*** **Onychomycosis**, although it is *still used* for **Dermatophytosis**.
Formulations; - **Microsize** OR **Ultramicrosize**; **capsules**, **tablets** or **suspension**.
Absorption; - **Ultramicrosize Griseofulvin**; **absorption** is almost ***complete***.
- **Microsize Griseofulvin**; **25-70%** of **oral dose** (***enhanced by*** **fatty meal**).
Dose; 2–6 weeks for **Dermatophytosis** (skin/hair infection), 4-6 months for **Onychomycosis** (nail infection).
- *Microsize*; 1000 mg/day (*Ultramicrosize*; 660 to 750 mg/day); orally in 2 to 4 divided doses.
Side effects; **Rash**, **urticaria**, **headache**, **GI disturbance** and **oral thrush**.
Contraindicated in ***patient with*** **porphyria**.

Terbinafine (Lamisil®)#

Terbinafine is an *Allylamines antifungal* used *orally* or *topically* act by ***inhibiting*** squalene epoxidase → ***blocking*** the **biosynthesis** of **ergosterol** (not act on CYP450).
Uses and *Doses*;
- **Onychomycosis** (*drug of choice*) 250 mg once daily for 6 weeks (fingernail) or 12 weeks (toenail).
- **Tinea Corporis**, **Tinea Cruris**; 250 mg/day orally in single dose or divided every 12hr for 2-4 weeks.
- **Tinea Pedis** (Off-label); 250 mg/day orally in single dose or divided every 12hr for 2-6 weeks.
- **Sporotrichosis**, **Lymphocutaneous** and **Cutaneous** (Off-label); 500 mg/day PO q12hr for 2-6 weeks; treat for additional 2-4 weeks after resolution of all lesions (resolution may take 3-6 months).
Pregnancy; **Category B** # *Lactating women*; ***Accumulates*** in **breast milk** and *should not* **used**.
Side effects; **Headache**, **GI disturbances** and **rash**.
Terbinafine is used with ***caution*** in **renal** and **liver** ***impairment***.

Topical Antifungals

Polyene Antifungal

Nystatin (Mycostatin®)#

Nystatin is a *polyene* **antifungal**, *similar to* **Amphotericin B**.
Nystatin is *negligibly* ***absorbed*** from **GIT**, and *not* **used** ***parenterally*** *due to* **systemic toxicity**; Liposomal Nystatin is also available *off-label* for **invasive fungal infections**.
Uses; * **Oropharyngeal Candidiasis**; * **1-12 months**; 200,000 *units* 4 *times* daily.
⁰ **Intestinal Candidiasis**; * **1-18 years**; 400,000 to 600,000 *units* 4 *times* daily.
⁰ **Oral tablets**: 500,000-1,000,000 *units* every 8 hours.
⁰ **Powder**: 1/8 to 1/4 teaspoonful in 1/2 cup of water (500,000-1,000,000 units) orally every 8 hrs.

Azole (Imidazole) Antifungals

Ketoconazole (Nizoral®)	**Miconazole** (Daktarin®)	**Econazole** (Pevaryl®)
Isoconazole (Travocort®)	**Clotrimazole** (Canesten®)	**Oxiconazole** (Tinox®)
Tioconazole (Trosyd®)	**Sertaconazole** (Dermofix®)	**Butoconazole** (Gynazole-1®)
Sulconazole (Exelderm®)	**Terconazole** (Terazol®)	**Bifonazole** (Mycospor®)

Topical **Imidazoles** have a ***variety*** of **uses**, *including*; **tinea corporis**, **tinea cruris**, **tinea pedis** and **oropharyngeal** and **vulvovaginal candidiasis**.

Allylamine Antifungals

Terbinafine (Lamisil®)#	**Naftifine** (Exoderil®)#
Butenafine (Derfina®)#	**Amorolfine** (Loceryl nail lacquer®)#

They are ***used for*** **topical treatment** of **tinea infections**.
Loceryl nail lacquer® is used *for* **fungal nail infection** ***once*** or ***twice*** **weekly**.

Others

Ciclopirox (Batrafen®)#	**Tolnaftate** (Tineacure®)#	**Clioquinol** (Betnovate-C®)#

Ciclopirox and **Tolnaftate** are used for **cutaneous mycotic infections**.
Clioquinol or **Iodochlorhydroxyquin** is an *antifungal* and *antiprotozoal drug*.

Antiviral Drugs

Anti-herpes Virus Drugs

Acyclovir (Zovirax®)# (Virustat®)

- Acyclovir (Zovirax®)# (orally, topically & injectable); is a **guanosine analogue** ***primarily used*** in; ***herpes simplex*** **virus** (**cold sores** or **herpes labialis**), **chickenpox**, & **shingles**. It may use in ***prevention*** of ***cytomegalovirus*** **infections** and ***severe complications of Epstein-Barr virus***.
- ***Dose***; - ***Adult***: **200 mg 1*5** ***daily*** - **400-800 mg 1*2** or **1*3** or **1*4** ***daily***; *according to infection.*
  - ***Child***: **200 mg Susp.** (10-20 mg/kg/dose) **1*4** ***daily***; *according to infection.*

Famciclovir (Famvir®)#	Valacyclovir (Valtrex®)#	Penciclovir (Denavir®)

- ***Used*** in ***treatments of herpes simplex*** **virus**, **chickenpox** and **shingles**.
- ***Dose***; - **Famciclovir**; **250-500 mg** ***orally*** **1*3**.
  - **Valacyclovir**; **1-2 g** ***orally*** **1*2** or **1*3**. ***May use*** in **CMV** ***Prophylaxis***.
  - **Penciclovir**; **1%** available as **topical cream**.

Cidofovir (Vistide®)	Ganciclovir (Cymevene®)	Fomivirsen (Vitravene®)
Foscarnet (Foscavir®)	Valganciclovir (Valcyte®)	

- ***Used*** in ***treatments of*** **cytomegalovirus** (**CMV**) ***retinitis*** in ***patients with*** **AIDS**.

Antivirals for Respiratory Viral Infections

Amantadine (PK-Merz®)# (Adamine®) (Symmetrel®)

Rimantadine (Rymanta®)	Tromantadine (Viru-Merz®)#

- ***Used*** ***only*** for **influenza A infections** (*no longer recommended*).
- ***Dose***; - **Amantadine**; **200 mg** ***orally*** **per day** *in* **1** *to* **2** ***divided*** **doses**.
  - **Rimantadine**; **> 10 years**; **100 mg** ***orally*** **1*2**. ***1-9 year***; **5 mg/kg** ***orally*** **1*1**.
  - **Tromantadine** (**Viru-Merz®**)#; ***topical cream*** **1*2**.

Oseltamivir (Tamiflu®)#	Zanamivir (Relenza®)

Used for **influenza A** and **B influenza** ***viruses***; *such as* **H1N1 flu** or "**Swine flu**"
Dose; - **Oseltamivir**; (**Tamiflu®**)#; ***Duration of therapy***: **5 days:**
  - **<15 kg**: **30 mg** ***orally*** **twice daily**.
  - **15-23 kg**: **45 mg** ***orally*** **twice daily**.
  - **23-40 kg**: **60 mg** ***orally*** **twice daily**.
  - **>40**: **75 mg** ***orally*** **twice daily**.
  - **Zanamivir** (**Relenza®** *Rotahalar*); **10 mg** (**2** ***inhalation tab.***) **twice** for **5 days**.
  - **Zanamivir** ***not used*** in **asthmatic patient** *due to* **bronchospasm** ***effect***.

Ribavirin

Used for **respiratory viral infections**, **hepatitis C**, and **viral haemorrhagic fever** (**Ebola virus**); ***guanosine analogue***.
Dose; **200 mg**, **400 mg** or **600 mg** orally **1*2**; *depend on weight*
  - *For* **hepatitis C** (not alone; in combination therapy); - <75 kg 1000 mg/day.
  - ⩾75 kg 1200 mg/day.
FDA "BLACK BOX" warnings;
  # ***Should not*** be **used** ***alone*** for **chronic hepatitis C virus infection**.
  # **Hemolytic anemia**; ***Should not*** be **used** in ***unstable*** **cardiac disease** (**Hb monitoring**).
  # **Teratogenic** (**Category X**); ***Avoid*** in **women** and **men** who are ***pregnant*** and ***after*** **6 months** of **therapy**.

Influenza Vaccine (Vaxigrip®)#

Dose; # **6** to **35 months** (***3 years***); **0.25 mL** ***once*** **yearly** (**second injection 0.25 mL** with **1 month** *interval* ***only*** in **first time of vaccination**).
  # **3** to **8 years**; **0.5 mL** ***once*** **yearly** (**second injection 0.5 mL** with **1 month** *interval* ***only*** in **first time of vaccination**).
  # **≥ 9 years**; **0.5 mL** ***once*** **yearly**.

Antivirals for Hepatitis B Virus (HBV)

Lamivudine (Zeffix®)# | **Adefovir** (Hepsera®)#

Entecavir (Baraclude®) | **Telbivudine** (Sebivo®) (Tyzeka®)

- Lamivudine (Zeffix®)#; hepatitis B virus (HBV) & human immunodeficiency virus (HIV);
  # *Dose*; HBV 100 mg *orally* 1*1 - AIDS; 150 mg *orally* 1*2 or 300 mg *orally* 1*1.
  # *Side effects*; constipation/diarrhea, headache and cough, hair loss and insomnia >>
  # *FDA warning*; Lactic acidosis, hepatomegaly & *severe acute* exacerbations of hepatitis.
- Adefovir (Hepsera®)# and Telbivudine; hepatitis B virus (HBV).
  # *Dose* (Hepsera®); 10 mg 1*1. # # *Side effects* (Hepsera®); Diarrhea & headache.
  # *FDA warning* (Hepsera®); *Severe acute* exacerbations of hepatitis and nephrotoxicity.

Hepatitis B Vaccine (Engerix-B®)#

Dose; Engerix-B®; # < 19 years; 3 doses (0.5 mL or 10 mcg *each*); 0-, 1-, 6-month.
> 20 years; 3 doses (1 mL or 20 mcg *each*); 0-, 1-, 6-month.

Hepatitis A Vaccine (Havrix®)#

Dose; Havrix®; # Children and adolescents; 2 doses (0.5 mL); 0-, 6 to 12-month.
Adult; 2 doses (1 mL); 0-, 6 to 12-month.

Hepatitis B + Hepatitis A Vaccine (Twinrix®)#

Dose; Twinrix®; # > 18 years (approved only); 3 doses (1 mL); 0-, 1-, 6-month.

Antivirals for Hepatitis C Virus (HBV)

PEG-interferon alpha or PegIFN-α

Dose; PegIFN-α2a; 180 µg/week. - PegIFN-α2b; 1.5 µg/kg/week.
Side effects; *Flu-like* symptoms, fatigue, mental *depression* and weight loss.

Ribavirin

- *See previous page* >> *Should be* used in *combination* with >>>>

Sofosbuvir (Sovaldi®)#

Dose; 400 mg (one tablet) *once per* day; 12-24 weeks.
Should be used in *combination with* Ribavirin or in *combination with* PegIFN and Ribavirin.
Metabolism; *not metabolised* by CYP450, but *interact with* Rifampin, Carbamazepine & Phenytoin.
Side effects; *with* Ribavirin; fatigue and headache.

Ledipasvir + Sofosbuvir (Harvoni®)#

Dose; *fixed-dose*; 400 mg Sofosbuvir + 90 mg Ledipasvir *once per* day; 12-24 weeks.
Side effects; fatigue and headache.

Simeprevir (Olysio®)# + Sofosbuvir (Sovaldi®)#

Dose; 150 mg (one tablet) *once per* day; 24 weeks; Genotype 1 and 4.
Should be used in *combination with* Ribavirin or in *combination with* PegIFN and Ribavirin.
Metabolism; by CYP3A4; # *Drug interactions*.
Side effects; *with* Ribavirin and PegIFN; photosensitivity.

Daclatasvir (Daklinza®)# + Sofosbuvir (Sovaldi®)#

Dose; 30 mg or 60 mg *once per* day; 12-24 weeks; *used in combination with* Sofosbuvir and *with* or *without* Ribavirin. *Metabolism*; by CYP3A4; # *Drug interactions*.

Ritonavir/Paritaprevir/Ombitasvir (Qurevo®)# (Viekira Pak®)# (Technivie®)

Dose; Ritonavir/Paritaprevir/Ombitasvir (50 mg/75 mg/12.5 mg per tablet) *once*/day; 12 weeks with Ribavirin in patients *without* cirrhosis.

Antivirals for HIV Infections (AIDS)

A) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Zidovudine (Retrovir®)#

Zidovudine is the *first drug* approved by **FDA** for **HIV**; is a *thymidine analog*.
It is **used** in ***treatment of*** **HIV** in **children** and **adults** and to ***prevent*** **perinatal transmission** of **HIV**, it is also **used** for ***prophylaxis***.
Most common side effects; **headache**, **nausea**, **vomiting** and **heartburn**.

Didanosine (Videx®)#

Didanosine is the *second drug* approved by the **FDA** for the *treatment of* **HIV**.
Like; **Zidovudine**.
Toxicity; **Peripheral neuropathy** and **pancreatitis** (*may be* **fatal**).

Stavudine (Zerit®)#

- **Stavudine** is a *thymidine analog*.
It is ***mainly*** **excreted** ***unchanged*** in the **urine** (renal impairment interferes with clearance).
#*Toxicity*; **Peripheral neuropathy**, **pancreatitis** and **lipoatrophy** (*loss of SC fat tissue*).

Abacavir (Ziagen®)#

- **Abacavir** is a *guanosine analog*.
Abacavir ***should be*** used in *combination* with *other* **antiretroviral agents**.
Serious side effects; **hypersensitivity reaction**.

Lamivudine (Zeffix®)#

Lamivudine *inhibits* the **Reverse Transcriptase** (**RT**) of ***both*** **HIV** and **HBV**.
Serious side effects; **Lactic acidosis** and **hepatomegaly**.

Emtricitabine (Emtriva®)

Emtricitabine is a *fluoro derivative* of **Lamivudine**, ***inhibits*** *both* **HIV** and **HBV RT**.
Toxicity; **Hyperpigmentation**, **lactic acidosis** and **hepatomegaly**.

Tenofovir (Viread®)#

Tenofovir ***inhibits*** *both* **HIV** and **HBV RT**.
Toxicity; **Lactic acidosis**, **hepatomegaly** and **Peripheral neuropathy**.

B) Non-nucleoside Reverse-transcriptase Inhibitors (NNRTIs)

Efavirenz (Sustiva®)#

Efavirenz is the *preferred* **NNRTI** and *widely* **used** to ***treat*** and ***prevent*** **AIDS**.
Should be **taken** on an *empty stomach* (*to reduce CNS side effects*).
Efavirenz is a ***potent*** **CYP450 inducer**.
Most common side effects; **CNS** (**dizziness**, **headache**, **vivid dreams**, loss of concentration and **depression**) and **skin rash**.

Nevirapine (Viramune®)#

Nevirapine is **used** in ***combination*** *with* other **antiretroviral drugs** for the ***treatment*** of **HIV** in **adults** and **children**.
Toxicity; *Severe* **hepatotoxicity** and *Severe* **skin rash** (**Stevens-Johnson syndrome** and **toxic epidermal necrolysis**).

Delavirdine (Rescriptor®)#

- **Delavirdine** is ***currently*** *rarely* **used**.

Etravirine (Intelence®)#

Etravirine is a *second-generation* **NNRTI** ***active against many*** **HIV strains** that are ***resistant*** to the *first-generation* **NNRTIs**; *approved in* **2008**.
Most common side effects; **skin rash**.

Rilpivirine (Edurant®)#

Rilpivirine is a ***second-generation*** **NNRTI**; *approved in* **2011**.
Rilpivirine is ***approved for*** **HIV treatment-naïve patients** in ***combination with*** other **antiretroviral agents**.
It **taken** ***orally*** with **meals** and has **pH-dependent** ***absorption*** (avoid co-administered with acid suppression therapy and antacids and requires dose separation).
Most common side effects; **Depression**, **headache**, **drowsiness** and **rash**.

C) Protease Inhibitors (PIs)

Common side effects of **PIs**; **Nausea**, **vomiting**, **diarrhea** and ***disturbances*** in **glucose** and **lipid metabolism** (*diabetes, hypertriglyceridemia and hypercholesterolemia*) and **fat redistribution** (*buffalo hump* and breast enlargement).
Drug interactions; **PIs** are ***substrates*** and ***potent inhibitors*** of **CYP450**.

Ritonavir (Norvir®)#

Ritonavir is **used** as a **pharmacokinetic enhancer** or "***booster***" of ***other*** **PIs**.

Saquinavir (Invirase®)#

Saquinavir is ***typically*** **used** with **Ritonavir** or **Lopinavir/Ritonavir**.

Indinavir (Crixivan®)#

Indinavir has a ***poor*** **pharmacokinetic profile**, so it is ***now rarely*** **used**.

Nelfinavir (Viracept®)#

Nelfinavir ***should be*** **taken** ***with*** **food** (bioavailability increased 2.5 to 5 times).

Amprenavir (Agenerase®)# | **Fosamprenavir** (Lexiva®)# (Telzir®)#

Fosamprenavir is a ***prodrug*** that is *metabolized to* **Amprenavir**.

Lopinavir (Kaletra®)#

Lopinavir *available as* a ***fixed-dose*** **combination** **Lopinavir/Ritonavir** (*booster*).

Atazanavir (Reyataz®)# | **Tipranavir** (Aptivus®)# | **Darunavir** (Prezista®)#

This agents are ***second*** **generation PIs**; ***preferred*** **PIs**.
Atazanavir ***inhibits*** **glucuronyl transferase**; cause **hyperbilirubinemia** & **jaundice**.
Tipranavir ***rarely*** cause **fatal hepatitis** and **intracranial hemorrhage**.

D) Entry (Fusion) Inhibitors

Enfuvirtide (Fuzeon®)# | **Maraviroc** (Selzentry®)#

Enfuvirtide *available as* ***injectable form***, while **Maraviroc** *available as* ***oral tablets***.
Maraviroc has ***black box warning*** for **hepatotoxicity**.

E) Integrase Strand Transfer Inhibitors (INSTIs)

Raltegravir (Isentress®)# | **Elvitegravir** (Vitekta®)# | **Dolutegravir** (Tivicay®)#

They are **used** as part of the ***combination*** **therapy**.

F) Common Fixed Dose Combination Brands

Truvada®; **Emtricitabine/Tenofovir**.
Kivexa®; **Abacavir/Lamivudine**.
Evotaz®; **Atazanavir/Cobicistat**.
Combivir®; **Lamivudine/Zidovudine**.
Atripla®; **Efavirenz/Emtricitabine/Tenofovir**.
Complera®, **Eviplera®**; **Emtricitabine/Rilpivirine/Tenofovir**.
Triumeq®; **Abacavir/Dolutegravir/Lamivudine**.
Trizivir®; **Abacavir/Lamivudine/Zidovudine**.
Stribild®; **Elvitegravir/Cobicistat/Emtricitabine/Tenofovir**.
Kaletra®; **Lopinavir/Ritonavir**.
Dutrebis®; **Lamivudine/Raltegravir**.
Prezcobix®; **Darunavir/Cobicistat**.

Antiparasitic Drugs

Anthelmintic Drugs

Anti-Nematodes (*Round Worm*)

- ***Most common*** Nematodes;
  - Hookworms; *Ancylostoma duodenale*.
  - Roundworms; *Ascaris lumbricoides*.
  - Pinworms; *Enterobius vermicularis*; Oxyuris.
  - Whipworms; *Trichuris trichiura*.
  - Tissue Nematode; as *Loa loa* (Filariasis).

Mebendazole (Antiver®)# (Vermox®)# | **Flubendazole** (Fluvermal®)# (Verm-All®)#

Dose; **100 mg *orally* twice** or **200 mg (2 tab** or **10 mL) once *for* 3 days**, and may ***repeated*** in **2 weeks**.
Mebendazole *dose in* **Giardiasis**; **200 mg 1*3 *daily*** for **5 days**; *not recommended*.
Mebendazole + **Metronidazole** ***interaction***; ***risk of*** **Stevens-Johnson syndrome**.
Side effects; **Headache, dizziness, fever, vomiting** and **temporary hair loss**.
Pregnancy; **Category C**.

Albendazole (Albenda®)# (Alzental®)# (Vermizole®)# (Bendax®)#

Albendazole effect ***against*** ***many types*** including; **Nematodes** and **Cestodes**.
Dose; **400 mg (2 tab. or 20mL) once** may ***repeated*** in **2 weeks** (***all ages***).
Pregnancy; **Category C**.

Anti-Cestodes (Tapeworms)

- ***Most common*** Cestodes;
  - Fish worm; *Diphyllobothrium latum*
  - Beef tapeworm; *Taenia saginata*
  - Pork tapeworm; *Taenia solium*
  - Dwarf tapeworm; *Hymenolepis nana*
  - Rat tapeworm; *Hymenolepis diminuta*
  - Tissue Cestoda; **Hydatidosis**

Niclosamide (Yomesan®)# (Niclosan®)#

FIRST CHOICE; in **Taeniasis, Diphyllobothriasis**, and ***other*** **cestode infections**; ***no longer*** **available** in **USA** ***according to*** **CDC** *recommendations* (***using*** **Praziquantel**)
Dose; **7 days** is ***recommended***; 500 mg **Chew. Tab**.
First day: - < 2 years; 1 tablet (500 mg) - 2-6 years; 2 tablets - >6 years; 4 tablets
Another six days: - < 2 years; 1/2 tablet - 2-6 years; 1 tablets - >6 years; 2 tablets

 # # # # # # # PATIENT COUNSELLING # # # # # # #

1) **Tablets *should be* chewed** *before* **swallowing** and ***washed down*** *with* a **little water**.
2) **Constipated patients *should receive*** a **purgative** the *previous* **evening**.

Pregnancy; **Category B**.

Anti-Trematodes (Flukes) Flatworms (Leaf-shaped)

- ***Most common*** Trematodes;
  - Intestinal flukes; *Heterophyes heterophyes* (**Heterophyiasis**).
  - Liver flukes; *Fasciola* (**Fascioliasis**).
  - Lung flukes; *Paragonimus* (**Paragonimiasis**).
  - Blood flukes; *Schistosoma* (**Schistosomiasis**).

Praziquantel (Biltricide®)# (Distocide®)# (Mirazid®)#

FIRST CHOICE for **Trematodes** and can ***used in*** **Cestodes**.
Dose; - **Schistosomiasis**; **20 mg/kg/dose** in **3 divided doses** (4-6 hrs) ***for*** **1 day**.
- **Taeniasis**; 5-10 mg/kg orally once. - ***Hymenolepis nana***; **25 mg**/kg orally once.
Pregnancy; **Category B**.

Antiprotozoal Drugs

- *Most common* **Protozoa**;
  - *Plasmodium*; **Malaria**.
  - *Giardia lamblia*; **Giardiasis**.
  - *Leishmania*; **leishmaniasis**.
  - *Entamoeba histolytica*; **Amoebiasis**.
  - *Trichomonas vaginalis*; **Trichomoniasis**.
  - *Toxoplasma Gondii*; **Toxopasmosis**.
  - **African sleeping sickness**.

Chloroquine (Chloroquine®)# (Resochin®)#

- **Chloroquine** is an ***antimalarial agent***, it is also ***used for*** **amebiasis** (*combination with* **metronidazole**) in **amoebic liver abscesses, rheumatoid arthritis & lupus erythematosus**.

Mefloquine (Lariam®)#

- **Mefloquine** is an ***effective*** and **widely used** for ***prophylaxis*** and ***treatment***.

Dose; **Lariam®**; - ***Prophylaxis***; **One tab. 250 mg *once* weekly**;
(**1-3 week *before* >> *during* >>> 4 weeks *after***).

- ***Treatments***; **1250 mg *orally* once**.

Side effects; **nausea, vomiting** and **dizziness**.

Pyrimethamine + Sulfadoxine (Fansidar®)#

- **Pyrimethamine + Sulfadoxine**; **Fansidar®**; **used** for ***prophylaxis*** and ***treatment***.

For Amoeba

Metronidazole (Flagyl®)# (Amrizole)#

- ***Uses***; **Trichomoniasis, Amebiasis, Giardiasis, Anaerobic Bacterial Infections, Sexually Transmitted Disease, Bacterial Vaginosis** and **Helicobacter Pylori**.

Dose (**Amebiasis**) - ***Adult***; **500-750 mg 1*3 *daily*** for **5-10 days**.
- ***Child***; **35-50 mg/kg/day**, *divided into* **3 doses** for **5-10 days**.

Side effects; **Metallic taste, dark urine, GI upset** and **Disulfiram-*Like reaction*** (Disulfiram-Like reaction occur when ingested with alcohol severe flushing, tachycardia and hypotension).

Metronidazole (**vegetative *more than* cystic**) + **Diloxanide** (**cystic *more than* vegetative**); **Furazol®**.

Pregnancy; **category B**; but ***many studies recommend***; ***not used*** in **first trimester**.

Tinidazole (Fasigyn®)# (Protozole®)# | Secnidazole (Flagentyl®)# (Amebazole®)#

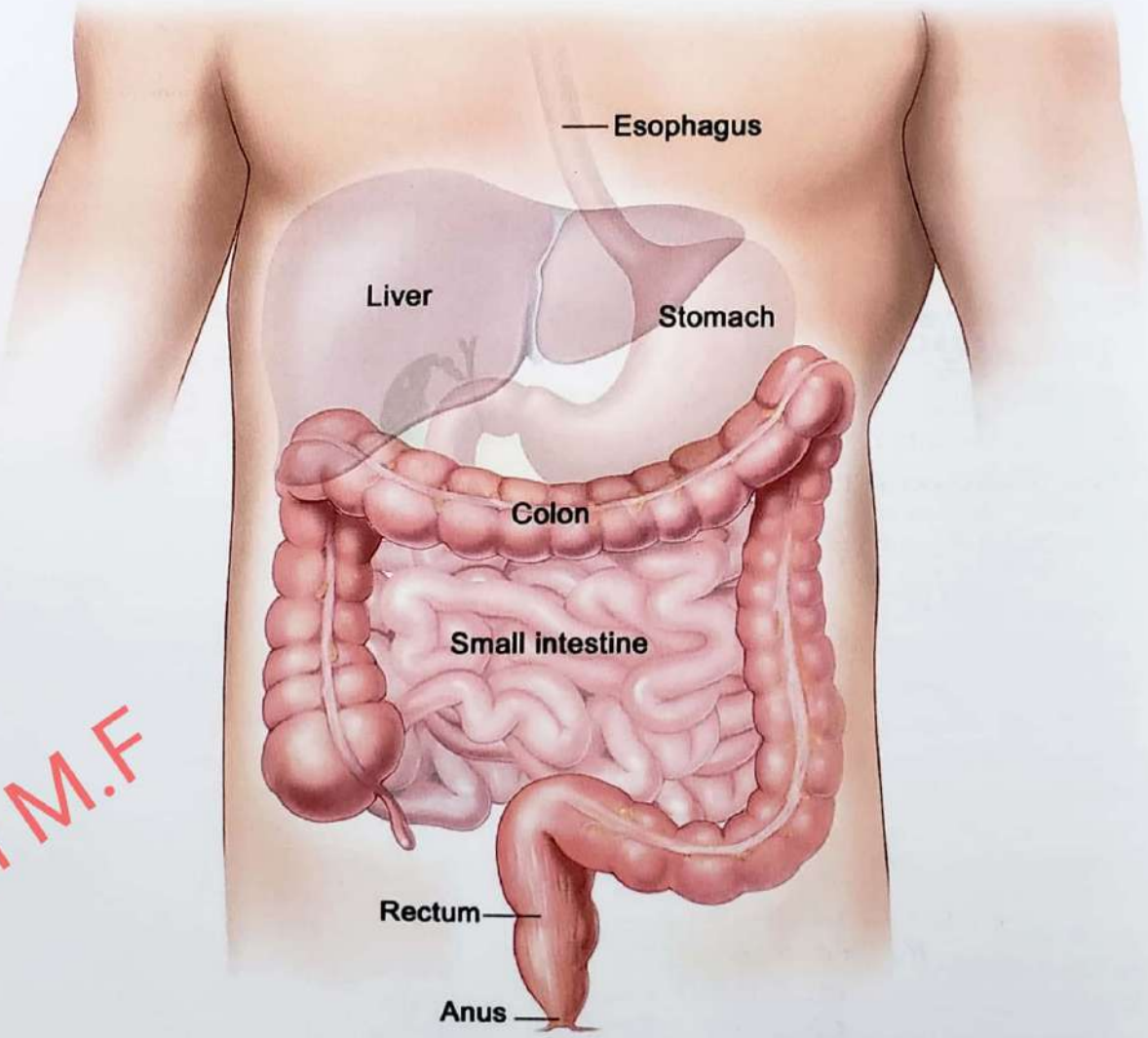
Dose; **2 g** (4 tab. 500 mg) **orally *once with* food** (for 3 days in **Amebiasis**).

Side effects; **Metallic taste, dark urine** and **Ataxia**.

➢ Dosage of Commonly Antimicrobial in Children:-

Amoxicillin or **Ampicillin**; 25–50 mg/kg/day
Ampicillin/Sulbactam; 300 mg/kg/day
Amoxicillin/Clavulanic; 20–90 mg/kg/day
Piperacillin/Tazobactam; 80-100 mg/kg/4-6 hrs
Cephalexin; 25–50 mg/kg/day
Cefadroxil; 30 mg/kg/day
Cephradine; 25–50 mg/kg/day
Cefaclor; 20–40 mg/kg/day
Cefuroxime; 30 mg/kg/day
Cefprozil; 15–30 mg/kg/day
Ceftriaxone; 50–75 mg/kg/day
Cefotaxime; 50–200 mg/kg/day
Ceftazidime; 30–50 mg/kg/8 hours
Cefixime; 8 mg/kg/day
Cefdinir; 14 mg/kg/day
Cefpodoxime; 10/kg/day
Linezolid; 10 mg/kg/8 hours
Erythromycin; 40–50 mg/kg/day
Clarithromycin; 15 mg/kg/day
Azithromycin; 10 mg/kg/day
Clindamycin; 8–20 mg/kg/day
Sulfamethoxazole; 8-10 mg **TMP**/kg/day
Fluconazole; 3–12 mg/kg/day
Nystatin; 1-12 months; 200,000 units/dose
1-18 years; 400,000-600,000 units/dose
Griseofulvin; Micro; 10-20 mg/kg/day
Ultra; 5-15 mg/kg/day
Acyclovir; 10–20 mg/kg/dose
Amantadine; 5–10 mg/kg/day
Lamivudine; 3 mg/kg/day
Adefovir; 10 mg/kg/day
Mebendazole; 200 mg/day; all ages
Flubendazole; 200 mg/day; all ages
Albendazole; 400 mg/day; all ages
Chloroquine; 8 mg/kg/dose
Mefloquine; 20–25 mg/kg/dose
Metronidazole; 35–50 mg/kg/day
Tinidazole; 50 mg/kg/day

Gastrointestinal Tract (GIT)



Drugs for Peptic Ulcer Disease (PUD)

- **Peptic Ulcer Disease (PUD)** *or* **Peptic Ulcer**, is a ***break in the lining of***;
  - * Stomach (**gastric ulcer**), *or*
  - * *First part of* **small intestine** (**duodenal ulcer**), *or*
  - * *Lower* **oesophagus**; *results from* ***chronic*** **gastroesophageal reflux disease (GERD)**
- ***Most common symptom*** *of* **PUD** is **epigastric pain**, *classically*, ***shortly*** **after meals** *with* **gastric ulcer** and **1-3 hours after meals** *with* **duodenal ulcer**.
- ***Symptoms of hyperacidity***; **heart burn, gases, indigestion** and **regurgitation**.
- ***Most common causes*** *of* **PUD** are ***Helicobacter pylori*** (***H. pylori***) **infection** and **NSAIDs**.

Lifestyle Modifications

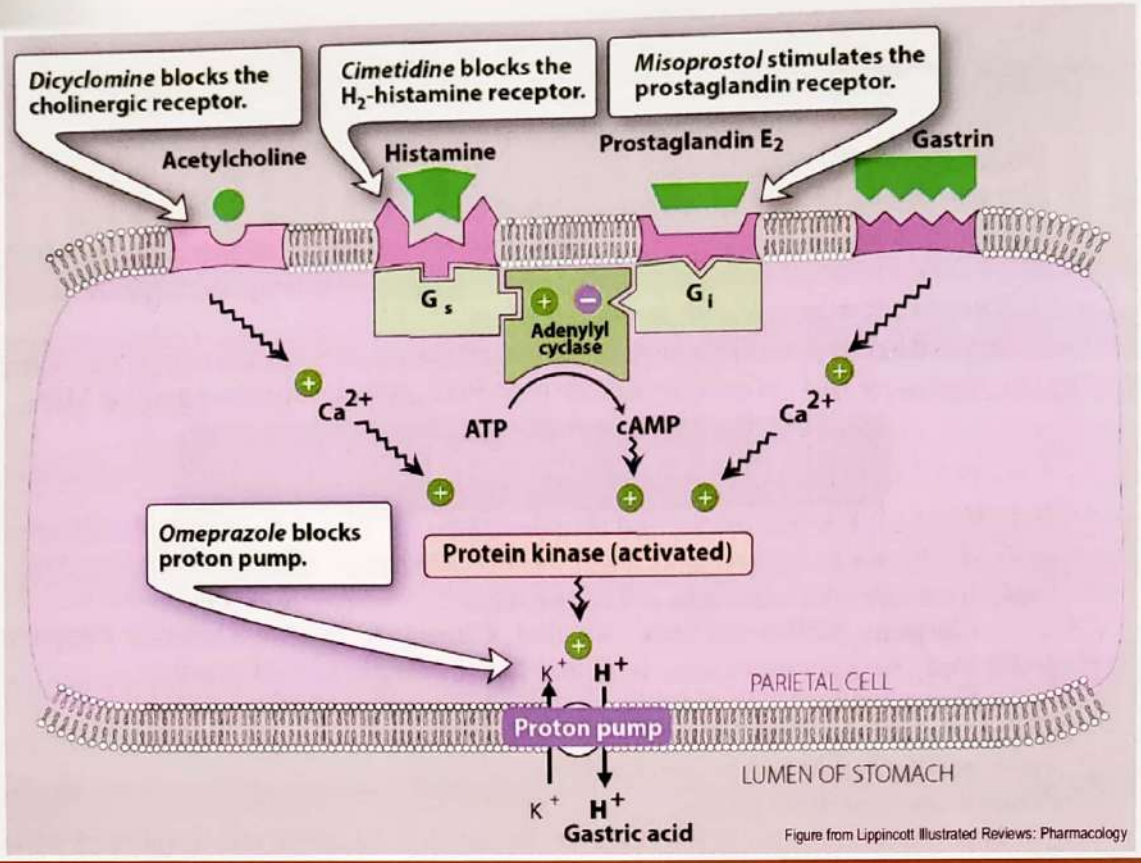
- ***Lifestyle Modifications***; **GERD, PUD,** and **Hyperacidity**
  - **A) Dietary modifications** (If symptoms are associated with certain foods or drinks);
    - * ***Avoid*** **foods/drinks** *may* ***reduce*** **LES pressure**;
      - **Caffeine** (**Coffee** and **Cola**), **Alcohol, Chocolate, Garlic, Onion** & **Peppermint**.
    - * ***Avoid*** **foods/drinks** *may* ***cause*** **irritants** to the **oesophageal mucosa**;
      - **Spicy foods, Orange juice, Tomato juice** and **Coffee**.
    - * ***Reduce*** **fat intake** (*high-fat meals slow gastric emptying*).
    - * ***Avoid*** **eating 2–3 hours before bedtime**.
    - * ***Remain*** **upright** ***after*** **meals**.
  - **B) Weight loss if overweight.** **C) Reduce or discontinue nicotine use in tobacco products.**
  - **D) Elevate head of bed.** **E) Avoid tight-fitting clothing** (decreases intra-abdominal pressure).
  - **F) Avoid medications *that may* reduce LES pressure, delay gastric emptying,** or cause **direct irritation**: **NSAIDs, Nicotine, Nitrates, Calcium Channel Blockers, Anticholinergics, Tetracycline, Theophylline, alpha/beta-blockers, Benzodiazepines, Opiates,** and **Tricyclic antidepressants**.

Pharmacological Therapy

Antacids

Aluminium Hydroxide [$Al(OH)_2$]	**Magnesium Hydroxide [$Mg(OH)_2$]**
Calcium Carbonate [$CaCO_3$]	**Sodium Bicarbonate [$NaHCO_3$]**

- # **Antacids**; are ***weak bases*** that *react with* **gastric acid** to form **water** and a **salt**.
- # ***reduce*** **pepsin** ***activity***, *because* **pepsin** is ***inactive*** at a **pH > 4**.
- # ***Mechanism of action***; **Neutralizing gastric acid** and ***decrease*** of **pepsin**.
- # # **Aluminium; Constipation** # # **Magnesium; Diarrhea**
- # # **Magaldrate**; is a **hydroxy-magnesium aluminate**; ***No*** **diarrhea** – ***No*** **constipation**
- # # ***Formulations***; **capsules, tablets, chewable tablets** and **suspensions**.
  - # # **Maalox®; Aluminium Hydroxide + Magnesium Hydroxide (Magaldrate)**.
  - # # **Maalox® plus; Magaldrate + Simethicone** (***anti flatulence***).
  - # # **Epicogel®; Magaldrate + Dimethicone** (***anti flatulence***).
  - # # **Mucogel®; Magaldrate + Oxethazaine** (***local anesthetic***).
  - # # # **Gaviscon®; Magaldrate + Alginic Acid** (***physical barrier*** *to* **acid**); ***anti-refluxant*** **Alginic Acid,** ***forms*** a ***viscous layer*** on ***top of*** **gastric contents** to act as a ***barrier***; ***before meal*** in **hyperacidity** & ***after meal*** in **GERD**.
- # # ***Advantages***; ***Rapid*** **onset of action**.
- # # ***Disadvantages***; ***Short*** **duration of action** (*need frequent dosing*).
- # # ***Drug interactions***; ***Chelation***; *reduce absorption of*; **Fluoroquinolones & Tetracyclines**.



H_2-receptor Antagonists (H2RAs)

- The **H_2 receptor antagonists (H_2RAs)** are ***reversibly inhibit*** **histamine-2 receptors**, ***block*** the ***stimulatory effect*** of **Histamine** on **gastric parietal cell**, ***decreasing*** the **production of gastric acid**.

Cimetidine (Tagamet®)	**Ranitidine** (Zantac®)#
Nizatidine (Ulcfree®)#	**Famotidine** (Antodine®)#

- **Cimetidine** is ***largely replaced*** by ***other*** **H_2 receptor blocker** *due to* **side effects**.
- ***Dose reduction*** is **required** in ***moderate*** to ***severe*** **renal dysfunction** and ***severe*** **hepatic impairment**.

Drug	Relative potency	Usual dose	Parenteral form
Cimetidine	1	400 mg twice or 800 mg at bedtime	50 mg
Ranitidine	4-10	150 mg twice or 300 mg at bedtime	50 mg
Nizatidine	4-10	150 mg twice or 300 mg at bedtime	Not available
Famotidine	20-50	20 mg twice or 40 mg at bedtime	20 mg

Therapeutic Uses;

1) **Peptic Ulcer Disease (PUD)**: **PPIs** have ***largely replaced*** **H_2RAs**
   - **H_2RAs** ***used*** in **Zollinger–Ellison Syndrome (ZES)**; is a ***gastrin-secreting tumor*** of the **pancreas** that ***stimulates*** the **acid-secreting cells** of the **stomach**, cause **mucosal ulceration**.
2) **Gastroesophageal Reflux Disease (GERD)**: **H_2RAs** is ***less efficacious than*** **PPIs**.
3) **Non-ulcer Dyspepsia**: ***Commonly used*** for **dyspepsia** ***not caused*** by **peptic ulcer**.
4) **Acute Stress Ulcers**: **IV infusion** (**PPIs** are ***favor*** for this indication).

H_2-antagonists are ***extremely*** **safe drugs**. ***Pregnancy*** ⇨ **FDA category B**.

Side effects; occur in > 3% of patient; **diarrhea**, **headache** & **fatigue**.

Cimetidine ***inhibits*** binding of **Dihydrotestosterone** to **androgen receptors** (***Anti-androgenic effect***) and ***increase*** **serum prolactin**, ***long term use*** may *cause*:
- In ***male***; **Impotence** (*Anti-androgenic effect*) and **Gynecomastia** (*Increase prolactin*).
- In ***female*** **Galactorrhea** (*Increase prolactin*) and **amenorrhea**.

- ***Rapid*** **IV infusion** of **H_2-antagonists** may ***rarely*** cause **bradycardia** and **hypotension**.

Proton Pump Inhibitors (PPIs)

Omeprazole (Losec®)# (Pepzol®)# (Omez)#	**Esomeprazole** (Nexium®)#
Lansoprazole (Lanzor®)#	**Dexlansoprazole** (Dexilant®)#
Pantoprazole (Controloc®)# (Pantoloc®)#	**Rabeprazole** (Pariet®)#

***All six* proton pump inhibitors (PPIs)** are *effective orally*.

All six* PPIs** are ***prodrugs.

All oral* PPIs** are ***formulated as* acid-resistant enteric coated** to ***protect them from ***premature* degradation** by **gastric acid**; The **coating** is ***removed*** in the **alkaline *duodenum***, & the ***prodrug***, a **weak base**, is ***absorbed* & *transported*** to the **parietal cell**.

Omeprazole, **Lansoprazole** and **Esomeprazole** is *also available as* a ***gastro-resistant granules*** as a ***powder for* oral suspension** or **tablet formulation** that ***disintegrates*** in the **mouth**, or it may *mixed with* **water**.

Omeprazole is also available as a ***powder formulation*** (**capsule** or **packet**) that contains **Sodium Bicarbonate** (**Zegerid®**) to ***raise* gastric pH** to ***protect* Omeprazole** *from* **acid *degradation***.

All* PPIs *should be administered *approximately* **30-60 minutes *before*** a **meal** (usually breakfast); ***bioavailability*** of all agents is decreased *approximately* **50%** by ***food***.

Full acid inhibiting are *occur* ***after* 3–4 days** of ***daily dose***, similarly, ***after stopping*** the drug, it takes **3–4 days** for ***full acid secretion*** to *return*.

Mechanism; - **Active drugs** of **proton pump inhibitors *blocks* proton pump** by ***forms*** a ***stable* covalent bond** (***irreversible***) with the **H^+/K^+-ATPase enzyme**.

- ***At least* 18 hours** are *required for* ***resynthesized*** of ***new* H^+/K^+-ATPase enzyme**, and **acid *secretion*** is ***inhibited*** *during this* **time**.

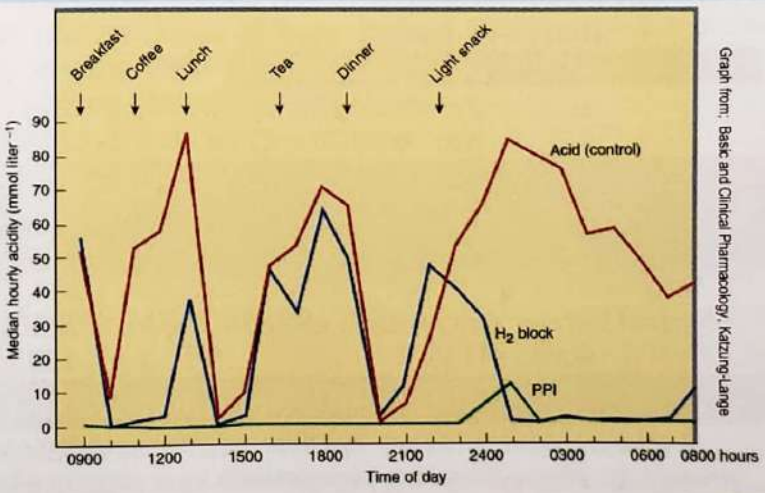
Drug	Relative potency	Usual dose	Parenteral form
Omeprazole	1	20-40 mg once/d	
Esomeprazole	1.6	20-40 mg once/d	IV 20, 40-mg/vial
Lansoprazole	0.9	15-30 mg once/d	IV 30 mg/vial
Dexlansoprazole	data not available	30-60 mg once/d	
Pantoprazole	0.23	20-40 mg once/d	IV 40 mg/vial
Rabeprazole	1.82	10-20 mg once/d	

Therapeutic Uses;

1) **Gastroesophageal Reflux Disease (GERD)**; **Gold-Standard**
2) **Non-ulcer Dyspepsia**; ***More rapid* symptom relief** and ***faster* ulcer healing** *than* **H_2 RAs**.
3) **Peptic Ulcer Disease (PUD)**.
4) **Acute Stress Ulcers**.

Red; Twenty-four-hour median intragastric acidity pre-treatment.
Blue; After 1 month of treatment with ranitidine, 150 mg twice daily.
Green; After 1 month of treatment with omeprazole 20 mg once daily (PPI).

- ***Notes***;
  - **H_2-receptor antagonists** have a ***marked effect*** on **nocturnal acid secretion** but only a ***modest* effect** on **meal-stimulated secretion**.
  - **Proton pump inhibitors (PPIs)** ***markedly suppress*** **meal-stimulated** and **nocturnal acid secretion**.



Side effects; PPIs are extremely safe, diarrhea, headache, and abdominal pain are reported only in 1–5% of patients.

Pregnancy ⇨ Enough data to suggest that PPIs therapy is safe during pregnancy, but Antacids and H_2-receptor antagonist are superior to use.

- Respiratory and Enteric Infections; Gastric acid is an important barrier to colonization and infection of the stomach and intestine from ingested bacteria.

Long-term side effects; ######## PATIENT COUNSELLING

{Hypochlorhydria or achlorhydria; low or absent HCl production}; Gastric acid is important for absorption of; Vitamin B_{12}, Iron, Calcium and Magnesium;

- Long term use of PPIs; risk for osteoporosis (Calcium Citrate is the preferred calcium supplement in patients taking PPIs and ensure adequate Vitamin D), severe life-threatening hypomagnesemia with secondary hypocalcemia.
- Effects of Vitamin B_{12} and Iron malabsorption is clinically insignificant.

Long term use of PPIs (especially Omeprazole) have also been associated with several cases of acute interstitial nephritis.

- All PPIs are metabolized by CYP2C19 and CYP3A4, because of the short half-lives of (about 1.5 hours) PPIs, clinically significant drug interactions are rare.

Drug Interactions; !!!

1) Drugs with pH-dependent absorption; Itraconazole & Protease inhibitors.
2) Inhibition of CYP450; Warfarin, Diazepam, Phenytoin and Theophylline.
3) Inhibition of CYP2C19 ##############
   - Clopidogrel (antiplatelet) is a prodrug that requires CYP2C19.
   - In 2009, the FDA issued a public-health warning about the possible interaction between Clopidogrel and Omeprazole.
   - Recent (2015) meta-analysis study; In summary, suggest that the highly controversial interaction between PPIs (Omeprazole) and Clopidogrel observed in platelet aggregation studies has no clinical significance.
4) high-dose IV Methotrexate; Higher risk of methotrexate toxicity; switch to Ranitidine if needed, for 2 days before and after Methotrexate administration.

- H_2 blockers can be used with PPIs in some severe cases; which of one taken first?

Prostaglandins

Misoprostol (Cytotec®)# (Misotac®)#

Misoprostol is a PGE_1 analogue, with oxytocic properties.
It is approved for use in the prevention of NSAID-induced gastric ulcers;
It produces uterine contractions and is contraindicated during pregnancy.
Off-label: labor induction, abortion, missed miscarriage & postpartum bleeding;

- Routes of administration; include oral, vaginal, sublingual, buccal, or rectal.
- In abortions mainly used in combination with Mifepristone (Antiprogestin).

Dear pharmacists; This drug is prescribed only by obstetricians and gynaecologists by a trusted prescription; So don't prescribe this drug by any way because may be used by prostitutes for abortion (illegally).

Mucosal Protective Agents

Sucralfate (Gastrofait®)#

Sucralfate is a sucrose sulfate-aluminium complex that binds to the ulcer, creating a physical barrier that protects ulcer from gastric acid, allowing the ulcer to heal.
Require acidic pH for activation. # # Dose; 1- 2 gm twice daily.

Bismuth Subsalicylate (Pepto-Bismol®)

Antimicrobial actions, inhibits pepsin activity, increases mucus secretion, coat and protect the ulcer. Bismuth compounds may cause a black discoloration of tongue & stool.

Treatment of *H. pylori* Associated Ulcers

First Line		
Standard Triple Therapy		
* PPI + Amoxicillin 1 g BID + Clarithromycin 500 mg BID ***OR*** * PPI + Metronidazole 500 mg BID + Clarithromycin 500 mg BID	10–14 Days	70–85%
Sequential Therapy		
* PPI + Amoxicillin 1 g BID for **5 days**, then PPI, Clarithromycin 500 mg BID + Tinidazole 500 mg BID for **5 days**	10 Days (5+5)	> 90%
Second Line		
Non–bismuth-based Quadruple Therapy		
* PPI + Amoxicillin 1 g BID + Clarithromycin 500 mg BID + Tinidazole 500 mg BID (*or* Metronidazole 500 mg BID)	10 Days	90%
Bismuth-based Quadruple Therapy		
* Bismuth Subsalicylate 525 mg QID + Metronidazole 500 mg TID + Tetracycline 500 mg QID + PPI BID	14 Days	75–90%
* {Bismuth Subcitrate 420 mg + Tetracycline 375 mg + Metronidazole 375 mg (Pylera®) QID} + PPI BID	10 Days	85–92%
Levofloxacin-based Triple Therapy		
* PPI + Amoxicillin 1 g BID + Levofloxacin 500 mg once daily	10 Days	-

PPI = Omeprazole 20 mg BID or Lansoprazole 30 mg BID or Esomeprazole 40 mg once daily or Rabeprazole 20 mg PO BID (Pantoprazole or Dexlansoprazole *not* FDA-approved indication for *H. pylori* eradication).

BID = twice daily; PO = orally; PPI = proton pump inhibitor; QID = 4 times/day; TID = 3 times/day

- Metronidazole can be *substituted for* Amoxicillin or Clarithromycin in patients with **penicillin** or **macrolide** ***allergy*** for the **triple-drug regimens**, treat for **14 days** in this instance.

Primary Prevention of NSAID-Induced Ulcers

→ If ***low*** **CV risk** and:
- ***Low*** **GI risk** → **NSAID** (*lowest dose*).
- ***Moderate*** **GI risk** → **NSAID + PPI *or* Misoprostol** (800 mcg/day in divided doses).
- ***High*** **GI risk** → **COX-2 inhibitor + PPI *or* Misoprostol** (800 mcg/day in divided doses).

→ If ***high*** **CV risk** (***requirement for*** *low-dose* **Aspirin**) and:
- ***Low*** **GI risk** → **Naproxen + PPI *or* Misoprostol**.
- ***Moderate*** **GI risk** → **Naproxen + PPI *or* Misoprostol**.
- ***High*** **GI risk** → **Avoid NSAIDs *or* COX-2 inhibitors**.

Secondary Prevention of NSAID-Induced Ulcers

1) **PPIs**; ***Drugs of choice***, **Combination product** may be used such as Vimovo® contains **Esomeprazole** with **Naproxen** in the ***same tablet*** (375 mg/20 mg or 500 mg/20 mg).
2) **Misoprostol**: *effective as* **PPIs** but require ***several*** **doses** *per* **day** and **high doses** *cause* **diarrhea** and **abdominal pain**.
3) ***Combination*** of a **COX-2 inhibitor + PPI**.
4) **H_2RAs**; ***less than*** **Misoprostol** and **PPIs** in ***healing*** and ***preventing*** **recurrence**.

Promotility (Prokinetic) Agents

- *Promotility* (*Prokinetic*) *agents* are a type of drug which ***enhance*** **gastric emptying** and ***enhance*** **intestinal contractions**.
- They are **used** to *relieve* **GI symptoms** such as **abdominal discomfort, bloating, constipation, heart burn, nausea** and **vomiting**.
- **Prokinetic Uses**; **Delayed stomach emptying** in *diabetes* or *following surgery* and **GERD, vomiting, indigestion, dyspepsia** and **hiccup**.

Metoclopramide (Primperan®)#

Metoclopramide is a *peripherally* and *centrally* ***dopamine antagonist***.
Metoclopramide ***increases*** **LES pressure** and ***accelerates*** **gastric emptying** (***does not improve*** **oesophageal clearance**).
Formulations; Tab, supp, syrup and injection (*not* SC).
Antiemetic properties; ***block*** **stimulation** of the medullary **chemoreceptor trigger zone (CTZ)** by **Dopamine** or **Dopamine-like agents** (**L-dopa** or **Apomorphine**).
Uses; - **Nausea** and **vomiting**.
- **Delayed stomach emptying** in *diabetes* (**diabetic gastric stasis**) or *following surgery* and in **GERD**.
- *Also used* to ***treat*** **migraine headaches**.

Dose in **GERD**; **10-15 mg orally** ***up to*** **4 times a day 30 min**. ***before*** **meals** & at **bedtime**.
Side effects; **Dizziness, fatigue, somnolence, drowsiness, extrapyramidal symptoms (EPS)** and **hyperprolactinemia**.
Children; **0.1-0.2 mg/kg/dose 1*3** or **1*4**.
FDA warning; **Metoclopramide** can ***cause*** **tardive dyskinesia** (***Treatment with*** **Metoclopramide** for ***longer than*** **12 weeks** ***should be*** **avoided**).

Domperidone (Motilium®)#

Domperidone is a *peripherally* ***dopamine antagonist***.
Formulations; Tab, supp, syrup, sachets and injection (*not* SC).
Domperidone ***may*** ***relieve*** **nausea** and **vomiting** by ***improve*** **upper GIT** ***motility***.
Domperidone ***promote*** **lactation** by ***blocks*** **dopamine receptors** in the *anterior* **pituitary gland** *increasing* ***release*** of **Prolactin** which in turn *increases* **lactation** (not covered by BBB).
Dose; **10 mg orally 1*3 a day 30 minutes** ***before*** **meals** and at **bedtime**.
Children; **0.25-0.5 mg/kg/dose 1*3** or **1*4**. # # # # **DON'T** ***use*** **30 mg Domperidone supp** in **children < 10 years**; ***Fatal*** **QT prolongation**.
Side effects; ***Fatal*** **QT prolongation** (mostly when used with CYP3A4 inhibitors such as; **Itraconazole** and **Ketoconazole, Erythromycin** and *certain other* **macrolide**).

Cisapride (Propulsid®)

- **Cisapride** is a *gastroprokinetic agent*, it acts ***as*** a *Serotonin* **5-HT4 receptor** *agonist*.
- ***Stimulation*** of the **serotonin** ***increases*** **Acetylcholine** ***release*** in the **enteric nervous system**.
- **Cisapride** ***improve*** **oesophageal clearance**.
- **Cisapride** is *no longer available*; *life-threatening* **cardiac arrhythmias**, when used in ***combination*** with drugs ***inhibiting*** **CYP3A4**.

Bethanechol (Urotone®)

- **Bethanechol** is a *parasympathomimetic choline carbamate* that ***selectively stimulates*** **muscarinic receptors** *without any* effect on **nicotinic receptors**.
- **Bethanechol** has *limited value* in the ***treatment of*** **GERD** because of *unwanted* ***side effects***, is ***not*** *routinely* ***recommended*** for **GERD**.
- It is *used* in **postoperative non-obstructive GIT** and **urinary tension**.
- *Side effects*; **Diarrhea, blurred vision, abdominal cramping**.

Antiemetic Agents

- *Nausea*: *Unpleasant sensation* of the ***imminent need*** *to* **vomit**; ***may*** or ***may not*** *lead to the act of* vomiting.
- *Vomiting* (*emesis*): *Involuntary forceful expulsion* of **gastric contents** *through the* **mouth**.
- **Nausea** and **vomiting** *may occur* ***separately*** or ***together***.
- *Nearly* **70-80%** of ***patients*** who undergo **chemotherapy** *experience* **nausea** and/or **vomiting**.
- About **50-80%** of **pregnant women** *experience* **nausea** and/or **vomiting** *during* the **first trimester** of **pregnancy** (due to *high levels* human chorionic gonadotropin; hCG).

Antiemetic Agents

Dopamine (D_2) Antagonists

Prochlorperazine (Compazine®)

- **Prochlorperazine** and **Promethazine** are **Phenothiazines** are ***antipsychotic agents***.
- **IV Phenothiazines** provided ***quicker*** and ***more complete*** **relief** in **emergency department**.
- ***Dose*** of ***antiemetic effect*** is *approximately* a ***third*** of that than its **dose** *for* **psychosis**.
- ***Formulations***; Tablets, syrup, suppositories and injection (*not* SC).
- ***Side effects***; **Extrapyramidal symptoms** (EPS) and **hypersensitivity reactions**.

Promethazine (Phenergan®)

- ***Antiemetic mechanism***; **antidopaminergic**, **anticholinergic** and **antihistaminergic** ***activity***.
- ***Formulations***; Tablets, suppositories and injection.
- ***Side effects***; **EPS**, **hypersensitivity reactions**, **sedation**, and **anticholinergic effects**.

Haloperidol (Haldol®)# | Droperidol (Inapsine®)

- ***Formulations***; **Haloperidol**; Injection, tablets. **Droperidol**; Injection.
- ***Side effects***; **Extrapyramidal symptoms** (EPS), ***fatal*** **QT prolongation** (ECG monitoring for 2 to 3 hours after administration).

Metoclopramide (Primperan®)#

Metoclopramide is a **Substituted Benzamides**; ***peripherally*** and ***centrally*** ***dopamine antagonist***.
Antiemetic mechanism; ***block*** **D_2 receptors** in **CTZ**.
Pregnancy; **US FDA category B**; ***not recommended due to*** **extrapyramidal symptoms (EPS)**.
Side effects; **extrapyramidal symptoms (EPS)**; *long-term use* (can **cause** **tardive dyskinesia**).

Domperidone (Motilium®)#

Domperidone is a ***peripherally dopamine antagonist***.
Domperidone ***may*** ***relieve*** **nausea** and **vomiting** by ***improve*** **upper GIT** ***motility***.
Domperidone ***promote*** **lactation** by ***blocks*** **dopamine receptors** in the *anterior* **pituitary gland** *increasing* ***release*** of **Prolactin** which in turn *increases* **lactation**.
Pregnancy; **US FDA category C**; ***not recommended due to*** **QT prolongation**.
Side effects; ***Fatal QT prolongation*** (mostly when used with CYP3A4 inhibitors such as; **Itraconazole** and **Ketoconazole**, **Erythromycin** and *certain other* **macrolide**).
Contraindications; **CYP3A4 inhibitors**, **Prolactin secreting pituitary tumor**, **Mechanical bowel disorders** (such as bowel obstruction, gastrointestinal hemorrhage or bowel perforation).

Olanzapine (Zyprexa®)#

- **Olanzapine** is an ***atypical antipsychotic***, it is ***block*** **5-HT_{2A}** and **D_2 receptors**.
- **Olanzapine** can be ***used*** in ***combination*** with to **standard antiemetics** such as **Palonosetron** and **Dexamethasone**, for ***prevent*** **acute chemotherapy-induced nausea & vomiting (CINV)**.

Serotonin 5-HT$_3$ Receptor Antagonists (5-HT$_3$-RAs)

Ondansetron (Zofran®)# (Danset®)#	**Granisetron** (Kytril®)# (EM-EX®)#
Dolasetron (Anzemet®)	**Palonosetron** (Aloxi®)

Uses; **nausea/vomiting**; **cancer chemotherapy**, **radiation therapy**, **surgery**, or **postoperative**.
Off-label used to treat **morning sickness** & **hyperemesis** in **pregnancy** (**category B**).
Formulations; - **Ondansetron**; Tablet, disintegrating tablet, solution and injection.
Ondansetron *injection* is *same* **concentration** but *different* **volume**.
- **Granisetron**; Tab., solution, patch & injection. - **Dolasetron**; Tab. & injection.

Antihistamines

Diphenhydramine (Dramenex®)#	**Dimenhydrinate** (Dramamine®)#
Meclizine (Navidoxine®)#	**Cyclizine** (Emetrex®)#
Doxylamine (Diclegis®)#	**Promethazine** (Phenergan®)#

This agents are ***most effective*** **antihistamines agents** for ***prevention*** of the ***symptoms*** of **motion sickness** and **vertigo** (***prevent*** **nausea** and **vomiting**), ***used*** **30–60 minutes** *before* **travel**.
Antiemetic mechanism; ***due to*** block **H$_1$** & **M$_1$ receptors** in ***vestibular system*** & may affect at **CTZ**.
Brands; **FIRST CHOICE**; **nausea and vomiting of pregnancy** (**NVP**)
Navidoxine®; **Meclizine** + **Vitamin B6** (**Pyridoxine**); **pregnancy category B**
Emetrex®; **Cyclizine** + **Vitamin B6**; **pregnancy category B**
Diclegis®; **Doxylamine** + **Vitamin B6**; **pregnancy category A**
Systemic acute **toxicity**, ***especially*** in **young children**, *including* **hallucinations**, **excitement**, **ataxia**, and **convulsions**. *So*, (**Emetrex® Ampoule**) is **NOT** recommended in **CHILDREN** younger than **6 years** to prevent vomiting (***serotonin antagonists*** such as **Ondansetron** is ***safer***).

Corticosteroids

Methylprednisolone (Depo-Medrol®)#	**Dexamethasone** (Epidron®)#

- *Acute* and *delayed* **nausea** and **vomiting** in *moderately* to *highly* **emetogenic chemotherapy**.
Brands; **Cortigen-B$_6$®**; **Corticoadrenal Extract** + (**Pyridoxine**) **Vitamin B$_6$** *was available* to ***control*** **nausea** and **vomiting** in and ***may use*** *during* **pregnancy** or in **children** or **paediatrics**.

Cannabinoids

Dronabinol (Marinol®)	**Nabilone** (Cesamet®)

Neurokinin-1 (NK$_1$) Receptor Blockers

Aprepitant (Emend®)	**Netupitant** (Akynzeo®)	**Rolapitant** (Varubi®)

Herbal

Ginger

Ginger may ***use*** to ***relieve*** **nausea** and **morning sickness** *during* **early pregnancy** (**NVP**), **women** ***should not*** *consume* **large amounts** of **ginger**, as it can cause **uterine contractions**.

Antidiarrheal Agents

- Diarrhea [dia-rrho-ea] or Diarrhoea; is *characterized by* **loose, watery stools** or a ***frequent*** **need** to ***have*** a **bowel movement**.
- Diarrhea *remains* the *second leading* **cause** of **mortality** ***after*** **pneumonia** in *infant*.
- *Most common* **cause** is an **infection** of the ***intestines*** (**virus, bacteria** or **parasite**).
- *Viral diarrhea* is ***most common*** in **young children** (*rotavirus* and *astrovirus*).
- *Management of diarrhea focuses on* ***preventing*** *excessive* **water** and **electrolyte** ***losses***, **dietary** ***care***, ***relieving*** **symptoms**, ***treating*** **curable causes**, and ***treating*** **secondary disorders**.

Definition; *Alteration in* a ***normal*** **bowel movement** *characterized by* an ***increase in*** the **water content**, **volume**, or **frequency** (*more than* **3** *per* **day**) of **stool**.

- *Acute Diarrhea*; ***Less than*** **14 days**. - *Chronic* (**or** *Persistent*) *Diarrhea*; ***More than*** **14 days**.

Pharmacological Therapy

Rehydration

- **Sodium** and **Glucose** are ***key ingredients*** of **oral rehydration solutions** because they have ***active uptake*** into the **intestinal mucosa** *even* ***during active*** **diarrhea**. This ***results in*** **water** being ***pulled back*** *into* **circulation**.

- *Dose* **and** *Administration* (Rehydran-N®);
  - ***Dissolve*** the **content** of this **sachet** in **200 ml** of **water** (glass of water) to *form* **Oral Rehydration Solution** (**ORS**).
    - For ***prevention***; Give 50 ml solution per stool motion.
    - For ***treatment***; Give the solution to the child to drink as he or she can, and continue breast feeding or normal feed.

Antimicrobial Agents

Antibiotics

- **Cefixime** (Suprax®); ***potent*** **oral** ***3rd generation cephalosporin*** with ***high*** **gram -ve coverage**.
- **Ceftriaxone** (Rocephin®) & **Cefotaxime** (Claforan®); are ***potent*** **injectable** ***3rd generation cephalosporin*** with *increased* **gram -ve coverage** and ***some*** **gram-*positive*** **bacteria**.
- **Fluoroquinolone antibiotics**; *such as* **Ciprofloxacin** (Cipro®) and **Levofloxacin** (Tavanic®); *Drug of choice* for **traveler's diarrhea**.
- **Azithromycin** (Zithromax®); ***good choice*** in **traveler's diarrhea** for ***pregnant women*** and **children**.
- **Rifaximin** (Xifaxan®); also used in **traveler's diarrhea**.
- **Sulfamethoxazole/Trimethoprim** (Septrin®); Can be used in **traveler's diarrhea** *prophylaxis*.
- **Vancomycin** (Vancomycin®); ***orally*** for **antibiotic-associated colitis** (pseudomembranous colitis).
- **Doxycycline** (Vibramycin®); is a ***good choice*** for ***Vibrio cholerae*** **infection** and Can be used in **traveler's diarrhea** *prophylaxis*.
- **Neomycin** (*not absorbed from GIT*) and **Streptomycin**; can be used ***orally*** in **traveler's diarrhea**.
- **Bismuth Subsalicylate** (Pepto-Bismol®); Used in **traveler's diarrhea** *prophylaxis*.
- **Nifuroxazide** (Antinal®); is an **oral** ***nitrofuran antibiotic***, is a ***broad spectrum*** **intestinal antiseptic** for the *treatment* of **diarrhea** & **gastroenteritis** (*poorly absorbed from the GIT, act mainly locally*).

Antiprotozoal

- **Nitazoxanide** (Alinia®); **diarrhea** due to **Cryptosporidiosis** or **Giardiasis**.
- **Metronidazole** (Flagyl®); is an ***antibiotic*** and ***antiprotozoal agent***, it is effective against wide range of microorganisms, is a ***good choice*** for **diarrhea** due to; **Amoebic dysentery** or **Amebiasis**, **antibiotic-associated colitis** and **Giardiasis**. **Tinidazole** (Fasigyn®), **Secnidazole** (Flagentyl®) and **Ornidazole** (Tibezole®); are an ***antibiotic*** and ***antiprotozoal agent*** like **Metronidazole**.

Antiparasitic

- **Albendazole** (Alzental®), **Mebendazole** (Antiver®) and **Flubendazole** (Fluvermal®); is a ***broad spectrum*** **anthelmintic agents** used in **diarrhea** *caused by* **worms**.

Antimotility Agents

WARNING: - *Avoid* antimotility agents in infection (*presence of high fever*).
- *Avoid* antimotility agents in bloody stool.

Loperamide (Imodium®)#

Loperamide is an OTC opioid drug, act as μ receptor *agonist* on *large intestine* (*not* pass BBB)
Pregnancy; Category B.
Side effects; *increase* risk of toxic megacolon (*acute colonic distension*) and paralytic ileus.
Contraindications; *high* fever, *bloody* or *black* stool and in children > 2 years.

Diphenoxylate/Atropine (Lomotil®)#

Diphenoxylate is a *prescription* opioid drug, act as μ receptor *agonist* (*cross* BBB and may cause physical dependence with high doses). *Pregnancy*; Category C.
Side effects; *Atropine like effects* (dry mouth, headache and blurred vision).
Overdose; convulsions and respiratory depression.
Contraindications; *high* fever, *bloody* or *black* stool and in obstructive jaundice.

Antisecretory Agents

Bismuth Subsalicylate (Pepto-Bismol®)

- Antisecretory, anti-inflammatory, and antibacterial *effects*.

Racecadotril (Hidrasec®)#

- Racecadotril is an *antisecretory agent* act as *peripherally* enkephalinase inhibitor, lead to *increase* Enkephalins (endogenous opioids) *levels*, *lead to inhibits* fluid/electrolyte depletion (NOT act on motility).
- Racecadotril is a *prodrug* which is *converted to* Thiorphan is the *active* metabolite.
Racecadotril is used as *adjuvant therapy* to oral rehydration solution (ORS) in acute diarrhea in children (*over 3 months*) and adult; *reduce frequency* and *duration* of diarrhea.
Dose; 1.5 mg/kg 3 times *daily* (10 mg sachet; infant – 30 mg sachet; child – 100 mg capsules; adult).

Adsorbent Agents

- These agents *act by* *adsorbing* (*binding*) intestinal toxins or microorganisms and/or by *coating* or *protecting* the intestinal mucosa.

Methylcellulose (Citrucel®)

- Methylcellulose is *not absorbed*, is a *hydrophilic colloid* which *absorbs* water in the intestines.

Kaolin-Pectin (Kapect®)#

- Kaolin/Pectin *mixture* is an off-white *suspension* *used for* diarrhea.
- Kaolin, is a *natural* hydrated aluminium silicate, *not absorbed*, act by *binds* to bacteria and toxic substances in the GIT.
- Pectin is a *polyuronic polymer* extracted from citrus fruits, the mechanism of action is *unknown*, but it may *decrease* stool softness (stool modifiers) and *increase* viscosity.

Alternative Therapies

Lactase Enzyme

- Lactase is an *enzyme* that *aids* in the *digestion* of Lactose.
Lactose is in *dairy foods*, this *enzyme supplement* is used to *break down* Lactose and *prevent* bloating, diarrhea, and gas of lactose intolerance.
Lactase *enzyme* *used* in lactose intolerance patient *taken with* milk or dairy product.

Probiotics (Bacterial Replacement Therapy) (Lacteol® forte)#

- Probiotics *restore* *normal* intestinal function & *suppresses* *growth* of pathogenic microorganism.
Probiotics have been shown to *decrease* the duration of infectious and antibiotic-induced diarrhea (*C. difficile*) in *adults* and *children* (*Not used in severely immunocompromised patients*).

Zinc

Zinc *reduce* the duration and severity of diarrhea, and to *prevent* subsequent episodes.
WHO recommendations; Children with diarrhea should provide with 20 mg per day of Zinc supplementation for 10-14 days (10 mg per day for infants under the age of six months).

Laxatives

- The **definition** of **constipation** *includes* the ***following***;
  - * **Infrequent bowel movements** (*typically* ***less than*** 3 **times** ***per*** **week**).
  - * **Straining** ***during*** **bowel movements** (***difficulty*** *during* **defecation**).
  - * ***Sensation*** of **hard dry stools**.
  - * ***Sensation*** of ***incomplete*** **defecation**.

- **Constipation** can be ***caused*** or ***exacerbated*** *by*;
  - A) **Diet**; Low-fiber diet, low liquid intake, dieting or overuse of coffee and tea may cause constipation.
  - B) **Metabolic** or **Hormonal**; Pregnancy, Diabetes, hyperparathyroidism & hypothyroidism.
  - C) **Structural** (morphological or anatomical); Colon cancer, anal fissures, proctitis (inflammation of the anus and the lining of the rectum), and pelvic floor dysfunction.
  - D) **Neurological**; Autonomic neuropathy, Multiple sclerosis, Parkinson's disease, Spinal cord injury & Stroke.
  - E) **Psychological**; Stress, Depression and Anxiety.
  - F) **Medications**;
    - **Opioids**
    - **Tricyclic antidepressants**
    - **Scopolamine**
    - **Bile acid sequestrants**
    - **Calcium** *supplements*
    - **Aluminium**-*containing drugs*
    - **Benzodiazepines**
    - **Antihistamines**
    - **Diuretics**
    - **Benztropine**
    - **Calcium channel blockers**
    - **Antacids** (Al, Ca)
    - **Iron** *supplements*
    - **Phenothiazines**

- **Laxatives**, **Purgatives** & **Cathartics**; are terms describing **drugs** that ***promote*** **evacuation** of the **intestine**.

	Laxatives +	Purgatives ++	Cathartics +++
Potency	Powerful	More powerful	Most powerful
Action	Eases defecation	Accelerates defecation	Urgency defecation
End-Stool	Soft stool	Liquefied stool	More liquid stool
Example	**Psyllium**	**Bisacodyl**	**Magnesium Sulfate**

Stimulant (or Irritant) Laxatives

- **Stimulant laxatives** are ***substances*** that act on the **intestinal mucosa** or **enteric nervous system**, ***altering*** **water** and **electrolyte** ***secretion*** and ***stimulate*** **peristaltic action**
- ***Long-term use*** of **stimulant laxatives** *could lead to* **dependence** and ***destruction*** of the **myenteric plexus**, resulting in **colonic atony** and **dilation**.
- ***Laxative Abuse***; some of the ***less significant*** **adverse effects** of **laxative abuse** include; **dehydration**, **hypotension**, **tachycardia**, **postural dizziness** and **syncope**.
- **Laxative abuse** *can lead* to ***potentially fatal*** **acid-base** and **electrolyte imbalances**.

Senna (Senokot®) (Senna lax®)#

- **Senna** is ***widely used*** **stimulant laxative**.
- ***Active ingredient***; **Sennoside** is an ***anthraquinone glycoside***.
Uses; - ***Short-term*** **relief of** ***acute*** ***or*** ***intermittent*** **constipation**.
- ***Evacuation*** of the **bowel** *before* **surgery** or **colonic examinations**.
- ***Prevention*** of **opioid-induced constipation**.
- ***Formulations***; **oral formula** and **suppository**.
- ***Administration***; **orally**; ***once daily*** at **bedtime**.
Onset; **6-12 hours** *when given* **orally** and *within* **2 hours** *when given* **rectally**.
Side effects; *May cause* **abdominal cramping**, # # **Electrolyte Disturbances** # #, **melanosis coli** (pigmentation of the wall of the colon).
- ***Pregnancy***; **category C**; ***not recommended***
- ***Lactation***; *Not excreted in milk* (safe).
- ***Contraindications***; **intestinal obstruction**, **acute intestinal inflammation**, **Crohn's disease**, **ulcerative colitis**, **appendicitis**, and **abdominal pain** of ***unknown origin***.
- ***Other anthraquinone derivatives***; **Cascara** and **Aloe** (not used now).

Bisacodyl (Dulcolax®) (Bisadyl®)# (Minalax®)#

- **Bisacodyl** is ***widely used*** **stimulant laxative**.
Uses; - ***Short-term*** **relief of** ***acute*** ***or*** ***intermittent*** **constipation**.
- ***Evacuation*** of the **bowel** *before* **surgery** or **colonic examinations**.
- ***Formulations***; **enteric-coated tab** & **suppository**.
- ***Administration***; **orally**; ***once daily*** at **bedtime**.
Onset; **6-10 hours** *when given* **orally** and *within* **30-60 minutes** *when given* **rectally**.
- ***Pregnancy***; **category B**.
- ***Lactation***; *no data on the excretion into human milk* (safe).

Sodium Picosulfate (Picolax®)# (Dulcolax® Pico)#

- **Sodium Picosulfate** is a ***prodrug***, *metabolised by* **gut bacteria** into the **active compound**, this compound is a ***stimulant*** **laxative** and ***increases*** **peristalsis** in **gut**.
Uses; - ***Short-term*** **relief of** ***acute*** ***or*** ***intermittent*** **constipation**.
- ***Evacuation*** of the **bowel** *before* **surgery** or **colonic examinations**.
- ***Administration***; **orally solution** ***once daily*** at **bedtime**.
Pregnancy; **category B** (**GOOD CHOICE**; *in* **acute cases ONLY**).
Onset; **6-12 hours**.

Castor Oil

- ***Mechanism of action***; **Castor Oil** is ***broken down*** in the **small intestine** by **pancreatic lipase** to **ricinoleic acid**, which is ***very irritating*** to the **stomach** and **promptly** ***increases*** **peristalsis**.
Uses; ***reserved*** for **total colonic evacuation**, *such as* **before** to ***surgery*** or ***radiologic*** or **endoscopy**.
- ***Administration***; **orally**, **16 hours** *before* **surgery**.
Onset; **6-10 hours**.
Pregnancy; ***should be avoid***, it may ***stimulate*** **uterine contractions**.

Bulk Forming Laxative

- **Bulk-forming laxatives** are ***indigestible***, ***hydrophilic*** **colloids** (indigestible parts of fruits & vegetables).
- They ***absorb*** **water**, ***forming*** **a bulky, emollient gel** in the **large intestine**, *causing* **water *retention*** and **intestinal *distension***, thereby ***increasing*** **peristaltic activity**.

Psyllium or Ispaghula (Fybogel®)# (Meta-mucil®)#	
Wheat Bran	**Wheat Dextrin** (Benefiber®)#
Methylcellulose (Citrucel®)#	**Inulin** (Fiber Choice®)#
Polycarbophil (FiberCon®)#	

- **Wheat Bran**; is an ***insoluble*** **fiber *extracted from*** **outer shell** (**bran**) of **wheat grain**.
- **Wheat Dextrin**; is a ***soluble*** **fiber *extracted from*** **wheat starch**.
- **Methylcellulose** is ***not absorbed***, is a ***hydrophilic colloid***.
- **Psyllium** [SILL-i-um] or **Ispaghula** [es-PAG-ula] is a form of fiber (***insoluble*** and ***soluble***) made from the ***husks*** of the *Plantago ovata* **plant's seeds**.
- **Polycarbophil** is an ***insoluble*** **fiber**.
- **Inulin** are a group of ***soluble*** *polysaccharide* **fibers** naturally occurring by many types of plants.

Brands; # **Benefiber®** ***powder***; **odourless** and can be ***used*** on **tea** or **juice** ,
Benefiber® ***Suspension***; **apple taste**.
Fybogel® and **Meta-mucil®** ***powder***; **Orange taste**.
Normacol® and **Agiolax®** ***powder***; **Granules *taken* directly** in the **mouth *then* drink *large* amount** of **water**.

Agiolax® granules; ***Plantago ovata*** + **Ispaghula husk** + ***Senna*** **pods**.
Onset of action; **12-72 hours**.
Uses; ***Intermittent*** or ***chronic*** **constipation**.
- ***Effectiveness***; - ***Least effective*** **laxatives**.
- ***Requires*** **adequate water intake** to be ***effective***.
- ***Less effective*** in **drug-induced constipation** & **slow-transit constipation (STC)**.

Safety; ***Safe*** in **renal** and **hepatic disease**, **pregnancy** and **geriatrics** (*old people*).
- ***Side effects***; May cause **gas** and **bloating**.

Osmotic Laxatives

- **Osmotic laxatives**; are **substances** that ***increases*** **osmotic pressure**, *causing* **fluid *accumulation***, **colon *distension***, ***soft*** **stools**, and ***stimulates*** a **bowel movement**.

Glycerin

- **Glycerin** is *usually* **administered** as ***suppository*** and ***exerts*** its ***effect*** by ***irritating*** the **lining** of the **intestine** and **osmotic action** in the **rectum**.

Onset of action; *within* **30 minutes**.
Uses; ***acute*** or ***intermittent*** **constipation**.
Glycerin is considered a ***safe laxative***, can be used in **pediatric patients**.

Lactulose (Duphalac®)#

Lactulose is a ***non-absorbable*** **disaccharide** (**Galactose** and **Fructose**) that is **used *orally*** or ***rectally*** in **constipation** & **hepatic encephalopathy** (reduce ammonia levels).
- ***Mechanism***; **Lactulose** is ***metabolized by*** **colonic bacteria** to low-molecular-weight acids (**Lactic**, **Formic** and **Acetic**) resulting in an **osmotic effect** & ***lowers*** the **pH** and ***increases*** **colonic *peristalsis***.

Lactulose is considered a ***safe laxative***, can be used in **pregnancy**.
Onset of action; **1-2 days** (may require multiple doses).
Uses; - ***Intermittent*** and ***chronic*** **constipation**, ***preferred*** in **chronic liver disease**.
- It ***may*** use for ***acute*** **constipation** or in ***patients*** with an ***inadequate*** **response** to ***increased*** **dietary fiber** and **bulking agents**.
- ***Side effects***; **nausea** and **abdominal discomfort** (**gas** or **bloating**).

Saline Osmotic Laxatives

- **Saline osmotic laxatives** or **saline cathartics** are ***non-absorbable*** **salts**, which produce their effects primarily by **osmotic action**, *causing* **fluid** ***accumulation***, **colon** ***distension*** and ***stimulates*** a **bowel movement**.

Sodium Phosphate	**Magnesium Citrate**
Magnesium Hydroxide	**Magnesium Sulfate**

Onset of action; 0.5-3 hours (oral), 2-15 minutes (rectal).
Uses; **Acute constipation**, ***preoperative*** or ***pre-procedure*** **bowel preparation**.
- ***Contraindications***; **renal impairment**, **heart failure** and **cirrhosis**.
- ***FDA warning***; **patients** who ***received oral*** **Sodium Phosphate** for **bowel preparations** to **colonoscopy** *can development* of ***acute*** **phosphate nephropathy**.
- **Magnesium hydroxide** ***provides additional*** **bulk** and **stimulates** ***increased*** **contractions**.

Stool Softeners (Emollient Laxatives or Surfactants)

- **Stool Softeners** (**Emollient Laxatives** or **Surfactants**) are ***anionic surfactants*** that become ***emulsified*** with the **stool** *produce* ***softer*** **feces** and ***ease*** **passage**.

Docusate (Colace®)

- **Docusate** or **Dioctyl Sodium Sulfosuccinate** is a ***stool softener***. It works by helping **fat** and **water** *into the* **stool mass** to ***soften*** the **stool** (***emulsified*** **stool**).
- **Docusate** ***typically*** comes in the form of a **Sodium**, **Calcium** or **Potassium** ***salts***.
- ***Onset of action***; 1-3 days (oral), 5-20 minutes (rectal).
- ***Uses***; ***prophylaxis*** *rather than* **acute treatment**; ***Prevention*** of **opioid-induced constipation** (in combination with **Senna**) or ***prevention*** of **straining** in **post-myocardial infarction**, **postsurgical**, and **pregnant patients**.
- **Stool softeners** ***requires*** **adequate water** ***intake*** to be **effective**.
- **Stool softeners** ***should not*** be **taken** ***concomitantly with*** **Mineral Oil** *because* of the ***potential for absorption*** of the **Mineral Oil**.

Lubricant Laxatives

- **Lubricant laxatives** are ***substances*** that ***coat*** the **stool** and ***facilitating*** the **passage** of **hard stools**.

Mineral Oil

- **Mineral Oil** or **Paraffin Oil** is a ***clear***, ***viscous oil*** *derivative* of **petroleum** that ***lubricates*** **faecal material**, ***retarding*** **water absorption** *from* the **stool**.
- **Mineral Oil** may be ***given*** **orally** or **rectally**.
- ***Warning***; **Mineral Oil** *should be* ***taken*** **orally** in an **upright position** to ***avoid*** its **aspiration** and ***potential for*** **severe lipid pneumonitis**.
- ***Long-term*** **use** can *impair* **absorption** of **fat-soluble vitamins** (A, D, E, K).

Drugs for Irritable Bowel Syndrome (IBS)

- **Irritable Bowel Syndrome** (**IBS**); is a **functional** (*not* structure) **GI disorder** ***characterized by*** **abdominal pain** and **altered bowel habits** in the ***absence*** of a **specific** and **unique** ***organic pathology***.
- **IBS** ***divides into*** the *following subtypes*;
  - **Diarrhea** *predominant* (**IBS-D**).
  - **Constipation** *predominant* (**IBS-C**).
  - **Mixed IBS** (**IBS-M**) or **Alternating IBS** (**IBS-A**); *features* of ***both*** **IBS-D** & **IBS-C**.
  - **Unclassified** (**IBS-U**).
- ***N.B.***; **Post-Infective syndrome** has consequently been ***termed*** "**Post-Infectious IBS**" (**IBS-PI**).
- ***Symptoms***; - ***In addition*** to **diarrhea** and/or **constipation**, **abdominal pain** is often a **component** of ***all subtypes***.
  - ***Other symptoms***; **bloating**, **distension**, **spasm** and **urgency**.
- ***Drugs for*** **Irritable Bowel Syndrome** (**IBS**);

Antispasmodics

- ***Antispasmodics***: Used mostly for ***short-term relief*** of **abdominal pain** ***but*** *may also* ***treat*** **diarrhea** in *patients with* **IBS-D**.

Atropine

- **Atropine** is a *prototype* of ***antimuscarinic agents***.
- ***Peripheral*** and ***central*** (*tertiary amine*) *effect*.
- ***Uses***; 1) **Ophthalmologic**; **Cyclopentolate** and **Tropicamide** *more preferred*.
  2) **Gastrointestinal**
     - ***Antispasmodic***; **Hyoscine N-Butylbromide** *more preferred*.
     - **Peptic ulcer**; **Pirenzepine** and **Telenzepine**; *more selective* but ***rarely*** **used**.
  3) **Urinary**; **Oxybutynin** and **Solifenacin** *more selective*.
  4) **Cardiovascular**; **bradycardia** and **AV heart block**; ***still used*** (***highly effective***).
  5) **Respiratory**;
     - **Pre-anesthetic medication**; ***still used and*** **Glycopyrrolate** *more preferred*.
     - **Asthma** and **COPD**; **Ipratropium** and **Tiotropium** *more selective*.
  6) **Cholinergic Poisoning/Organophosphate Poisoning**; **DRUG OF CHOICE**.
  7) **Central Nervous System**;
     - **Parkinson's disease (Adjuvant therapy)**; **Benztropine** *more selective*
     - **Motion sickness**; **Scopolamine** **DRUG OF CHOICE**.
- ***Common side effects***; **dry mouth**, **blurred vision**, **tachycardia**, **urinary retention** & **constipation**.

Dicyclomine or **Dicycloverine** (Bentyl®)#	**Hyoscine N-Butylbromide** (Buscopan®)#
Drotaverine (Do-Spa®)#	**Tiemonium Methylsulfate** (Visceralgine®)#
Clidinium (Librax®)#	**Peppermint Oil** (Colpermin®)#

- **Hyoscine butylbromide** (**Buscopan®**); ***most popular antispasmodic drug***.
- **Tiemonium Methylsulfate** (**Visceralgine®**); ***now*** is the ***most widely*** **used**.

Dicyclomine ***should not*** be used *during* **lactation**; *may cause* **baby** ***convulsions***.

- **Librax®**; **Clidinium** + **Chlordiazepoxide** (*benzodiazepine derivative*; **Anxiolytics**); ***used*** for ***short-term relief*** to **reduce** the **abdominal pain** in **irritable bowel syndrome (IBS)** (in some patient if comorbid anxiety exists); ***Long-term*** **use** may cause **dependence** and **tolerance**. ***Side effects***; **anticholinergic side effects**. **Warnings**; Concomitant use of **benzodiazepines** (*including* **Librax®**) and **opioids** may result in **sedation**, **respiratory depression**, **coma** and **death**.
- ***Side effects***; **anticholinergic** *side effects*.

Peppermint oil; may ***worsen*** **GERD** but may ***improve*** **symptoms** in **IBS**.

Mebeverine (Duspatalin®)# (Coloverin®)#

- Mebeverine is an *antispasmodic drug* *without* anticholinergic *side-effects* (this relieves painful muscle spasms of the gut, without affecting its normal motility).

It *used* to **reduce** the **abdominal pain** in **irritable bowel syndrome (IBS).**

Brands;

Duspatalin® and Coloverin® 135; Mebeverine **135 mg** 1*3 **20 min**. *before* meal.

Coloverin® SR 200; Mebeverine **200 mg** 1*2 **20 min**. *before* meal.

Coloverin®-A; Mebeverine **135 mg** + Chlordiazepoxide (*Anti-anxiety*) **5 mg**; 1*3 **20min**. *before* meal.

Coloverin®-D; Mebeverine **135 mg** + Dimethicone (*Antiflatulent*) **40 mg**; 1*3 **20min**. *before* meal.

Pinaverium (Spasmopinaver®)#

Pinaverium is an *antispasmodic drug* acts as a **calcium channel blocker**.

Tricyclic Antidepressants

Tricyclic Antidepressant; Used to *relief* **pain**, *improve* **global symptoms**, and *slow* motility in *patient with* **IBS-D**, *but can* be used in **IBS-C** *but* may *worsen* **constipation**, *especially if comorbid* **depression** or **anxiety exists**.

Imipramine (Tofranil®)# | Amitriptyline (Tryptizol®)# | Nortriptyline (Pamelor®)#

- Imipramine, Amitriptyline and Nortriptyline are the *most studied*.
- *Actions in IBS*; at **doses** ***sub-therapeutic*** for **antidepressive actions**.
  - ***Increases*** **pain threshold** in the **gut** (providing a visceral analgesic effect).
  - ***Delayed*** **gastric emptying** and ***decrease*** **stool frequency**.
- *Precautions*; **anticholinergic effects**, **sedation**, **CV effects** & **drug interactions**.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin Reuptake Inhibitors (*SSRIs*); Used to *relief* **pain**, *improve* **global symptoms**, *similar to Tricyclic Antidepressant*. ***Used for*** *both* **IBS-D** and **IBS-C**.

Fluoxetine (Prozac®)# | Sertraline (Lustral®)# | Paroxetine (Seroxat®)#

Citalopram (Cipram®)# | Escitalopram (Cipralex®)#

- Fluoxetine, Sertraline, Paroxetine, Citalopram & Escitalopram; *all* ***viable*** **options**.

Probiotics

- ***Some*** **evidence** to ***support*** probiotics in ***improvement*** in **global symptoms**, **bloating** and **flatulence**.

Antiflatulent Drugs

Simethicone (Disflatyl®)# | Charcoal (Eucarbone®)# | Herbal Volatile Oil

Disflatyl®; **1-2 tab** ***chewable*** 1*4 or ***after*** **meals** and ***before*** **bed**.

Digestive Drugs

Digestive Enzymes or Zymogen (Digestine®)# (Spasmo-digestin®)# (Digenorm®)#

Dose; **1-2 tab** ***immediately before*** **meals** 1*3

Spasmo-digestin®; Dicyclomine *should not* be used **during lactation**; *Convulsions*.

Probiotics (Lacteol® forte)#

Stimulation of the ***intestinal*** **flora** which ***increase*** **digestibility**.

- ***N.B.***; **Sulpiride** (Dogmatil®) is an ***atypical antipsychotic*** some physicians can prescribe it for ***some*** IBS patients; relief abdominal pain, anxiety, depression and correct stool.

Drugs for IBS-C

Laxatives

- **Laxatives** *was* **discussed** in the ***previous topic***.
Psyllium has ***best evidence***; however, it may cause **bloating** and **gas formation**.
Avoid **stimulant laxatives** because they may ***worsen*** **abdominal pain**.

Chloride Channel Activators

Lubiprostone (Amitiza®)#

- **Lubiprostone** it is a ***derived from*** **Prostaglandin E_1**.
- ***Used*** in **Irritable Bowel Syndrome** *with* **Constipation (IBS-C)** in **women** ≥18 years.
- ***Most common side effects***; **nausea**, **diarrhea**, **headache** and **abdominal pain**.

Serotonin Agonists

Tegaserod (Zelmac®)#

- **Tegaserod** is a **5-HT_4 partial agonist** in the **enteric nervous system (ENS)** in the **GIT**, which ***stimulates*** **GI motility**. ***Used*** for **IBS-C**.
- ***Efficacy***; ***Improves*** **pain**, **global symptoms**, and **motility**.
It is ***removed*** from the market in 2007 due to FDA concerns about possible ***increased risks*** of **heart attack** (In **US** **Tegaserod** is ***available only*** on an **emergency-use**).

Mosapride (Fluxopride®)#

- **Mosapride** is a **5-HT_4 partial agonist** and ***indirectly*** as a **parasympathomimetic** (***increase*** **ACh release**); ***gastroprokinetic agent***.
- It is ***used*** for the treatment of **irritable bowel syndrome** with **constipation (IBS-C)**.
Drug interaction: **LMEIs** (e.g. **Erythromycin**) ***may cause*** ⇨ **QT interval** ***prolongation***.

Guanylate Cyclase-C Agonists

Linaclotide (Linzess®)

- **Linaclotide** is a ***Guanylate cyclase-C agonist***, *approved in* 2012.
- ***Used*** in **Irritable Bowel Syndrome** *with* **Constipation (IBS-C)**

Drugs for IBS-D

Antibiotics

A ***short course*** (10–14 days) of **non-absorbable antibiotic** (**Rifaximin**) may ***improve*** **global symptoms** of **IBS**, ***especially*** **bloating** in **IBS-D**.

Antimotility Agents

- **Antimotility Agents** *was* **discussed** in the ***previous topic***.

Loperamide (Imodium®)# | Diphenoxylate/Atropine (Lomotil®)#

- **Loperamide** and **Diphenoxylate** is an **opioid drug**, act as **μ receptor** ***agonist***.
- May be used as an ***adjunct*** to **other therapies** in **IBS-D**.
Contraindications; ***high*** **fever**, ***bloody*** or ***black*** **stool** and in **children > 2 years**.

Serotonin Antagonists

Alosetron (Lotronex®) | Cilansetron (Calmactin®)

- **Alosetron** and **Cilansetron** are **5-HT_3 receptor antagonist** ***used*** for the management of severe **irritable bowel syndrome** with **diarrhea (IBS-D)**.
- **Alosetron** ***used only*** in **women**, ***but*** **Cilansetron** effective in **men** as well as **women**.
- ***Side effects***; **Alosetron**; ***serious*** (***life-threatening***) **constipation** e.g. **ischemic colitis** *may lead to* **obstruction**, (**Cilansetron** is **constipation**, ***less*** or ***self-limited***).

Drugs for Inflammatory Bowel Disease (IBD)

- **Inflammatory Bowel Disease** (**IBD**); is a ***group of*** **inflammatory conditions** of the **colon** and **small intestine**.
- *Two major types* of **IBD** are **ulcerative colitis** (**UC**) & **Crohn's disease** (**CD**).
- **Ulcerative colitis** (**UC**), which is ***limited to*** the **colon** and **rectum**.
- **Crohn disease** (**CD**); which can ***affect any segment*** of the **GIT** *from the* **mouth** *to the* **anus**.
- ***Common*** **symptoms** in **both diseases** (**UC** and **CD**) *include*;
  - **Fever**.
  - **Abdominal pain**.
  - **Diarrhea** (*may be* **bloody**, **watery** or **mucopurulent**).
  - **Rectal bleeding**.
  - **Weight loss**.

➢ **Medications Used to Treat IBD:-**

Aminosalicylates

- **Aminosalicylates** was the ***first agents*** used to **treat IBD**.
- **Aminosalicylates** are drugs that ***contain*** **5-aminosalicylic acid** (**5-ASA**).
- **Used** for ***both***;
  1) ***Induction*** of **remission** (relieve symptoms and inflammation).
  2) ***Maintenance*** of **remission** (prevent the disease from becoming active again).
- **Aminosalicylates** are ***believed*** to **work** ***topically*** (not systemically).

Azo Compounds

Sulfasalazine (Azulfidine®)#	**Balsalazide** (Colazal®)	**Olsalazine** (Dipentum®)

Sulfasalazine is a ***prototype agent***, *cleaved by* **colonic bacteria** to the **active portion** (**5-ASA**) and the ***inactive*** **carrier** molecule **Sulfapyridine**.
Balsalazide and **Olsalazine** are ***non-sulfa azo compounds***.
- ***Efficacy***; ***best*** in **colonic disease** (because of the colonic activation of the drug).
Mechanism of action; ***Inhibits*** **prostaglandin** and **leukotriene synthesis** (*local* anti-inflammatory).
- ***Dose***; - **Sulfasalazine**; 4–6 g/day for induction and 2–4 g/day for maintenance.
  - **Olsalazine**; 1–3 g/day. **Balsalazide**; 2–6.75 g/day.

Side Effects (dose-related); **GI disturbance**, **headache**, **arthralgia** and **folate malabsorption**.
Contraindications; **Sulfasalazine** is ***avoid*** in *patients with* a **sulfa allergy**.
- ***Monitoring/Follow-Up***; **folate supplements**, **Renal function**, **CBC** & **creatinine level/3-6 months**.

Mesalamine Compounds

Mesalamine

(Pentasa®)# (Rowasa®) (Canasa®) (Delzicol®) (Asacol® HD) (Lialda®) (Apriso®)

Mesalamine is ***designed to*** *deliver* **5-ASA** to ***different*** **segments** of the **small** or **large intestine**.
In general; ***better*** **tolerated** than **Sulfasalazine**; *considered* ***first line*** in **mild–moderate UC & CD**.

- *Formulations*; **Product *selection*** *depends on* **location** of **disease**.

Product	Formulation	Daily Dosage (g)	Site of Action
Pentasa®	Timed-release microgranules	2-4	- Small intestine - Colon
Delzicol®	Delayed-release capsules	1.6-4.8	- Distal ileum - Colon
Asacol®	Delayed-release resin (dissolves at pH >6-7)		
Apriso®	Enteric-coated granules in a delayed-release polymer matrix (dissolves at pH >6-7)	0.375-1.5 once	- Colon
Lialda®	Delayed-release Multi Matrix (MMX) System tablet (dissolves at pH >6-7)	2.4-4.8 once	- Colon
Canasa®	Suppository	1	- Rectum
Rowasa®	Enema	4	- Rectum - Terminal colon

Antibiotics

Ciprofloxacin (Cipro®)# | **Metronidazole** (Flagyl®)#

- The ***most commonly*** used agents (alone or in combination) are:
  - # **Metronidazole**; 500-750 mg orally 3 every 8 hours.
  - # **Ciprofloxacin**; 500-750 mg orally every 12 hours.

Indications of **antibiotics** in **IBD**;
- # ***Adjunctive*** **treatment** *along with* ***other*** **medications** for **active CD**.
- # **Treatment** for ***complications*** in **CD** (e.g.; **fistulas**, **perianal disease**).
- # **Prophylaxis** of **CD** ***recurrence*** in **post-operative patients**.

- **Note**; that **antibiotics** ***do not*** have a **role** in the **management** of **UC**.

Glucocorticoids

Prednisone (Hostacortin®)# | **Prednisolone** (Hostacortin-H®)#

Methylprednisolone (Depo-Medrol®)# | **Hydrocortisone** (Solu-Cortef®)#

Budesonide (Entocort®)#

Corticosteroids are ***rapid-acting*** **anti-inflammatory agents**.
Efficacy; are indicated ***only*** for **acute flares** (no role in the maintenance of remission).
Corticosteroids are ***not useful*** for ***maintaining*** **disease remission**.
- ***Administration***; by ***various*** **routes** *depending on* the **location** and **severity** of **disease**;
  - **IV**; **Methylprednisolone** (15-48 mg/day)
    Hydrocortisone (100 mg every 8 hours).
  - **Orally**; **Prednisone** (20–60 mg/day)
    Prednisolone (20–60 mg/day)
    Budesonide (9 mg/day)
  - **Topically**; Enema, suppository or foam preparations.

Side effects; **adrenal suppression**, **glucose intolerance**, **hypertension**, **sodium/water retention**, **osteoporosis**, **cataracts**, and **impaired wound healing**.

Immunomodulators

6-Mercaptopurine (6-MP) (Purinethol®)# | Azathioprine (AZA) (Imuran®)#
Methotrexate (MTX)

Immunomodulators have a ***slower*** **onset** (> 3 months); ***not*** ***used for*** **induction** of **remission**.
Efficacy; Used for **maintenance of remission** in **patients** ***intolerant*** of or ***not responsive*** to **Aminosalicylates**.
- ***Doses***;
  - **Azathioprine**; 2–2.5 mg/kg/day orally.
  - **Mercaptopurine**; 1–1.5 mg/kg/day orally.
  - **Methotrexate**; 15–25 mg/week intramuscularly (Crohn's disease only).

Side effects; **Bone marrow suppression, anemia, nausea, diarrhea, rash** and **hepatotoxicity**.
Folate ***supplementation*** *reduces* the **risk** of these events *without* **impairing** the **anti-inflammatory action**.

Biologic Agents

TNF-α Inhibitors

Tumor necrosis factor alpha (TNF-α) is a ***pro-inflammatory cytokine***.
5 TNF inhibitors; **Etanercept, Infliximab, Adalimumab, Certolizumab** and **Golimumab**.

Anti-TNF PRECAUTIONS

Risk of **serious infections**, or ***history of*** **recurring infections**; black box warning.
Recent malignancies; *especially* **lymphoproliferative cancer**; black box warning.
Congestive heart failure (CHF); New York Heart Association (NYHA) class III or IV heart failure
Demyelinating diseases; *like* **multiple sclerosis**.
Avoid **vaccination** *with* **live vaccines**.

Infliximab (Remicade®)#

- **Infliximab** is a ***recombinant*** **DNA-derived** **chimeric** **human-mouse** **IgG_1 monoclonal antibody**.
- ***Efficacy***; - **Maintenance of remission of moderate–severe CD** and **UC**.
  - **Perianal fistulizing CD**.
- ***Dose***; IV Infusion, 5 mg/kg as single dose, followed by 5 mg/kg at 2 and 6 weeks, then every 8 weeks as maintenance. (Patients losing response with time may be treated with a 10-mg/kg dose).
- **Infusion site reactions** ***may*** **occur** and may ***correlate with*** **anti-infliximab antibodies** ***formation*** (antihistamines may prevents some of these reactions).

Adalimumab (Humira®)#

- **Adalimumab** is a ***recombinant*** ***fully*** **human IgG_1 monoclonal** ***antibody***.
- ***Efficacy***; **Maintenance of remission of moderate–severe CD** and **UC**, in **patients** ***unresponsive*** to **conventional therapy**; also *indicated for* **patients** who no **longer** *respond to* **Infliximab**.
- ***Dose***; Induction; 160 mg SC on day 1 (given as four separate 40-mg injections) or two 40-mg/day injections for 2 consecutive days, followed by 80 mg SC 2 weeks later (day 15). Then, can decrease dose to 40 mg SC every 2 weeks starting on day 29 of therapy.

Certolizumab Pegol (Cimzia®)#

- **Certolizumab** is a ***unique*** **TNF-α blocker** that contains a ***recombinant***, ***humanized*** **antibody Fab fragment** ***conjugated to*** a **Polyethylene Glycol (PEG)** (not contain IgG_1) with ***specificity*** for ***human*** **TNF-α**.
- ***Efficacy***; **Maintenance of remission of moderate–severe CD**, in **patients** ***unresponsive*** to **conventional therapy**.
- ***Dose***; 400 mg **SC** initially and repeat at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.

Golimumab (Simponi®)#

- **Golimumab** is a ***human*** **monoclonal antibody** with a ***high*** **affinity** for ***soluble*** and ***membrane-bound*** **TNF-α**.
- ***Efficacy***; **Maintenance of remission of moderate–severe UC**, in **patient's** ***unresponsive*** to in **previous therapies** or ***requiring*** *continuous* **steroid therapy**.
- ***Dose***; 200 mg subcutaneously at week 0, then 100 mg at week 2, then 100 mg every 4 weeks.

Anti-integrin Agents

Natalizumab (Tysabri®)#

Natalizumab is a ***humanized*** **monoclonal antibody** ***against*** the **α-4 subunit of integrin molecules** (*leukocytes*), ***used*** in the ***treatment of*** **multiple sclerosis** & **Crohn's disease**.

- ***Efficacy***; **Maintenance of remission of moderate–severe CD**, in **patients** ***unresponsive*** to **conventional therapies** and **TNFα** ***inhibitors***.
- ***Dose***; 300 mg IV infusion over 1 hour every 4 weeks, the treatment cost is very expensive.
- ***Precautions***; **Progressive Multifocal Leukoencephalopathy**; **PML** (viral CNS infection, John Cunningham virus; JCV); rapidly progressive and usually results in death or permanent disability;
  - The ***risk of PML***;
    1) History of previous immunosuppression.
    2) Long duration of **Natalizumab** treatment, beyond 2 years.
    3) JC virus antibody positivity.

Vedolizumab (Entyvio®)#

- **Vedolizumab** is a ***humanized*** **monoclonal antibody** ***against*** the **α4β7-integrin of integrin molecules** (*leukocytes*).
- ***Efficacy***; **Maintenance of remission of moderate–severe CD** and **UC** in **patients** ***unresponsive*** to **conventional therapies** and **TNFα** ***inhibitors***.
- ***Dose***; 300 mg IV given at 0, 2, and 6 weeks, then given every 4 weeks. Discontinue if no evidence of improvement at 14 weeks.
- ***Precautions***; similar to that of **Natalizumab**, ***but*** with ***lower risk*** of **PML**.

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➢ Pancreatic Enzyme Replacement Therapy (PERT):-

- ***Exocrine* pancreatic insufficiency** is ***most commonly*** *caused by* **cystic fibrosis, chronic pancreatitis** or **pancreatic resection**.
- *If* **secretion** of **pancreatic enzymes** *below* **10%** of **normal**; **fat** and **protein** ***digestion*** is ***impaired*** & can lead to **steatorrhea, azotorrhea, vitamin malabsorption & weight loss**.
- The **Pancreatic Enzyme Products** (**PEPs**) or **Pancrelipase** ***used in*** **PERT** are *extracts of* **porcine pancreas** that contain ***all* 3 pancreatic enzymes** (**amylase, protease** and **lipase**) in ***varying proportions***, are ***used for*** **pancreatic enzyme insufficiency**.
- The are **6 PEPs** have been ***approved*** by the **US FDA**;

Pancreatic Enzyme Products (PEPs) or Pancrelipase

Brand	Lipase (units)	Amylase (units)	Protease (units)	Formulation
Creon®	3000	15,000	9500	Capsules with enteric-coated microspheres
	6000	30,000	19,000	
	12,000	60,000	36,000	
	24,000	120,000	76,000	
	36,000	180,000	114,000	
Viokace®	10,440	39,150	39,150	Immediate-release tablet
	20,880	78,300	78,300	
Pertzye®	8000	30,250	28,750	Capsules with enteric-coated microspheres
	16,000	28,750	57,500	
Zenpep®	3000	16,000	10,000	Capsules with enteric-coated beads
	5000	27,000	17,000	
	10,000	55,000	34,000	
	15,000	82,000	51,000	
	20,000	109,000	68,000	
	25,000	136,000	85,000	
	40,000	218,000	136,000	
Ultresa®	13,800	27,600	27,600	Capsules with enteric-coated mini-tablets
	20,700	41,400	41,400	
	23,000	46,000	46,000	
Pancreaze®	2600	10,850	6200	Capsules with enteric-coated micro-tablets
	4200	17,500	10,000	
	10,500	43,750	25,000	
	16,800	70,000	40,000	
	21,000	61,000	37,000	

- ***Dosing***; based on **lipase content** (units) in the product;
  - ***Initial***; 500 units/kg/meal.
  - ***Dose range***, 500-2500 units/kg/meal.
  - ***Maximum dose***; 10,000 units/kg/day.
  - ***Usually adult doses***; 30,000–40,000 units/meal, with one-half dose for snacks.
- ***Administration***; orally before or during meal.
- ***Dose monitoring***; ***increased*** in **weight gain** and ***decreased*** in **steatorrhea**.
- ***May need*** to ***add*** **proton pump inhibitors** (**PPIs**); *if* **maximal response** is ***not seen***.
- ***Side effects***;
  - **Nausea** or **abdominal cramping**.
  - **Allergy** in patients with *pork allergy*.
  - **Hyperuricosuria, hyperuricemia**.
  - **Fibrosing colonopathy** (generally seen with doses greater than 10,000 units/kg/day)
- ***Pregnancy***; **category C**.

Gallstones

- **Bile** is a ***complex*** of **fluid** *containing* **water**, **electrolytes** and ***organic molecules*** *including* **bile acids**, **cholesterol**, **phospholipids** and **bilirubin**.
- ***Bile Function***; - **Bile acids**, ***help for*** **digestion** and **absorption** of **fats** and **fat-soluble vitamins** in the **small intestine** (*by acting as a surfactant that emulsifies them into micelles*). *Many* **waste products**, *including* **bilirubin**, are *eliminated from* the **body** by **secretion** into **bile** and *elimination in* **feces**.
- **Gall bladder** ***stores*** and ***concentrates*** **bile** and **cholesterol** is ***soluble*** in **bile**.
- **Gallstone** (**Cholelithiasis**); is a ***stone formed within*** **gallbladder**, *about* **80%** of **patients** are *asymptomatic*.
- **Gallstones**, ***most of which*** are **composed** *predominantly of* **cholesterol**.
- **Gallstones** ***develop*** when **bile** *contains* ***too much*** **cholesterol** and ***not enough*** **bile salts**.
- ***Common Symptoms***; **biliary colic** (**crampy pain**; ***right*** **upper** **abdominal pain**, *usually* ***after*** **heavy meals** and *lasts* **1-4 hours**), ***more than*** **5 hours** → **Complication**.
- **Complications**; **cholecystitis**, **cholangitis** and **acute pancreatitis**.
- ***Complication signs***; **biliary colic** ***more than*** **5 hours**, **fever**, ***persistent*** **tachycardia**, **hypotension** and **jaundice** (yellowish skin).
- **Surgery**; ***rapid*** **treatment** of **complications** is **cholecystectomy** (**gallbladder** ***remove***).
- ***Medical treatments*** of **asymptomatic gallstones** is **oral bile salt** (**Ursodeoxycholic acid**);

Ursodeoxycholic Acid or Ursodiol (Ursofalk®)#

Ursodeoxycholic Acid (**UDCA**) or **Ursodiol** is a ***naturally occurring*** **bile acid** found in *small quantities* in *normal* **human bile** and in ***larger quantities*** in the **bile** of *certain species* of **bears**.

Mechanisms; **1**) **Ursodiol** ***regulate*** **cholesterol** by;

* ***Reducing*** **intestinal cholesterol** ***absorption***.

* ***Reducing*** **hepatic cholesterol** ***synthesis*** and ***secretion***.

2) **Ursodiol** is a **hydrophilic bile acid** that ***solubilizes*** **cholesterol** and ***promotes*** its **dispersion** in **aqueous fluids**, ***reducing*** **viscosity** and ***improving*** **bile flow**.

- ***From 1 and 2***, ***results***; **Ursodiol** *reduces* **cholestasis**, ***prevents*** **formation** and ***promotes*** **dissolution** of **cholesterol-containing gallstones**.

Indications; **Cholelithiasis**, **Primary Biliary Cholangitis** (**PBC**), **Cholestasis** (slowing or stopping of bile flow) in **cystic fibrosis**, **new-born infants** and **pregnant women** (relieve itching).

- **Chenodeoxycholic Acid** (**Chenodiol**) is an ***epimer of*** **Ursodeoxycholic Acid**, ***but*** have ***potential*** **hepatotoxicity** and ***poor*** **response**.

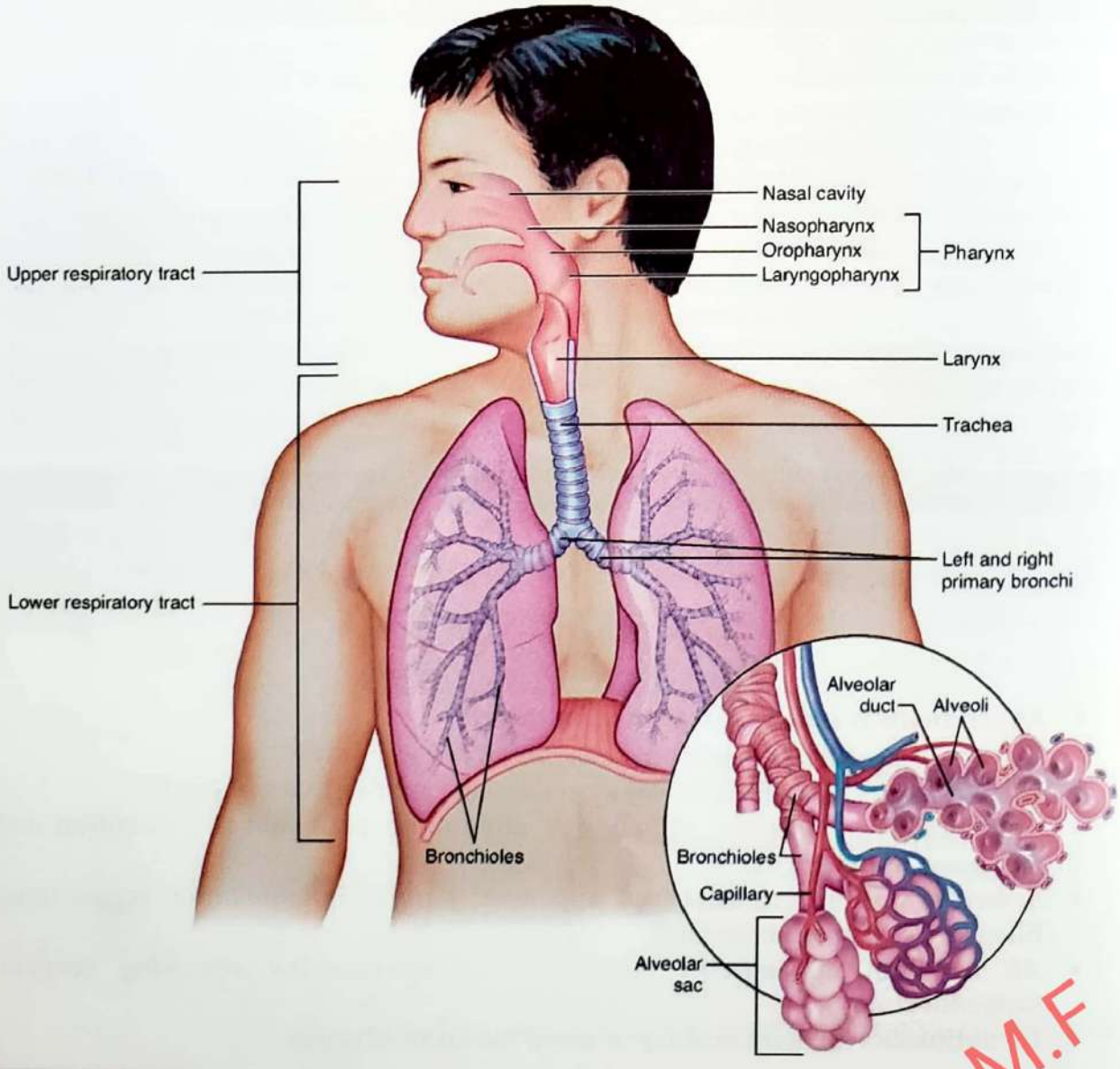
Rowachol®#

#**Rowachol®** ***contains*** **essential oils** (**Pinene**, **Camphene**, **Cineol**, **Menthone**, **Menthol**, **Borneol**) that ***may help*** to ***dissolve*** or ***break up*** **cholesterol-based gallstones**.

Appendicitis

- **Appendicitis** is ***inflammation*** of the **appendix**.
- **Appendix** is a **tube** ***of*** **tissue** that ***extends from*** **large intestine**.
- There is ***no accurate*** **function** of **appendix** and we ***can*** **live** ***without*** **it**.
- **Appendicitis symptoms**; ***right*** **lower** **abdominal pain**, **nausea**, **vomiting** and ***decreased*** **appetite**.
- ***Severe complications***; **ruptured appendix**; ***painful inflammation***, **sepsis** (pus-filled abscess) and can be **fatal**.
- ***All cases*** of **appendicitis** are treated as **emergencies**, ***requiring*** **surgery** (**appendectomy**).
- **IV antibiotics** are used to ***delay*** or ***avoid*** the **onset of sepsis**.

Respiratory



Antihistamines

Histamine

- **Histamine** is formed by ***decarboxylation*** of the amino acid **L-histidine**, a reaction catalyzed by **histidine decarboxylase enzyme**.
- ***Once formed***, **Histamine** is either **stored *or* *rapidly* inactivation**.

Storage:

* ***Tissues***; It is found in ***most*** tissues but is present in ***high*** conc. in the **lungs**, **skin** and **fundus** of the **stomach** (Enterochromaffin-Like; ECL cells).

* ***Cells***; It is found largely in **mast cells** and **basophils**.

* ***Neurons***; Histaminergic neurons in the **brain**.

Release;

A) Immunologic Release:

- **Hypersensitivity reaction (Type I) (immediate hypersensitivity)**: **Antigen** (***allergen***) react with **antibody (IgE)** on the mast cell ⇨ these reaction increase release of histamine from mast cells.

B) Chemical and Mechanical Release;

- **Morphine** and **Tubocurarine**, can ***displace*** **histamine** from its bound form within cells. This type of release is not associated with mast cell injury or degranulation.

- **Histamine** exerts its ***biological actions*** by combining with **specific cellular receptors** located on the surface membrane.
- **Histamine** exerts ***powerful effects*** on **smooth** and **cardiac muscle**, on certain **endothelial** and **nerve cells**, on the **secretory cells of the stomach**, and on **inflammatory cells**.

Histamine Antagonists

1) **Physiological Antagonist of Histamine**: #
   # **Adrenaline** having ***apposite*** to those **histamine** on **H_1 receptor** due to cause **bronchodilatation** (β_2) and **vasoconstriction** (α_1).
2) **Mast Cell Stabilizers** # (***Inhibit*** **histamine release**); ⇨ ***Decrease*** **histamine release** from **mast cell** ⇨ ***used as*** **prophylactics in asthma**.
   A) Cromolyn (or **Cromoglycate**), **Nedocromil** and **Ketotifen**.
   B) β_2-adrenoceptor agonists e.g. **Salbutamol**.
   C) Methylxanthines e.g. **Theophylline**.
3) **Histaminase Enzyme** (**Diamine Oxidase**): ⇨ ***Responsible for*** **histamine *metabolism***.
4) **Histamine Receptors Blockers**:
   A: **H_1**-receptor blockers.
   B: **H_2**-receptor blockers.
   C: **H_3**-receptor blockers.
   D: **H_4**-receptor blockers.

H_1-receptor Antagonists (Antihistamine)

The ***term*** **antihistamine** ***refers primarily*** to the classic **H_1-receptor blockers**.

- The ***new*** classification of **H_1-receptor blockers**; ***First-***, ***Second-*** & ***Third-generation***.

First Generation (Sedating Antihistamines)

The *older* **first-generation** drugs are still ***widely used*** *because*; **effective** & **inexpensive**
Most of these drugs ***penetrate the CNS*** (lipophilic) and ***cause*** **sedation**.
Short duration of action (4-6 hours); **3** ***times*** **daily**.
Some of these drugs have another actions in addition of H_1-blockers e.g. ***Anticholinergic***, ***Antiemetic***, ***Antiserotonin*** and ***local anesthetic effects***.

Chlorpheniramine (Anallerge®)#	**Brompheniramine** (VaZol®)
Hydroxyzine (Atarax®)#	**Triprolidine** (Actifed®)#
Clemastine (Tavegyl®)#	**Dimethindene** (Fenistil®)#
Pheniramine (Avil®)#	**Mequitazine** (Primalan®)

Chlorpheniramine, **Triprolidine**; ***slight*** **sedation**, ***common component*** of **cold medication**.
Hydroxyzine; ***marked*** **sedation**.
- **Brompheniramine**, **Dimethindene**, **Clemastine**, **Pheniramine** & **Mequitazine**; ***slight*** **sedation**

Diphenhydramine (Dramenex®)#	**Cyclizine** (Emetrex®)#
Dimenhydrinate (Dramamine®)#	**Doxylamine** (Donormyl®)#
Meclizine (Navidoxine®)#	**Promethazine** (Phenergan®)#

Diphenhydramine, **Dimenhydrinate**, **Cyclizine**, **Meclizine**, **Doxylamine** and **Promethazine** are the ***most effective*** agents for ***prevention*** of the symptoms of **motion sickness** and **vertigo** (***prevent*** **nausea** and **vomiting**). ***Antiemetic action***; ***due to block central*** **H_1** and **M_1 muscarinic receptors**.
Diphenhydramine, **Dimenhydrinate** and **Promethazine**; ***marked*** **sedation**.
Cyclizine and **Meclizine**; ***slight*** **sedation**.
Doxylamine (**Donormyl**®)#; ***strong*** **sedation**, ***used*** in the ***treatment*** of **insomnia**.

Cyproheptadine (Triactin®)#

Cyproheptadine (**Triactin**®)# # also acts as a ***serotonin antagonist*** on the ***appetite center*** and is sometimes ***used*** *off-label* as an **appetite stimulant**; ***widely used***

Second Generation (Non-sedating Antihistamines)

The ***newer*** **second-generation** drugs are **expensive**.
They are made **polar** mainly by adding carboxyl groups, the second-generation agents ***don't pass*** **the BBB**, causing ***less*** **CNS sedation**.
Long duration of action (**12** to **24 hours**); ***once*** **daily** *at* **bed time**.
More **selective** (***no*** anticholinergic, ***no*** antiemetic & ***no*** antiserotonin activity).

Cetirizine (Zyrtec®)#	**Loratadine** (Claritin®)#	**Acrivastine** (Semprex®)
Ebastine (Kestine®)	**Mizolastine** (Zolim®)	

Cetirizine is a ***partially*** **sedating** ***second-generation agents***.
- **Loratadine**, **Acrivastine**, **Ebastine** and **Mizolastine**; ***least*** **sedation**.

Ketotifen (Zaditen®)#	**Alcaftadine** (Lastacaft®)#	**Bepotastine** (Talion®)#
Emedastine (Emadine®)	**Azelastine** (Azelast®)#	**Olopatadine** (Patanol®)#

[Ophthalmic Antihistamines]

Ketotifen, **Alcaftadine**, **Bepotastine**, **Emedastine**, **Azelastine** and **Olopatadine**; ***ophthalmic formulations*** and used for the ***treatment*** of **allergic conjunctivitis**.
Azelastine and **Olopatadine** ⇨ have ***intranasal*** **formulations**.
Ketotifen ⇨ has ***oral formulations***.
Azelastine and **Ketotifen**; have **mast cell** ***stabilizing effects*** in addition to their **H_1-blocking effects**.

Third Generation (Non-sedating Antihistamines)

Third-generation are the ***active enantiomer*** (**Levocetirizine**) or ***metabolite derivatives*** (**Desloratadine** & **Fexofenadine**) of ***second-generation drugs*** intended to have ***increased*** **efficacy** with ***fewer*** **adverse drug reactions**.
They are ***more*** **expensive** ***than*** **second-generation**.
Don't pass **the BBB**, causing ***no*** OR ***less*** **CNS sedation** ***than*** **second-generation**.
Long duration of action (**24 hours**); **1*1 at bed time**
Pure **selective** for **H_1-receptors**.

Levocetirizine (Allear®)#	**Desloratadine** (Aerius®)#	**Fexofenadine** (Telfast®)#

Levocetirizine is the ***active enantiomer*** of **Cetirizine**, and cause ***partially*** **sedation**.
Desloratadine, **Fexofenadine**, are the ***least*** **antihistamines sedation**.
Desloratadine is an ***active metabolite*** of **Loratadine**.
Fexofenadine is an **active metabolite** of **Terfenadine**.
- Terfenadine (Prodrug) is metabolized to **Fexofenadine** (Active drug), liver microsomal enzyme inhibitors (e.g. Erythromycin) inhibit this metabolism, lead to ↑ concentration of Terfenadine in the blood ⇨ Block K^+ channels in the heart ⇨ cardiac arrhythmia (QT interval prolongation). (No cardiotoxicity with fexofenadine).

Pharmacodynamics;

1) **Sedation**;
   # A ***common effect*** of **first-generation**; ***useful*** as "**sleep aid**".
   # At ***very high toxic*** **dose**, marked stimulation; ***convulsions***.
2) **Antinausea and antiemetic actions**;
   # ***Several*** **first-generation**; **prevention motion sickness**.
3) **Anticholinoceptor actions**;
   # ***Many*** **first-generation**; **Diphenhydramine**, **Clemastine**, **Dimenhydrinate** and **Doxylamine** have significant **atropine-like effects** (**dry mouth**, **urinary retention** and **blurred vision**).
4) **Adrenoceptor-blocking actions**;
   # **α_1 blocking effects** can *demonstrated for* many **first-generation** ***especially*** **Promethazine**, may ***cause*** **orthostatic hypotension**.
5) **Serotonin-blocking action**;
   # **Cyproheptadine**, it is ***used*** **off-label** as an **appetite stimulant**.
6) **Local anesthesia**;
   # ***Several*** **first-generation** are ***potent*** **local anesthetics** especially **Diphenhydramine** and **Promethazine** they **block Na^+ channels** in ***excitable*** **membranes**.

Therapeutic Uses;

1) **Allergic Reactions**;
   # **Allergic rhinitis** (**hay fever**); **ONLY** **2nd/3rd generation**.
   # **Urticaria** & **dermatitis**; **1st generation** **sedative effects** (↓ itching).
2) **Dry Cough**; **ONLY** **1st generation** (*unknown central mechanism*); ***especially*** **Diphenhydramine**, **Promethazine** and **Chlorpheniramine**.
3) **Motion Sickness** *and* **Vestibular Disturbance**;
   # **Scopolamine** & ***some*** **1st generation** ***especially*** **Diphenhydramine** and **Promethazine** are **most effective agents**.
   # **Cyclizine** and **Meclizine** ***also effective*** with ***less*** **sedation** than **Diphenhydramine**.
4) **Nausea and Vomiting of Pregnancy (NVP)**;
   # **Meclizine**, **Cyclizine** and **Doxylamine** are ***combined with*** **V-B6**.
5) **Somnifacient (Hypnotic)**;
   - **1st generation**; especially **Doxylamine** and **Diphenhydramine**.

PATIENT COUNSELLING

Antihistaminic especially **1st generation** is ***contraindicated*** in the ***individuals*** **working** in **jobs** in ***which*** **wakefulness** is ***critical*** such as **drivers** and **worker in dangerous machines**.

Systemic Acute **Toxicity** **Emetrex®** **Ampoule**; is **NOT** ***recommended*** in **CHILDREN** ***younger than*** **6 years** to ***prevent*** **vomiting** (***serotonin antagonists*** such as **Ondansetron** is ***safer***).

H_3-receptor Antagonists

Betahistine (Betaserc®)#

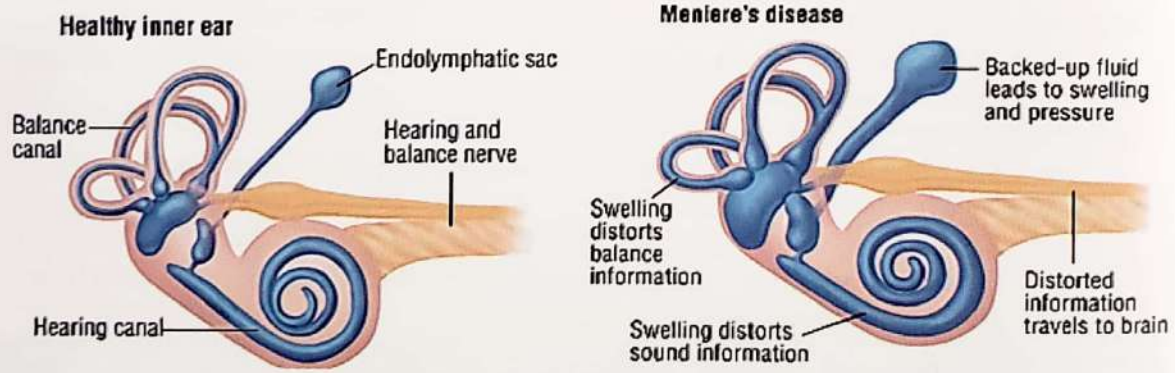
Betahistine is an **anti-vertigo** drug ***used*** in **balance disorders** or **relieve vertigo** symptoms associated with **Ménière's** [men-YEERS] **disease**.

Mechanism;

- **Betahistine** has a ***very strong*** **affinity** as an ***antagonist for*** **histamine H_3-receptors** and a ***weak affinity*** as an ***agonist for*** **histamine H_1-receptors**.
- **Betahistine** seems to ***dilate*** the **blood vessels** *within* the **inner ear** which can ***relieve*** **pressure** from ***excess*** **fluid** and act on the **smooth muscle**.

Dose; - **Betaserc® 8 mg tab**; **1-2 tab 1*3**
- **Betaserc®16 mg tab**; **½-1 tab 1*3**
- **Betaserc® 24 mg tab**; **24-48 mg** ***divided*** **over the day** (***max dose***; **48 mg**).

- **Ménière's disease** is a disorder of the inner ear that causes spontaneous episodes of vertigo, fluctuating hearing loss, ringing in the ear (tinnitus) and affects only one ear.



Eicosanoids

- **Eicosanoids** are ***oxygenation*** products of **polyunsaturated long-chain (20 C atom) fatty acids**.

There are ***multiple subfamilies***; **Prostaglandins (PGs)**, **Thromboxanes (TXs)** and **Leukotrienes (LTs)**.

- **Eicosanoids** are ***not stored*** within cells, ***but*** are **synthesized as required**.

Cysteinyl LTs (LTC_4, LTD_4 and LTE_4) ⇨ ***bronchospasm*** (**1000 times** ***more potent*** **than Histamine**).

Bronchospasm occur bout **10%** of **people taking** **NSAIDs**, ***because*** of a ***shift*** in **arachidonic acid** ***from*** **COX** ***to*** **5-LOX**; **Leukotrienes** ***formation***.

Asthma and COPD

Asthma; is a ***chronic inflammatory disorder*** of the **airways** *causing* ***recurrent*** **episodes** *of*; **wheezing**, **breathlessness**, **cough** and **chest tightness**, *particularly* at **night** or ***early*** in the **morning**.

Chronic Obstructive Pulmonary Disease (**COPD**); is a ***chronic*** **limitation** ***in*** **airflow** ***encompassing*** **emphysema** and **chronic bronchitis**;

1) **Chronic bronchitis**; *consists of* ***persistent*** **cough** ***plus*** **sputum production** for ***most days*** of **3 months** in ***at least*** **2 consecutive years**.
2) **Emphysema**; is ***abnormal permanent*** **enlargement** of the **airspaces distal** to the **terminal bronchioles**, *accompanied by* ***destruction of*** **their walls** and ***without*** **obvious fibrosis**.

Cigarette smoking ***causes*** about **80-90%** of ***all*** **COPD cases**.

Asthma is *caused by* a ***combination*** of **complex** and ***incompletely understood*** **environmental** and **genetic** ***factors***;

- **Environmental allergens** (e.g.; house dust mites; animal allergens, especially cat and dog and cockroach allergens and fungi).
- **Viral respiratory tract infections**.
- **Aspirin** or **NSAIDs**.
- **Exercise** or **hyperventilation**.
- **Chronic sinusitis** or **rhinitis**.
- **Environmental pollutants** or **smoking**.
- **Obesity**.
- **Gastroesophageal reflux disease** (**GERD**).
- **β-blockers** (*including ophthalmic*).
- **Emotional factors** or **stress**.
- **Irritants** (household sprays or paint fumes).
- **Genetics**.

Asthma Medications

Asthma Medications are *generally* ***divided into*** **two categories**:

1) **Quick relief** (**reliever medications**); *relieve acute asthma exacerbations*;
   - **Short-acting β_2-agonists** (**SABAs**).
   - **Systemic** (**Oral**) **Corticosteroids**.
   - **Anticholinergics** (***only for severe exacerbations***).
2) **Long-term control** (**controller medications**);
   - **Inhaled Corticosteroids**.
   - **Long-acting β_2-agonists** (**LABAs**).
   - **Long-acting Anticholinergics**.
   - **Methylxanthines**.
   - **Leukotriene Modifiers**.
   - **Mast Cell Stabilizers**.

β_2-adrenoceptor Agonists

β_2-***agonists*** are the ***most effective*** **bronchodilators** ***available***.

- ***In general activation*** of **β_2-adrenergic receptors** ☞
  - **Smooth muscles**; **bronchodilatation** and **uterine muscle** ***relaxation***.
  - **Skeletal muscles**; **vasodilatation** and **tremors**.
  - **Heart**; **heart muscle** ***contraction***.
  - **Mast cells**; ***inhibition*** of **mast cell** ***degranulation***.
  - **Metabolic**; **glycogenolysis**, **gluconeogenesis**, **lipolysis**, **hypokalemia** & ↑ **lactate**.

Side Effects; **Tremor**, **Tachycardia**, **Hypokalemia**, **Hypomagnesemia** and **Hyperglycemia**.

Short-acting β_2-adrenoceptor Agonists (SABA); Acute Asthma

Salbutamol or Albuterol (Ventolin®)#

Levosalbutamol or Levalbuterol (Xopenex®)

Terbutaline (Bricanyl®)# | **Pirbuterol** (Maxair®)

Salbutamol or **Albuterol** is the ***most commonly*** used **bronchodilator** that is ***available*** in **multiple forms** (e.g.; solution for nebulization, metered-dose inhaler, and oral solution).

- **Salbutamol** ***Dose***; ***Metered-dose inhaler*** (***MDI***); 2 puffs every 4 to 6 hours as needed. ***Inhalation capsules***; 200 mcg inhaled every 4 to 6 hours (may increase to 400 mcg inhaled every 4 to 6 hours, if necessary). ***Nebulizer***; 1.25–5 mg in 3 cc of saline every 4 to 8 hours as needed. **Tablet** and **syrup**; 2-4 mg orally every 6-8 hours (not to exceed 32 mg/day).

Long-acting β_2-adrenoceptor Agonists (LABA); Chronic Asthma

LABA ***should not*** **use** ***for*** **acute asthma**.

LABA ***used for*** **prevention** (such as; **nocturnal asthma** or **exercise-induced asthma**).

LABA ***must be*** ***used in*** **chronic asthma** in ***combination with another long-term asthma-control medicine*** (e.g. **Inhaled Corticosteroids** (**ICS**) such as **fluticasone** and **budesonide**); to ***prevent*** **ASTHMA-RELATED DEATH**.

LABA in **COPD**; ***may be*** used as **mono-therapy** *or* in **combination** with **Corticosteroids**.

Formoterol (Foradil®)# | **Salmeterol** (Serevent®)#

Formoterol and **Salmeterol** ***duration of action*** may ***extended up*** to **12 hours**.

- ***Dose***; 1 puff or 1 inhalation capsule 2 times daily.
- **β_2-Agonist/Inhaled Corticosteroid Combinations**;

Product	Corticosteroid	β_2-Agonist
# Symbicort®	Budesonide	Formoterol
# Dulera®	Mometasone	Formoterol
# Fostair®	Beclomethasone	Formoterol
# Advair® - Seretide®	Fluticasone	Salmeterol
# Breo® Ellipta®	Fluticasone	Vilanterol

- **Vilanterol** an **ultra-long-acting β_2 agonist** (**ultra-LABA**), it was ***approved by*** **FDA** in **2013** for **COPD**. In **2015**, ***approved*** **once-daily treatment** *for* **asthma** in **people ≥ 18 years**. Breo® Ellipta ***contraindicated*** in ***patients with*** **severe milk protein allergy**. **Indacaterol** is the ***first*** **ultra-LABA**, **approved** ***only*** for **long-term control** of **COPD** ***symptoms*** (***not used*** in **chronic asthma**).

Corticosteroids

Benefits of ***corticosteroids*** in **asthma**;

1) ***Increasing*** **number** and **sensitivity** of **β_2 receptors**.
2) ***Reducing*** **mucus** ***production*** and **hypersecretion**.
3) ***Reducing*** **airway edema** and **exudation**.
4) ***Reducing*** **bronchial hyperresponsiveness** (**BHR**).

Mechanisms of ***corticosteroids*** in **asthma**;

1) ***Suppress*** **several proinflammatory cytokines** → ***reducing*** **inflammatory cell** ***activation*** and ***infiltration*** → ***decreasing*** **vascular permeability**.
2) ***Prevent*** **action** of **proinflammatory cytokines** *on the* **cell**.
3) ***Increase*** **β_2 Receptor density** (within 4 hours of corticosteroid administration) and ***improve*** **responsiveness** of **β_2-agonists** (within 2 hours of corticosteroid administration).
4) ***Reversal increased*** **BHR** (requires at least 1 week of therapy).

Side Effects of **Chronic Systemic Glucocorticoid Administration**;

- Hypothalamic–pituitary-adrenal suppression
- Skeletal muscle myopathy
- Aseptic necrosis of bone
- Pseudotumor cerebri
- Sodium and water retention
- Hypertension
- Impaired wound healing
- Posterior subcapsular cataracts
- Central redistribution of fat
- Growth retardation
- Osteoporosis/fractures
- Pancreatitis
- Psychiatric disturbances
- Hypokalemia/hyperglycemia
- Skin striae
- Inhibition of leukocyte & monocyte function
- Glaucoma
- Moon facies

Oral (Systemic) Corticosteroids; Acute Asthma

Prednisone (Hostacortin®)# | **Prednisolone** (Hostacortin-H®)#

Methylprednisolone (Solu-Medrol®)#

Prednisone is a ***prodrug***; ***converted*** via *liver metabolism* to **Prednisolone** (***active***).

Oral Corticosteroids are ***used for*** **short courses** (3-10 days) to control **acute asthmatic episodes**.

Dose; 40–80 mg in 1 or 2 divided doses.

Inhaled Corticosteroids (ICSs); Chronic Asthma

Beclomethasone (QVAR®) | **Fluticasone** (Flovent®) (Flixotide®)#

Mometasone (Asmanex®) | **Budesonide** (Pulmicort® Flexhaler)# (Miflonide®)#

Triamcinolone (Azmacort®)# | **Flunisolide** (Aerospan®)

ICS are the ***first line*** (**drugs of choice**) for ***long-term control any degree*** of **persistent asthma**.

ICS are given as ***long-term*** to ***avoid*** **adrenal insufficiency**, ***but*** **high doses** of ICS *may cause* **adrenal suppression**.

Onset of improvement; **5–7 days** (additional benefit may occur over several weeks).

ICS *have* ***few systemic*** **side effects** (consider **Calcium** and **Vitamin D** ***supplements*** in **adults**, particularly in premenopausal women).

ICS ***local*** **side effects**; due to **ICS** deposition on the **oral** and **laryngeal mucosa** *can cause*;

 # # # # # # # PATIENT COUNSELLING # # # # # # #

1) **Oropharyngeal candidiasis** (**Thrush**); due to local immune suppression.
2) **Hoarseness** (**Dysphonia**); due to myopathy of the vocal cords.

Patients ***should be*** **gargle water** and **spit** ***after*** *each* **inhaled treatment** to ***decrease*** the **chance** of these ***local*** **adverse events**.

Ciclesonide (Alvesco®)#

Ciclesonide is ***recently approved*** **ICS** as a **prodrug** ***activated by*** **esterases** in **lung** to ***form*** its **active metabolite** (**Desciclesonide**)

Because it is ***not activated*** **until** it ***reaches*** the **lung**, **Ciclesonide** *may cause* ***fewer*** **local side effects**.

Desciclesonide is ***tightly*** **bound** to **plasma proteins**, and so has ***little*** **access** to **glucocorticoid receptors** in **skin**, **eye** and **bone**, ***minimizing*** its **risk** of *causing* ***systemic*** **side effects**.

Anticholinergics

- A *number* of the **triggers** and **mediators** of **asthma** (i.e., **Histamine**, **Prostaglandins**, **Sulfur dioxide**, **Exercise** and **Allergens**) *produce* **bronchoconstriction** in part *through* **vagal reflex mechanisms** (parasympathetic stimulation).
- The **anticholinergic agents** *block* **vagally** *mediated contraction* of **airway smooth muscle** and **mucus secretion**.

Side effects; **Headache**, **flushed skin**, **blurred vision** and **tachycardia**.

Ipratropium (Atrovent®)#

Ipratropium is a *non-selective* **muscarinic receptor blocker**, **quaternary ammonium derivatives** (*not cross BBB*).

Indications;

Off-label; 1) *Acute* **severe asthma** in **patients** *not completely* **responsive** to β_2-**agonists** *alone*.

Approved; 2) **Chronic Obstructive Pulmonary Disease** (**COPD**).

- *Onset of action*; **30–60 minutes** (β_2-**agonists**; **5–10 minutes**).
- *Duration of action*; **4-8 hours**.
- *Dose for Acute* **severe asthma** (**emergency**); ***Off-label***
  - *Metered-dose inhaler* (*MDI*); 8 puffs every 20 min as needed for up to 3 h.
  - *Nebulizer*; 500 mcg (1 unit dose vial) every 30 min for 3 doses, then every 2–4 h as needed.
- *Anticholinergic combinations*; **Ipratropium** + **Salbutamol** (**Combivent®**)#
- A *longer-acting* **antimuscarinic agent** such as **Tiotropium** and **Aclidinium**; are *approved* and *used only* in **COPD** (*not used* in **asthma**), *but recently* **Tiotropium** **studies well** in **chronic asthma** and is *approved*; **Spiriva® Respimat** ***only***.

Tiotropium (Spiriva® Respimat)#

Tiotropium is a *selective* **muscarinic receptor blocker** (***mainly on*** M_3), used in *management* of **COPD**.

- *Recently* **Tiotropium** **studies well** in **chronic asthma** and is *approved*; **Spiriva® Respimat** [inhaled spray] ***only*** is used in **chronic asthma**; **Spiriva® HandiHaler** [inhaled capsule] *used* in **COPD** but *NOT used in* **chronic asthma**.
- *Dose for* **chronic asthma** (**Spiriva® Respimat**); **2 puffs** *once* **daily**.

Methylxanthines

- The **3** ***important*** **methylxanthines** are **Theophylline**, **Theobromine** and **Caffeine**.
- The ***importance*** of **Theophylline** as a ***therapeutic agent*** in the ***treatment*** of **asthma** and **COPD**.
- **Aminophylline** is a **Theophylline** ***complex with*** **Ethylenediamine** is ***less potent*** and ***shorter-acting***. **Aminophylline** is the ***preferred*** **injectable product** owing to ***increased*** **solubility**.
- *Mechanism of actions*; **Methylxanthines** have ***several*** **mechanisms**, the ***main*** **mechanisms** are;
  1) ***Inhibits*** **phosphodiesterase enzyme** → ***increase*** **cyclic adenosine monophosphate** (**cAMP**);
     - *In* **smooth muscle** → ***relaxation*** (**bronchodilatation**).
     - *In* **cardiac muscle** → ***contraction*** (***increase*** **heart rate**).
  2) ***Block*** **adenosine receptors**; - *In* **heart** → ***increase*** **heart rate**. - *In* **brain** → **Stimulant effect**.

Methylxanthines have been used for **asthma** for ***more than*** **50 years**, but their use in ***recent years*** has ***declined markedly*** owing to the ***high risk*** of ***severe*** **life-threatening toxicity** and ***numerous*** **drug interactions**, as well as ***decreased*** **efficacy** ***compared with*** **ICSs** and **LABAs**.

Theophylline (Quibron®)#

- Theophylline *relieves* airflow obstruction in chronic asthma and *decreases* its symptoms.
- *Dose*; - Adult; 300–600 mg/day.
  - Children; Start at 10 mg/kg/day.
  - Pediatric; Start; 5 mg/kg/day.

Side effects; *At therapeutic levels*; Insomnia, GI upset and agitation.

Toxicity; *At high levels*: Nausea, vomiting, CNS stimulation, headache, cardiac arrhythmias and seizures.

Drug interactions; Theophylline is *metabolized* in the liver by CYP1A2 and CYP3A4; Ketoconazole, Cimetidine and Erythromycin (*increase* Theophylline effect). Phenytoin and Barbiturates (*decrease* Theophylline therapeutic effect).

Leukotriene Modifiers (LTMs)

- Leukotrienes (LTs) *result from* the *action of* 5-lipoxygenase enzyme *on* arachidonic acid.
- LTs are *synthesized by* (*not stored*) a *variety of* inflammatory cells in the airways, *including* eosinophils, mast cells, macrophages and basophils.
- Cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4); are a *potent* bronchoconstrictor (1000 times more potent than histamine), *increased* bronchial reactivity, mucosal edema, and mucus *hypersecretion*.

Bronchospasm *occur bout* 10% of people taking NSAIDs, *because* of a *shift* in arachidonic acid *from* COX *to* 5-LOX.

Leukotriene Receptor Antagonists (LTRAs); Chronic Asthma

Zafirlukast (Accolate®)# | Montelukast (Singulair®)#

- Zafirlukast and Montelukast are *selective* antagonists of the cysteinyl leukotriene-1 receptor ($CysLT_1$ receptor for leukotrienes; LTC_4, LTD_4 and LTE_4).

Zafirlukast and Montelukast *used for* the *prophylaxis* and chronic *treatment* of asthma.

Montelukast *used in* exercise-induced bronchospasm and *seasonal* & *perennial* allergic rhinitis.

Doses; - Montelukast; once in the *evening*;
- Adults and children ≥15 years: 10 mg/day.
- Children 6 to <15 years: 5 mg/day. - Children 1 to <6 years: 4 mg/day.

Zafirlukast; 10–20 mg orally *twice* a day, 1 hour *before* or 2 hours *after* meals (*Bioavailability decreases with food*).

Leukotriene Receptor Antagonists (LTRAs) PRECAUTIONS

- Neuropsychiatric events; behavior and mood changes; agitation, insomnia, hallucinations, depression, irritability, restlessness, suicidal thinking and tremor.
- Churg-Strauss syndrome; is a *rare* systemic vasculitis *accompanied by worsening* asthma, pulmonary infiltrates, and eosinophilia in *people with* asthma who are steroid-dependent and who are *treated with* leukotriene receptor *antagonists* upon reduction in their *oral steroid dose*.
- Hepatotoxicity *with* Zafirlukast *only* (*monitor symptoms*).
- Acute asthma attacks; *not used* in reversal bronchospasm in acute asthma attacks (but continuous used; if acute attack occur during long term control).

Drug interactions; Warfarin, Erythromycin and Theophylline *with* Zafirlukast *only*; Zafirlukast *inhibits* CYP3A4 and CYP2C9.

5-lipoxygenase Inhibitors; Chronic Asthma

Zileuton (Zyflo®)#

- **Zileuton** is a ***5-lipoxygenase inhibitor***, *inhibits* **leukotrienes formation**.
Indications; ***prophylaxis*** & **chronic *treatment*** of **asthma** in **adults** & **children** ≥ 12 y.
- ***Dose***; extended release tablets; 1200 mg orally *twice* a day.
Warnings and Precautions; ######## PRECAUTIONS
  - Neuropsychiatric events. - Churg-Strauss syndrome.
  - Hepatotoxicity; Liver Function Tests; LFTs (*transaminases*); ***should be monitoring***.
  - Acute asthma attacks.
- ***Drug interactions***; **Warfarin**, **Propranolol** & **Theophylline**; It is *weak inhibitor* of CYP1A2.

Monoclonal Antibody

Omalizumab (Xolair®)#

Omalizumab is a ***recombinant*** **anti-IgE** (**human immunoglobulin E**) **antibody** *approved for* the **treatment** of **allergic asthma** ***not well controlled*** on **oral corticosteroids** or **ICSs**.
Mechanism of action; **Omalizumab** *decrease* **binding** of **IgE** to *its* **receptor** on the *surface of* **mast cells** and **basophils**.
- ***Elimination half-life***; 17 to 22 days.
Indications; 1) **Allergic Asthma** 2) **Chronic Idiopathic Urticaria (CIU)**
Dose; 150–375 mg SC *every* 2–4 **weeks**; 1 or **more** ***injections*** (Do not inject >150 mg per injection site)
Side effects; **Injection site reactions** (urticaria, thrombocytopenia, malignancy and rare anaphylaxis).

Mast Cell Stabilizers

- **Mast Cell Stabilizers** act by ***stabilize*** the **mast cell** ***membrane***, and ***inhibit*** the **activation** and **release** of **mediators**.
- They *inhibit* **acute responses** to **cold air**, **exercise** and **sulfur dioxide**.

Cromolyn Sodium (Intal®) | Nedocromil Sodium (Tilade®)

Cromolyn and **Nedocromil** are ***mast cell stabilizers***, widely used as ***eye drops*** in **allergic conjunctivitis**.
Cromolyn (**Intal®**) and **Nedocromil** (**Tilade®**) are an ***inhaled anti-inflammatory*** **agent** for the ***prophylaxis*** and ***management*** of **asthma**.
- ***Due to*** its ***short*** **duration of action**, this agent ***requires*** dosing **3** or **4 times daily**, which affects adherence and ***limits*** **its use**.
- ***Side effects*** are ***minor*** and *include* **cough**, **irritation**, and **unpleasant taste**.

COPD Managements

1) Smoking Cessation Therapies

Smoking cessation is the ***most important*** **therapeutic intervention** for **COPD**.
Smoking cessation has the ***greatest capacity*** to **influence** the **natural history** of **COPD**.
Long-term **quit smoking** ***success rates*** of ***up to*** **25%** can be *achieved*.

Nicotine Replacement Therapies

Nicotine (Nicorette®)#

Nicorette® ***products*** (***chewing gum***, ***lozenges***, ***patches***, ***oral spray inhalator***, ***sublingual tablets*** and ***nasal spray***) ***aid in smoking cessation***.
- **Nicotine replacement therapy** ***should be*** **started > 2 weeks** ***after*** a **cardiovascular events** (such as acute coronary syndrome).
- The ***effectiveness*** and ***safety*** of **e-cigarettes** as a **smoking cessation** ***aid*** is ***uncertain at*** **present**.

Varenicline

Varenicline (Chantix®)# (Champix®)#

- Chantix® in the USA and Champix® in Canada Europe and other countries.

Varenicline is an **oral drug** ***used to*** **quit smoking** ***(treat nicotine addiction)***. ***Act as*** a **partial agonist** in the **nicotinic receptors** (*especially CNS*).

Dose: - **Days 1 to 3** ⇨ 0.5 mg orally once a day.
- **Days 4 to 7** ⇨ 0.5 mg orally twice a day.
- **Days 8 to end of treatment** ⇨ 1 mg orally twice a day.

☞ Patients ***should be*** treated with **Varenicline** for **12 weeks**.

Most common side effects; ☞ **Nausea, vomiting, headache, constipation, sleep disturbance** and **unusual dreams**. **Varenicline** are **category C** ***in pregnancy***.

Bupropion

Bupropion (Wellbutrin®)#

Bupropion is a ***weak*** **norepinephrine-dopamine** ***reuptake*** **inhibitor** (**NDRI**), the ***exact*** **mechanism** of action remains **unknown**.

Dose; - ***Initial dose***; 150 mg orally once daily for 3 days.
- ***Maintenance dose***; 150 mg orally twice a day.
- ***Duration of therapy***; **12 weeks**, up to 6 months.

Most common side effects; ***increased*** **risk of seizures, insomnia, anxiety, irritability, headache**, and ***decreased*** **appetite**.

Warning; ***should not be*** **prescribed** to individuals with **epilepsy** (***lower*** the **seizure threshold**).

2) Vaccinations

All patients with COPD should receive the **influenza vaccine** ***yearly*** (*see page;* 36) and the ***polysaccharide*** **pneumococcal vaccine** (**PCV**) ***once*** *before* **age 65**; then a **one-time** ***revaccination*** **5 years** or ***more*** *after* the ***first*** **vaccination**;

PCV-7 (**Prevnar®**); ***contains*** **7 different** ***types*** of **pneumococcal bacteria**.
PCV-10 (**Synflorix®**); ***contains*** **10 different** ***types*** of **pneumococcal bacteria**.
PCV-13 (**Prevnar-13®**); ***contains*** **13 different** ***types*** of **pneumococcal bacteria**;
- Is routinely given to children at 2, 4, 6, and 12–15 months of age.
- It is also recommended for children and adults 2 to 64 years of age with high risk.
- It is also recommended for all adults 65 years of age and older.

3) Pharmacologic Therapy

β_2-agonists

Short-acting β_2-adrenoceptor Agonists (SABA); 4-6 hours

Salbutamol or Albuterol (Ventolin®)#

Levosalbutamol or Levalbuterol (Xopenex®)

Terbutaline (Bricanyl®)# | **Pirbuterol** (Maxair®)#

Long-acting β_2-adrenoceptor Agonists (LABA); 12 hours

Formoterol (Foradil®)# | **Salmeterol** (Serevent®)# | **Arformoterol** (Brovana®)

Ultra-Long-acting β_2-adrenoceptor Agonists (Ultra-LABA); 24 hours

Indacaterol (Onbrez® Breezhaler®)#

Olodaterol (Striverdi® Respimat®)# | **Vilanterol** (Breo® Ellipta®)# (Anoro® Ellipta®)#

Anticholinergics

Short-acting Muscarinic Antagonist (SAMA); <12 hours

Ipratropium (Atrovent®)#	**Oxitropium** (Oxiven®)#

Long-acting Muscarinic Antagonist (LAMA); 12-24 hours

Tiotropium (Spiriva®)#	**Umeclidinium** (Incruse® Ellipta®)#
Aclidinium (Tudorza®)#	**Glycopyrronium** (Seebri® Breezhaler®)#

Methylxanthines

Theophylline (Quibron®)#

Combining Bronchodilators

Product	β_2-agonist	Anticholinergic
# Combivent®	Salbutamol (SABA)	Ipratropium (SAMA)
# Atrovent® Comp	Fenoterol (SABA)	Ipratropium (SAMA)
Duaklir® - Brimica®	Formoterol (LABA)	Aclidinium (LAMA)
Bevespi Aerosphere®	Formoterol (LABA)	Glycopyrronium (LAMA)
Utibron® Neohaler®	Indacaterol (LABA)	Glycopyrronium (LAMA)
Anoro® Ellipta®	Vilanterol (LABA)	Umeclidinium (LAMA)
Stiolto® Respimat®	Olodaterol (LABA)	Tiotropium (LAMA)

Inhaled Corticosteroids (ICSs)

Beclomethasone (QVAR®)	**Fluticasone** (Flovent®) (Flixotide®)#
Mometasone (Asmanex®)#	**Budesonide** (Pulmicort® Flexhaler)#
Triamcinolone (Azmacort®)#	**Flunisolide** (Aerospan®)

Ciclesonide (Alvesco®)#

- β_2-Agonist/Inhaled Corticosteroid Combinations;

Product	Corticosteroid	β_2-Agonist
# Symbicort®	Budesonide	Formoterol
Dulera®	Mometasone	Formoterol
Fostair®	Beclomethasone	Formoterol
Advair® - Seretide®	Fluticasone	Salmeterol
Breo® Ellipta®	Fluticasone	Vilanterol

Triple Inhaled Therapy (ICS/LABA/LAMA)

- *Recommendations*;
  - * *Triple therapy* **ICS/LABA/LAMA** *improve* **lung function**, **symptoms** and **health status** and *reduce* **exacerbations** *compared to* **ICS/LABA** or **LAMA** *monotherapy*.
- *Products*;
  - **Triohale®** pressurized Metered-Dose Inhaler (pMDI); **Ciclesonide/Formoterol/Tiotropium** has been marketed as the ***world's first*** **triple-combination inhaler** to be taken only **once** a **day** and is already available in **India**.
  - .....®; **Fluticasone Furoate/Umeclidinium/Vilanterol**; *Preregistration* by **GSK**.
  - .....®; **Mometasone/Indacaterol/Glycopyrronium**; *Preregistration* by **Novartis**.
  - .....®; **Budesonide/Formoterol/Glycopyrronium**; *Preregistration*.
  - .....®; **Beclomethasone/Formoterol/Glycopyrronium**; *Preregistration*.

Oral Glucocorticoids (OCSs)

- *Recommendations*;
  * *Chronic treatment* with **OCSs** *should be* **avoided** because of an *unfavorable* **benefit-risk ratio**.
  * **OCSs** used treating *acute exacerbations* in **hospitalized patients**, or *during* **emergency**.

Phosphodiesterase-4 (PDE_4) inhibitors

Roflumilast (Daxas®)# (Daliresp®)

Roflumilast is a *phosphodiesterase-4 inhibitor*, is an *anti-inflammatory*, *not* **bronchodilator**.

Mechanism; *Reduces* **inflammation** through *inhibition* of the **breakdown** of **intracellular cyclic adenosine monophosphate (cAMP)**, *no* **direct bronchodilator activity**.

Indication: *reduce* the *risk* of **COPD exacerbations** in *patients with* **severe COPD** *associated with* **chronic bronchitis** and a **history of exacerbations**.

Dose; **500 mcg orally** *once daily*.

Side effects; **Diarrhea**, **weight loss** (*monitoring body weight*) or *decreased* **appetite**, **nausea**, **headache**, **back pain**, **influenza**, **insomnia** and **dizziness**.

- *Contraindications*: *Moderate* to *severe* **liver impairment**.
- *Drug interactions*: With *strong* **CYP450 enzyme** *inducers* or *inhibitors*.

Antibiotics

Azithromycin | Erythromycin

- *Recommendations*;
  * **Azithromycin** (250 or 500 mg/day three times per week) or **Erythromycin** (500 mg two times per day) for *one year* in **patients** *prone to* **exacerbations** *reduced* the *risk of* **exacerbations** *compared to* **usual care**.
  * **Azithromycin** use was *associated with* an *increased* *incidence of* **bacterial resistance** and *impaired* **hearing tests**.

Mucolytic and Antioxidant Agents

- In **COPD** patients *not receiving* **inhaled corticosteroids**, *regular treatment* with **Mucolytics** such as **Carbocysteine** and **N-acetylcysteine (NAC)** may *reduce* **exacerbations** and *improve* **health status**.
- *Recommendations*;
  * *Regular* **use** of **NAC** and **Carbocysteine** *reduce* the *risk of* **exacerbations** in **selected patients**.

Alpha-1 Antitrypsin Augmentation Therapy

Alpha-1 Proteinase Inhibitor (Zemaira®)

- Patients *with* **α_1-antitrypsin deficiency (AATD)** *usually* are **white**, usually *develop* **COPD** at a **young age** (*younger than* **45 years**), and have a *strong* **family history**.
- **IV** *augmentation therapy* has been *recommended for* *individuals with* **AATD**.
- *Recommendations*;
  * **IV** *augmentation therapy* may *slow down* the *progression of* **emphysema**.

Allergic Rhinitis Medications

- **Allergic rhinitis** (**AR**); is an ***inflammatory***, **IgE-*mediated* disease** *characterized by* **nasal congestion**, **rhinorrhea** (nasal drainage), **sneezing** and/or **nasal itching**.
- ***Pharmacological Management***;
  1) ***Intranasal* Corticosteroids** (***strong recommendation***); **1st line**; Moderate-Severe
  2) ***Oral* Antihistamines** (***strong recommendation***); **1st line**; Mild-Moderate
  3) ***Oral* Leukotriene Receptor Antagonists** (***recommendation***); Coexistent asthma
  4) ***Intranasal* Antihistamines** (***option***); If symptoms not improved with oral antihistamines
  5) **Decongestants** (***option***); Short term-use if congestion not improved with INCs
  6) ***Intranasal* Mast-Cell Stabilizer** (***option***); Before exposure to specific known allergy
  7) ***Intranasal* Anticholinergics** (***option***); For sever persistent rhinorrhea
  8) ***Combination* Therapy** (***option***); If inadequate response with monotherapy

1) *Intranasal* Corticosteroids (INCs)

First Generation

Beclomethasone (Becol®)#	**Triamcinolone** (Nasacort® AQ)#
Flunisolide (Nasarel®)#	**Budesonide** (Rhinocort® Aqua)#

Second Generation

Fluticasone Furoate (Avamys®)#	**Fluticasone Propionate** (Flonase®)#
Mometasone (Nasonex®)#	**Ciclesonide** (Omnaris®)
Betamethasone (Betnesol®)	

***First generation* intranasal corticosteroids** are ***more* bioavailable** and tend to *produce* ***more* systemic adverse effects** than ***second generation* intranasal corticosteroids** are ***less* bioavailable** and have ***limited* systemic adverse effects**.
Mechanism; act by ***decreasing*** the ***influx of* inflammatory cells** and ***inhibiting*** the ***release of* cytokines**, thereby ***reducing* inflammation** of the **nasal mucosa**.
Onset of action; ***within* 12 hours**. # ***Maximum Effectiveness***; **2-4 weeks** *of use*.
Pregnancy; ***only* Budesonide** has an **FDA pregnancy *category* B** & ***others*** are **C**.
Local side effects; **throat irritation**, **epistaxis**, **stinging**, **burning** and **nasal dryness**.
Systemic side effects; ***No*** or ***limited* effects** on **Hypothalamic-pituitary-adrenal (HPA) *axis*** *suppression* and ***decreased* vertical growth** of **children** [***all*** intranasal corticosteroids ***carry*** a warning that ***long-term use*** may ***restrict*** growth in children].

2) *Oral* Antihistamines

Second Generation

Cetirizine (Zyrtec®)#	**Loratadine** (Claritin®)#	**Acrivastine** (Semprex®)#
Ebastine (Kestine®)#	**Mizolastine** (Zolim®)#	

Third Generation

Levocetirizine (Allear®)#	**Desloratadine** (Aerius®)#	**Fexofenadine** (Telfast®)#

Second and ***third*-generation antihistamines** have a ***better* adverse effect *profile*** and *cause* ***less* sedation**, with the ***exception of* Cetirizine** (**Zyrtec®**) [***partially* sedating**].
Onset of action; **15** *to* **30 *minutes***.
Oral Antihistamines; **safe** for children **≥ 2 years**.
Pregnancy; **Cetirizine** and **Loratadine** are **FDA pregnancy *category* B**, while **Desloratadine** and **Fexofenadine** are ***category* C**.

3) Oral Leukotriene Receptor Antagonists

Montelukast (Singulair®)#

Montelukast; can be *used* in *children* < 2 years for **allergic rhinitis** and may be ***most beneficial*** in patients who also have **asthma**.

- ***Pregnancy***; **Montelukast** has an **FDA pregnancy *category* B**.

4) Intranasal Antihistamines

Azelastine (Astelin®)#

Intranasal* antihistamines** are an ***option for **patients *with seasonal*, *perennial*** and ***episodic* allergic rhinitis**.

Benefits; is **targeted delivery** and ***increased* dosage** to **nasal tissues**.

Efficacy; ***similar*** or ***superior*** to **oral antihistamines** for **nasal *symptoms*** & ***may improve* congestion**.

- **Children**; may *use* for children ≥ 5 years.

- ***Pregnancy***; **Azelastine** has an **FDA pregnancy *category* C**.

Recommendations; **Intranasal antihistamines** are an ***option*** if symptoms ***do not*** improve *with* **oral *second/third-generation* antihistamines**; *because*; **Azelastine** *twice* daily dosing, *more expensive*, and *decreased* effectiveness *compared with* **intranasal corticosteroids**.

Local side effects; **bitter taste, epistaxis, headache, somnolence** and **nasal *burning***.

5) Decongestants (Oral/Topical)

Pseudoephedrine	Phenylephrine
Oxymetazoline (Afrin®)#	Xylometazoline (Otrivin®)#

- **Oral** and **intranasal decongestants** *improve* **nasal congestion** *associated with* **allergic rhinitis** by *acting on* α_1-**adrenergic receptors**, which causes *vasoconstriction* in the **nasal mucosa**.

- ***Most common* decongestants** are **Pseudoephedrine, Phenylephrine** & **Oxymetazoline**

- ***Common side effects*** of **intranasal decongestants**; **sneezing** and **nasal dryness**.

Duration of therapy; ***not more than* 3-5 days**; *because* may *develop* **Rhinitis Medicamentosa (RM)**, or **rebound rhinitis** or **recurring congestion**.

Patient Counselling; **Patients** *using* **topical decongestants** *should understand* that if the **agents** are **used** *longer than* 3 **days**; *rebound* **congestion** [**Rhinitis Medicamentosa (RM)**] *will* **develop**.

Oral decongestants; *may cause* **headache**, *elevated* **blood pressure** and **intraocular pressure, tremor, urinary retention, dizziness, tachycardia** and **insomnia**.

Pseudoephedrine ***should be used cautiously*** in **patients *with* cardiovascular disease, hypertension, diabetes, hyperthyroidism, closed-angle glaucoma** or **bladder neck obstruction**.

Recommendations; **Decongestants** may be *considered for* **short-term use** in *patients without* improvement in congestion with **intranasal corticosteroids**.

6) Intranasal Mast-Cell Stabilizer

Cromolyn (Nasalcrom®)#

- **Cromolyn**; **safe** for children ≥ 2 years. - ***Pregnancy***; **FDA pregnancy *category* B**.

7) Intranasal Anticholinergics

Ipratropium (Atrovent®)#

- **Ipratropium** has ***anti-secretory properties***, and when ***applied*** **locally**, ***inhibits*** **secretions** from **glands** *lining* the **nasal mucosa**.

- **Ipratropium** ***may cause*** **dry nose** and **mouth, pharyngeal irritation**.

8) Combination Therapy

- ***Combination* therapy** is an ***option*** for **patients *with severe*** or ***persistent* allergic rhinitis** who have ***inadequate*** **response** to **monotherapy**.

Cough Medications

Cough; is a *defense mechanism* that *clear* the **respiratory tract** *from* **mucus** and **irritants** such as **dust** or **smoke**.
- **Coughing** is either ***voluntary*** or ***involuntary***.
Cough reflex is ***stimulated from*** **afferent cough receptors** *located in* the **upper** and **lower respiratory tract, pericardium, oesophagus, diaphragm** and **stomach**.
- **BEFORE treating cough**; ***identification*** of its **cause** is **important** to ***ensure*** that **antitussive treatment** is ***appropriate***.
Cough Classifications;
  * *According to* **durations**;
    - **Acute** (***sudden onset***); if it is present ***less than*** **3 weeks**.
    - **Subacute**; if it is present ***between*** **3** and **8 weeks**.
    - **Chronic**; when **lasting** ***longer than*** **8 weeks**.
  * *According to* **character**;
    - **Dry**; ***non-productive*** (***no*** **phlegm** or **mucus** or **sputum** is **produced**).
    - **Productive** or **wet**; **coughs** that ***produce*** **phlegm** or **mucus** or **sputum**.
The **FDA** ***does not*** **recommend OTC cough** and **cold drugs** (containing nasal decongestants, antihistamines, cough suppressants and expectorants) for use in **children** ***younger than*** **6 years** for ***treatment of*** **URTI symptoms**.
For children, the ***only*** **products** that can be **beneficial** *are* **Honey** (older than 1 year) and **VaporRub®** (older than 2 year).

Antitussives or Cough Suppressants

Cough suppressants ***must not be used*** to ***treat*** **productive cough**, which is ***considered to*** be a **useful protective mechanism**.

Central Antitussives

- *Mechanism of action*;
  1) ***Depression*** of **medullary cough center**.
  2) ***Increased*** **threshold** of **cough center**.

Opioid/Narcotic/Addicting Antitussives

Potent Addictive Opioids

Morphine

Less Addictive Opioids

Codeine

Non-Addictive Opioids

Dextromethorphan

Dextromethorphan is ***free*** of **addictive properties** and produces ***less*** **constipation** than **Codeine**.
It is ***one*** of the **active ingredients** in ***many*** **OTC cough medications**.
The ***primary*** ***use*** of **Dextromethorphan** is as a **cough suppressant** (***antitussive***).
Dextromethorphan is the ***most commonly*** **used** ***agent*** as **antitussive**.
Dose; **15-30 mg orally** ***every*** **6-8 hours**. - ***Pregnancy category***; **C**.
At ***high*** **doses** **Dextromethorphan** acts as an **NMDA** ***antagonist*** (**Hallucinations**).
Dextromethorphan and **Codeine** are ***available alone*** or in ***combination with*** **Guaifenesin**.

Noscapine

- Noscapine is a *non-narcotic* alkaloid *derived from* opioids, with *mild* analgesic, antitussive, and *potential* antineoplastic *activities*.
- Noscapine, and its *synthetic derivatives* called Noscapinoids (*new class* of anticancer drugs) are known to *interact with* microtubules and *inhibit* cancer cell *proliferation*.
- *Dose*; 15-30 mg orally 3-4 times daily. ### *Pregnancy category*; X.

Non-opioids/Non-narcotic/Non-addicting Antitussives

Diphenhydramine | Promethazine | Chlorpheniramine

First generation antihistamines (cross BBB; central mechanism) are *now can used as* antitussives.
Mechanism; They *relieve* cough *due to their* sedative (*central*) and anticholinergic actions, *but* lack *selectivity* for cough center.
Many antihistamines have been *added to* antitussive/expectorant *formulations*.

Butamirate (Sinecod®)#

Butamirate is a *central non-narcotic* antitussive.
- *Mechanism*; *depress* cough center *with moderate* bronchodilator *effect*.
Butamirate *can be used even* in infants (Sinecod® *drops*).
Butamirate produce *efficacy similar to* Dextromethorphan with *safe profile*.
- *Adult dose*; 7.5 mg orally 3-5 times daily. - *Pregnancy category*; C.

Cloperastine (Notussil®) | Dropropizine (Tussapine®)#

Clobutinol (Silomat®)#

Clobutinol has the *potential* to *prolong* the QT interval, it was voluntarily *withdrawn* from *some* countries (Germany).

Oxeladin (Paxeladine®)#

Oxeladin is a *highly potent* and *effective* antitussive drug used to treat *all types* of cough *because* it *helps to clear* the respiratory tract *from excess* secretions.

Pentoxyverine (Solotuss®) (Cabella®)#

Pipazethate or Pipazetate (Selgon®)#

Pipazethate is a *central and peripheral* antitussive by *inhibition of* cough center and peripheral neural *receptors* in the lung. It has a *bronchodilator effect* which *reduce spasm during* cough.
- It may be *used* at every age (*available as* drops, tablets and supp.).
- *Adult dose*; 20 mg orally *3 times daily*.
- *Pregnancy category*; N (FDA has not classified the drug).

Benproperine (Pectipro®)#

Peripheral Antitussives

Peripheral Cough Reflex Inhibitors

Benzonatate (Tessalon®)

- Benzonatate *suppresses* the cough reflex through *peripheral* action.
Benzonatate is chemically *related to* the ester-linked class of local anesthetic drugs.
- It *works by* anesthetizes *peripheral* neural receptors (stretch receptors) in the lung.
- *Adult dose*; 100-200 mg orally *3 times daily*.
- *Pregnancy category*; C.
- *Excessive* absorption of Benzonatate in the oral mucosa will result in the *rapid development* of numbness of the mouth and throat.

Others

Honey; *effective for relieving* **cough**, and *improving* **sleep** in **children**. *Dose*; **8.5 mg (½ tsp)** for *ages* **2-5 years**, **17 mg (1 tsp)** for *ages* **6-11 years**, and **34 mg (2 tsp)** for *ages* **12-18 years**, *administered as* a **single dose 30 minutes** *before* **bedtime**; *Should not* be used in **children < 1 year** *because* of possible *contamination with Clostridium botulinum*.

Chest rub; **Vicks® VaporRub®** ; is a *topical* **petrolatum-based gel** *contains* **Menthol**, **Eucalyptus oil** and **Camphor**, *applied* **once** to the **upper chest** and **neck** *before* **sleep** at a dose of **5 mL** for **children** *ages* **2-5 years** and **10 mL** for **children** *ages* **6-11 years**.

NSAIDs; **Naproxen**; The ***only* NSAID** ***recommended*** in the **guidelines** for treatment of **cough** ***associated with*** **common cold** (because it was the only NSAID studied in this setting).

Inhaled **Ipratropium**; ***recommended in post-infectious*** **cough** or **chronic bronchitis**.

ICS; ***recommended in post-infectious*** **cough** if ***Inhaled*** **Ipratropium** is ***not effective***.

- **N.B.**; ***Central-acting*** **antitussives**; are ***recommended in post-infectious*** **cough** if *both* ***Inhaled*** **Ipratropium** and **Inhaled Corticosteroids** (**ICS**) are ***ineffective***.

Mucolytics/Mucoregulators/Mucokinetics

N-AcetylCysteine (NAC)

N-Acetylcysteine (**NAC**) is a **mucolytic** and **antidote** (**Paracetamol** toxicity) **drug**, with ***antioxidant*** and ***anti-inflammatory properties***.

- ***Mechanism of action***;
  - ***Decreases*** **thickness** (**viscosity**) of **mucous secretions** in **lung**; by ***breaks*** **disulphide bonds** in ***mucoprotein*** (**mucin**) in **sputum**.
  - ***Protects*** **liver** by ***maintaining*** or ***restoring*** **glutathione** ***levels***.

Uses; - ***Adjuvant therapy*** for ***patients with*** **abnormal mucous secretions**; *such as* **emphysema**, **cystic fibrosis** and **chronic obstructive pulmonary disease** (**COPD**).
  - ***Prevention*** or ***decreasing*** of **liver damage** after **Paracetamol toxicity**.

Dose; in ***abnormal*** **mucous** ***secretions***;
  - ***Inhalation***; 1-2 mL of 10% solution may be given as often as every hour.
  - ***Direct instillation*** (into respiratory tract); 2-5 mL of the 20% solution.
  - ***Nebulization***; 3-5 mL of 20% solution or 6-10 mL of the 10% solution 3 to 4 times a day; DON'T mix with antibiotics in the same nebulizer.

Pregnancy category; **B**.

#There are ***several*** **similar compounds** that **contain sulfhydryl groups** *such as*, **MethylCysteine** and **N-Acystelyn** (**lysine salt** *alternative to* **NAC**) that can ***effectively depolymerize*** **mucin polymers**.

Erdosteine (Mucotec®)#

Erdosteine is a **mucolytic** *agent* with ***antioxidant properties***.

Erdosteine is ***prodrug*** *contains 2* blocked **sulfhydryl (SH) groups** which are ***released following*** **first-pass metabolism**. The **3 active metabolites** ***exhibit*** **mucolytic** and ***antioxidant*** **activity**.

- ***Dose***; **150-300 mg orally twice** *daily*.

Bromhexine (Bisolvon®)#

Bromhexine is a **mucolytic expectorant** ***agent*** with ***antioxidant properties***.
- ***Dose***; **4-8 mg orally 3-4** ***times daily***. # ***Pregnancy*** ***category***; **A**.

CarboCysteine or Carbocisteine or CarboxyMethylCysteine (Mucosol®)#

CarboCysteine (**Carbocisteine** or **CarboxyMethylCysteine**) is the ***most frequently*** **prescribed mucoactive agent** (**mucoregulator**) for ***long-term*** **COPD** ***use***.
CarboCysteine has ***antioxidant*** and ***anti-inflammatory properties***.
Carbocisteine is ***available as*** an ***oral formulation*** and *achieves* ***good*** **penetration** into **lung tissue** and **bronchial secretions**.
- ***Mechanism of action***; ***Not act*** **directly** *upon the* **mucus structure**, in ***contrast to*** **NAC**.
  - ***Increase*** the **synthesis** of **sialomucins** (important structural components of mucus) → ***restoring*** the **viscoelastic properties** of **mucus**.
  - ***Increase*** **chloride** ***transport*** *across the* **airway epithelium**, which may *contribute towards* its **mucoregulatory** ***action***.
- ***Dose***; **20 mg/kg orally** ***daily*** in *divided doses*. - ***Pregnancy*** ***category***; **C**.

Ambroxol (Mucosolvan®)#

Ambroxol is a **secretolytic** (**mucolytic**) and **secretomotoric drug** that ***restore*** the **physiological clearance** ***mechanisms*** of the **respiratory tract**.
Ambroxol is a ***metabolite of*** **Bromhexine**.
- ***Dose***; - ***Adult***: **60-120 mg** ***daily*** in **2-3** ***divided doses***.
- ***Child***: **2-5 years**: **7.5 mg 3 times** ***daily***. - **6-12 years**: **15 mg** ***twice*** or **3 times** ***daily***.
Pregnancy; ***avoid use*** *during* the **first trimester** of **pregnancy**.

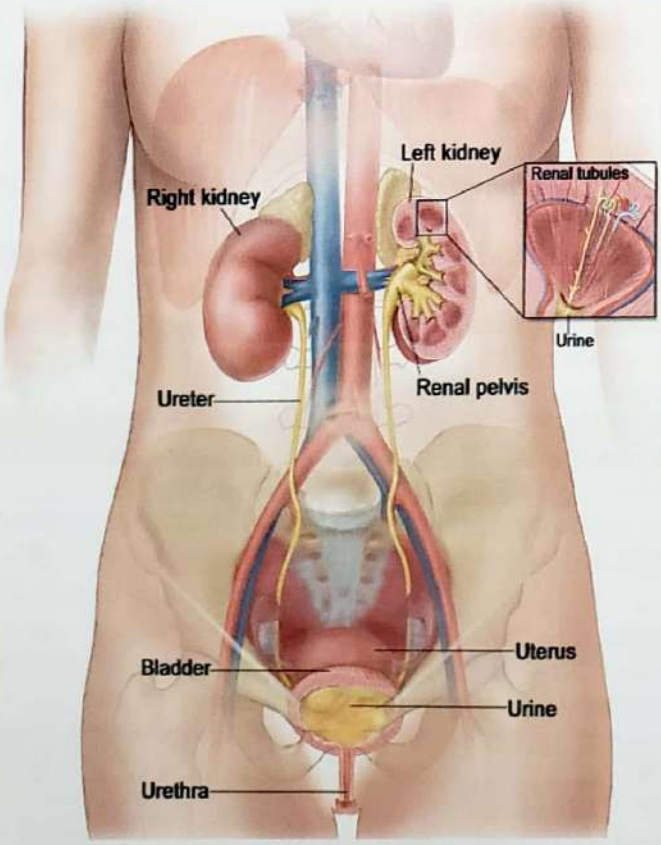
Expectorants

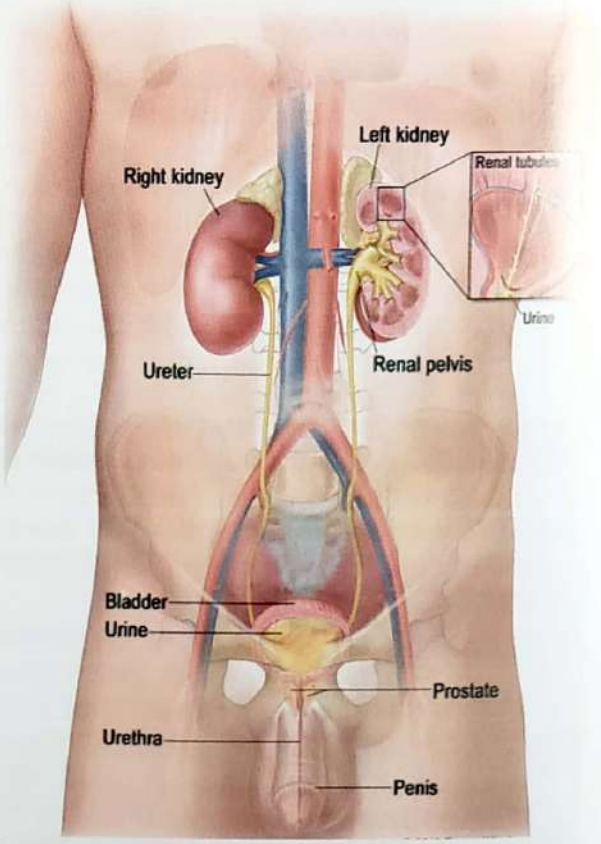
- **Expectorants**; **Drugs** that ***expulsion*** of **mucus** ***from*** the **respiratory tract**. This ***typically*** **requires** a **coughing** ***action*** to ***loosen*** and **bring up** the **mucus** *from* the **respiratory tract**.
  - **Guaifenesin** (**glyceryl Guaiacolate**) is an ***expectorant drug*** **sold OTC**.
  - **Syrup of ipecac** (***Ipecacuanha***); is a ***powerful*** **emetic**, used in ***cough mixtures*** as an **expectorant** or an **emetic** from the 18th until the early 20th century.
  - **Hypertonic saline**; ***Aerosol inhalation*** of **Saline** or **Mannitol** has been ***previously*** *thought to* ***induce*** **ciliary motility**, **proteolysis** and **mucus liquefaction** by **osmosis**.
  - ***Aerosol inhalation*** of **Ammonium chloride/bicarbonate**, **Sodium/Potassium citrate** and **Potassium iodide**; ***promote*** the **secretion** of **airway fluids**. **Potassium iodide** ***should not*** be *administered to* **pregnant** or **hyperthyroid**.

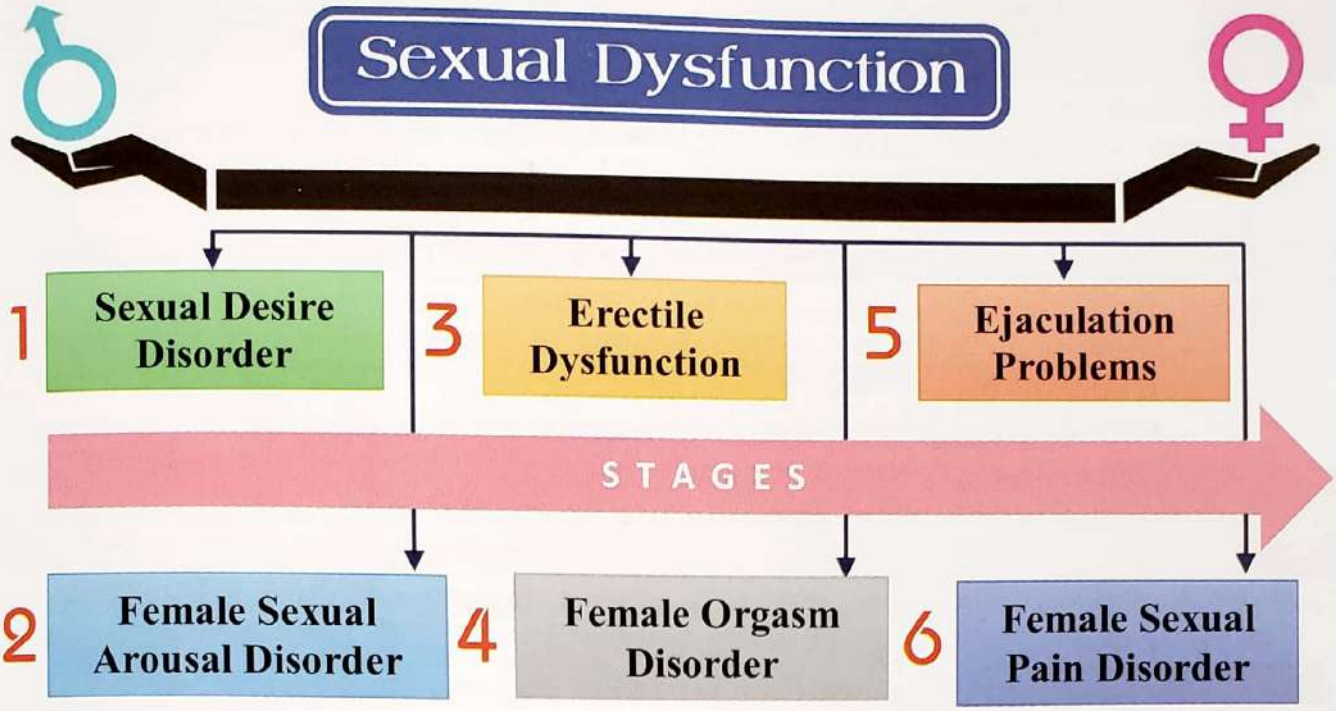
Guaifenesin or Guaiphenesin or Glyceryl Guaiacolate

Guaifenesin [gwye-FEN-e-sin] is an **expectorant drug** ***sold*** **OTC**.
Guaifenesin has ***no*** **mucolytic** ***action*** but may ***reduce*** **bronchial sputum surface tension** and is *sometimes* ***combined with*** **antitussives**.
- ***Mechanism of action***;
  - ***Increasing*** **volume** and ***reducing*** **viscosity** of **bronchial secretions**.
  - ***Increasing*** **ciliary** ***movement*** and ***increase*** the **efficiency** of the **cough reflex** → ***facilitate*** **removal** of **secretions**.
Guaifenesin has **muscle relaxant** and **anticonvulsant** ***properties*** ***increases*** the **analgesic effect** of **Paracetamol** and **Aspirin**, *increases* **sedative effects** of **alcohol**, **tranquilizers** and **anesthetics**.
- ***Adult dose***; - *Immediate release*; **200-400 mg orally** ***every*** **4 hours**.
  - *Sustained release*; **600-1200 mg orally** ***every*** **12 hours**.
Pregnancy ***category***; **C**.
Guaifenesin (**expectorant**) + **Oxomemazine** (***sedative*** **antihistamine**); **Toplexil®**.

Genitourinary (GU)







Sexual Dysfunction; is ***difficulty*** *experienced by* an **individual** or a **couple** *during* ***any*** **stage** of a ***normal*** **sexual activity**, including; **libido** (Desire), **arousal**, **erection**, **orgasm** or **ejaculation**.
Sexual Dysfunction ***require*** a ***minimum*** **duration** of *approximately* **6 months**.
Sexual Dysfunction is ***more prevalent*** for **women** (43%) than **men** (31%); 1999 NHSLS

Drugs for Sexual Dysfunction (Male & Female)

1) Hypoactive Sexual Desire Disorder (HSDD)

Hormone Replacement Therapy

Testosterone

Transdermal Testosterone is **used** ***off-label*** for **short-term therapy** to ***increase*** **libido** in **postmenopausal women** (***little evidence*** to ***support*** **long-term use**; longer than 6 months).
Testosterone in **women**, ***may cause*** **weight gain**, **clitoral enlargement**, **acne** and ***excess*** **body hair**.

Estrogen

Local Estrogen therapy in **postmenopausal women** can ***improve*** **clitoral** and **vaginal sensitivity**, ***increase*** **libido** and **arousal**, ***decrease*** **vaginal dryness** and **pain** *during* **intercourse**.

Dehydroepiandrosterone (DHEA)

- **Dehydroepiandrosterone (DHEA)** is a ***precursor to*** **Estrogen** & **Testosterone**.
DHEA is *available as* an **OTC supplement** and has been reported to ***increase*** **libido** in **postmenopausal women** (***off-label***); in dose ***less than*** **100 mg/day**.

Female Viagra (Pink Pill)

Flibanserin (Addyi®)#

Flibanserin is the ***first medication approved*** (August, 2015) for the ***treatment*** of **Hypoactive Sexual Desire Disorder (HSDD)** in ***pre-menopausal*** **women**.
Flibanserin was ***originally*** *developed as* an ***antidepressant***, ***before*** being **using** for **HSDD**.
Flibanserin is *classified as* a ***multifunctional serotonin agonist antagonist*** (MSAA).
- ***Mechanism of action***;
  - **Flibanserin** ***helps restore*** **rebalancing** of **neurotransmitters** that ***influence*** **sexual desire**.
  - **Flibanserin** ***act as*** **5-HT_{1A}** ***agonist*** and **5-HT_{2A}** ***antagonist*** → ***increases*** **Dopamine** and **Norepinephrine** (both responsible for sexual excitement) and ***decreasing*** **Serotonin** (responsible for sexual inhibition).

Dose; **100 mg orally once** ***per*** **day** at **bedtime** (discontinue after 8 weeks if no response).
Most common side effects; **dizziness**, **nausea**, **fatigue**, **sedation** or **insomnia** and **hypotension**.
FDA ***warning***;
- **Flibanserin** + **Alcohol** ***intake increases*** the **risk** of ***severe*** **hypotension** and **syncope**.
- ***Contraindicated*** with *strong* or *moderate* **CYP3A4 Inhibitors**.
- ***Contraindicated*** in *patients with* **hepatic impairment**.

Other

Bremelanotide or PT-141

- ***Unlike*** **Sildenafil**, it ***does not*** act by **vasodilatation**, but ***directly*** **increases sexual desire** and **arousal** via ***acting*** in the **brain**.
- ***Mechanism***; ***non-selective*** **agonist** of ***all*** of the **Melanocortin** ***receptors*** *except* MC_2.
- ***Uses*** (***not*** **approved**); - **Hypoactive Sexual Desire Disorder (HSDD)**.
  - **Female Sexual Arousal Disorder (FSAD)**.
  - ***Mixed*** **FSAD/HSDD**.

2) Female Sexual Arousal Disorder (FSAD)

Hormone Replacement Therapy

Estrogen

- **Local Estrogen therapy** in **postmenopausal women** can ***improve*** **clitoral** and **vaginal sensitivity**, ***increase*** **libido** and **arousal**, ***decrease*** **vaginal dryness** and **pain**.

Vasodilator

Sildenafil (Viagra®)#

Topical **phosphodiesterase inhibitors** such as **Sildenafil** have been shown to have ***limited benefit*** in **women** with **sexual arousal disorder**.

Alprostadil (Caverject®)#

- **Alprostadil** is a **prostaglandin E_1 (PGE_1)** ***analogue*** used in **male erectile dysfunction** as an **intracavernous** ***injection*** or **urethral** ***suppository***.

Topical **Alprostadil** has been shown to ***increase*** **blood flow** to the **vaginal area** by **vasodilation** and ***shows efficacy*** in **Female Sexual Arousal Disorder** (***off-label***).
- ***Adverse reactions***; **vaginal burning** and **irritation**.

Other

Apomorphine

- Apomorphine is a *dopamine agonists* that are *approved for* the *treatment of* Parkinson's disease.
- *Sublingual* Apomorphine (2-3 mg) *thought to* ***enhance*** sexual response *due to* stimuli in FSAD.

Bremelanotide or PT-141

- Bremelanotide is *effective* in Female Sexual Arousal Disorder.

3) Erectile Dysfunction (ED)

Hormone Replacement Therapy

Testosterone

ONLY used *if* Testosterone *levels* are *found to be* low.

Dose and Formulations;

- # Oral Testosterone *should not* be used *because* of *potential* liver toxicity.
- # *Depot* IM injection of Testosterone Enanthate 200 mg or Cypionate 300 mg every 2–3 weeks.
- # Transdermal patches (Androderm®) *placed* daily and Testosterone 1% gel (AndroGel®) *applied every* morning; *apply to* shoulders, *upper* arms *only* (*should not be applied to genitals, chest or back*).
- # Topical solution (Axiron®): *apply to* underarms *once daily*.
- # Pellet implanted (Testopel®); *provides* hormone for 3–4 months.
- # Buccal system (Striant®); *Placed on* gum tissue *twice* daily.

Side effects; *increase* blood pressure, acne, *enlarged* prostate, liver *toxicity*, cholesterol *changes*, edema and polycythemia.

Contraindication; prostate cancer.

Monitoring; *monitor* serum Testosterone *within* 1–3 months and at 6-12 month *intervals*.

- *If* ***no improvement*** *after* 3 months, may *discontinue* treatment.

Phosphodiesterase Type-5 (PDE5) Inhibitors

Sildenafil (Viagra®)#

Phosphodiesterase type-5 (*PDE5*) *Inhibitor* are First-Line drug therapy.

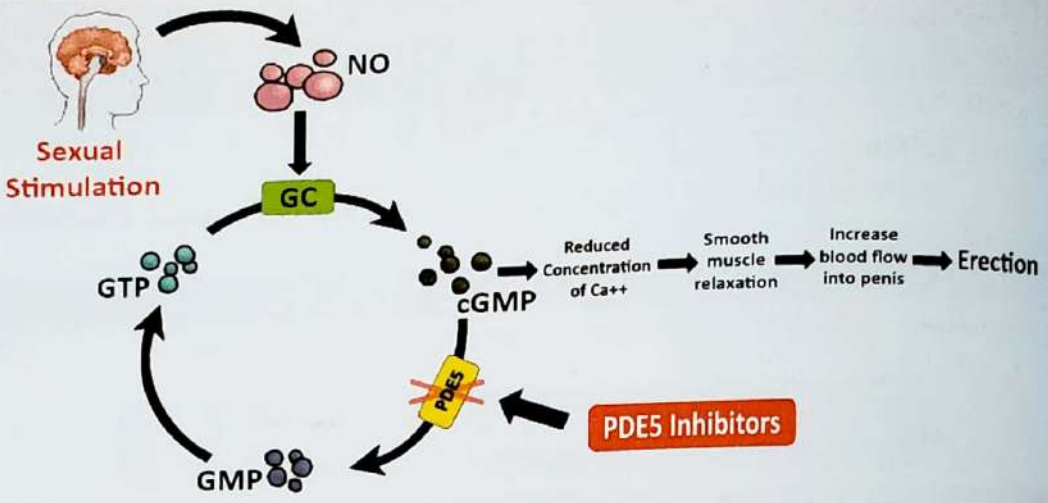
Sildenafil is a *phosphodiesterase type-5* (*PDE5*) *Inhibitor*.

- Early 1990s; Pfizer completes *several early* trials of Sildenafil citrate for its use as a heart disease *treatment*, but volunteers in the clinical trials are *reporting* ***increased*** erections several days after taking a dose of the Sildenafil.

In 1998 the FDA approved Viagra® (Blue pill) to *treat* Erectile Dysfunction (ED) and Pulmonary Arterial Hypertension (PAH).

Mechanism of Action;

- *During* sexual stimulation ⇨ *Stimulate* release of nitric oxide (NO) in the corpus cavernosum in the penis.
- NO *release* ⇨ *activate* guanylate cyclase (GC) ⇨ ↑ cyclic guanosine monophosphate (cGMP) ⇨ ↓ Ca^{2+} *influx* ⇨ *relaxation* of blood vessels smooth muscle ⇨ VD ☞ Erection.
- Phosphodiesterase type-5 *responsible for* degradation of cGMP into GMP.
- Sildenafil is a *selective PDE5 Inhibitor* ⇨ *accumulation* of cGMP ☞ Erection.
- Sildenafil has *no effect* in absence of sexual stimulation.



Pharmacokinetics;
- *Absorption*; ***rapidly*** **absorbed** (*orally*).
- *Maximum* **plasma concentrations** *within* **30-120 minutes**.
- *Metabolism*; ***predominantly*** by **CYP3A4**.
- *Excretion*; feces (80%) and urine (13%).

Uses;- **Erectile Dysfunction (ED)**.
- **Pulmonary Arterial Hypertension (PAH)**; It relaxes the arterial wall, leading to decreased pulmonary arterial resistance and pressure.
- **Sildenafil** (**Respatio**®) can ***improve*** **fetoplacental perfusion** in **pregnancies**.

Dose;
Usual Adult Dose for Pulmonary Hypertension:
- **20 mg *orally*** 1*3.

Usual Adult Dose for Erectile Dysfunction:
- **50-100 mg *orally once*** a day, ***as needed***, **1 hour prior** to ***sexual activity***.

Dose *Adjustments* (erectile dysfunction):
- **Geriatric**: **25 mg 1 hour prior** to ***sexual activity***.
- ***Mild*** ***to*** ***moderate*** **renal dysfunction**: No adjustment recommended.
- **Severe renal dysfunction** (CrCl less than 30 mL/min): 25 mg.
- **Hepatic impairment** (any degree): 25 mg.
- With **alpha blockers** or with **CYP450 3A4 inhibitors** (**Ketoconazole** or **Erythromycin**): 25 mg.

Most Common Side Effects:
- **Headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness** and **rash**.
- **Abnormal vision**: ***due to*** **inhibition** of **PDE-6**.

Contraindications;
In **patients** ***who taking*** **Nitrates**.
Severe **hepatic impairment** *or* ***severe*** **renal impairment**.
Hypotension, ***recent*** **stroke** *or* **heart attack**.
Retinal disorders (genetic disorders of retinal phosphodiesterases).

FDA Warning;
Patients ***should stop*** **Sildenafil** if a **sudden loss of vision** occurs in ***one*** or ***both*** **eyes**, *which could be a sign of* **Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)**.
Patients ***should stop*** **Sildenafil** in the ***event*** of **sudden** ***decrease*** or ***loss*** of **hearing**.

Vardenafil (Levitra®)# — Tadalafil (Cialis®)#

- Vardenafil & Tadalafil are *selective* PDE-5 inhibitors *used for* Erectile Dysfunction.
- *Structurally* Vardenafil is *similar to* Sildenafil, while Tadalafil is *very different*.
- Vardenafil is *may* be effective in the *treatment of* Premature Ejaculation!!

Tadalafil *used for* in treatment of Pulmonary Arterial Hypertension and *symptoms of* Benign Prostatic Hyperplasia (BPH).

Vardenafil is *more selective* than Sildenafil and Tadalafil to PDE-5.

- *Brief comparison*:

	Sildenafil	Vardenafil	Tadalafil
FDA approval date	March 27, 1998	August 19, 2003	November 21, 2003
Dosage form	25mg, 50mg, 100mg tablets	2.5mg, 5mg, 10mg, 20mg tablets	5mg, 10mg, 20mg tablets
Efficacy	82-84%	80%	81%
Onset of action	30 minutes (effect delayed by food)	25 minutes (effect delayed by fatty meal)	16-45 minutes (effect NOT delayed by food)
Recommended dose	50 mg, may be adjusted to 100 mg or 25 mg	10 mg, may be adjusted to 20 mg	10 mg, may be adjusted to 20 mg
Duration of action	4 to 5 hours	4 to 5 hours	36 hours
Food Interactions	- Less effective after high-fat meal	- Less effective after high-fat meal - Moderate-fat meal does not reduce its effectiveness	- Works without regard to what eat
Most common side effects	Facial flushing, headache, indigestion	Facial flushing, headache	Headache, indigestion
Less common side effects	Altered vision, dizziness, nasal congestion	Indigestion, nausea, dizziness, nasal congestion	Back pain, muscle aches, nasal congestion, facial flushing, dizziness

Vardenafil is *also available* in an Orally Disintegrating Tablets (ODT); *not* affected by high-fat meals *with fast* onset of action. (Levitra® ODT) (Staxyn®).

Avanafil (Stendra®)# (Erovanafile®)#

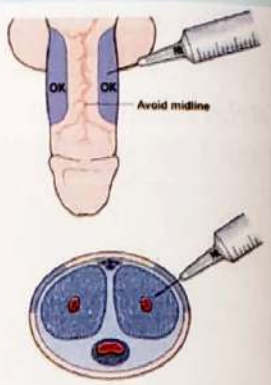
- Avanafil is a *selective* is a PDE-5 inhibitor *approved for* Erectile Dysfunction by FDA on April 27, 2012.
- *Onset of action*: **15 minutes** (***Fast onset of action***).
- *Duration of action*: ***up to*** **6 hours.**
- *Dosage form*: ***Tablets***: **50, 100** and **200 mg**.
- *Side effects* *same as* Sildenafil.

Prostaglandin Analogues

Alprostadil (Caverject®)

#Alprostadil is a **prostaglandin E_1 (PGE_1)** *analogue* used in **male erectile dysfunction** (*second-line therapy if* PDE-5 inhibitors *fail*), *increases* **cAMP → smooth muscle** *relaxation*.

Dosage form: **urethral suppositories** and **injection**.
  # MUSE® **penile suppository**; **125–1000 mcg** *inserted into* the **urethra**.
  # Caverject®; **2.5-40 mcg injected** *directly into* **corpus cavernosum**.
Onset of action: **5-10 minutes**.
Duration of action: ***Injection*** ⇨ **1-3 hours**, *supp.*⇨ **30-60 min**.
Common side effects: **penile pain** (*place of injection*) or **urethral pain** (*suppository only*), **priapism** and **hypotension**.



Priapism; erect penis *does not* return to its flaccid state, *potentially* painful and is *considered* a medical emergency; Phenylephrine, Pseudoephedrine, Terbutaline & Methylene blue can be used.

- *Drug interactions*: ***Not used*** *with* **PDE inhibitors**.
Topical **Alprostadil cream** (Vitaros®) has been ***approved in*** **Canada** as a ***first-line treatment*** **ED**.

Other (*off-label*)

Yohimbine (Yohimbex®)

- **Yohimbine** is a ***selective competitive*** **α_2-blocker**, *derived from* bark of ***yohimbe*** **tree**.
Uses: **mydriatic**, **erectile dysfunction** & **fat burner** (***promoting*** **lipolysis**; Lipo-6®).
Dose; 5.4 mg orally 3 times daily.
Common side effects: **Tachycardia**, **hypertension**, ***increased*** **motor activity**, **tremor** & **dizziness**

- In **1983**, **Penile erection** could be *induced by* the ***Intracavernosal injection*** of **vasoactive drugs** such as Papaverine, Phentolamine and Phenoxybenzamine.

Papaverine (Papacon®)

Papaverine is an ***opium alkaloid*** **antispasmodic drug**, ***used*** *primarily* in the ***treatment*** of **visceral spasm**, **vasospasm** and in the ***treatment*** of **erectile dysfunction**.
- *Mechanism* (not clear); **Papaverine** is a ***non-specific*** **phosphodiesterase inhibitor**.
Papaverine ***injection*** (**Intracavernosal**) and **topical gel** is *also* **available**.
- *Dose*; 7.5-60 mg **Intracavernosal injection**.
- *Common side effects*: **Priapism**, **corporal fibrosis**, **hypotension** and **hepatotoxicity**.

Phentolamine (Rogitine®)

- **Phentolamine** are **non-selective** ***reversible competitive*** **α-antagonist**.
- *Administration*; **intracavernosal injection**.
- **Phentolamine** ***monotherapy*** is ***avoided*** because **large doses** are ***required*** for an **erection**, and at these **large doses** can cause ***systemic*** **hypotension**.
- *Common side effects*: **Priapism**, **corporal fibrosis** and **hypotension**.

Apomorphine (Ixense®) (Uprima®)

- ***Sublingual*** **Apomorphine** has ***demonstrated*** some ***benefit*** in **erectile dysfunction**.

4) Premature (Early) Ejaculation (PE)

Topical Desensitizing

Lidocaine/Prilocaine (EMLA®)#

Topical desensitizing products *applied* to the **penis** *about* **20–30 minutes** *before* **intercourse**.
Condom *can* **used** *to* ***minimize*** the **effect** of the **cream** on **vaginal** ***sensation***.
Side effects; **Hypoanaesthesia** of the **penile shaft** and **vaginal numbness** (if a condom is not used or not adequately washed off the penis).
Contraindications; **man** or ***his*** **partner** has an **allergy** to **product component**.

Antidepressants

The ***most effective*** **pharmacologic therapy** for **premature ejaculation** is **selective serotonin reuptake inhibitors** (**SSRIs**).
- ***Some*** **tricyclic antidepressants** (**TCAs**) have the ***same*** **effect** of **SSRIs**, but have ***more*** **side effects**.
- **Ejaculatory** ***delay*** to **6–20 times** ***greater than*** *before* **medication**.

Clomipramine (Anafranil®)#

Clomipramine is a ***tricyclic antidepressants***.
Dose; - **Daily Therapy**; **25-50 mg/day**.
- **On-demand Therapy** (*before* **sexual activities**); **25 mg 4-24 hours**.
Clomipramine is ***more effective*** for **premature ejaculation** *than* ***many*** **SSRIs**.
Clomipramine now, it *has* ***largely*** been ***replaced by*** **SSRIs** *because* it is ***side effects***; **hypotension, fatigue, dizziness, dry mouth** and **QT prolongation**.

Paroxetine (Seroxat®)# | Sertraline (Lustral®)#

Fluoxetine (Prozac®)# | Escitalopram (Cipralex®)#

SSRIs may be **used** to ***treat*** **premature ejaculation**, **patients** *may* **report symptom** ***improvement*** *within* a **few days** of ***starting*** **therapy**, with ***best*** **effects** noted ***after*** about **4 weeks** of **treatment**.
Mechanism (*unclear*); ***probably*** **revolves** *around* ***activation*** of the **5-HT$_{2C}$ receptor**.
- ***Dose***; - **Paroxetine**; ***Daily***; **10-40 mg/day**. ***On-demand***; **20 mg 3-4 hr** *before* **sexual activities**.
- **Sertraline**; ***Daily***; **25-200 mg/day**. ***On-demand***; **50 mg 4-8 hr** *before* **sexual activities**.
- **Fluoxetine**; ***Daily***; **5-20 mg/day**. - **Escitalopram**; ***Daily***; **20-40 mg/day**.
Side effects; **GI side effects, headache, anxiety, fatigue**, and **sleep disturbances**.
Mild **erectile dysfunction**, ***reduced*** **libido** and ***increased*** **suicide risks** may occur with ***high*** **doses** and ***long-term*** **use** of **SSRIs**.

Dapoxetine (Priligy®)# (Joybox®)# >>

Dapoxetine is a ***short-acting*** **SSRI** and it was the ***first*** **drug** ***developed*** **specially** for the ***treatment*** of **premature ejaculation** as an **on-demand therapy**.
Dapoxetine is the ***only*** **approved drug** in the ***treatment*** of **premature ejaculation**, in ***many*** **countries** (***not approved*** in US).
Dapoxetine is the **Ideal Compound** for the ***treatment of*** **premature ejaculation**, ***because*** it has a **unique pharmacokinetic profile**; ***rapid*** **absorption**, ***adequate*** **availability** at the **target site**, and ***rapid*** **elimination** and ***minimize*** the *incidence* of **side-effects**.
Dose; **30-60 mg 1-3 hours** *before* **sexual activities** (***on-demand only***).

Some studies have demonstrated that ***combining*** **PDE-5 inhibitors** *with* **SSRIs** ***provides*** **better results**

Other Agents

Tramadol (Contramal®)#

Tramadol is a **μ receptor** *agonist* and **norepinephrine/serotonin reuptake** *inhibitor*.
Tramadol may be *prescribed* when **SSRIs** *haven't been* **effective** in *treatment of* **premature ejaculation**, but *can't* be used in *combination with* an **SSRI**.
Dose; **50 mg 1-3 hours** *before* **sexual activities** (on-demand *only*).
Tramadol has been *associated with misuse* (*delay* **ejaculation** and **wakefulness**) and *abuse*.
Long-term use of *high* **doses** will *cause dependence* and a *withdrawal syndrome*.

Pindolol (Visken®)

- Pindolol is a *non-selective* **β-blockers** used in *combination* with **Paroxetine** for **premature ejaculation** *refractory to* **Paroxetine** *alone*.

5) Retarded (Delayed) Ejaculation (RE)

Amantadine (PK-Merz®)# (Symmetrel®)

- Amantadine has *benefit* in *treating* **delayed ejaculation** by *potentiate* **dopaminergic function**.
- *Dose*; - **Daily Therapy**; **100-200 mg** *twice* **daily**.
  - **On-demand Therapy**; **100-400 mg/day** *for* **2 days** *before* **sexual activities**.
- *Side effects*; **Hypotension**, **dizziness** and **insomnia**.

Bupropion (Wellbutrin®)#

- Bupropion is a *weak* **norepinephrine-dopamine** *reuptake* **inhibitor** (**NDRI**).
- *One* **clinical study** *found* **Bupropion** SR **150 mg** *once* **daily** given for **2 months** to **men** with *lifelong* **delayed ejaculation** increased *overall* **ejaculation**.
- *Side effects*; *increased* **risk of seizures**, **insomnia**, **anxiety**, **headache**, and *decreased* **appetite**.

Buspirone (Buspar®)#

- Buspirone is a *selective* **5-HT1A agonist**, which is an **antianxiety agent**.
- Buspirone has *minimal* **data supporting** *its* use for **delayed ejaculation**.

Yohimbine (Yohimbex®)#

- Yohimbine has been associated with *improvements* in **delayed ejaculation**.

Cyproheptadine (Triactin®)#

Cyproheptadine acts as a *serotonin antagonist* and *used* **off-label** as an **appetite stimulant**.
Cyproheptadine has been associated with *improvements* in **delayed ejaculation**.
- *Dose*; **4-12 mg 3-4 hours** *before* **sexual activities**. *Side effects*; **drowsiness** and **dizziness**.

Pseudoephedrine

- Pseudoephedrine may be *used for* **delayed ejaculation** because of its *agonistic* **action** on **α receptors** and its *ability to increase* **norepinephrine**; *easy* **contraction** for **ejaculation**.
- *Dose*; **60-120 mg 1–2 hours** *before* **sexual activities**.

Oxytocin

- Oxytocin *plays* a **role** in *regulating* **orgasms** *through* **several pathways**.
- *Dose*; **24 international units** of *intranasal* **Oxytocin** *just* **minutes** *before* **sexual activities** (quick onset of action) has been suggested for *possible* *treatment* of **delayed ejaculation**.

6) Retrograde Ejaculation

Imipramine	Pseudoephedrine	Chlorpheniramine

- *These* **medications** *can be* **used** in **retrograde ejaculation**, *because* are *tighten* the **bladder neck muscles** and *prevent* **semen** from **going** *backwards into* the **bladder**.
- *Usually* **taken** *at least* **1–2 hours** *before* **sexual activities**.

Sexual Transmitted Disease (STD) Regimens

Genital Herpes (*Herpes Simplex Virus*; HSV Infection)

- Treatment; 2015 STDs Guidelines *from* Centers for Disease Control and Prevention (CDC).
  - Acyclovir (Zovirax®) **400 mg** orally 1*3 daily for 7–10 days.
  - OR Acyclovir (Zovirax®) **200 mg** orally 1*5 daily for 7–10 days.
  - OR Valacyclovir (Valtrex®) **1 g** orally 1*2 daily for 7–10 days.
  - OR Famciclovir (Famvir®) **250 mg** orally 1*3 daily for 7–10 days.

Syphilis

- Treatments; 2015 STDs Guidelines *from* Centers for Disease Control and Prevention (CDC).
  - Primary syphilis/Secondary syphilis;
    - Benzathine Penicillin G; 2.4 million units IM in a single dose (adults).
    - *If penicillin allergy*: Doxycycline 100 mg 1*2 daily or Tetracycline 500 mg 1*4 daily for 2 weeks.
  - Latent syphilis/Tertiary syphilis
    - Benzathine Penicillin G 2.4 million units IM every week for 3 weeks.
    - *If penicillin allergy*: Doxycycline 100 mg orally 1*2 or Tetracycline 500 mg 1*4 daily for 4 weeks.

Chlamydia Infection

- Treatments; 2015 STDs Guidelines *from* Centers for Disease Control and Prevention (CDC).
  - Azithromycin **1 g** in a ***single dose*** OR Doxycycline **100 mg *twice* daily** for **7 days**.
  - *Alternatives*: Erythromycin base 500 mg orally 1*4 daily for 7 days OR Erythromycin ethylsuccinate 800 mg orally 1*4 daily for 7 days OR Ofloxacin 300 mg orally 1*2 daily for 7 days OR Levofloxacin 500 mg/day 1*1 for 7 days.
- **Abstain** *from* **sexual intercourse** for *at least* **7 days** and *until* **sexual partners** are ***adequately*** **treated**.

Gonorrhoea (Gonococcal Infection)

- Treatments; 2015 STDs Guidelines *from* Centers for Disease Control and Prevention (CDC).
  - *Uncomplicated* gonococcal infections of pharynx, cervix, urethra and rectum;
    - ***Single doses*** of Ceftriaxone 250 mg IM + Azithromycin **1 g**.
    - *Alternative*; ***single doses*** of Cefixime 400 mg orally + Azithromycin **1 g**.
    - ***Allergy*** to **cephalosporins**; ***single doses*** of ***oral*** Gemifloxacin 320 mg + ***oral*** Azithromycin **2 g**.
- **Abstain** *from* **sexual intercourse** for *at least* **7 days** and *until* **sexual partners** are ***adequately*** **treated**.

Pelvic Inflammatory Disease (PID)

- Treatments; 2015 STDs Guidelines *from* Centers for Disease Control and Prevention (CDC).
  - Parenteral Regimens; discontinued 24 hours after clinical improvement and changed to oral therapy for 14 days.
    - Cefotetan 2 g IV every 12 hours + Doxycycline 100 mg orally or IV every 12 hours
    - OR Cefoxitin 2 g IV every 6 hours + Doxycycline 100 mg orally or IV every 12 hours
    - OR Clindamycin 900 mg IV every 8 hours + Gentamicin loading dose IV or IM (2 mg/kg), followed by a maintenance dose (1.5 mg/kg) every 8 hours.
    - *Alternative*; Ampicillin/Sulbactam 3 g IV every 6 hours + Doxycycline100 mg orally or IV /12 hr.
  - Intramuscular/Oral Regimens;
    - Ceftriaxone 250 mg IM in a ***single dose*** + Doxycycline 100 mg orally twice a day for 14 days ***WITH*** or ***WITHOUT*** Metronidazole 500 mg orally twice a day for 14 days.
    - Cefoxitin 2 g IM in a ***single dose*** and Probenecid, 1 g orally administered concurrently in a ***single dose*** + Doxycycline 100 mg orally twice a day for 14 days ***WITH*** or ***WITHOUT*** Metronidazole 500 mg orally twice a day for 14 days.

Bacterial Vaginosis (BV)

- Treatments; 2015 STDs Guidelines *from* Centers for Disease Control and Prevention (CDC).
  - *Non-pregnant women*;
    - Metronidazole 500 mg orally twice daily for 7 days.
    - OR Clindamycin 2% cream, 1 full applicator intravaginally at bedtime for 7 days.
    - OR Metronidazole 0.75% gel one full applicator intravaginally once daily for 5 days.

- *Alternatives*: - Clindamycin ovules 100 mg intravaginally at bedtime for 3 days.
  - OR Clindamycin 300 mg orally twice daily for 7 days.
  - OR Tinidazole 2 g orally once daily for 2 days.
  - OR Tinidazole 1 g orally once daily for 5 days.
- *Pregnant women*;
  - Metronidazole 500 mg orally twice daily for 7 days.
  - OR Metronidazole 250 mg orally three times daily for 7 days.
  - OR Clindamycin 300 mg orally twice daily for 7 days.
- *Do not* use Clindamycin *cream* ***during*** pregnancy because of the ***increased*** risk of preterm deliveries.

Vulvovaginal Candidiasis (Vaginal Thrush)

- Treatments; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention (CDC)**.
  - *Therapeutic Regimens*;

Drug	Dose	Length of Therapy
Butoconazole	2% cream: 5 g intravaginally	1 dose
Clotrimazole	1% cream: 5 g intravaginally at bedtime	7–14 days
	2% cream: 5 g intravaginally at bedtime	3 days
Miconazole	2% cream: 5 g intravaginally at bedtime	7 days
	4% cream: 5 g intravaginally at bedtime	3 days
	100-mg vaginal suppository at bedtime	7 days
	200-mg vaginal suppository at bedtime	3 days
	1200-mg vaginal suppository	1 dose
Nystatin	100,000-unit vaginal tablet at bedtime	14 days
Terconazole	0.4% cream: 5 g intravaginally at bedtime	7 days
	0.8% cream: 5 g intravaginally at bedtime	3 days
	80-mg vaginal suppository at bedtime	3 days
Tioconazole	6.5% ointment: 5 g intravaginally	1 dose
Fluconazole	150-mg oral tablet	1 dose

  - *Recurrent* vulvovaginal candidiasis (**four** or ***more*** **episodes** a **year**);
    - ***Longer*** **duration** of **initial therapy**;
      - **7–14 days** of **topical therapy**.
      - 100 150 or 200-mg oral dose of Fluconazole ***every*** **third day** for a total of **3 doses**.
    - ***Maintenance regimen***; Oral Fluconazole 100, 150, or 200 mg/week for 6 months.
  - *Pregnant women*; ***Drugs of choice*** is **topical azole**, *applied for* **7 days**.

Trichomoniasis

Treatments; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention (CDC)**.
- Metronidazole 2 g orally in a ***single dose*** OR Tinidazole 2 g orally in a ***single dose***.
- *Alternative*; Metronidazole 500 mg orally twice daily for 7 days.
- ***All sexual*** **partners** *should be* **treated**.

Human Papillomavirus (HPV) infection

- Treatments; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention (CDC)**.
  - *External Anogenital Warts* (**penis**, **groin**, **scrotum**, **vulva**, **perineum**, **external anus** and **perianus**);
    - ***Patient-Applied***:
      - Imiquimod 3.75% (*every night*) OR 5% (*3 times a week*) **once** at bedtime, *for up to* **16 weeks**
      - OR Podofilox® (Podophyllotoxin) 0.5% solution or gel; twice a day for 3 days, followed by 4 days of no therapy, this cycle can be repeated, as necessary, for up to four cycles.
      - OR Sinecatechins 15% (green-tea extract) ointment; three times daily until complete clearance of warts is achieved (should not be continued for longer than 16 weeks).
    - ***Provider-Administered***:
      - Cryotherapy with **liquid nitrogen** or **cryoprobe**.
      - OR Surgical removal.
      - OR Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80%–90% **solution**.
      - *Alternative*; Podophyllin resin, Interferon, photodynamic therapy, and ***topical*** Cidofovir.
  - Regimens for Urethral Meatus Warts; Cryotherapy with ***liquid nitrogen*** OR Surgical removal.
  - Recommended Regimens for Vaginal, Cervical and Intra-anal Warts;
    - Cryotherapy with **liquid nitrogen**.
    - OR Surgical removal.
    - OR Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80%–90% **solution**.
- Podofilox® (Podophyllotoxin), Podophyllin & Sinecatechins ***should not*** be **used** ***during*** **pregnancy**.

HIV/AIDS and hepatitis are ***sexually transmitted disease; see Antiviral agents***

Drugs for Kidney Stones

➢ Classification:-

Kidney stone type	Prevalence	Circumstances	Crystal shape	Color
Calcium oxalate	80%	Acidic urine	Envelope	Black/dark brown
Calcium phosphate	5-10%	Alkaline urine	Amorphous	Dirty white
Uric acid	5-10%	Acidic urine	Diamond or barrel	Yellow/reddish brown
Struvite (Magnesium Ammonium Phosphate)	10-15%	Infections in the kidney (ammonia-producing bacteria)	Coffin-lid	Dirty white
Cystine	1-2%	Cystinosis; genetic disorder	Hexagon	Pink/yellow

➢ Prevention:- *depend on stone type*

Calcium Oxalate Stones

Lifestyle modifications; # # # # # # # PATIENT COUNSELLING # # # # # #

- ***Adequate* fluid intake** (2.5–3 L of fluids per day).
- ***Moderate dietary* calcium *intake***.
- ***Avoid* oxalate *containing* foods**; **spinach**, **rhubarb**, **nuts** and **wheat bran**.
- ***Limit* animal protein**; ***decrease* animal protein *intake* → 1) *increase* citrate *excretion* 2) *decrease* urate *excretion* 3) *decrease* calcium *excretion***.
- ***Limit* sodium intake**; ***decrease* sodium *intake* → *decrease* calcium *excretion***.
  - Check food labels for ingredients and hidden sodium, such as; Monosodium glutamate (MSG), Sodium bicarbonate (baking soda & baking powder), disodium phosphate, sodium alginate and sodium nitrate or nitrite.

Drug therapy;

A) Thiazide diuretics; ***Reducing* calciuria & stone *recurrence*** (risk for uric acid stones)

B) Alkalinizing agents; Citrate Treatment

Magnesium Citrate (Epimag®)#	Potassium Citrate (Urocit-K®)
Citric Acid or Citrate	

1) **Citrate salts**; are ***metabolized by* liver** and **kidney** and ***produce* Bicarbonate → *raise* urine pH → *inhibits*** the **formation** and ***growth*** of **CaOx crystals**.
2) **Citrate ion *bind*** with **calcium** in **urine → form *soluble* citrate complex → *inhibits* formation** and ***growth*** of **calcium crystals**.

- **N.B.; Citrate treatment *raise* urine pH**, and this ***may* increase** the ***risk*** for **calcium phosphate stones** if ***urine* calcium *remains* high** and **fluid intake** is ***not maintained***.
- **Citrocid Magnesium Plus®** (**Citric acid + Magnesium + pyridoxine**); ***Adequate* quantities** of **B-complex vitamins** and **Magnesium** can ***prevent* calcium oxalate stone formation**.

C) Allopurinol (**Zyloric®**); ***some* patients** with **calcium oxalate *stones*** have **hyperuricosuria**. **Uric acid *facilitates*** the **precipitation** of **calcium oxalate *crystals***.

Calcium Phosphate Stones

- The ***common cause*; *high* urine pH** (**alkaline urine**) and **hypercalciuria**.

Lifestyle modifications; # # # # # # # PATIENT COUNSELLING # # # # # #

- ***Adequate* fluid intake** (2.5–3 L of fluids per day).
- ***Moderate dietary* calcium *intake***. - ***Limit* animal protein** and **sodium intake**.

Drug therapy;

A) Thiazide diuretics; ***Reducing*** **calciuria** and **stone** ***recurrence***.

B) Acidifying urine; by ***large dose*** of Vitamin C (Vitacid®); 1 g eff. 1*2 or 1*3

C) Citrate Therapy; is *controversial* (*not backed by any trials*);

- *Benefits*; Citrate in the **urine** ***forms*** a *soluble* ***complex*** with Calcium.
- *Risk*; Citrate ***raise*** **urine pH** (***increase*** **calcium phosphate stone** ***formation***).

Uric Acid Stones

Lifestyle modifications; ####### PATIENT COUNSELLING

- ***Adequate*** **fluid intake** (2.5–3 L of fluids per day).
- ***Limit*** **Purine-Rich Foods**;
  - **Organ meats**; Liver, kidneys, brain and heart.
  - **Game** (hunting) **meats**; rabbit and venison.
  - **Fish**; herring, mackerel, sardines and sprats.
  - **Seafood**; mussels, shellfish and caviar.
  - **Yeast extracts**; beer (not wine).
  - **High-fructose foods**.

Drug therapy;

A) Alkalinizing agents;

Potassium Sodium Hydrogen Citrate (Uralyt-U®)#

Sodium Citrate + Citric Acid (Bicitra®)

- Citrates are ***metabolized by*** liver and kidney and ***produce*** Bicarbonate → ***raise*** urine pH → dissolve and ***inhibits*** the formation and ***growth*** of Uric Acids crystals.

Piperazine Citrate (Urosolvine®)#

- Urosolvine® effervescent; introduced in 1949; contains Piperazine ***anthelmintic agent***; increase the solubility of urates, Colchicine; brings rapid relief in cases of acute gout attacks and Atropine; relieves spasms of the urinary tract.

B) Allopurinol (Zyloric®); ***decrease*** Uric Acid production by ***competitively inhibiting*** xanthine

Renal Colic Managements

Pain Management

NSAIDs

Diclofenac (Voltaren®) (Cataflam®) is often the FIRST CHOICE NSAID for renal colic.

Dose; Diclofenac **75 mg** (3 mL) **injection, IM**, ***repeated once*** (***may be given*** **30 minutes** later *if required*, in the ***opposite side***).

May also be ***combined with*** **oral** Diclofenac to a ***maximum*** of **150 mg**, daily, for a ***maximum*** of **two days**. **Oral** or **rectal** Diclofenac, **75-150 mg, daily**, ***can be*** **prescribed**.

Diclofenac is ***contraindicated*** in **patients** who have a **cardiovascular risk**. ***Other*** NSAIDs, e.g. Ibuprofen or Naproxen, ***should*** *provide* **effective pain management** for ***patients*** with **renal colic** in ***these*** **situations**.

Opioids

Morphine 5-10 mg, IM *every* 4 hours; is an ***alternative*** **treatment** to **NSAIDs**.
Morphine is ***preferred*** **over NSAIDs** in **pregnant women**.

Antiemetic Therapy

Metoclopramide (**Primperan**®) is the ***only*** **antiemetic** that has ***been*** **specifically studied** in the ***treatment*** of **renal colic**, ***usual*** **adult** ***dose*** is **10 mg IV** or **IM** ***every*** **4-6 hours** as ***needed***.

Antispasmodic Therapy

Antispasmodic ***most commonly*** in ***combination*** *with* **pain management agents**.
Hyoscine N-butylbromide (**Buscopan**®) ***reduces*** **amount** of **opioids** ***required*** in **renal colic**.
Drotaverine (**Do-Spa**®) is an **antispasmodic** ***without*** **antimuscarinic** ***adverse effects***.
- **Aminophylline** is a ***methylxanthine***, it ***relaxes*** **smooth muscles**.

Medical Expulsive Therapy (MET)

- **MET** is ***useful for*** **stones diameter** ***less than*** **10 mm**.
- **MET**; ***includes*** **α-blockers**, **Calcium Channel Blockers**, **Corticosteroids** and **Phosphodiesterase-5 (PDE5) Inhibitors**.
- **NSAIDs** ***have*** **ureteral-relaxing effects** and *can be* **considered** a ***form of*** **MET**.

* **α-blockers**; **Tamsulosin** (**Flomax**®) is a ***selective*** **α_{1A} receptor** ***antagonist*** *making it* the ***most commonly*** *prescribed* **α- blocker**, **Silodosin** (**Rapaflo**®) is *another* ***selective*** **α_{1A} receptor** ***antagonist*** can be **used**.
* **Calcium Channel Blockers**; **Nifedipine** (**Epilat**®) is the ***only*** **calcium channel blocker** that has ***shown*** *some* **benefit** in **stone expulsion** (**Tamsulosin** ***better than*** **Nifedipine**).
* **Corticosteroids**; have been *reported to* ***facilitate*** **stone expulsion**.
* **Phosphodiesterase-5 (PDE5) Inhibitors**; ***Relaxing*** **effects** of **ureteral muscle tension** have been observed in patients ***receiving*** **Vardenafil** (**Levitra**®), **Sildenafil** (**Viagra**®) and **Tadalafil** (**Cialis**®).

Miscellaneous Agents

* **Antibiotics**; can be **used** if ***infections*** are **present**, *such as*;
  - **Ciprofloxacin** (**Cipro**®) and **Sulfamethoxazole/Trimethoprim** (**Septrin**®)
* **Urinary Tract Antiseptics**; can be **used** if ***infections*** are **present**, *such as*;
  - **Nitrofurantoin** (**Uvamin**®) ***concentrated*** in the **urine**, *leading to* ***higher*** and ***more*** **effective levels** in the **urinary tract**, it works by ***damaging*** **bacterial DNA**.
  - **Hexamine** ***decomposes*** at an **acidic pH** to form **formaldehyde** and **ammonia**, and the **formaldehyde** is ***bactericidal***.
* **Other Agents**;
  # **Halphabarol** (**Proximol**®) (*Cymbopogen proximus*) (Halfa bar); is an ***antispasmodic*** and ***used widely*** in **management** of **renal colic**.
  # **Khellin** (*Ammi Visnaga*); *work by* ***decrease*** **calcium oxalate stone** ***formation***, **antibacterial** ***activity***, ***antispasmodic*** and ***acting as*** a **diuretic**.
  # **Cystone**®; *work by* ***decrease*** **kidney stone** ***formation***, **antibacterial** ***activity***, ***antispasmodic*** and ***acting as*** a **diuretic**.
  # **Rowatinex**®; *work by* **urinary muscle** ***relaxant***, ***facilitating*** **ureteral stone** ***passage*** and ***decrease*** **calcium oxalate stone** ***formation***.

Drugs for Benign Prostatic Hyperplasia (BPH)

Lower Urinary Tract Symptoms (LUTS); *group of* **medical symptoms** *caused mainly by;* benign **prostatic hyperplasia (BPH), urinary tract infection (UTI)** and **chronic prostatitis.**

A) Storage (Irritative) Symptoms;

- **Urinary frequency**; increased frequency of urination.
- **Urinary urgency**; increased urgency of urination.
- **Dysuria**; painful urination.
- **Nocturia**; excessive passage of urine at night.

B) Voiding (Obstructive) Symptoms;

- **Poor stream** (unimproved by straining); decreased force.
- **Hesitancy** (worsened if bladder is very full); a delay between trying to urinate and the flow actually beginning.
- **Dribbling**; loss of small amounts of urine due to a poor urinary stream.

- ***N.B.***; **LUTS** as an ***independent*** **risk factor** for **erectile dysfunction** and **ejaculatory dysfunction.**

Medication can cause LUTS;

- **α-Adrenergic agonists**; ***Decongestants*** and **Pseudoephedrine**.
- **Anticholinergics**; **Antispasmodics**, **Antihistamines**, **Tricyclic Antidepressants** and **Phenothiazines**.
- **Diuretics**.
- **Testosterone**.

Benign Prostatic Hyperplasia (BPH) or **Benign Prostatic Hypertrophy**; is a ***noncancerous*** *increase* in **size** of the **prostate**, is a ***common*** in **older men**.

- **BPH Managements:-**

1) Watchful Waiting

- **Watchful waiting** is ***recommended*** in **men** who have **mild symptoms**.

2) α_1-Receptor Antagonists

Prazosin (Minipress®)#	**Doxazosin** (Cardura®)#	**Terazosin** (Hytrin®)
Alfuzosin (Xatral®)#	**Tamsulosin** (Flomax®)# (Omnic-Ocas®)#	**Silodosin** (Rapaflo®)

- **Prazosin, Doxazosin** and **Terazosin** are a ***non-specific selective*** **α_1 blocker**; ***acts on*** **blood vessels** (lower blood pressure) and **prostate** (relax prostate and urethra muscles and relax bladder neck), ***used in*** **symptoms of BPH (LUTS)** and **hypertension.**

Alfuzosin is a ***specific selective*** **α_1 blocker** in the **prostate** and **bladder**, ***approved only*** for **symptoms of BPH (LUTS)**, ***not indicated*** for the **treatment** of **hypertension.**

Tamsulosin and **Silodosin** are a ***specific selective*** **α_1 blocker** that has ***preferential selectivity*** for *the* **α_{1A} receptor** in the **prostate** *versus* the **α_{1B} receptor** in the **blood vessels** ***approved only*** for **symptoms of BPH (LUTS)**, ***not indicated*** for the **treatment** of **hypertension.**

All **α-blockers** ***relieve*** **symptoms** in **men** ***with*** **moderate** to **severe BPH**.

Side effects;

- ***All*** **α-blockers** can ***cause*** **orthostatic hypotension** (non-specific >>> specific); Therapy with ***non-specific*** **agents** ***should*** begin at a **low dose** and then be ***titrated*** **upward**. **Sildenafil** (or ***other*** **PDE-5**) in doses ***greater than*** **25 mg** should not be taken ***within*** **four hours** of **alpha-blocker** use.
- ***All*** **α-blockers** can ***cause*** **ejaculation changes, headaches, nasal congestion** and **weakness.**
- **Patients** ***taking*** **Tamsulosin** are prone to a ***complication known*** as **floppy iris syndrome** during **cataract surgery**, ***should avoid*** *until* their **cataract surgery** is **completed.**

# *Doses*;	
Prazosin	***Start*** at 1 mg twice daily; ***usual*** 2–10 mg in two to three divided doses.
Doxazosin	***Start*** at 1 mg daily; ***usual*** 1–4 mg daily; ***maximum*** 8 mg.
Terazosin	***Start*** with 1 mg taken at bedtime; ***usual*** 1–10 mg daily; ***maximum*** 20 mg.
Alfuzosin	10 mg daily as a single dose.
Tamsulosin	0.4–0.8 mg daily as a single dose.
Silodosin	8 mg daily as a single dose - 4 mg daily if CrCl 30–50 mL/minute.

Drug interactions; ***All*** **α-blockers** are ***metabolized through*** the **CYP3A4** ***pathway*** and have **drug** ***interactions*** with ***strong*** **CYP3A4 inhibitors** and **inducers**.

3) 5-α-Reductase Inhibitors

Finasteride (Proscar®)# | **Dutasteride** (Avodart®)#

Finasteride and **Dutasteride** are a *5-α-reductase inhibitors*.
- They inhibits ***5α-reductase enzyme*** which ***convert*** **Testosterone** into the ***more potent androgen*** **Dihydrotestosterone (DHT)**; *lead to* ↓ **prostate size** & ↑ **urinary flow**.

Most beneficial; in **men** *with* **prostates** ***larger than*** **40 g**.
Should not use in **men** *with* **LUTS** ***secondary*** to **BPH** ***without*** **prostatic enlargement**.
Onset of benefits; *approximately* **6 months** of **therapy**.
Doses; **Finasteride**; 5 mg daily. - **Dutasteride**; 0.5 mg daily.
Side effects; ***decreased*** **libido**, **ejaculatory problems** and **erectile dysfunction**.

4) Combination Therapy

Dutasteride + Tamsulosin (CombAT®) (Duodart®) (Jalyn®) (Combodart®)

It *contains*; **Tamsulosin** 0.4 mg + **Dutasteride** 0.5 mg.
Indications; **severe symptoms** of **BPH** in **enlarged prostate** ***larger than*** **40 g**.

5) Phosphodiesterase Type-5 (PDE5) Inhibitors

Tadalafil (Cialis®)#

Tadalafil are *selective* **PDE-5 inhibitors** *used for* **Erectile Dysfunction** and it is ***approved for*** use in **BPH** in **2011** or *both* **BPH** and **Erectile Dysfunction**.
- *Mechanism* (*exact mechanism unknown*).
- *Doses*; 5 mg once daily. *Combination of* **Tadalafil** and **α_1-blockers** is a ***risk of*** **hypotension** ***but*** it can **safe** in **proper instructions**.

6) Antimuscarinics

Oxybutynin (Ditropan®)# (Uripan®)#

Tolterodine (Detrusitol®)# | **Solifenacin** (Sofenacin®)#

- ***Used*** to ***improve*** **irritative voiding symptoms** (e.g., **urinary frequency**, **urgency**), which **α_1-blockers** and **5-α-reductase inhibitor** ***does not improve*** **these symptoms**.

7) Phytotherapy or Alternative Therapy

(Pepon®)# (Lycomen®)# (ProstaCure®)#

- **Saw Palmetto** (*Serenoa repens*) **extract**; *most commonly used* and *studied*; ***mild*** to ***moderate*** **improvement** in **LUTS**; some of urologists preferred **saw palmetto** over pharmacotherapy.
- **Stinging nettle** (*Urtica dioica*), **South African stargrass** (*Hypoxis rooperi*), **pumpkin seed** (*Cucurbita pepo*), and **African plum** (*Pygeum africanum*); *can be used*, but the **AUA** ***does not*** **recommend** the *use of* **Phytotherapy**.

8) Surgery

Surgery is ***preferred*** in **men** ***with*** **severe symptoms** and in those ***with*** **moderate symptoms** who have ***not adequately*** **responded** to **medical options**.

Drugs for Urinary Incontinence (UI)

Antimuscarinics

Oxybutynin (Ditropan®)# (Uripan®)#	**Tolterodine** (Detrusitol®)#
Solifenacin (Sofenacin®)#	**Flavoxate** (Genurin S.F®)#
Trospium (Spasmolyt®)	**Propiverine** (Mictonorm®)

- **Anticholinergic Drugs**; **Oxybutynin**, **Tolterodine**, **Fesoterodine**, **Trospium**, **Solifenacin** and **Darifenacin**; They ***reduce*** **detrusor over-activity** by ***antagonizing*** **M_3 muscarinic receptors** in the **bladder**. ***Longer*-acting formulations** may be ***better*** **tolerated**.

Oxybutynin & **Tolterodine** are ***most commonly used***.

Oxybutynin is available as a transdermal system (topical patches).

Fesoterodine is a ***prodrug***. It is broken down into its **Tolterodine**.

Solifenacin by CYP3A4 ⇨ ***drug interaction***; with ***LME inhibitors***. May also ***prolong the QT interval*** ⇨ ***Contraindicated*** in patient with ***long QT interval***.

Flavoxate is ***indicated for*** symptomatic relief of **interstitial cystitis**, dysuria, urgency, nocturia, supra-pubic pain, frequency and incontinence as may occur in **cystitis**, **prostatitis** and **urethritis**, **urethrocystitis/urethrotrigonitis**.

- **Trospium** ***should be*** **taken** ***at least*** **1 hour** ***before*** **meals** or *given on* an **empty stomach**.

Emepronium may cause ***ulceration of oesophagus***, so it ***should be taken*** in **orthostatic position** ***with sufficient*** **amounts** of **liquids**.

Antidiuretic Hormone (ADH)

Desmopressin (Minirin®)#

Desmopressin is a ***synthetic*** **replacement** for **antidiuretic hormone** (**ADH**) or **vasopressin**, the **hormone** that ***reduces*** **urine** ***production*** *during* **sleep**.

Desmopressin is the ***first-line treatment*** for **enuresis** in **children** ***older than*** **5 years**.

Dose; in **Nocturnal enuresis**.

  # **Minirin®**; **Regular tablets**; 0.2 mg one hour before bedtime, if needed after 10 to 14 days, the dose may be increased by 0.2 mg to a maximum dose of 0.6 mg.

  # **Minirin®-melt**; **Oral melt tablets**; 120 µg sublingual are given 30 to 60 minutes before bedtime; if needed after 10 to 14 days, the dose may be increased by 120 µg to a maximum dose of 360 µg.

Uses; **Nocturnal enuresis**, **coagulation disorders** and **central diabetes insipidus**.

Side effects; **Nausea**, **headaches**, **flushing**, **hyponatremia** and **seizures**.

β_3-Agonist

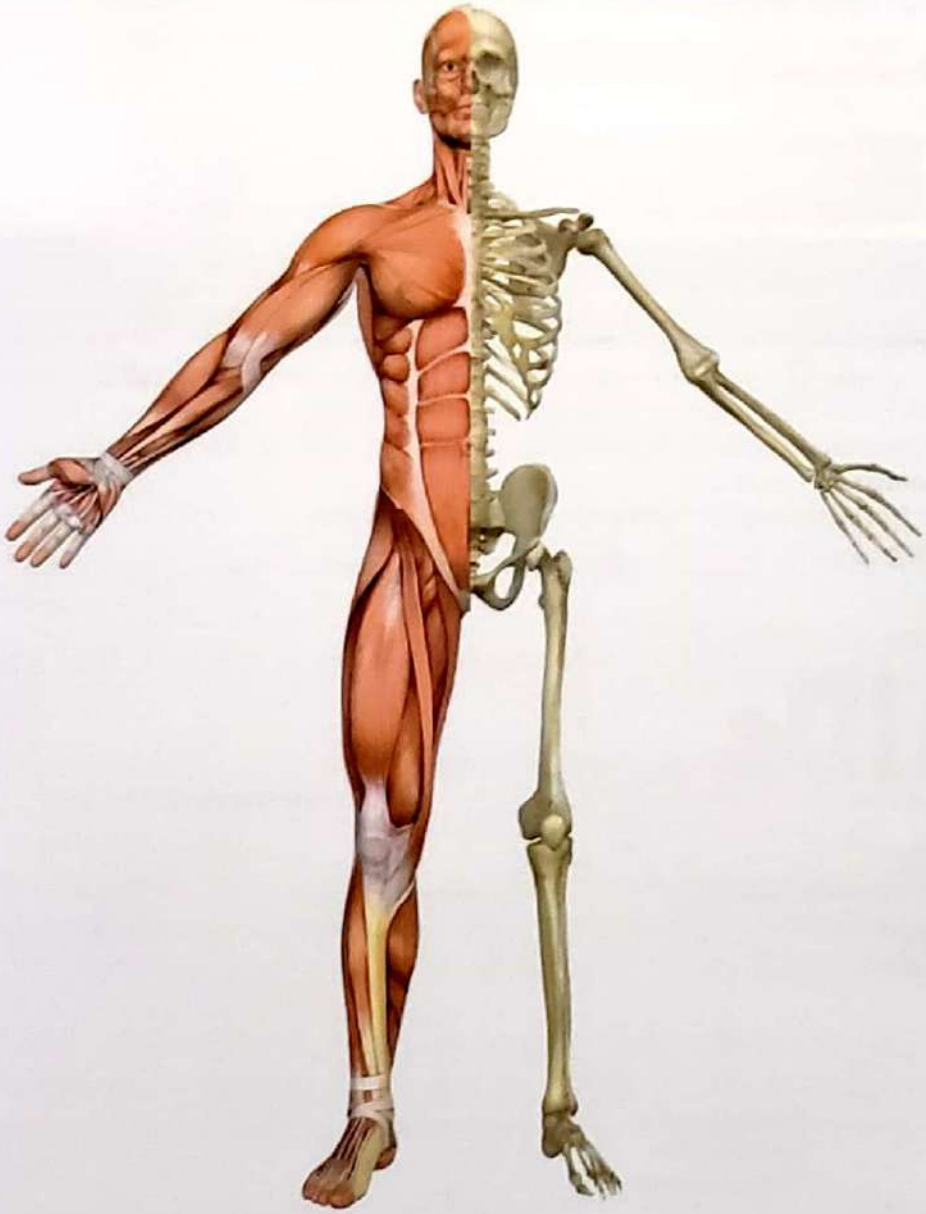
Mirabegron (Myrbetriq®)# (Betmiga)#

Mirabegron; ***approved by*** the **FDA** in **2012**, **Mirabegron** act on **β_3-adrenergic receptors** to ***relax*** the **detrusor**.

Dose; **25-50 mg** ***orally*** **once**.

Common adverse effects are **nausea**, **diarrhea**, **constipation**, **dizziness**, and **headache**. ***Increased*** **blood pressure** ***can*** **also** *occur*, and **Mirabegron** ***should not*** be used in **patients** with ***uncontrolled*** **hypertension**.

Musculoskeletal

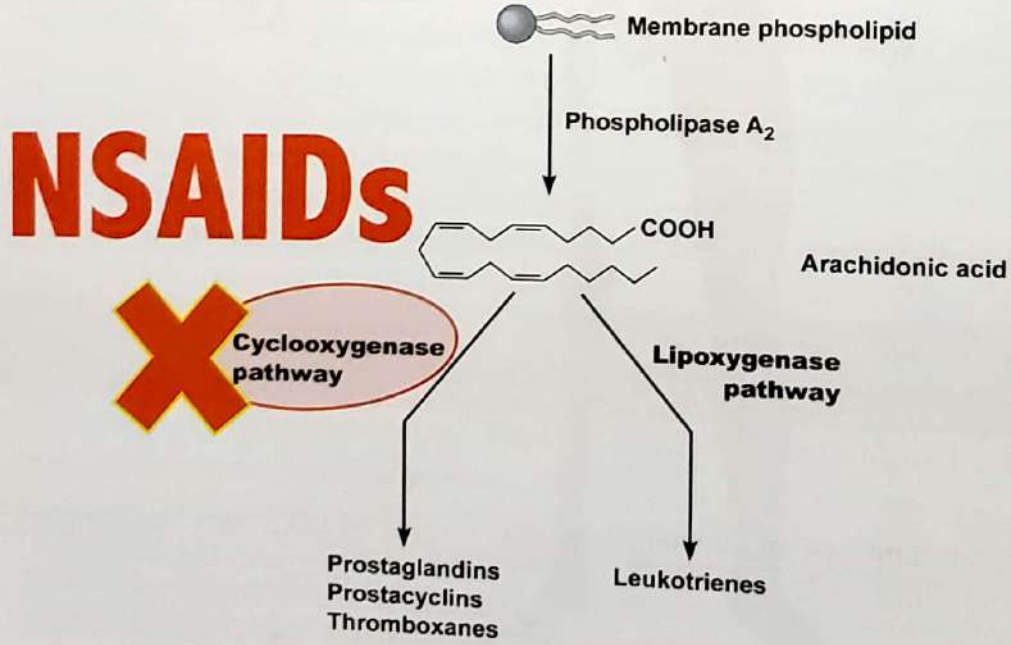


Pain Management

Pain can be **either** **acute** or **chronic** and is a consequence of **complex neurochemical processes** in the **peripheral** and **central nervous systems (CNS)**.
- **Analgesic** or **painkiller** is *any group* of drugs used to ***achieve*** **analgesia**, ***relief from*** **pain**
Types of pain;
  - *According to duration*;
    - **Acute pain**; ***less than*** **30 days**.
    - **Chronic pain**; ***more than*** **6 months**.
    - **Subacute pain**; ***from*** **1-6 months**.
  - *According to type of damage*;
    - **Nociceptive pain**; ***tissue damage***; skin, muscles, visceral organs, joints, tendons, or bones.
    - **Neuropathic pain**; ***nerve damage***; spinal cord injury, multiple sclerosis and diabetic neuropathy.
- **Breakthrough pain**; ***just occurs***, *without* any ***obvious*** **trigger**; type of cancer pain.
Analgesic choice is also ***determined by*** the **type of pain**; **for example**;
  - **Mild** to **moderate pain**; **Simple** (non-opioid) **analgesics** **such as nonsteroidal anti-inflammatory drugs** (**NSAIDs**) are **often effective**.
  - **Neuropathic pain**; **Responds *best*** to **anticonvulsants** and **tricyclic antidepressants**.
  - **Severe** or **chronic malignant** or **non-malignant pain**; **Opioid analgesics** are considered **part** of the **treatment plan** in select patients.
Major Classes of Analgesics;
  - **NSAIDs** and **Paracetamol**.
  - **Opioid Analgesics**; **Agents** that **produce morphine-like effect**.
  - **Specific agents**; **Anticonvulsants** and **tricyclic antidepressants**.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs; are a ***group*** of **chemically** ***dissimilar*** **agents** that ***have*** **analgesic** (*pain-killing*) and **antipyretic** (*fever-reducing*) and **anti-inflammatory** ***effects***.
Paracetamol (**Acetaminophen**) is ***generally*** ***not*** **considered** an **NSAID** because *it has* ***only little*** **anti-inflammatory activity**.
The **NSAIDs** *act by* ***inhibiting*** the **synthesis** of **prostaglandins**.



Major Roles of Eicosanoids;

- Prostaglandins (PGs);
  - *Modulate* pain, inflammation and fever.
  - *Control* acid secretion and mucus production *in the GIT*.
  - *Control* renal blood flow.
  - *Control* uterine contractions.
- Prostacyclin (PGI_2);
  - *Inhibit* platelet aggregation.
  - *Induce* vasodilation.
- Thromboxane-A_2 (TXA_2);
  - *Induce* platelet aggregation.
  - *Induce* vasoconstriction.
- Leukotrienes (LTs);
  - *Powerful* bronchoconstriction.
  - *Increase* vascular permeability.

- PGI_2 & PGE_1; ↓ platelet aggregation & VD
- PGE_2; VD, uterine contractions & ↑ platelet aggregation.
- PGD_2; inflammatory response, bronchoconstriction & VD.
- $PGF_{2\alpha}$; VC, bronchoconstriction & uterine contractions.
- TXA_2; ↑ platelet aggregation, VC & bronchoconstriction.
- LTB_4; chemotaxis and T-cell proliferation.
- LTC_4, LTD_4, LTE_4; VC and bronchoconstriction.

Two forms of cyclooxygenase (COX); COX-1 and COX-2.

- COX-1 is *expressed constitutively* in gastric mucosa, kidney and platelets
- COX-2 is *expressed* in macrophages and monocytes *in response* to inflammation.

Aspirin is an *irreversibly inhibitor* of cyclooxygenase (COX) *enzyme*, *while other* NSAIDs are *reversible* inhibitors.

Selectivity for COX-1 *versus* COX-2 is *variable* and *incomplete* for the *older* NSAIDs, but *selective* COX-2 *inhibitors* (*such as* Celecoxib) *have been synthesized*.

I) Aspirin and other NSAIDs

Acetylsalicylic Acid (Aspirin) (Aspirin®)#

- Aspirin is the *prototype* of the NSAIDs, it is a *weak* organic acid that is unique (*only*) NSAIDs in *irreversibly inactivating* cyclooxygenase (COX-1 and COX-2), *other* NSAIDs (*including other salicylates*), are *all reversible inhibitors* of cyclooxygenase.

Aspirin is *now rarely* used as anti-inflammatory, and used *only* as anti-platelet (75-325 mg/d).

- *Salicylates* (*except* Diflunisal) *cross both* BBB & placenta.

Mechanism; Aspirin *irreversibly inhibits* COX; *synthesis* of *new* COX *replaces* the *inactivated* enzyme *lasts* 6-12 hours.

Antiplatelet effect; Aspirin *irreversibly inhibits* COX *within* the platelets ⇨ *blocks* the *formation* of TXA_2, *Antiplatelet effect* of Aspirin *lasts* 8-10 days (*the life of the platelet*).

Therapeutic Actions of NSAIDs; 3 *major* therapeutic actions;

1) *Anti-inflammatory actions*; *decrease* prostaglandins *synthesis* ⇨ *inhibits* inflammation.
2) *Analgesic action*; *decrease* PGE2 synthesis ⇨ *decrease* pain sensation.
3) *Antipyretic action*; *decrease* PGE_2 synthesis ⇨ thermoregulatory center ⇨ ↑ heat loss *by peripheral* vasodilation & sweating in *patients with* fever.

GIT; * Ulceration and GI Bleeding *

- NSAIDs *inhibit* COX-1 ⇨ *reduce* beneficial *effects* of PGs in the GIT.
- Patients with a *high* risk for GI events, NSAIDs *should be* used *concomitantly* with proton pump inhibitors or Misoprostol (*PGE_1 analogue*) to *prevent* NSAID-induced ulcers.
- *Selective COX-2 inhibitors*, have *less effect* on GI ulceration and bleeding.

Platelets; * Antiplatelet Effect *

- Aspirin inhibits the synthesis of TXA_2 by *irreversible acetylation* of COX enzyme.
- *Other* NSAIDs also *inhibit* COX *but* have a *shorter duration* of inhibitory action *because* they *cannot* acetylate COX; that is their action is *reversible*.
- The *recommended dose*; ranges from **75-325 mg/d**.
- Aspirin inhibit platelet function *within* 60 min.
- *N.B.*; *Concomitant administration* of *other* NSAIDs can *diminish* the antiplatelet effects of *low-dose* Aspirin, *increase* the risk of thromboembolic effects.
- Aspirin *not given* at *least* 1 week *before* surgery (*Antiplatelet effect of* Aspirin *lasts* 8-10 days).

Kidney; * *Decrease* Renal Blood Flow *

- NSAIDs *inhibit* COX-1 ⇨ *reduce* beneficial PGs in the Kidneys ⇨ *decrease* renal blood flow due to *constriction* of *afferent* arterioles.
- *Selective COX-2 inhibitors*, have *less effect* on renal blood flow.

Heart;

- NSAIDs with a *very high degree* of COX-1 *selectivity* (such as Aspirin); have a cardiovascular protective effect, due to *decrease* TXA_2 production *mediated by* COX-1.
- NSAIDs with a *very high degree* of COX-2 *selectivity* (such as Rofecoxib), have a *high risk* for cardiovascular events (MI and stroke), due to *decrease* PGI_2 production *mediated by* COX-2.
- Aspirin in *high dose* (> 325) *inhibit* PGI_2 production *mediated by* COX-2 and may carry a *risk* for CVS events.

Lung; * *Bronchospasm* *

- NSAIDs cause *shift* in arachidonic acid *from* COX pathway *to* LOX pathway ⇨ leukotrienes *formation* ⇨ bronchospasm *may occur* (about 10% of people taking NSAIDs).
- Leukotrienes receptor *antagonists* (Montelukast) are *used* to *overcome* NSAIDs *induced* bronchospasm.

NSAIDs *should be* used at the;
***lowest* effective dose** for the ***shortest possible* duration of therapy**

Uses of NSAIDs;

A) **Anti-inflammatory** and **analgesic**; such as; **rheumatoid arthritis (RA), osteoarthritis (OA) & gout, headache, toothache, backache, menstrual cramps (dysmenorrhea)** and **cold/flu**.

B) **Antipyretic**; **Aspirin** is *contraindicated* in **children** (*under 20 years*) as **antipyretic** *with* **viral infections** such as chickenpox or influenza), due to *increased* **risk** for **Reye syndrome**.

C) **Antiplatelets**; ***Low-dose* Aspirin** *used* in the ***prophylactic treatment* of transient cerebral ischemia and thromboembolic stroke**, and ***reduce* the incidence of recurrent MI**.

D) **Pregnancy**; ***Low-dose* Aspirin *may be beneficial*** in **pregnancies** at ***risk for*** the ***development*** of **pregnancy-induced hypertension** and **pre-eclampsia**, and in **fetuses with intra-uterine growth retardation**.

D) **Topical**;

1) **NSAIDs** may be **used topically as anti-inflammatory** and **analgesic**.
2) **Salicylic acid** is a ***keratolytic***, **used *topically*** to ***treat* corns, calluses** and **warts**.
3) **Methyl salicylate** is a **counterirritants**, **used *topically* arthritis** and **sports rubs**.

General side effects for *all* NSAIDs (*commonly dose related*);
- **CNS**: headaches, tinnitus and dizziness.
- **CVS**: hypertension, fluid retention, edema and risk for CV events.
- **GIT**: abdominal pain, dysplasia, nausea, vomiting, ulcers or bleeding.
- **Kidney**: renal insufficiency, renal failure, hyperkalemia & proteinuria.
- **Lung**: asthma.
- **Hematologic** (*rare*); thrombocytopenia and aplastic anemia.
- **Hepatic**: (*rare*) abnormal liver function tests and liver failure.
- **Skin**: rashes

Reye's syndrome; ***rare serious*** **condition** ***characterized by acute*** **encephalopathy** ***and*** **hepatic dysfunction; Reye's syndrome** ***typically affects*** **children** and **teenagers** ***after*** a **viral infection** (*flu* or *chickenpox*), and is ***associated with*** the ***use of*** **Aspirin** ***during*** the **illness**.

Pregnancy;
- ***Most*** **NSAIDs** are **category C** in the ***first*** and ***second*** **trimesters**.
- ***All*** **NSAIDs** ***should not*** (**category D**) be **used** in **third trimester**, may ***increases*** the **risk** of **pulmonary hypertension** in **newborns**, ***due to premature*** **closure of the ductus arteriosus** (**NSAIDs** ***block*** the *synthesis* of **PGE_1** & **PGE_2**, which are ***needed to*** **keep** ***open*** the **ductus arteriosus**).

Lactating women;
- ***Most*** **NSAIDs** ***displace*** **bilirubin** and are ***contraindicated*** if a **neonate** ***with*** **jaundice**.
- **Ibuprofen**, **Indomethacin** and **Naproxen** ***safe*** in **breastfeeding women**.

II) Specific Agents

Salicylates

Diflunisal (Dolobid®)

Diflunisal is a **difluorophenyl** ***analogue*** of **salicylic acid**; ***not cross*** **BBB**.
- It is ***used*** in **rheumatoid arthritis** (**RA**), **osteoarthritis** (**OA**) and **muscle pain**.
- **Diflunisal** also had the ***advantage*** of a **twice daily** ***dosage***.
- It ***reported*** causes ***less*** **GIT ulceration** and **tinnitus** *than* **Aspirin**.
- **Diflunisal** **oral ointment** is a clinically ***useful*** **analgesic** for ***painful*** **oral lesions**.

Propionic Acid Derivatives

Ibuprofen (Advil®)#	**Dexibuprofen** (Extragesic®)	**Ketoprofen** (Ketofan®)#
Dexketoprofen (Dextrafast®)	**Flurbiprofen** (Nalfon®)	**Fenoprofen** (Nalfosab®)
Loxoprofen (Roxogesic®)	**Naproxen** (Aleve®)#	**Oxaprozin** (Daypro)

All ***of these*** **drugs** ***possess*** **anti-inflammatory**, **analgesic** and **antipyretic** ***activity*** and *may be* **used** in ***chronic treatment*** of **rheumatoid** and **osteoarthritis**; because ***their*** **GI side effects** are ***generally*** ***less*** **intense** ***than*** that of **Aspirin**.

Ibuprofen; ***lowest*** **risk** of causing **GI bleeding** (*this advantage is lost at high doses*). It has ***about*** **4 times** the ***analgesic potency*** of **Aspirin**. It is ***available*** in ***multiple*** **formulations**. **Ibuprofen** and **Indomethacin** are ***effective*** in ***closing*** **patent ductus arteriosus** ***in*** **preterm infants**.

Dexibuprofen is the ***active*** **dextrorotatory** ***enantiomer*** of **Ibuprofen**.

Ketoprofen; ***higher*** **COX-1 selectivity** and **LOX** (*lipoxygenase*), ***less*** **potent** ***than*** **Indomethacin**, ***maximum dose*** is **300 mg/day**.

Dexketoprofen is the ***active*** **dextrorotatory** ***enantiomer*** of **Ketoprofen**.

Flurbiprofen is ***available*** in an ***ophthalmic formulation*** for ***inhibition of*** **intraoperative miosis**, as well as it is also ***orally*** for ***available*** **arthritis**.

Naproxen; It is the ***only*** **NSAID** presently as a ***single*** **enantiomer**, has a ***lowest*** **risk** of **CV events** (*but not without risk*), ***intermediate*** **risk**. It ***may be used alone*** in **menstrual migraine** ***prophylaxis*** or in ***combination*** (**Sumatriptan/Naproxen Treximet®**) in **migraine** ***acute attack***, ***like other*** **NSAIDs** used for ***mild*** to ***moderate*** **pain** & for **rheumatoid**, **osteoarthritis** and **primary dysmenorrhea**. It has been associated with ***pseudoporphyria*** and ***photosensitivity*** in ***some patients***.

Oxaprozin is a ***unique*** *among the* **propionic acid group** of **NSAIDs**, ***because*** it has a ***rapid*** **onset of action** and a ***prolonged*** **duration of action** (half-life 50–60 hours). It also has ***mild*** **uricosuric properties** and is ***more useful*** in **gout** ***than*** some ***other*** **NSAIDs**.

Acetic Acid Derivatives

Indomethacin (Indocid®)#	**Diclofenac** (Voltaren®)#	**Aceclofenac** (Bristaflam®)#
Ketorolac (Ketolac®)#	**Etodolac** (Etodine®)	**Sulindac** (Clinoril®)
Tolmetin (Rumatol®)	**Nabumetone** (Nabuxan®)	

Indomethacin; is a ***very potent*** ***non-selective*** **COX inhibitor** (***one*** **of the** ***most potent*** **NSAIDs**), It is also a ***more*** **potent** ***antipyretic*** than *either* **Aspirin** or **Paracetamol**, and it has ***about*** **10 times** the ***analgesic potency*** of **Aspirin** and about ***6 times*** the ***analgesic potency*** of **Ibuprofen**. **Indomethacin** may also ***inhibit*** **phospholipase A** and **C**, ***reduce*** **neutrophil** ***migration*** and ***decrease*** **T-cell** and **B-cell proliferation**, *so it is* **mainly** ***used for*** **acute gout** *and* **rheumatoid arthritis**. **Indomethacin** are ***effective*** in ***closing*** **patent ductus arteriosus** ***in*** **preterm infants**. It has been ***used for*** ***many*** **other conditions**, ***ophthalmic preparation*** is efficacious for **conjunctival inflammation** and to ***reduce*** **pain** ***after*** **traumatic corneal abrasion**, **Indomethacin** ***oral rinse*** are ***used for*** **gingival inflammation**. **Indomethacin** has ***moderate*** ***high*** **risk** of **CV events**, has a ***very high*** **risk** of **GI complications** and ***many*** **CNS side effects**. [**Indomethacin suppositories** ***should be used*** with ***extreme caution*** in **CHILDREN** ***younger than*** **15 year old** (*safety and effectiveness in these children have not been confirmed*).]

Diclofenac is **one** of the ***most potent*** **NSAIDs**, is ***more potent*** **anti-inflammatory** *than* **Indomethacin** and **Naproxen**. **Diclofenac** may also be a ***unique member*** of the **NSAIDs**, it ***inhibits*** the **lipoxygenase pathways** and also may ***inhibit*** **phospholipase A2** with ***higher*** **COX-2 selectivity**, it ***used widely*** in the treatment of **pain** ***associated with*** **renal stone** (*first choice NSAID for renal colic*). It has been ***used for*** ***many*** **other conditions**, ***very high*** **risk** of **CV events** and ***moderate*** **risk** of **GI complications**. [*Don't waste your time to differentiate between diclofenac sodium and potassium*], [**Diclofenac suppositories** ***should be used*** with ***caution*** in **CHILDREN** ***younger than*** **3 year old** (*safety & effectiveness in these children have not been confirmed*). **Diclofenac** & **Sulindac** cause ***elevation*** of **liver enzymes**, ***increased*** **risk** of **liver toxicity** *compared with* ***other*** **NSAIDs**.

Aceclofenac is the **glycolic acid ester** of Diclofenac. The ***incidence*** of GI complications of Aceclofenac has been reported to be ***significantly lower than*** that of the ***other*** **NSAIDs**, for instance, **2-folds** ***lesser than*** Naproxen, **4-folds** ***lesser than*** Diclofenac, and **7-folds** ***lesser than*** Indomethacin.

Ketorolac is the ***most potent*** and ***most effective*** NSAID analgesic, with **efficacy** ***comparable to*** **opioids** (The analgesic effect of 30 mg of Ketorolac is similar to 10 mg of Morphine), it ***used widely*** in ***short-term treatment*** of ***moderately severe pain*** (*usually after surgery*), due to ***highest*** ***incidence*** **of side effects**, Ketorolac ***should not use for more than 5 days*** (**oral**, **parenteral** and **intranasal**), the **oral formulation** is ***only*** to be ***used as*** **continuation** to **IV** or **IM therapy**.

Etodolac is a *potent* NSAIDs, The *anti-inflammatory* potency of Etodolac was found to lie ***between*** that of Sulindac and Piroxicam. Etodolac has a *low incidence* of GI complications.

Sulindac is an *analog* of Indomethacin (*sulfoxide prodrug*), ***developed as*** a *less* toxic, with *similar* anti-inflammatory *potency*, Sulindac is *unique* NSAIDs in ***lesser inhibiting PGs synthesis*** in the **kidneys** (Kidneys can ***deactivate*** the **active metabolite** of Sulindac be ***reoxidize*** the **sulfide** to the ***inactive*** *sulfoxide prodrug*) So, it may be *one* of the *safest NSAIDs* drugs for ***treating*** **osteoarthritis** in ***older people***. Like Diclofenac, Sulindac may cause *elevation* of liver enzymes.

Tolmetin is a NSAIDs with a short half-life (1-2 hours) and *used in* **osteoarthritis** and **rheumatoid arthritis** and **juvenile rheumatoid arthritis**, with *mild* GI complications and *less* tinnitus.

Nabumetone is a non-acidic NSAID, is a *prodrug* which ***contains*** the **non-acidic ketone**, which is ***quickly*** **metabolized to** give the **naphthyl-acetic acid derivative** (it was designed to ***decrease*** some of the **GI problems** normally associated with the acidic functionality of these agents), ***long*** **half-life** (*more than 24 hours*), is a *more potent* ***inhibitor*** of **COX-2**, is *very similar* to **other NSAIDs**, with *less* GI complications and *less* risk of CV events (Effects of Nabumetone on blood pressure control in hypertensive patients on ACE inhibitors is also good).

Enolic Acid Derivatives (Oxicams)

Piroxicam (Feldene®)#	**Tenoxicam** (Epicotil®)#	**Lornoxicam** (Xefo®)#
Meloxicam (Mobic®)#		

Piroxicam is an oxicam (***nonselective COX inhibitor***), at ***high concentrations*** also ***inhibits*** **polymorphonuclear leukocyte migration**, ***decreases*** **oxygen radical production**, and ***inhibits*** **lymphocyte function**. Its ***long*** **half-life** (*once-daily*), ***very high*** **risk** of **GI complications**.

Tenoxicam is an oxicam, there is ***no significant difference*** between Tenoxicam and Piroxicam (*some studies found* Tenoxicam ***more*** **effective** and ***better*** **tolerated** than Piroxicam).

Lornoxicam is *unique among the* enolic acid derivatives of **NSAIDs** in that it has a *rapid onset* of **action** and a *relatively short* **half-life** (3-4 hours).

Meloxicam has a ***higher*** **COX-2 selectivity** (it was initially introduced as a selective COX-2 inhibitor), it has a ***fewer*** **risk** of **GI complications** with ***high moderate*** **risk** of **CV events**. It is ***available in*** **7.5mg** and **15mg doses**. ***October, 2015***; FDA approved a ***new formulation*** of Meloxicam (Vivlodex®) contains *microparticles* of Meloxicam (using Solu-Matrix Fine Particle Technology) to *reduce* **dose** (5mg and 10mg) and *decrease* **toxicity** for the ***treatment of*** **osteoarthritis**.

Droxicam is a *prodrug* of Piroxicam.

Long-term use of Oxicams and Ketorolac is ***associated with*** an *increased* **risk** of **chronic kidney disease**.

Fenamic Acid Derivatives

Mefenamic Acid (Ponstan®)# | **Meclofenamic Acid** (Meclomen®)

Tolfenamic Acid (Fastgraine®)

Mefenamic acid is a ***non-selective* COX inhibitors** (**COX-2 >> COX-1**) and also *may* ***act as* prostaglandins receptor *antagonist***, these effects may also be ***responsible for*** its ***effectiveness*** in the ***treatment of* primary dysmenorrhoea**. **Mefenamic acid** is also ***used in* osteoarthritis** and **rheumatoid arthritis**.

- **Meclofenamate** or **Meclofenamic acid** as **Mefenamic acid** ***used for*** treatment of **dysmenorrhoea**, **osteoarthritis** and **rheumatoid arthritis**.
- **Tolfenamic acid** is ***used to*** treat **migraines** and **severe headaches**, It is available in some countries for humans and for animals.

Other Agents

Nimesulide (Sulide®)#

Nimesulide is a ***sulfonanilide derivatives***, is a ***relatively* COX-2 *selective***, it has ***analgesic***, ***antipyretic*** and **anti-inflammatory effects**. It has ***low incidence*** of **GI complications**.

- It ***primary used*** as ***short term*** in the ***treatment*** of ***acute* pain**, and ***primary* dysmenorrhea**.

Nimesulide ***should not*** be ***taken*** as **long-term**, (*like* **arthritis**), ***due to*** its ***association with*** an ***increased risk*** of **liver toxicity**.

- ***Due to risk*** of **hepatotoxicity**, **Nimesulide** has been ***withdrawn from* market** in ***several* countries**.

Metamizole (Dipyrone) (Novalgin®)#

Metamizole (Dipyrone) is a ***non-opioid analgesic drug***.

Metamizole is an ***ampyrone sulfonate*** (***pyrazolone derivatives***) ***analgesic***, ***antispasmodic*** and ***antipyretic***. ***Like* Paracetamol**, it has ***minimal* anti-inflammatory effects**, this agent is ***still* incorrectly *classified as*** a **NSAID**.

It was ***first used*** in1922 (Novalgin®) and for ***many years*** it was available **OTC** in ***most countries***, ***until* several reported cases** of **Agranulocytosis**, *but it is still available OTC in some countries.*

Selective COX-2 Inhibitors (Coxibs)

Celecoxib (Celebrex®)#	**Rofecoxib** (Vioxx®)
Valdecoxib (Bextra®)	**Parecoxib** (Dynastat®)
Etoricoxib (Arcoxia®)	**Lumiracoxib** (Prexige®)

Celecoxib is a ***reversible selective* COX-2 inhibitor** (about 10–20 times more selective for COX-2 than for COX-1). **Celebrex®** was one of Pfizer's ***best-selling drugs***.

Celecoxib is ***approved for*** the treatment of **rheumatoid arthritis**, **osteoarthritis**, and ***acute mild*** to ***moderate* pain** (has similar efficacy to NSAIDs in the treatment of pain).

Celecoxib is ***associated with* less GI complications *than* other NSAIDs**. ***Like other NSAIDs***, it has a ***similar* risk** of **CV events**, it has a **sulfonamide *structure*** (***contraindicated*** for ***patients*** with **sulfa allergy**). **Celecoxib *metabolism*** is ***primarily by* CYP2C9**, **Fluconazole** and **Fluvastatin**, may ***increase*** serum levels of **Celecoxib**.

Rofecoxib; **Merck & Co.** ***withdrew* Vioxx®** from market **voluntarily**, due to an ***increased* risk** of **CV events**; **heart attack** and **stroke** (**Rofecoxib** inhibits COX-2 80 times more than the COX-1).

- **Valdecoxib**; **Pfizer** ***withdrew*** **Bextra**® from the US market on recommendation **by the FDA** due to an ***increased*** **risk** of **CV events**.
- **Parecoxib** is a ***water-soluble*** and ***injectable*** ***prodrug*** of **Valdecoxib**, It is marketed in the Europe.
- **Etoricoxib** is ***approved in some countries*** (*not in the US*) by **Merck & Co.**
- **Lumiracoxib** is still sold in ***few countries*** by **Novartis**.

NSAIDs *should be* used *at the*;

 # *Lowest effective* dose *for the*;

 # *Shortest possible* duration of therapy.

➢ Special Populations:-

Population or Disease State	Preferred Agents
- Pregnancy	- 1st, 2nd trimesters; *Most* NSAIDs are Category C - 3rd trimesters; *All* NSAIDs are Category D
- Patent Ductus Arteriosus (PDA)	- Indomethacin or Ibuprofen.
- Primary Dysmenorrhoea	- Mefenamic acid, Ibuprofen and Naproxen.
- High CV Risk (Coronary Diseases)	- *All* NSAIDs are *should be avoided*. - *If must be used*, Naproxen appears to be the *least* CVS risk.
- High GI Risk (ulcers or bleeding)	- *All* NSAIDs are *should be avoided*. - *If must be used*, Ibuprofen and Celecoxib appears to be the *least* GI risk and used as co-therapy with Misoprostol or *proton pump inhibitors* (e.g. Omeprazole).
- Asthma and COPD	- NSAIDs can *prescribed to* patients with asthma who *have no previous* history of NSAID-associated symptoms. - *About* 8-20% of adult asthmatics *experience* bronchospasm *following ingestion* of NSAIDs. - People who *have had* a *hypersensitivity reaction* to a NSAID *should avoid all* NSAIDs.
- Renal Diseases	- *All* NSAIDs are *should be avoided* in *people* with Chronic Kidney Disease (CKD). - *If must be used*, Sulindac, Aspirin and Ibuprofen appears to be the *least* nephrotoxic risk.
- Renal Stone (Renal Colic)	- Diclofenac (*strongest in effectiveness in renal* colic).
- Children	- Ibuprofen is the *most appropriate* NSAID *for* children.

- **COX-Inhibiting Nitric Oxide Donators** (**CINODs**); Are a new class of non-steroidal anti-inflammatory drug (NSAID) with a nitric oxide (NO)-donating moiety by improving vascular safety, most likely via vasodilatation such as Naproxcinod (NO-naproxen).

Paracetamol

Paracetamol or Acetaminophen (Panadol®)# (Tylenol®)# (Calpol®)#

- Acetaminophen is the name **generally** ***used in*** the **US** and **Japan**, Paracetamol is used in ***internationally***.
- ***Both*** *come from* a **chemical name**;
  - Para-acetylaminophenol; **Acetaminophen**.
  - Para-acetylaminophenol; **Paracetamol**.

Tylenol® is an ***American*** **brand** of Acetaminophen; ***derived from*** the chemical name; N-acetyl-para-aminophenol (APAP) (or para-acetylaminophenol); Tylenol®.

Panadol® is one of GlaxoSmithKline's (GSK) trade names for Paracetamol.

Calpol® is a brand of Paracetamol children's medicine sold in the UK & other countries

It is ***typically by*** **oral route** ***but*** is ***also available*** **rectally** and **intravenously** (perfalgan®).

- **After** ***more than*** **100 years**, the ***exact*** ***mechanism*** of Paracetamol is ***still*** **unclear**.

Paracetamol is an **analgesic/antipyretic** ***of choice*** for;
  - **Children**, with **viral infections** or **chickenpox**; Due to the risk of Reye syndrome with aspirin.
  - **Pregnancy** and **breastfeeding women**.
  - ***Patients with*** **CV risk** or **GI complications**.
  - **Asthmatic patients**.

Therapeutic Uses;
  - **Fever**, **Pain** (***mild*** *to* ***moderate pain***)
  - **Headaches**; Paracetamol in ***combination with*** Caffeine is ***highly effective*** in treatment of **tension** or **migraine headache**.
    - Caffeine ***accelerates*** **absorption** and ***enhances*** the **analgesic effect** of Paracetamol.
  - **Osteoarthritis**; In 2012 the American College of Rheumatology ***recommends*** Paracetamol with ***other*** **several options** for ***people with*** **osteoarthritis**.

Dose;
  - *Medicines and Healthcare products Regulatory Agency (MHRA) guidelines for IV Paracetamol dosing (most accurate and updated);*

Weighing	Dose per administration	Max. daily dose
< 10 kg	7.5 mg/kg	30 mg/kg
10-33 kg	15 mg/kg	60 mg/kg (max. 2gm)
33-50 kg	15 mg/kg	60 mg/kg (max. 3gm)
>50 kg	1 gm	4 gm

 # N.B.; - ***Maximum*** ***single*** ***adult dose***: **1 gm** (oral or IV).
- ***Minimum*** ***dosing interval***: ***every*** **4 hours**.
- ***Acute*** ***ingestion*** of **15 g** of Paracetamol ***may be*** **fatal**, **death** being ***caused by*** ***severe*** **hepatotoxicity**, *sometimes associated with* **acute renal tubular necrosis**.

Toxic Dose; ***Acute*** ***ingestion***; > 150-200 mg/kg in children or 7 g in adult is considered potentially toxic.

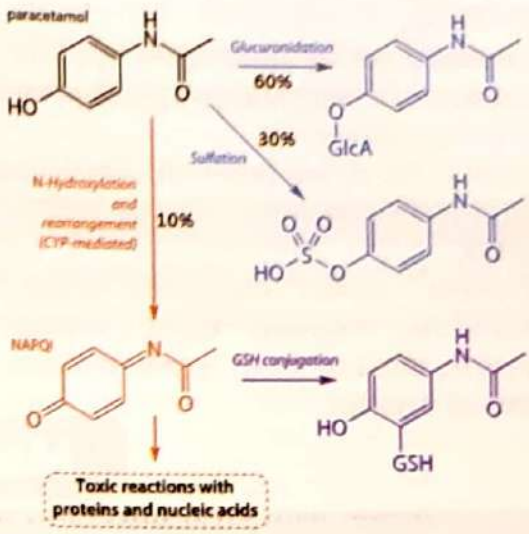
- ***Severe renal impairment*** (CrCl less than 30 mL/min); ***Longer*** **dosing intervals** and a ***reduced*** **total daily dose**.
- ***Severe hepatic impairment***; Paracetamol is ***contraindicated***.

Mild to ***moderate*** **hepatic impairment**: ***Used with*** **caution** (***reduce*** **total daily dose** and/or ***used in combination with*** **glutathione analogues** such as; Methionine (is an essential amino acid which serves as a precursor for the amino acid Cysteine which will be incorporated in glutathione "GSH" synthesis.

At normal therapeutic doses, **Paracetamol** is ***virtually free*** of ***significant*** **side effects**. *With large doses*; **Hepatic necrosis** (a ***very serious*** and ***potentially*** **life-threatening condition**) ***may occur***.

☛ ***Metabolism in therapeutic dose***;

- *About 60%* of **Paracetamol** by **glucuronidation** and ***about 30%*** by **sulfonation** ⇨ to ***inactive*** **products**.
- *About 10%* by **cytochrome P450** (CYP3A4 and CYP2E1) ⇨ to **alkylating metabolite** ***known as*** **NAPQI** (N-acetyl-p-benzoquinone imine) ⇨ ***Highly toxic <u>but</u> rabidly*** **detoxified** by ***irreversibly conjugated*** with the **sulfhydryl groups** of **glutathione**.



☛ ***Metabolism in toxic dose***;

- ***High dose*** of **Paracetamol** cause ⇨ ***<u>saturation</u>*** of **glucuronidation** ⇨ ***shunting metabolism*** to **cytochrome** ⇨ ***increase amount*** of **NAPQI** ⇨ **glutathione system** ***not able*** to **detoxify NAPQI** ***due to depletion*** of **–SH group** ⇨ **Acute hepatic necrosis**.

- ***Clinical manifestation during toxicity***;
  - **Phase I** (during 24 hours);
    - **Nausea, vomiting** and ***may be*** **asymptomatic**.
    - ***Normal*** **hepatic transaminases ALT** and **AST**.
    - ***Normal*** **hepatic transaminases ALT** and **AST**.
  - **Phase II** (24-72 hours after ingestion);
    - Signs of ***liver damage*** are ***increased*** e.g. **right upper quadrant pain** and ***mild*** **increase** in **ALT** and **AST**.
  - **Phase III** (3-4 days after ingestion);
    - ***Symptoms of*** **hepatic necrosis**; **hepatic encephalopathy, jaundice, coagulopathy** and **hypoglycemia**.
    - **Acute renal failure** ***may*** **develops**.
    - **Death** ***may occur*** from **multiorgan** ***failure***.
  - **Phase IV** (3-4 weeks) (**recovery phase**):
    - **Clinical recovery** may take up to **21 days**; however, ***complete*** **hepatic histologic** ***recovery*** requires ***several*** **months**.

Antidote;

- *N*-acetylcysteine (NAC) is ***nearly*** **100% hepatoprotective** ***within*** **8 h.** ***after*** an ***acute*** **Paracetamol ingestion**;
  - Oral NAC; ***loading dose*** of 140 mg/kg, ***followed by*** 70 mg/kg, every 4 hours for 17 doses.
  - IV NAC; - ***loading dose***: 150 mg/kg IV in 200 mL of 5% dextrose and infuse over 1 h.
    - ***Dose 2***: 50 mg/kg IV in 500 mL 5% dextrose over 4 h.
    - ***Dose 3***: 100 mg/kg IV in 1000 mL 5% dextrose over 16 h.

Opioid Analgesics

- **Opioids**; are **natural**, **semisynthetic**, or **synthetic compounds** that **produce morphine-like effects**.
All opioids act by binding to specific **opioid receptors** to **produce effects** that mimic the action of **endogenous opioid peptide neurotransmitter** (**Endorphins**, **Dynorphins** and **Enkephalins**).
- **Opium**; is the **dried latex obtained from** the **opium poppy** (***Papaver somniferum***).
- **Opium latex**; contains **Morphine**, may used chemically to produce **Heroin** and **other opioids**.
- **The term "opioid"** originated in the 1950s. It combines **"opium"** + **"-oid"** meaning **"opiate-like"** ("opiates" being morphine and similar drugs).
- **Narcotic**; derived from words meaning **numbness** or **sleep**, is **now** a **legal term** that **refers to opioids**.

Morphine

Morphine (MS Contin®)#

- **Morphine** (***prototype***) is a **phenanthrene** (*chemical class*) ***strong* μ receptor *agonist***.
* **Clinical Use of Opioid** (**Morphine** and ***other opioids***) **Analgesics** *
  1) **Analgesia** (***relief* pain *without* loss of consciousness**).
  2) **Acute Pulmonary Edema**.
  3) **Cough Suppression**.
  4) **Diarrhea**.
  5) **Preanesthetic Medication**.
Side effects; **Tolerance**, **dependence** and **acute side effects** (**Respiratory depression**, **nausea**, **vomiting**, **allergic reactions**, **bronchoconstriction** and **constipation**).

Specific Agents

Strong Agonists

Phenanthrenes

Hydromorphone (Dilaudid®)#

Hydromorphone is a ***semi-synthetic* Morphine *derivative***, is ***hydrophilic like***, ***more* water soluble**.
Oral* Hydromorphone** (*usual oral dose* 1.5 mg) is *approximately* **8-10 times *more potent than **Morphine** (*usual oral dose* 10 mg).
Extended-release (*once-daily*) **formulation** of **Hydromorphone** (**Exalgo®**) is *available*.
- **Morphine** are ***contraindicated*** in **renal failure**, while **Hydromorphone** is **used *with caution***.

Oxymorphone (Opana®)#

- **Oxymorphone** is a ***semi-synthetic* Morphine *derivative***, is ***more* lipid *soluble*** than **Morphine**, resulting in a ***rapid onset of action*** when given in **oral route**.
- **Oxymorphone**, ***Parenterally***; *approximately* **10 times *more potent*** than **Morphine**.
  Orally; *approximately* **3 times *more potent*** than **Morphine**.
Extended-release (*once-daily*) **formulation** of **Oxymorphone** (**Opana® ER**) is *available*.

Methadone (Dolophine®)#

- Methadone is a *synthetic* **opioids, structurally *unrelated*** to Morphine.
- *Uses*; - **Pain** (neuropathic pain is ***included*** due to ***non*-opioid mechanisms**).
  - **Control withdrawal symptoms of opioid dependency** (Methadone Maintenance Treatment; MMT), induced ***less*** **euphoria, tolerance & physical dependence** develop ***more slowly*** & **withdrawal symptoms** are ***milder*** than Morphine.
- *N.B.*; - Methadone can ***prolong*** the **QT interval**.

Meperidine or Pethidine (Demerol®)#

- Meperidine or Pethidine is a ***synthetic*** **opioid, structurally *unrelated*** to Morphine, but ***related*** to Atropine, it is ***very*** **lipophilic** and has *anticholinergic effects*, ***increased*** **incidence** of **delirium**.
- It is ***metabolized to*** an **active metabolite** Normeperidine (***neurotoxic*** and ***serotonergic effects***).
- It is a **κ *agonist*** and also has **local anesthetic *effects***.

It is the ***preferred*** **opioid** in *some countries* ***used*** in **labour** and **delivery**.

- *Due to* **anticholinergic effects**, It is preferred in **pain *associated with*** **biliary spasm** or **renal colic**.
- Serotonin syndrome has also been ***reported*** in patients receiving both Meperidine and **SSRIs**.

Fentanyl (Duragesic®)#

Fentanyl is **one** of the *most widely synthetic opioids* **used**.

- It is *approximately* **80-100 times *more* potent *than*** Morphine and *approximately* **40-50 times *more* potent *than*** Heroin, it is ***highly*** **lipophilic** and has a ***rapid*** **onset** and ***short*** **duration** of **action**.

Common Routes and Formulations;

- *IV injection*; ***duration***; 30-60 minutes, ***used for*** **adjunct *to an*** **anaesthetic** (**analgesic** and **sedative effects**) and **analgesia** for ***moderate*** and ***severe*** **pain**.
- *Transdermal patch*; ***duration***; 72 hours, ***used for*** **chronic pain**.
- *Transmucosal*; Fentanyl **lozenges** (Actiq®), ***duration***; 1-2 h, ***used in*** **breakthrough pain** (*sudden flare of pain*), e.g. **breakthrough cancer pain (BTCP), nasal spray, sublingual spray, sublingual tablets** and **buccal tablets** are **transmucosal *drug delivery*** and are also ***available*** and ***used*** in **breakthrough pain**.

- Fentanyl may **produce *more prolonged* respiratory depression** than other opioid analgesics, (*especially* Fentanyl **skin patches**).
- Fentanyl is ***metabolized to*** **inactive metabolites** by the **CYP3A4, CYP3A4 *inhibitors*** can ***potentiate*** Fentanyl **effects**. ***Inactive*** **metabolites** are *eliminated* **renally**.
- Fentanyl appears to be *safe* to ***use in*** **renal failure**.

Alfentanil (Alfenta®) | Sufentanil (Sufenta®) | Remifentanil (Ultiva®)

- Sufentanil, a *potent analgesic* (5-10 times more potent than Fentanyl).
- **These agents** are ***mainly*** **used** for **adjunct** *to an* **anaesthetic** (analgesic and sedative effects) ***during*** **surgical procedures**. Sufentanil appears to be *safe* to ***use in*** **renal failure**.

Mild to Moderate Agonists

Codeine

Codeine (3-Methyl-Morphine) is a *natural* **opioid alkaloid** (2% of opium) and is a *weak agonist*. Codeine is ***converted to*** Morphine by **CYP2D6 enzyme** in the liver.
It is *typically* ***used*** to ***treat*** ***mild*** to ***moderate*** **pain**, and ***commonly*** used in ***combination with*** Paracetamol (Tylenol® No.3) or Aspirin (Co-codaprin®).
Codeine exhibits ***good antitussive activity*** at **doses** that ***do not cause*** **analgesia**.

Hydrocodone (Lortab®) | Oxycodone (Oxycontin®)

- Hydrocodone and Oxycodone are *semi-synthetic* Codeine ***derivative***. Hydrocodone is ***stronger than*** Codeine (about 50%), while Oxycodone is ***stronger than*** Hydrocodone (about 50%).
- Hydrocodone & Oxycodone are used to treat ***moderate*** to ***severe*** **pain**, and ***sometimes*** used in ***combination with*** **NSAIDs**. ***Extended release*** **formulations** are available.

Partial Agonists and Mixed Agonist-Antagonist

Buprenorphine (Subutex®)#

- Buprenorphine is a *partial agonist*, at **μ receptor**, and *antagonist* at **κ & δ**.
It **cause** ***mild*** **withdrawal symptoms** and ***little*** **sedation**, **respiratory depression** or **hypotension** ***even at*** **high doses** (*advantage over* Methadone), so it is ***widely used*** to ***treat*** **opioid addiction** (**opioid detoxification**) or **opioid dependence**, and may ***use*** to treat ***moderate*** to ***severe*** **pain**,
Routes of administration; **Injection** and **transdermal patch** are ***indicated for*** **pain**, while **sublingual tablet** is ***indicated for*** **opioid dependence**.
Buprenorphine also **available** in a ***combination with*** Naloxone (***opioid antagonist***) (Suboxone®) at a 4:1 ratio, **sublingual tablet** is ***used*** for **opioid dependence** (*see withdrawal symptoms*).

Nalbuphine (Nubain®)#

- Nalbuphine is a *mixed agonist-antagonist*.
It is ***used*** **parenterally** ***for***; ***moderate*** to ***severe*** **pain**, ***supplement*** to **balanced anesthesia** (preoperative and postoperative analgesia) and **obstetrical analgesia**.

Butorphanol (Stadol®)#

- Butorphanol is a *mixed agonist-antagonist*.
- It ***produces*** **analgesia** ***equivalent to*** Nalbuphine & Buprenorphine ***but*** it ***produce more*** **sedation**.
Butorphanol **intranasal spray** is ***indicated for*** **migraine**, Butorphanol **injection** is ***indicated for moderate*** to ***severe*** **pain**, ***supplement*** to **balanced anesthesia** and **obstetrical analgesia**.

Pentazocine (Talwin®)#

- Pentazocine is a *mixed agonist-antagonist*, **κ receptor** ***agonist*** & ***weak*** **μ receptor** ***antagonist***.
Pentazocine **injection or oral** ***alone*** (Talwin®) or **oral** ***combination with*** Naloxone (Talwin® NX) (Naloxone not absorbed orally *but* used to prevent drug abuse if injected), is ***indicated for moderate-severe*** **pain**, ***supplement*** to **balanced anesthesia** & **obstetrical analgesia**.
- ***High*** **doses** ***increase*** **blood pressure** and can cause **hallucinations** (**psychotomimetic** ***effects***; due to its ***action*** at the **κ receptors**).
- Pentazocine **should** be ***used with*** **caution** in ***patients with*** **coronary artery disease**.

Other Opioid Analgesics

Tramadol (Contramal®)#

- Tramadol is a μ receptor *agonist* and norepinephrine/serotonin reuptake *inhibitor*.
- It is *metabolized by* CYP2D6, CYP3A4 and CYP2B6, *leading to* an active metabolites with a *much higher* affinity for the μ receptor than Tramadol, metabolites are *eliminated primarily* by the kidneys (dose *reduction* in renal and hepatic *impairment*).

It is *used for* *moderate* to *moderately severe* pain, for *severe pain* it is *less* effective than Morphine.

- Its respiratory depressant *activity* and constipation is *less than* that of Morphine.

Toxicity of Tramadol are *associated with* seizures (*contraindicated* in patients with a history of epilepsy and for use with *other* drugs that *lower* the seizure threshold).

Risk of *serotonin syndrome*, are *increased* *especially* if selective serotonin reuptake inhibitor (SSRI) antidepressants are *co-administration* with Tramadol.

Tramadol has been *associated with* *misuse* (*delay* ejaculation and wakefulness) and *abuse*.

Long-term use of *high* doses of Tramadol will *cause* *dependence* and a *withdrawal syndrome*.

- Tramadol and *active* metabolites may be *detected* in the blood to *monitor for* abuse.
- *Fatalities* with Tramadol *overdose* *have been* reported.

In 2014, Tramadol has been *placed into* Schedule IV.

Tapentadol (Nucynta®)#

- Tapentadol is a *newer* analgesic was *approved by* FDA in 2008.
- *Mechanism of action*; *modest* μ receptor *agonist*, *significant* norepinephrine reuptake *inhibitor* (NRI), and *weak* effects on serotonin reuptake. *Metabolism*; Tapentadol metabolites are *inactive*.

It is *used for moderate* to *severe* pain, it is also *indicated for* diabetic neuropathy pain (NRI).

#Tapentadol carries *risk for seizures* and for the *development of serotonin syndrome*.

- *In 2015*, Nucynta® *annual sales* are $166 million.
- Tapentadol *not* be placed *under* international control *but* remain *under* surveillance.

Black box warning; *May cause serious*, *life-threatening* respiratory depression and *risk for* addiction, abuse or misuse.

Other Opioids Not Used as Analgesics

Dextromethorphan

- Dextromethorphan (DXM or DM) is the *dextrorotatory* of Levomethorphan, which is the *methyl ether* of Levorphanol, *both* opioid analgesics.
- It is *free* of addictive properties and produces *less* constipation than Codeine.
- It is *one* of the active ingredients in *many* over-the-counter (OTC) cold and cough medicines.

The *primary use* of Dextromethorphan is as a cough suppressant (*antitussive*).

Usual antitussive dose is 15-30 mg 3 or 4 times *daily*.

At *high* doses Dextromethorphan acts as an NMDA receptor *antagonist* (Hallucinations).

- It is *should not* be taken with MAO inhibitors due to the *potential for* serotonin syndrome.

Diphenoxylate

- **Diphenoxylate**, is an **opioid drug** act as ***antiperistaltic drug*** (***Antimotility Agent***).
Diphenoxylate + **Atropine** (**lomotil**®) ***combination used*** to treat ***severe*** **diarrhea**.

Loperamide (Imodium®)#

Loperamide, is an **OTC opioid drug** act as ***antimotility Agent***.
- **Loperamide** is a **μ receptor** ***agonist*** on the **large intestine**.
Loperamide ***does not cross*** the **BBB**, ***concurrent*** **administration** of **P-glycoprotein** ***inhibitors*** (*mechanism prevents* **Loperamide** *from crossing the BBB*) such as **Quinidine** allow **Loperamide** to cross the BBB, and may produce **respiratory depression**.
- **Loperamide** is effective for the ***treatment*** of a ***many types*** of **diarrhea** (acute nonspecific diarrhea, traveler's diarrhea, irritable bowel syndrome and chronic diarrhea in inflammatory bowel disease).
Drug avoided in ***high*** **fever** and if **stool** is ***bloody*** or ***black***.
It *may* ***increase*** **risk** of **toxic megacolon** (*acute colonic distension*) and **paralytic ileus**.

Opioid Antagonists

Naloxone (Narcan®)#

Naloxone is a ***pure opioid antagonist***, it is used to ***reverse*** the **coma** and **respiratory depression** of **opioid overdose**.
- ***Onset***; ***Within*** **30 seconds** of **IV injection** of **Naloxone**, the **respiratory depression** and **coma** of **morphine** **high doses** are ***reversed***.
- ***Half-life***; **30-81 minutes**, ***shorter than*** the **half-life** of ***some*** **opiates**, ***repeat*** **dosing** ***may require***.
- It is *primarily* ***metabolized*** by the **liver** and ***excreted*** in the **urine**.
- ***In 2014***, the **US FDA** ***approved*** **Evzio**®, a **hand-held automatic injector** **Naloxone**, can be used in non-medical settings such as in the home.
- ***In 2015***, the **US FDA** ***approved intranasal*** **spray** **Naloxone**, ***easy-to-use*** to ***treat*** **opioid overdose**.
- The ***major uses*** of **Naloxone** is in the ***treatment*** of **acute opioid overdose**.
- It may be ***useful*** as an ***adjunctive agent*** in the ***management*** of **septic shock**.
N.B.; **Naloxone** ***cannot be*** **absorbed** ***orally***, so it is *commonly* ***combined*** with a number of oral opioids, including **Buprenorphine** (**Suboxone**®) and **Pentazocine** (**Talwin NX**®), ***so*** that when **taken orally** just the **opioid** has an **effect**; ***but*** if ***misused*** by **injecting**, the **Naloxone** ***blocks*** the **effect** of the **opioid**.

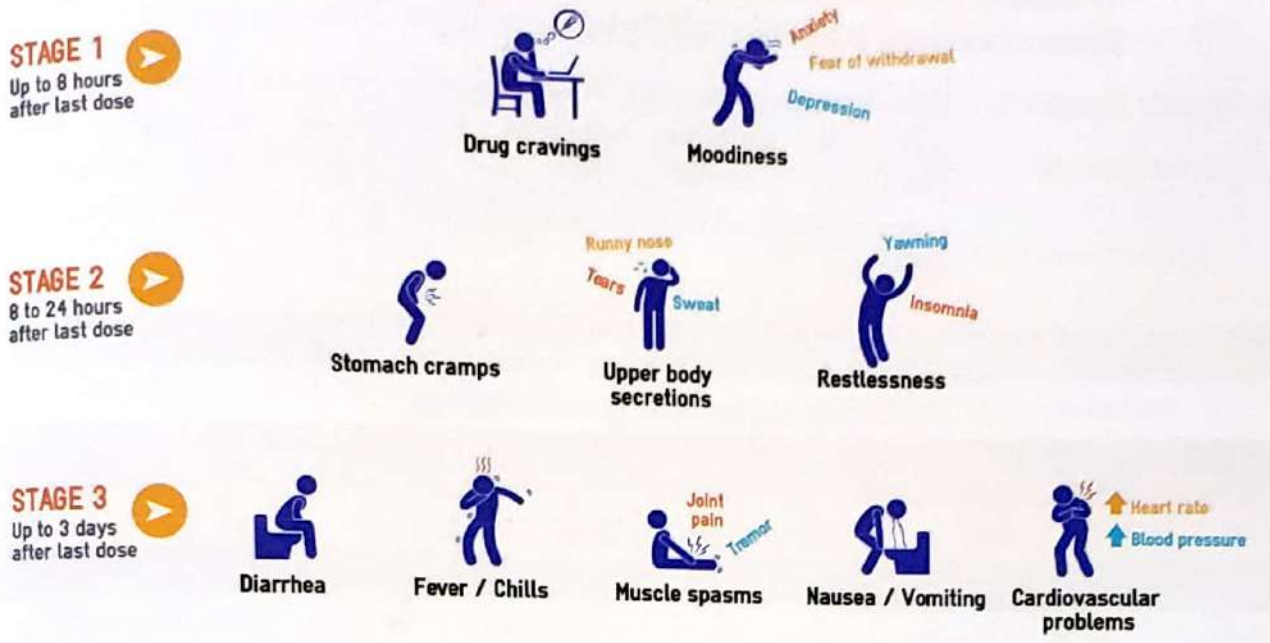
Naltrexone (Anarcol®)#

- **Naltrexone** has **actions** ***similar to*** those of **Naloxone**.
It is ***orally active*** and has a ***longer duration of action*** than **Naloxone** (***single*** **oral dose** of **Naltrexone** ***blocks*** the ***effect*** of ***injected*** **Heroin** for ***up to*** **24 hours**).
It is ***used primarily*** in the ***management*** of **alcohol dependence** (**alcoholism**, *unknown mechanism*) and **opioid dependence**. **Naltrexone** in ***combination with*** **Clonidine** (and sometimes with **Buprenorphine**) is ***used for*** **rapid opioid detoxification**.
- **Naltrexone** has been reported to cause **hepatotoxicity** (*dose-dependent*).

Nalmefene (Revex®)#

- Nalmefene, is a *derivative* of Naltrexone (*similar* in both **structure** and **activity**) *but* is **available** *only* for IV *administration*, *but* has a *longer* **half-life**, and *no* **dose-dependent liver toxicity**.
- It is *used* in the *management* of **alcohol dependence** and **opioid dependence**.

Heroin Withdrawal Timeline #



Opioid Detoxification

1) Methadone Maintenance Treatment (MMT)

Methadone maintenance has been *used* to *treat* **opioid dependence** for *more than* **45 years ago**.
- ***Long-term*** use of **Methadone** as a ***substitute*** (***drug replacement therapy***) to the **opioid** on which the **patient** was ***dependent***.
- ***Dose*** of **Methadone** in **maintenance treatment** *range from* **80-120** mg orally per day.

2) Buprenorphine Maintenance Treatment (BMT)

Some formulations of **Buprenorphine** (**Suboxone®** - **Zubsolv®**) are ***combined with*** the **opiate antagonist Naloxone** to ***protect*** the **pill**; ***prevent*** **people** from ***crushing*** the **sublingual tablets** and **injecting** ***them***.
- May 26, 2016, ***FDA approve*** **Probuphine®** **implant** to releases a steady six-month dose of **Buprenorphine**.

3) Levacetylmethadol or Levo-α-acetylmethadol (LAAM) (OrLAAM®)

LAAM is a ***long-acting*** (thrice-weekly dosing) **derivative** of **Methadone**, is a ***second-line*** **treatment**, if patients ***fail*** to **respond** to **Methadone** or **Buprenorphine**.
- It may cause ***life-threatening*** **QT interval prolongation**.

4) Opioid Antagonist

- **Naltrexone** (***monthly injection***) ***for*** **relapse prevention** of **alcohol** and **opioid**.

5) α_2-adrenergic Agonist

- **Clonidine** and **Lofexidine** are used to ***control*** **sympathetic symptoms**

 # # N.B.; Tropicamide (***antimuscarinic***) containing eye drops, ***used to*** produce ***short-acting*** **mydriasis** and **cycloplegia** is ***currently*** **abused**, as an ***inexpensive*** **euphoric deliriant drug**. It is usually ***mixed*** with **Heroin** and ***other*** **opioids** to ***increase*** the **efficacy** and ***decreasing*** or ***delaying*** the **withdrawal symptoms**.

Skeletal Muscle Relaxants

Muscle relaxants are **two major groups**, **Neuromuscular Blockers** and **Spasmolytics**;
Neuromuscular blockers (**NMBs**) act by **blocking nicotinic acetylcholine receptors** at the **neuromuscular junction** and have **no CNS activity**, they are often **used during surgical procedures** and in **intensive care**.
Spasmolytics; are **centrally acting muscle relaxants**, are **used** to **relief spasms** (***musculoskeletal pain***) and **spasticity** (*neurological conditions*).

Muscle Spasticity; **Muscle tone caused by brain** or **spinal problems**, **such as cerebral palsy** and **multiple sclerosis**. **Treated by**; **Antispastic drugs**, **Baclofen**, **Tizanidine** (first line) and **Dantrolene** and **Diazepam** (***second line***), **Botulinum toxin** (**Botox®**) have been shown to be **effective**.

Muscle Spasms; **Muscle tone caused by musculoskeletal conditions**, **such as back** and **neck pain** and **fibromyalgia**. **Treated by**; **Antispasmodic drugs** such as **Cyclobenzaprine** and **Orphenadrine**.

A) Centrally Acting Skeletal Muscle Relaxants

Centrally Antispasticity Agents

Diazepam (Valium®)#

- **Diazepam** ***facilitate*** the **action** of **GABA** in the **CNS** (*both* **brain** and **spinal cord**).
- **Diazepam** has been ***effective*** for **short-term use**, **tolerance** and **addiction** ***can occur***.
- ***Dose***; usual adult dose of **Diazepam** for **muscle spasms*** and **muscle spasticity*** (**antispasmodic** and **antispasticity agent**); 2-10 mg orally 3-4 times daily, OR 5-10 mg IV/IM initially.
- ***Other*** **benzodiazepines** *may* be **used** as **spasmolytics**, ***but*** **clinical experience** with them is ***limited***.

Baclofen (Lioresal®)#

- **Baclofen** is a ***derivative*** of **GABA** (***chlorophenyl*-GABA**) **antispasticity agent**, was ***designed*** to be an **orally active GABA-*potentiating agent***.
- **Baclofen** is an ***agonist*** at **$GABA_B$ receptors**, ***hyperpolarization*** ($\uparrow K^+$) ⇨ ***presynaptic*** **↓ calcium influx** and **↓** ***release*** of **excitatory transmitters** in CNS (*both* **brain** and **spinal cord**) ⇨ **↓ muscle tone** *as well as* **pain** *associated with* **spasticity**.
- ***Uses***; It is ***primarily*** **used** for the ***treatment*** of **muscle spasticity***, ***especially*** in instances of **spinal cord injury** (**SCI**), **cerebral palsy** and **multiple sclerosis** (**MS**).
- ***Dose***; 5 mg 3 times daily for 3 days ⇨ 10 mg 3 times daily for 3 days ⇨ 15 mg 3 times daily for 3 days ⇨ 20 mg 3 times daily for 3 days (Max, 80 mg daily).
- ***Side effects***; **confusion**, **headache**, **insomnia**, **nausea**, **constipation** & ***increase*** **urinary frequency**.
- ***Warning***; ***Abrupt*** **discontinuation** of **Baclofen** can be ***associated with*** a **withdrawal syndrome**; **hallucinations** and **seizures**.

Tizanidine (Sirdalud®)#

Tizanidine is a *centrally acting* α_2 **adrenergic agonist** (as **Clonidine**), is an **antispasticity agent**.

- **Tizanidine** ***reduce*** **spasticity** at ***doses*** that *cause* ***fewer*** **cardiovascular effects** ***than*** **Clonidine**.

Uses; *Like* **Baclofen** it is ***primarily*** **used** for the ***treatment*** of **muscle spasticity*** (***some*** **physicians** ***used*** **Tizanidine** in **muscle spasms**).

- *Dose*; ***Initial***; 2mg orally 3-4 times daily, ***maintenance***; 8mg orally 3-4 times daily, ***max***.; 36mg/day.
- *Side effects*; **hypotension**, **sedation** and **dry mouth** (*dose-related*).
- *Warning*; **Hepatotoxicity** (*monitor liver function tests*) and **abrupt discontinuation** can be associated with **rebound hypertension**.
- *Drug interactions*; **CYP1A2 inhibitors**, *such as* **Ciprofloxacin** and **Fluvoxamine**.

Centrally Antispasmodic Agents

Orphenadrine (Norflex®)#

- **Orphenadrine** is an ***anticholinergic drug*** *closely related to* **Diphenhydramine**
- **Orphenadrine** is the ***first*** **agent** used in the ***treatment*** of **Parkinson's disease** in **1940s**.
- *Uses*; as an ***adjunct*** to **rest**, **physical therapy** and ***other*** **measures** for the ***relief*** **muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions**.

Orphenadrine also ***combine*** with analgesics; **NSAIDs** (**Aspirin** + **Caffeine**; **Norgesic Forte®**) or with **Paracetamol** (**Norgesic®**).

- *Common Side effects*; **Confusion**, **constipation**, and **urinary retention** (*Anticholinergic effects*).

Cyclobenzaprine (Flexeril®) (Multi-Relax®)#

- **Cyclobenzaprine** is ***structurally related*** to **tricyclic antidepressants**.
- *Uses*; It is ***approved*** for **muscle spasms*** *associated with* ***acute*** **musculoskeletal conditions**, It is often used *off-label* for **fibromyalgia**.
- *Dose*; ***Initial***; 5 mg orally 3 times a day (***max***.; 10 mg orally 3 times a day).
- *Side effects*; **Drowsiness**, **dry mouth** (*Anticholinergic effects*), **fatigue** and **headache**.
- *Precautions*; ***Use in*** the **elderly** and **patients** *with* **hepatic dysfunction**.
- *Drug interactions*; **MAO inhibitors** (or *within* **14 days** *after discontinuation*).
- *Risk*; **serotonin syndrome**.

Carisoprodol (Soma®) (Myorelax®)#

- **Carisoprodol** is a ***carbamate derivative***.
- *Uses*; **Muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions**.
- *Metabolism*; Extensively metabolized by **CYP2C19**, one of its metabolites, **Meprobamate**, is an ***anxiolytic agent*** (**Meprobamate** is a drug of **abuse** and **dependence**)
- *Effects*; **analgesia**, **anxiolytic**, **muscle relaxation**, **sedation** and **somnolence**.
- *Dose*; 250-350 mg orally 3 times a daily.
- *Side effects*; **Drowsiness** and **dizziness** (*CNS depression*).
- *Precautions*; ***Use*** **patients** *with* **renal** or **hepatic dysfunction**.
- *Warning*; **Abuse**, **dependence** and **withdrawal**.

Methocarbamol (Robaxin®) (Ibuflex®)# (Dimra®)# (Methorelax®)#

- Methocarbamol is a *carbamate derivative* of Guaifenesin (*expectorant*).
- *Uses*; as an *adjunct* to **rest, physical therapy** and *other* **measures** for the *relief* **muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions, and** ***control*** of **neuromuscular manifestations** of **tetanus**.

Methocarbamol also *combine* with analgesics; **NSAIDs** (**Ibuprofen**; **Ibuflex®**, **Diclofenac Potassium**; **Dimra®**) or with **Paracetamol** (**Methorelax®**).

- *Metabolism*; by **dealkylation** and **hydroxylation** and **conjugation** (*unlike* **Carisoprodol, Methocarbamol metabolites** *not* has **greatly abuse potential**).
- *Formulations*; **oral** and **parenteral**.
- *Dose*; ***Initial***; 1500 mg orally 4 times daily for the first 2 to 3 days, ***followed by*** 750 mg orally 4 times daily.
- *Side effects*; **lightheadedness, dizziness** and **drowsiness**.
- *N.B.*; **black, brown** or **green urine** are *possible*.

Metaxalone (Skelaxin®)

- Metaxalone is a ***muscle relaxant*** **agent**.
- *Mechanism of action*; **unknown**, but may be ***due*** to ***general*** **CNS depression**.
- *Uses*; as an ***adjunct***, for the ***relief*** **muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions**.
- *Dose*; 800 mg 3-4 times daily.
- *Side effects*; **Drowsiness, dizziness, nausea** and **vomiting**.
- *Contraindications*; ***severe*** **hepatic** and **renal dysfunction**.

Chlorzoxazone (Parafon®)# (Myofen®)#

- Chlorzoxazone is a ***muscle relaxant*** **agent**.
- *Mechanism of action*; ***Not fully understood***, but it ***works*** **primarily** in **spinal cord** and **subcortical areas** of the brain ⇨ ***inhibits*** **multi-synaptic reflex arcs** involved in ***producing*** and ***maintaining*** **skeletal muscle spasm**.
- *Uses*; **symptomatic** ***treatment*** of **muscle spasms*** and **pain** *associated with* ***acute painful*** **musculoskeletal conditions**.

Chlorzoxazone is ***available*** in a ***combination*** with **analgesics** to ***relief*** **pain** *associated with* **muscle spasms**; **NSAIDs** (**Ibuprofen**; **Myofen®**) or with **Paracetamol** (**Parafon® - Myolgin®**).

- *Dose*; 250-750 mg orally 3 to 4 times daily.
- *Side effects*; **Dizziness, lightheadedness, malaise, nausea** and **vomiting**.
- *Warning*; **Serious** (or **fatal**) **hepatocellular toxicity**, ***especially*** if used with **Paracetamol**.

B) Peripherally Acting Skeletal Muscle Relaxants

Neuromuscular Blockers (NMBs)

- These drugs **block cholinergic transmission** between ***motor nerve endings*** and the ***nicotinic receptors on the skeletal muscle***.
- NMB are clinically useful **during surgery** to facilitate tracheal intubation and provide ***complete muscle relaxation*** at lower anesthetic doses (*lower anesthetic doses*; allowing for more rapid recovery and reducing postoperative respiratory depression).
- *Uses*;
  - **Surgical relaxation**; As adjuvants during general anaesthesia.
  - **Endotracheal intubation**; by relaxing pharyngeal and laryngeal muscles.
  - **Electro-convulsion therapy (ECT)**; to control muscle contraction.

- *Classification according to mechanism of action*;

Non-Depolarizing NMB (Competitive)		
Tubocurarine (Tubarine®)	**Atracurium** (Tracrium®)	**Cisatracurium** (Nimbex®)
Mivacurium (Mivacron®)	**Doxacurium** (Nuromax®)	**Metocurine** (Metubine®)
Rapacuronium (Raplon®)	**Rocuronium** (Esmeron®)	**Vecuronium** (Norcuron®)
Pancuronium (Pavulon®)	**Pipecuronium** (Arduan®)	**Gallamine** (Flaxedil®)

- **Curare** is the *first drug* known to block the skeletal NMJ, which native South American hunters of the Amazon region used to paralyze prey.
- **Tubocurarine** is the ***active agent*** of one of the forms of **Curare**, but it has been ***replaced by*** **other agents** with ***fewer*** **side effects**.
Atracurium is an ***intermediate*-duration of action**, it ***cause*** *slight* **histamine release** (*hypotension* and *bronchospasm*) and is ***metabolized to*** **toxic metabolite** called **Laudanosine** ⇨ which can cause *seizures*. It has been ***replaced by*** its isomer ⇨ **Cisatracurium**.
Cisatracurium is ***one isomers*** of the **Atracurium**, one of the *most commonly used* (*most popular*) and it have *fewer side effects than* **Atracurium** (*less* **histamine release** & *less* **Laudanosine**).
Mivacurium is a ***shortest*-duration of action** of ***all*** **non-depolarizing NMB**, it *cause* **histamine release**. *Clearance by* **plasma cholinesterase enzyme** and may be *prolonged* in **patient with impaired renal function** (due to; decrease in cholinesterase enzyme). ***No longer used***.
Doxacurium is use has *not been popular* because of ***considerably*** **long duration of action**, *cause* **histamine release** and ***metabolized into*** **Laudanosine**, ***greater accumulation*** in **individuals** with **renal failure**.
Rapacuronium ***is a short*** **acting amino-steroid compounds** and *used in* ***short*** **surgical operation**, *side effects include*; **hypotension**, **tachycardia** and **fatal bronchospasm**.
- **Rocuronium** and **Vecuronium** are ***metabolized in*** the **liver** and ***clearance*** *may* be ***prolonged*** in *patient with* **hepatic disease**.
- **Pancuronium** is the one of three drugs administered during most **lethal injections**.
Gallamine ***cause*** **tachycardia** and occasionally ↑ in **blood pressure** ***because***; **1)** it has strong **parasympatholytic effect** on the cardiac vagus nerve (Atropine like effect on the heart via block M_2 receptors). **2)** It has **sympathomimetic effect** via ↑ **norepinephrine (NE)** release (Tyramine like effect). It has ***no*** **histamine release**.
All neuromuscular-blockers are ***highly*** **polar** (*not pass* **BBB**) and ***inactive*** **orally**; they **must be administered** ***parenterally***.
- **Atracurium** and **Cisatracurium** can be used in **renal** and **hepatic** ***impairment***.
Side effects; - **Tubocurarine** > **Mivacurium** > **Atracurium** ⇨ **Hypotension**.
- **Gallamine** > **Pancuronium** ⇨ **Tachycardia**.

Drug interactions;
- **Cholinesterase inhibitors**; *such as* **Neostigmine** and **Physostigmine**; overcome the action.
- **Inhaled anesthetics**; *such as* **Halothane** and **Desflurane**; enhance NMB effect.
- **Aminoglycoside antibiotics**; *such as* **Gentamicin** and **Tobramycin**; ***Synergistic effect***.
- **Calcium channel blockers**; enhance NMB effect.

Depolarizing NMB (Non-Competitive)

Succinylcholine (Succinylcholine®) | **Decamethonium** (Syncurine®)

Side effects; **Prolonged apnea, bradycardia, myalgias,** *increase* **IOP,** and **hyperkalemia** and **malignant hyperthermia.**

Botulinum Toxin (BTX)

Clostridium botulinum toxin type A (Botox®)#

- **Botulinum toxin** is a ***neurotoxic*** **protein** *produced by* the **bacterium** ***Clostridium botulinum.***

Botulinum toxin is the ***most powerful*** **neurotoxin** *known to date* (Only one single molecule of it is needed to stop one neuron working. *In fact*, 1 gram of botulinum toxin would be enough to kill 14,000 people (if ingested), 1.25 million people if inhaled, or a staggering 8.3 million people if injected).

- ***Clostridium botulinum*** is an **anaerobic, Gram positive, spore-***forming* **rod.**
- **Botulinum toxin** acts by ***blocking*** **nerve function** by ***inhibition*** **Acetylcholine** ***release*** from the **presynaptic neuromuscular junctions.** This causes **skeletal muscle** ***paralysis*** and **respiratory failure** by paralysing the muscles of the chest.
- There are **2 commercial types** of **BTX**; **Botulinum toxin type A** and **Botulinum toxin type B.**

Most common applications (***Uses***) or **Botulinum toxin type A** (**Botox®**);

Cosmetics; ***Prevent*** **development** of **wrinkles** by paralyzing facial muscles.

Medical uses; **Muscle spasticity***, **dystonia, overactive bladder, chronic migraine, axillary hyperhidrosis, blepharospasm, strabismus,** and **anal fissure.**

Botulinum toxin type B (**Myobloc®**); used in **cervical dystonia.**

- **Heptavalent Botulism AntiToxin** (**HBAT**); was approved in 2010 as **botulism anti-toxin** that effectively neutralizes all 7 known botulinum nerve toxin serotypes (types A, B, C, D, E, F and G).

C) Direct Acting Skeletal Muscle Relaxants

Dantrolene (Dantrium®)# (DantRelax®)#

Dantrolene is a ***hydantoin derivative*** related to **Phenytoin** that has a ***unique peripheral mechanism*** of ***spasmolytic activity.***

Mechanism of action; **Dantrolene** is the ***only*** (***unique***) **drug** available that ***inhibits*** Ca^{2+} ions ***release*** from **sarcoplasmic reticulum.**

Uses; - ***Treatment*** of **chronic muscle spasticity*** of upper **neuronal disorders,** including spinal cord injury, multiple sclerosis, and cerebral palsy.

- ***Dose***; 25 mg orally once daily for 7 days, then 25 mg three times a day for 7 days, then 50 mg three times a day for 7 days, then 100 mg three times a day.

- **Malignant hyperthermia;**
  - ***Dose***; **IV**; bolus 2.5 mg/kg, then 1 mg/kg IV every 4-6hr OR 0.25 mg/kg/hr IV infusion.

- ***Most common side effects***; drowsiness, dizziness, fatigue and diarrhea.
- ***Black box warning***; ***potential for*** **hepatotoxicity.**

Drugs for Gout and Hyperuricemia

Gout is a ***sudden***, ***severe*** **attacks** of **pain**, **redness** and **tenderness** in **joints** (often **big toe**).
Hyperuricemia; is an ***abnormally*** **high level** of **Uric Acid (UA)** in the **blood**;
Reference range; **Male**; 3.5–8.0 mg/dL. **Female**; 2.5–6.5 mg/dL.
Gout Risk Factors; # # # # # # # # **PATIENT COUNSELLING** # # # # # # #

- ***Alcohol Consumption***; ***higher risk*** of **incident gout** & ***higher rate*** of **gout flares**.
- ***Dietary***;

** *Avoid*;	** *Limit*;
- **Organ meats**; Liver, kidneys, brain & heart.	- **Meat**; beef, lamb chicken, pork.
- **Game** (hunting) **meats**; rabbit and venison.	- **Poultry**; chicken and duck.
- **Fish**; herring, mackerel and sardines.	- **Dried peas, beans** and **legumes**.
- **Seafood**; mussels, shellfish and caviar.	- **Mushrooms**.
- **High-fructose drinks or foods**.	- **Some vegetables**; cauliflower and spinach.

- ***Drugs***;
  - **Thiazide** & **loop diuretics** (***higher risk*** of **incident gout** & ***higher rate*** of **gout flares**).
  - ***Low-dose*** **Aspirin** (***may also*** be a ***risk factor*** for **gout**).
  - **Xanthine oxidase inhibitors** (**XOIs**) and **uricosuric agents**; ***only in initial therapy***.
- ***Medical conditions***; **Hyperuricemia**, **obesity**, **diabetes**, **hypertension**, **dyslipidemia**, **renal insufficiency** and **early menopause**.
- ***Other conditions***; **Trauma**, **surgery**, **starvation**, **dehydration** and **family history**.

Non-pharmacological Therapy

- **Dietary Modifications** (*see risk factors*).
- **Maintaining adequate fluid intake**.
- **Weight loss** (*if obese*).
- **Exercise** (regular aerobic exercise program).
- **Smoking cessation**.

Pharmacological Therapy

Drugs for Gout Attacks

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Indomethacin (Indocid®)#	**Naproxen** (Aleve®)#	**Sulindac** (Clinoril®)#

NSAIDs are the ***first-line treatment of*** **acute gouty attacks**.
Indomethacin has been ***historically favored*** as **NSAID** of ***choice for*** **acute gout**.
- ***Only*** **FDA-approved**; **Indomethacin**, **Naproxen** and **Sulindac** for the ***treatment of*** **acute gouty attacks**, **BUT** ***other*** **NSAIDs** *may be* as **effective**.
- **Celecoxib** is an ***option*** in ***patients*** with ***contraindications*** or ***intolerance*** to **NSAIDs**.

Common Side Effects; **GIT** (gastritis and bleeding), **kidneys** (renal dysfunction), **CVS** (risk of CV events in susceptible patients and hypertension).
Consider **co-administration** with a **proton-pump inhibitor** (**PPI**) for ***patients*** at ***risk for*** **gastrointestinal bleeding**.

Colchicine

Colchicine (Colchicine® 500 mcg)#

Colchicine, is an *antimitotic drug*, is a *plant alkaloid*, *used for* the *treatment of* acute gouty attacks and familial Mediterranean fever (FMF).
Colchicine *relieves* the pain and inflammation of gouty arthritis in 12–24 hours *without altering* the metabolism or excretion of urates and *without other analgesic* effects (*not an analgesic*).
- Colchicine is used *less often than* NSAIDs, and *may be* reserved as a second-line therapy when NSAIDs are *contraindicated* or *ineffective*.
Side Effects; - *Dose-related GI side effects*; nausea, vomiting & diarrhea (50-80%).
- *Chronic use*; myopathy, neutropenia, aplastic anemia and alopecia.
Dose; ***Recently***, lower dose of colchicine are used; 1.2 mg; *then* 0.6 mg 1 hour *later*; *then* 0.6 mg *once* or *twice* daily *until* attack resolves (Colchicine *was* used in higher doses, *hourly* dosing *until* gastrointestinal symptoms *become develops* such as diarrhea).
Contraindications; *Co-administration* of Colchicine with *strong* CYP3A4 inhibitors (Erythromycin or Clarithromycin) in renal or hepatic impairment (*fatal toxicity*).

Corticosteroids (CSs)

- Corticosteroids *may be* an *appropriate alternative* for patients who *cannot* tolerate NSAIDs or Colchicine, *however*, *recent* evidence *indicates* that corticosteroids are *equivalent to* NSAIDs in the *treatment* of acute gout flares.
1) Oral corticosteroid (OCS) *used for all* cases of gout (oral route is a *first-line*);
   - Prednisone 0.5 mg/kg (30-60 mg) per day for 5–10 days.
     OR (*to reduce the risk of a rebound flare*), Prednisone 0.5 mg/kg for 2–5 days, then *tapered gradually* over 10 to 14 days, then discontinue (i.e.; 40 mg for 4 days, then 20 mg for 4 days, then 10 mg for 4 days).
   - Methylprednisolone Dose Pack; Six days of pre-dosed 4 mg package.
2) IM corticosteroid; *Single dose* of Triamcinolone (60 mg) *followed by* OCS.
3) Intra-articular corticosteroid; Triamcinolone is *limited to* one or two large joints;
   - Large joint; 40 mg of Triamcinolone. - Medium joint; 30 mg of Triamcinolone.
   - Small joint; 10 mg of Triamcinolone.
- *N.B.*; Intra-articular CSs *can be* used in *combination with* OCSs, NSAIDs or Colchicine.

Drugs for Gout Prevention and Hyperuricemia

Xanthine Oxidase Inhibitors (XOIs)

Allopurinol (Zyloric®)# (Zyloprim®)

Allopurinol, a *xanthine oxidase inhibitor*, is a *purine analog*; *decrease* Uric Acid production by *competitively inhibiting* xanthine oxidase *enzyme.*
Uses; Gout and hyperuricemia *secondary to* chemotherapy.
- *Dose*; - *Starting Dose*; < 100 mg/day; *Reduces* early gout flares and *risk* of hypersensitivity syndrome.
  - *Dose Titration*; *gradually titrate* dose every 2–5 weeks.
  - *Maintenance Dose*; can be *higher than* 300 mg daily.
- *Side effects*; *About* 20% of patients on Allopurinol report *side effects*;
  - *GI Side Effects*; Nausea, vomiting, and diarrhea.
  # # # Allopurinol hypersensitivity syndrome (AHS); *Mortality; 20–25%.*
  - *Severe* hypersensitivity reactions; urticaria, Stevens-Johnson syndrome, hepatotoxicity and eosinophilia.
- *Drug interactions*; 6-mercaptopurine, Azathioprine and Theophylline

Febuxostat (Uloric®)# (Feburic®)#

- Febuxostat, a *xanthine oxidase inhibitor*, is ***structurally unrelated*** to Allopurinol.
- *Mechanism*; ***Selective*** **direct non-competitively blocking** of **xanthine oxidase**.

Febuxostat VS Allopurinol;

- *Cost*; Febuxostat ***more expensive***.
- *Mechanism*; - Allopurinol; **Competitive**. - Febuxostat; **Non-competitive**.
- *Side effects*; Allopurinol ***more severe***.
- Chronic Kidney Disease; Allopurinol require dose adjustment.

- *Dose*; - Febuxostat is *approved at doses* of 40, 80 or 120 mg.
  - ***Starting dose***: 40 mg once daily.
  - ***If goal serum urate not reached***; dose may increase dose to 80 mg once daily.
- *N.B.*; Use with caution in severe renal impairment (CrCl <30 mL/minute); insufficient data.

Uricosuric Agents

- *Uricosuric Agents*; are **substances** that ***increase*** the **excretion** of Uric Acid in the ***urine***.

Probenecid | Sulfinpyrazone (Anturane®)

- *Indications*; ***If*** **XOIs is** ***contraindicated*** **or** ***not tolerated***.
- *Dose*;- Probenecid; ***Initial***; **250 mg** ***twice*** **a day** for **1-2 weeks** and then **500 mg** ***twice*** **a day** for **2 weeks** (when initiating, increase fluid intake or urine alkalinization).
  - Sulfinpyrazone; ***Initial***: 100-200 mg ***twice***, *with* **meals** or **milk**, ***gradually*** **increasing** ***when*** **necessary** to ***full*** **maintenance dosage** (200-400 mg ***twice***) **in 1 week**.
- *Most Common Side Effects*; **GI disturbances**.
- *Contraindications*; Probenecid ***contraindicated*** in **patients** *with* **CrCl** < 50 mL/min.
- Secondary Uricosurics *(second-line)*; Losartan and Fenofibrate *(off-label use)*.

Selective Uric acid Reabsorption Inhibitor (SURI)

Lesinurad (Zurampic®)

- *Approval*; ***FDA*** approval on December, 2015. ***European Union*** on February 2016.
- *Indications*; In ***combination with*** a **xanthine oxidase inhibitor (XOI)** for the ***treatment of*** **hyperuricemia** ***associated with*** **gout** in ***patients*** who have ***not achieved*** **target serum uric acid levels** with a **xanthine oxidase inhibitor** ***alone*** [**NOT USED ALONE**].
- *Recommended Dose*; **200 mg once daily** in ***combination with*** a **xanthine oxidase inhibitor**, including Allopurinol or Febuxostat.
- *Contraindications*; - **Severe renal impairment** (CrCl less than 30 mL/min).
  - **Tumor lysis syndrome (TLS)** or **Lesch-Nyhan syndrome**.
- *FDA WARNING*; - Renal events (**acute renal failure** ***more common*** when **used alone** ***without*** **XOIs**).
  - Cardiovascular events.

Recombinant Urate Oxidase (UO) "Uricase"

- Urate Oxidase (UO) ***enzyme*** or Uricase, is ***absent*** in **humans** (found nearly all organisms except humans) and ***catalyzes*** the ***oxidation*** of Uric Acid ***to*** Allantoin.
- Allantoin is an ***inactive*** (nontoxic) and ***more soluble*** **metabolite** and ***easily*** **excreted**.

Pegloticase (Krystexxa®)#

- *Indications*; ***treatment of*** **severe, refractory** or **resistant chronic gout**.
- *Dose*; 8 mg IV infusion every 2 weeks.

FDA warning; Anaphylaxis and infusion reactions and *Life-threatening* hemolysis.

Rasburicase (Elitek®)#

- *Indications*; ***Prevention & ttt*** of **hyperuricemia** ***caused by*** **Tumor Lysis Syndrome**.
- *Dose*; 0.2 mg/kg as a 30-minute IV infusion once a day for up to 5 days.

FDA warning; Anaphylaxis and infusion reactions and *Life-threatening* hemolysis.

Disease Modifying Antirheumatic Drugs (DMARDs)

Disease Modifying Antirheumatic Drugs (DMARDs) [dee-MAAR-D]; Used for **rheumatoid arthritis**.

1) **Non-biologic DMARDs**;
   - *Most common*; **Methotrexate, Leflunomide, Hydroxychloroquine** and **Sulfasalazine**.
   - *Less common*; *such as*; **Gold Salts, Azathioprine, Cyclosporine** and **D-Penicillamine**.
2) **Biologic DMARDs**;
   - *TNF inhibitors*; **Etanercept, Adalimumab, Infliximab, Certolizumab & Golimumab**.
   - *Non-TNF Biologic*; **Abatacept, Rituximab, Anakinra, Tocilizumab** and **Tofacitinib**.

Disease Modifying Antirheumatic Drugs (DMARDs)

Non-biologic (Traditional) DMARDs

Methotrexate (Methotrexate®)

- **Methotrexate (MTX)** is a *synthetic antimetabolite* (**Folic acid** *antagonist*).
- It was *originally* ***used as*** a **chemotherapy** ***treatment for*** **cancer** (first made in 1947), ***used in much lower doses*** for **rheumatoid arthritis** and *other* **rheumatic diseases** (such as systemic lupus erythematosus and Sjögren's syndrome).

MTX ***now considered*** the *first-line* **DMARD** for ***treatment of*** **rheumatoid arthritis**.

- **MTX** may be ***combined with other*** **DMARDs** or ***with*** a **biologic agent** if **MTX alone** ***does not*** **adequately control a patient's disease**.
- *Uses*; 1) *Cancer Chemotherapy*; **MTX** is an ***antimetabolite*** used in the *treatment of* ***certain*** **cancers**.
  2) *Autoimmune Diseases*; **MTX** is used as a ***disease-modifying agent*** for *some* **autoimmune diseases**, including; **rheumatoid arthritis, juvenile dermatomyositis, psoriasis, psoriatic arthritis, lupus, sarcoidosis, Crohn's disease**.
  3) *Abortion*; US FDA pregnancy category X; **MTX** is an ***abortifacient agent*** during the ***early stages***, *generally* in ***combination with*** **Misoprostol**. It is ***used to treat*** **ectopic pregnancies**.
- *Dose*; *Doses* of **MTX** *required for* **RA** treatment are ***much*** **lower than** those needed in **cancer chemotherapy** and are given ***once*** a **week**, *thereby* ***minimizing*** **adverse effects**;
  - **MTX** may be given **IM, SC** or **orally**.
  - ***Dosing regimen for*** the treatment of **RA 7.5-15** mg ***once*** a **week**.
  - *Onset of effect*; *within* **3-6 weeks** of ***starting*** **treatment**.

Side effects; - *Most common*; **Mucosal ulceration** and **nausea**.
- *Other side*; **leukopenia, anemia, stomatitis, GI ulcerations** and **alopecia** (*due to inhibiting cellular proliferation*), **halitosis** (bad breath odour).
- *Dose-related side effects*; **hepatotoxicity**.
- *Rare side effects*; **acute pneumonitis** and **kidney failure**.

- *Monitoring*; **Liver enzyme tests, complete blood counts**, and **monitoring** ***for*** **signs of infection**.

Taking **Folinic acid (leucovorin®) 24 hours** ***after*** *each* **weekly dose** or by the use of ***daily*** **Folic acid** (not in the same day; ***off-days***), although this may ***decrease*** the **efficacy** of **Methotrexate** by about 10%, ***but*** this ***reduces severity*** of **adverse effects**.

N.B.; **Folinic acid** ***should be distinguished from*** **Folic acid**. **Folinic acid** ***does not*** require the action of **dihydrofolate reductase** for its ***conversion***.
- **Levoleucovorin (Fusilev®)** is an **enantiomerically** ***active form*** of **Folinic acid**.

- *Drug Interactions*; **Penicillins, Aminoglycosides, Omeprazole & Valproate NSAIDs**

Leflunomide {Original brand (Arava®)#} {Egypt brand (Avara®)#}

- Leflunomide, *like* MTX, is an *immunomodulatory non-biologic* DMARD.
- Arava® was developed by Sanofi Aventis and approved by the US FDA in 1998.
- Leflunomide has *efficacy similar to* MTX for *treating* RA.
- Teriflunomide (*active metabolite of* Leflunomide) was approved by the FDA in 2012 for the *treatment of patients with* **relapsing forms of multiple sclerosis (MS)**.
- *Dose*; - *Loading dose*: **100 mg** orally *once* a **day** for **3 days**.
  - *Maintenance*: **20 mg** orally *once* a **day** (may be decreased to 10 mg orally once a day).

Most common side effects (up to 10%); **Respiratory infection, diarrhea, nausea, headache, hypertension, alopecia, rash, weight gain & *abnormal* liver function tests**.

Pregnancy; Category X (Leflunomide and Teriflunomide); **# PRECAUTIONS #**

- Women should wait to become pregnant for at least 2 years after discontinuation of treatment and plasma levels of A771726 should be less than 0.02 mg/L).
- *Or* Administer Cholestyramine 8 grams, 3 times daily for 11 days, verify plasma levels less than 0.02 mg/L by 2 separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L, additional Cholestyramine treatment should be considered.
- Men who are planning parenthood and are being treated with Leflunomide should undertake Cholestyramine washout and wait for at least one and possibly three spermatic cycles before inseminating their spouse.

Hydroxychloroquine (Plaquenil®)#

- Hydroxychloroquine is an *antimalarial drug*.
- *Onset of effects*; **6 weeks** to **6 months** (> 6 months without a response = therapeutic failure).
- *Main advantage*; *less toxicities* on the **liver, kidney** and **immune system** than *other* **DMARDs**, which *simplifies* **monitoring**.

Hydroxychloroquine is very ***extensively*** **tissue-bound**, particularly in ***melanin-containing*** **tissues** such as the **eyes** (**OCULAR TOXICITY**).

- *Dose* in **RA**; Oral: 200-300 mg twice daily, after 1–2 months may to 200 mg twice or once daily.
- *Most common side effects*; **GI effects**; *mild* **nausea, dyspepsia**, and **diarrhea** (can be managed by taking doses with a food or a glass of milk). *Chronic use side effects*; **skin pigmentation, hair bleaching, alopecia skin rash** and **CNS disturbances**.

Serious side effects; *Ocular toxicity*; accommodation defects, benign corneal deposits, blurred vision, scotoma (small areas of decreased or absent vision in the visual field) and night blindness.

Monitoring; **Ophthalmoscopy** every 9–12 months and Amsler grid test at home every 2 weeks.

- *Contraindications*; **G6PD deficiency, retinal** or **visual field changes** and ***long-term*** in **children**.
- N.B.; Chloroquine is ***another antimalarial agent*** that is also ***sometimes*** **used**.

Sulfasalazine (Azulfidine®)

- Sulfasalazine (SSZ) is a *prodrug*, is a *sulfa drug cleaved by* **bacteria** in the **colon** into Sulfapyridine and Mesalazine (5-Amino-Salicylic Acid; 5-ASA).

Sulfapyridine is *probably* the ***active moiety*** in ***treating*** **RA** (*unlike* **inflammatory bowel disease**, Mesalazine (Pentasa®) is the ***active moiety*** in treating this disease).

- *Dose* in **RA**; **500 mg** to **1 g** *twice daily*.
- *Most common side effects*; **nausea, vomiting, headache** and **rash**.
- *Contraindications*; **G6PD deficiency**, or ***hypersensitivity*** to **sulfa drugs** and **urinary obstruction**.
- *Drug interactions*; **Warfarin, oral hypoglycemic, antibiotics** and **iron supplements**.

Other Non-biologic DMARDs

Gold Salts	**Cyclophosphamide** (Cytoxan®)# (Endoxan®)#
Chlorambucil (Leukeran®)#	**Azathioprine** (Imuran®)#
Cyclosporine (Sandimmune Neoral®)#	**D-penicillamine** (Artamin®)#

- ***Although*** **these drugs** can be ***effective***, **BUT** they are **used** ***less frequently*** **today** *because of* **toxicity**, ***lack of*** **long term benefit or both.**

Cyclophosphamide (**Endoxan®**); ***Alkylating Agent.***
- ***Uses***; **Certain cancers and autoimmune diseases.**
- ***Side effects***; **Nausea, vomiting, *increased risk of*; developing certain cancers and risk of infections, anemia** (bone marrow suppression), **alopecia and infertility** (in males and females).

Chlorambucil (**Leukeran®**); ***Alkylating Agent.***
- ***Uses***; **Certain cancers and autoimmune diseases.**
- ***Side effects***; **Nausea, vomiting, *increased risk of*; developing certain cancers and risk of infections, anemia** (bone marrow suppression), **alopecia and infertility** (in males and females).

Azathioprine (**Imuran®**); ***Immunosuppressive Drug.***
- ***Uses***; **Organ transplantation and autoimmune diseases.**
- ***Side effects***; **Nausea, vomiting, hepatitis, pancreatitis, *increased risk of*; infections & developing certain types of cancers.**

Cyclosporine (**Sandimmune Neoral ®**); ***Immunosuppressive Drug.***
- ***Uses***; **Organ transplantation and autoimmune diseases.**
- ***Side effects***; **Nausea, vomiting, hepatitis, pancreatitis, *increased risk of* infections.**

D-Penicillamine (**Artamin®**); ***Chelating Agent*** (Chelates gold, copper, mercury and arsenic).
- ***Uses***; **Wilson disease** (accumulation of copper in tissues) **and rheumatoid arthritis.**
- ***Side effects***; **Nausea, vomiting, diarrhea and bone marrow suppression.**

Biologic DMARDs

- **Biologic DMARDs** are ***genetically engineered*** **protein molecules** that ***block*** the **proinflammatory cytokines**;

* ***These drugs*** may be ***effective*** *when* ***other*** **DMARDs** (non-biologic) ***fail*** to ***achieve*** **adequate responses** but are ***considerably*** **more expensive** ***to use.***

* ***Most*** of **these drugs** are ***increased*** an ***incidence*** of ***risk of*** **tuberculosis infection** (tuberculin skin testing is recommended).

* **Live vaccines** ***should not*** be **given** to ***avoid*** the **risk** of **infection.**

TNF-α Inhibitors

Tumor necrosis factor alpha (**TNF-α**) is a ***pro-inflammatory cytokine*** *produced by* **macrophages** and **lymphocytes**. It is *found in* ***large quantities*** in **rheumatoid joint.**

TNF *antagonists* were the ***first*** of **biological DMARDs** approved for **RA.**

Anti-TNF agents began to ***enter the market*** for **RA** in **1999.**

There are ***currently*** **5 TNF inhibitors** FDA *approved for* **RA**; listed in order of their approval for **RA**; **Etanercept, Infliximab, Adalimumab, Certolizumab & Golimumab.**

Anti-TNF PRECAUTIONS

Risk of **serious infections**, or ***history of*** **recurring infections**; black box warning.
Recent malignancies; *especially* **lymphoproliferative cancer**; black box warning.
Congestive heart failure (CHF); New York Heart Association (NYHA) class III or IV heart failure
Demyelinating diseases; *like* **multiple sclerosis.**
Avoid **vaccination** *with* **live vaccines.**

- ***Response*** was seen in **60-75%** of **patients.**
- ***Onset of effect***; ***rapid onset of action*** sometimes with **improvements** seen ***within*** **2-4 weeks**, however, ***additional improvements*** can be seen ***over*** **3-6 months.**
- ***Pregnancy***; **category B.**
- The global market for TNF inhibitors in 2008 was $13.5 billion and $22 billion in 2009.

Etanercept (Enbrel®)#

- Etanercept is a *recombinant*, *fully* human receptor *fusion* protein.
Indications; RA, ankylosing spondylitis, psoriasis and psoriatic arthritis.
- *Dose*; 25 mg SC *twice* weekly or 50 mg SC weekly.
Methotrexate, Glucocorticoids or NSAIDs *may be* continued *during* treatment (70% of patients taking Etanercept are also using Methotrexate).
** *Precautions* or *Contraindications*; *increase risk for* infections, malignancy and worsening heart failure (DON'T *forget* the anti-TNF precautions).

Infliximab (Remicade®)#

- Infliximab is a *recombinant* DNA-derived chimeric human-mouse IgG_1 monoclonal antibody.
Indications; RA, Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis and ankylosing spondylitis.
- *Dose*; 3–5 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks; may be increased to 10 mg/kg.
- *N.B.*; The immune system in patients *treated with* Infliximab *may develop* antibodies to this *foreign* protein of Infliximab (*called* anti-infliximab antibodies); *reduced efficacy*.
Methotrexate *should be* given *as long as with* Infliximab to *decrease* or *prevent* the *formation* of anti-infliximab antibodies.
- Infusion site reactions *may* occur and may *correlate with* anti-infliximab antibodies *formation* (antihistamines may prevents some of these reactions).
** *Precautions* or *Contraindications*; *Like other* TNF-α blocking agents.

Adalimumab (Humira®)#

- Adalimumab is a *recombinant fully* human IgG_1 monoclonal *antibody*.
- *Mechanism*; *Like* Infliximab, *but* Adalimumab is *fully* human (*not* chimeric), *no* foreign protein in Adalimumab, is *less antigenic than* Infliximab.
Indications; RA, Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis and ankylosing spondylitis, hidradenitis suppurativa and juvenile idiopathic arthritis.
- *Dose*; *usual dose* is 40 mg SC every other week (14 days).
** *Precautions* or *Contraindications*; *Like other* TNF-α blocking agents (*serious TB infection*).

Golimumab (Simponi®)#

- Golimumab is a *human* monoclonal antibody with a *high* affinity for *soluble* and *membrane-bound* TNF-α.
Indications; RA, ulcerative colitis, psoriatic arthritis and ankylosing spondylitis.
- *Dose*; - Simponi®; 50 mg SC monthly.
  - Simponi® Aria; 2 mg/kg IV infused over 30 minutes at weeks 0 and 4, then every 8 weeks.
** *Precautions* or *Contraindications*; *Like other* TNF-α blocking agents.

Certolizumab Pegol (Cimzia®)#

- Certolizumab is a *unique* TNF-α blocker that contains a *recombinant*, *humanized* antibody Fab fragment *conjugated to* a Polyethylene Glycol (PEG) (not contain IgG_1) with *specificity* for *human* TNF-α.
Indications; RA, Crohn's disease, psoriatic arthritis and ankylosing spondylitis.
- *Dose*; 400 mg SC initially and repeat at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.
** *Precautions* or *Contraindications*; *Like other* TNF-α blocking agents.

T-Cell Activation Blockade

Abatacept (Orencia®)#

- Abatacept is a ***soluble recombinant*** **fusion protein** *composed of* the **Fc region** of the **immunoglobulin IgG_1** ***fused to*** the **extracellular domain** of **CTLA-4** (CTLA4-Ig).

Indications; ***Monotherapy*** (***first-line therapy***) or in ***combination*** (*not with other biologic drugs*) with ***other*** **DMARDs** in patients with ***moderate*** to ***severe*** **rheumatoid arthritis**.

Abatacept may use in **autoimmune type 1 diabetes** to ***protect*** surviving **beta cells** from **autoimmune** ***attack***.

- ***Dose***; **IV infusion** based on patient weight (<60 kg; 500 mg. 60–100 kg; 750 mg. >100 kg; 1,000 mg) every 2 weeks for two doses after and then every 4 weeks.
- ***Pregnancy***; **category C**.
- ***Common side effects***; **headache**, ***upper*** **respiratory infections**, **nasopharyngitis** and **nausea**.

N.B.; ***Concomitant use*** Abatacept with anti-TNF-α is ***not recommended*** due to the ***increased incidence*** of **serious infection**.

B-Cell Depletion

Rituximab (Rituxan®)#

- Rituximab is a ***genetically engineered*** ***chimeric*** (murine/human) **monoclonal antibody** directed ***against*** the CD20 antigen *found on* the ***surface*** of **normal** and **malignant B lymphocytes**, ***resulting*** in **B-cell depletion**. Rituximab ***was originally*** *developed to* treat **non-Hodgkin's lymphoma**.

Indications; **Hematological cancers**, **autoimmune diseases** and **organ transplantation**.

- ***Dose***; in **RA**; Two infusions of 1,000 mg are given 2 weeks apart. **Methylprednisolone** 100 mg should be given 30 minutes prior to reduce the incidence and severity of infusion reactions.

Recommendations; Rituximab is used in ***combination*** with **Methotrexate** in patients who ***failed to*** **one** or **more** ***types*** of **treatment** (***including anti-TNF***).

- ***Pregnancy***; **category C**.

Common side effects; **Infusion reactions** (urticaria, hypotension and angioedema).

IL-1 Inhibitors

Anakinra (Kineret®)#

- Anakinra is a ***recombinant*** IL-1 receptor ***antagonist*** (*E.coli-derived product*).

Indications; **RA** and **neonatal-onset multisystem inflammatory disease (NOMID)**.

- ***Recommendations***; The **American college of rheumatology** ***guidelines did not include*** Anakinra in ***their*** **RA** ***treatment recommendations*** *due to* its ***infrequent*** **use** in **RA** and ***lack of*** **new data** since 2012, ***but some patients*** could ***benefit*** from **treatment** with ***this*** **drug** (patients who have failed one or more DMARDs).
- ***Dose***; 100 mg SC daily.
- ***Pregnancy***; **category B**.

** ***Precautions*** or ***Contraindications***; **Neutropenia**, ***severe*** **renal impairment**, *increased* **risk for infections** and **malignancy**.

IL-6 Inhibitors

Tocilizumab (Actemra®)#

- Tocilizumab is a ***humanized*** **monoclonal antibody** that ***block*** **IL-6 receptor**.
Indications; **RA** and **juvenile idiopathic arthritis**.
- *Recommendations*; *Monotherapy* (*first-line therapy*) or in *combination* (*not with other biologic drugs*) with ***other*** **DMARDs** such as **Methotrexate**.
- *Dose*; - **IV *infusion***; 4-8 mg/kg every 4 weeks.
  - **SC**; <100 kg: 162 mg SC every other week, may by an increase to every week.
    ≥100 kg: 162 mg SC every week.
- *Pregnancy*; **category C**.
- *Common side effects*; **Infusion reactions**, ***increased*** **risk of infection**, and ***increased*** **plasma lipids** and ***risk of*** **GI perforation**.

Janus Kinase (JAK) Inhibitors

Tofacitinib (Xeljanz®)#

- Tofacitinib is an ***oral*** *inhibitor* of **Janus kinases** (***first oral biologic***).
- JAK is a *human* **tyrosine kinase** essential for ***signaling*** for *certain types* of **cytokines**.
Indications; *Moderate* to ***severe*** **active RA**.
- *Recommendations*; *second-line treatment* as **monotherapy** or in **combination** ***with*** **MTX** or ***other*** **non-biologic DMARDs** or ***potent*** **immunosuppressive agents** (**Azathioprine** and **Cyclosporine**).
- *Pharmacokinetics*;
  - ***Bioavailability***: 74%. - ***Protein Bound***: ~40%
  - ***Metabolism***; CYP3A4 and CYP2C19 (**dosage adjustments** in ***potent*** **inhibitors** or **inducers**).
  - ***Clearance***: ~70% hepatic metabolism and 30% renal excretion.
- *Dose*; 5 mg orally 2 times a day (*immediate release*) or 11 mg orally once a day (*extended release*).
- *Dose adjustment*;
  - ***Moderate-severe*** **renal impairment**; Not to exceed 5 mg per day.
  - ***Moderate*** **hepatic impairment**; Not to exceed 5 mg per day.
  - ***Severe*** **hepatic impairment**; Not recommended.
- *Pregnancy*; **category D**.
** *Precautions* or *Contraindications*;
  - **Hemoglobin *concentrations*** must be ***greater than*** **9 g/dL** *before* ***start*** **Tofacitinib**.
  - ***Increase*** *risk for* **infections** and **malignancy**.
- *Monitoring*; **Hemoglobin *concentrations***, **lymphocyte** and **neutrophil** *counts* ***should be*** **checked *during* treatment**.

.....
.....
.....

Drugs for Osteoarthritis

- **Osteoarthritis (OA)** is the ***most common* joint disease**.
It is ***characterized by breakdown*** of the **cartilage**, **bony *changes*** of the **joints**, ***deterioration*** of **tendons** and **ligaments**, and ***various degrees*** of **inflammation** of the **joint lining** (***synovium***).
- The ***daily stresses applied to*** the **joints**, *especially* the **weight-bearing joints**, ***play*** an ***important role*** in the ***development*** of **osteoarthritis**.
Main symptoms; **stiffness & locomotor restriction**.
- **Pharmacological therapy** in **OA** is *targeted at* **relief of pain**; *see* ***pain management*** **topic**
  # For ***mild*** or ***moderate pain***, **topical analgesics** or **Paracetamol** ***up to*** **4 gm/day** (**Panadol Joint®**), **NSAIDs** *may be useful*.
  - ***Low-dose*** **opioid analgesics** *can be useful* for **patients** who experience ***no*** **pain relief** with **Paracetamol**, **NSAIDs**, **intra-articular glucocorticoid injections** or **topical therapy**.
- ***Other Therapies*** (***not recommended by guidelines***);

Glucosamine and Chondroitin

Glucosamine *and* Chondroitin (Move Free®)# (Osteo Bi-Flex®)# (Genuphil®)# >>

- **Glucosamine** ($C_6H_{13}NO_5$) is an ***amino sugar*** (*amino-saccharide*).
- **Glucosamine**, acting as a ***substrate*** for the **biosynthesis** of **glycosaminoglycan *chains***, **aggrecan** and *other* **proteoglycans** of **cartilage**.
- **Chondroitin** is a **Glycosaminoglycan (GAG)** *composed of* a chain of ***alternating sugars*** (**N-acetylgalactosamine** and **Glucuronic acid**).
- **Chondroitin** is an ***important structural* component** of **cartilage**.
The ***exact role*** of **Glucosamine**, **Chondroitin**, or a ***combination*** of the two products is ***still unclear***.
Dosing *should be* at ***least* 1,500 mg/day** of **Glucosamine** and **1,200 mg/day** of **Chondroitin**.
Glucosamine and **Chondroitin** are marketed in the **US** as ***dietary supplements*** and ***not approved*** by the **FDA**.

 # # # # # # # # PRECAUTIONS # # # # # # # #

Glucosamine *may*; 1) ***Increase*** *risk of* **bleeding**.
2) ***Increase* blood pressure**.
3) ***Affect* insulin resistance** and/or **blood sugar *levels***.
4) ***Increased* cataract** *risk* or **dry eyes**.
5) ***Use cautiously*** *in people who* have **asthma**, **kidney disorders**, ***active* peptic ulcer disease** and **depression**.

Hyaluronates Injection

Hyaluronic Acid (HA)	**Hyaluronate Sodium**

- **Hyaluronic Acid (HA)** or **Hyaluronate Sodium** are available for ***intra-articular injection*** for treatment of **knee OA**.
Main functions; as a ***tissue lubricant***.
HA injections ***temporarily*** and ***modestly increase* viscosity**.
- ***Intra-articular* HAs** ***approved by*** the **FDA** for the treatment of **osteoarthritic knee pain**.
- **HA *preparations***: *these agents are* ***expensive***;
  # **Hyalgan®** (20 mg sodium hylaronate/2 mL); weekly for 5 injections.
  # **Supartz®** (25 mg sodium hylaronate/2.5 mL); weekly for 5 injections.
  # **Euflexxa®** (20 mg sodium hylaronate/2 mL); weekly for 3 injections.
  # **Synvisc®** (16 mg hylan polymers/ 2 mL); weekly for 3 injections.
  # **Synvisc®-One** (48 mg hylan polymers/6 mL); single dose with efficacy up to 26 weeks.
  # **Orthovisc®** (30 mg hyaluronan/2 mL); weekly for 3 injections.
- ***Other uses*** of **HA**;
  # In **Ophthalmic Viscosurgical Device (OVD)**; is ***viscoelastic solution*** used in **eye surgery**.
  # **Skin care** and **lip augmentation**; ***creams***, ***serums***, ***injections*** (**Restylane®**) and as ***oral supplements***; **increases in skin moisture** and **decrease wrinkles**.

Drugs for Osteoporosis

- Osteoporosis is a *metabolic bone disorder* characterized by ***low*** **bone density**, ***decreasing*** its **strength** and ***resulting in increased*** **risk** *for* **bone fracture**.
- It is the ***most common*** **reason** for a **broken bone** in ***elderly***.
- ***Typically***; ***no symptoms***, ***until*** a **broken bone** ***occurs***.
- **Bone loss** ***increases*** ***after*** **menopause** (**postmenopause**) *due to* ***lower levels*** of **Estrogen**.

Non-pharmacological Therapy

Bone-Healthy Lifestyle

- *Diet*; * **Calcium and Vitamin D**; **Calcium** *and* **Vitamin D**.
  - **Vitamin K**; **Vitamin K** is a cofactor for ***carboxylation*** (*activation*) of proteins, such as **Osteocalcin**, which are involved in **bone formation**.
  - **Dietary Soy**; **Soy Isoflavones** are naturally occurring ***selective*** **estrogen receptor modulators**, with ***potential*** **bone protective** ***effects***.
- *Avoid* ***Alcohol*** and *Decrease* ***Caffeine***, ***Sodium*** *and* ***Smoking***.
- ***Carbonated Beverages***; **Phosphorus** intake (*soft drinks such as Cola*): ***reduced*** **bone mineral density (BMD)** and ***increased*** **fracture risk**.
- ***Exercise***; ***decrease*** the **risk of falls** and **fractures**.
- ***Fall Prevention***; **Patients** *should be* ***educated*** on **personal** and **home** ***safety options*** to ***decrease*** **falls**.

Drugs for Osteoporosis

Calcium & Vitamin D Supplementation

Calcium (Osteocare®)# (Marcal®)# (Caldin-C®)# (Calcitron®)# >>>

- ***Commonly used*** **Calcium supplements** include **Calcium Carbonate** & **Calcium Citrate**.
- **Calcium Carbonate** is generally ***less*** **expensive** and has ***better absorption*** *with* **food**.
- **Calcium** ***dietary*** **intake** *needs* to be known to ***calculate*** **correct** ***safe*** **supplemental dose**.
- ***Common side effects***; **Constipation**, **bloating**, **gas**, **stomach upset** and *rare* **kidney stones**.
- ***Common drug interactions***;
  - **Calcium** ***decrease*** **absorption** of **Iron**, **Tetracycline**, **Quinolones**, **Bisphosphonates**, **Phenytoin** and **Levothyroxine**.
  - **Calcium** ***increase*** the **effects** of **Digoxin**.
  - **Calcium** ***induce*** **hypercalcemia** with **Thiazide Diuretics**.
  - **Calcium** ***decrease*** the **effects** of **Calcium Channel Blockers** (**Diltiazem** and **Verapamil**).

Vitamin D Preparations

- **Vitamin D_2** & **Vitamin D_3** are ***not bioequivalent*** & ***should not*** be ***considered interchangeable***.
- **Vitamin D_3** is ***preferred over*** **Vitamin D_2**, because of its ***shorter half-life*** and ***decreased*** **potency** and **toxicity** (*little evidence*).
- ***Both*** **Vitamin D_2** and **Vitamin D_3** need to ***activation*** by ***hepatic metabolism*** to **25 (OH) vitamin D_3** and ***then*** ***renal metabolism*** to **1α,25(OH)$_2$ vitamin D_3** (**Calcitriol**; *the active moiety*).
- ***Common side effects***; **Hypercalcemia**, (weakness, headache, somnolence, nausea, cardiac rhythm disturbance) and **hypercalciuria**.
- ***Common drug interactions***;
  - **Phenytoin**, **Barbiturates**, **Carbamazepine**, **Rifampin** ***increase*** **Vitamin D** ***metabolism***.
  - **Cholestyramine**, **Colestipol**, **Orlistat** and **Mineral oil** ***decrease*** **Vitamin D** ***absorption***.

Ergocalciferol (Drisdol®)# (Sterogyl®)#

- **Ergocalciferol** is an ***inactive form*** of **vitamin D (vitamin D_2)**.

Indications; ***treatment of*** **hypoparathyroidism, vitamin D resistant rickets and familial hypophosphatemia.**

- ***Dose***; - **Vitamin D Resistant Rickets**: 12,000 to 500,000 IU units daily.
  - **Hypoparathyroidism**: 50,000 to 200,000 IU units daily.
  - **Dose for vitamin D deficiency**; 50,000 units (1.25 mg) once to twice weekly for 8–12 weeks; repeat as needed until therapeutic concentrations; occasionally 50,000 units monthly for maintenance.

Sterogyl® 15 "A"; Oral solution 600,000 IU/1.5 ml: (alcohol-based, colorless) Ampoule-vial filled to 1.5 ml, unit pack; in a ***single dose***, ***once*** a **year**.

Sterogyl® 15 "H": Oral and IM injection solution 600,000 IU/1.5 ml (oil-based, light yellow): Ampoule-vial filled to 1.5 ml, unit pack; in a ***single dose***, ***once*** a **year**.

Cholecalciferol (Devarol-S®)# (Vi-De 3®)# (Vidrop®)#

- **Cholecalciferol** is an ***inactive form*** of **vitamin D (vitamin D_3)**.
- ***Indications***; **Vitamin D deficiency prevention and treatment.**

Dose; 400–1,000 units/day orally **or** 1,000–2,000 units IM every 3-6 months to achieve adequate intake.

Alfacalcidol or 1-hydroxycholecalciferol [1α (OH) D_3] (One-Alpha®)#

- **Alfacalcidol** is an ***inactive form*** of **vitamin D [1α (OH) D_3]**.
- ***Activation***; **Alfacalcidol** need only to ***activation*** by ***hepatic metabolism***.
- ***Indications***; ***Most commonly*** for **Vitamin D deficiency in *patients with* end stage renal disease** (due to impaired renal second hydroxylation step).
- ***Dose***; 0.25-1 µg/day orally **or** injection.

Calcitriol or 1,25-dihydroxycholecalciferol [1,25-$(OH)_2$ D_3] (Rocaltrol®)#

- **Calcitriol** is an ***active form*** of **vitamin D [1α, 25 $(OH)_2$ D_3]**.
- ***Activation***; **Calcitriol *not need activation***.
- ***Indications***; **hypocalcemia, renal osteodystrophy, hypoparathyroidism and secondary hyperparathyroidism.**
- ***Dose***; 0.25–0.5 mcg orally **or** 1–2 mcg/mL intravenously daily.

Dihydrotachysterol (Hytakerol®)

- **Dihydrotachysterol (DHT)** is a ***synthetic vitamin D analog***.
- ***Activation***; ***activated*** in the **liver** that ***does not*** **require renal activation**.
- ***Indications***; **hypocalcemia, hypophosphatemia, rickets, osteomalacia, hypoparathyroidism, renal osteodystrophy** and **osteoporosis.**
- ***Dose***; ***in*** **osteoporosis**; 0.6 mg orally once a day.

- **19-nor-1,25-dihydroxyvitamin D2 (Paricalcitol)** and **Calcipotriene** or **Calcipotriol** are ***analogs of*** **Calcitriol** are ***approved for*** **treatment** of ***secondary hyperparathyroidism*** in *patients with* **chronic kidney disease**. **Calcipotriene** is ***approved for*** **topical treatment** of **psoriasis.**

Antiresorptive Medications

- *Antiresorptive*; agents that act by ***slowing*** **bone loss** by ***inhibiting*** the ***function*** of **osteoclasts**.

Bisphosphonates (BPs)

Bisphosphonates are ***potent*** **bone resorption inhibitors** and ***most commonly*** *prescribed* **antiresorptive medications** and ***remain*** **first-line** ***treatment for*** **osteoporosis**.

- **Bisphosphonates** (P-C-P) are ***biological analogues*** of naturally occurring **pyrophosphates** (P-O-P)
- They are *called* **bisphosphonates** because they have ***two*** **phosphonate** ***groups***.

Pyrophosphates are byproducts of ATP metabolism but have no biological activity because of the ubiquitous presence of pyrophosphatases

Bisphosphonates are ***used*** to treat **osteoporosis**, **Paget's disease** and ***certain types*** of **cancer** (***such as*** **bone metastasis** and **multiple myeloma**).

Oral and *intravenous* formulation of **Bisphosphonate** are ***available***.

Alendronate (Fosamax®)#	**Ibandronate** (Boniva®)#	**Risedronate** (Actonel®)#
Zoledronic acid (Zometa®)#	**Pamidronate** (Aredia®)#	**Clodronate** (Loron®)#
Etidronate (Didronel®)#	**Neridronate** (Nerixia®)#	**Tiludronate** (Skelid®)#

- **Alendronate**, **Neridronate**, **Ibandronate**, **Pamidronate**, **Risedronate** and **Zoledronic acid** have a ***nitrogen group*** and are *called* **nitrogen-containing BPs** (2nd and 3rd generation).
- ***Non*-nitrogen-containing BPs** are **Etidronate**, **Clodronate** & **Tiludronate** (1st generation).

Alendronate, **Ibandronate**, **Risedronate** and **Zoledronate** are the ***most popular first-line*** **bisphosphonate** used in **osteoporosis** and **Paget's**.

Oral BPs; **Alendronate**, **Ibandronate**, **Risedronate**, **Clodronate**, **Etidronate** & **Tiludronate**.

IV BPs; **Ibandronate**, **Zoledronic acid**, **Pamidronate**, **Neridronate** & **Tiludronate**.

Oral bisphosphonates are ***dosed on*** a **daily**, **weekly** or **monthly**.

IV bisphosphonates are ***dosed on*** **quarterly** (3 months) or **yearly**.

Bisphosphonates have an ***extremely high affinity*** for **bone tissue**.

Absorption of **oral bisphosphonates** is ***very poor*** (<1-10%), **food** and ***other*** **medications** (*such as* Calcium & Iron) *significantly* ***decrease absorption***.

20-80% of ***absorbed rapidly uptake*** by **bone** and the **remainder** ***rapidly excreted*** in the **urine**.

Bisphosphonates ***once bound*** to **bone**, they are ***cleared over*** a *period of* **hours** to **years**.

Bisphosphonates ***decrease*** **osteoclastic bone resorption** ***through*** an ***increase*** in **osteoclastic apoptosis** (*programmed cell death*) and ***decrease*** **osteoclast activity**.

Side effects;

- **Oral bisphosphonates**;
  - # **Stomach upset**, **inflammation** and **erosions** ***of the*** **esophagus** (main problem of oral N-containing preparations; *see precautions and patient counselling*).
  - # **Musculoskeletal pain**.
- **IV bisphosphonates**;
  - # **Fever** & **flu-like symptoms** (*acute inflammatory response*) after the ***first*** **infusion**.
  - # **Osteonecrosis** ***of the*** **jaw** (**ONJ**) *especially with higher doses for treatment cancer*.

Bisphosphonates PRECAUTIONS

1) ***Before starting bisphosphonates***; ***evaluation for*** **hypocalcemia, vitamin D deficiency** and **renal impairment**; hypocalcemia and/or vitamin D deficiency must be corrected.

2) ***Each*** **oral dose** ***should be*** taken ***alone*** on an ***empty stomach*** [*morning*] with ***at least*** **240 mL** of **tap water** (not coffee, juice, mineral water or milk) [enteric-coated delayed-release formulation (weekly) needs to be taken with only ~100mL] ***at least*** **30** (60 for **Ibandronate**) **minutes** ***before*** **consuming** ***any*** **food, supplements** (**Calcium**) or **medications** [*because bioavailability is very poor and to minimize GI side effects*].

3) **The patient** ***should be*** ***remain*** **upright** (*sitting or standing*) for ***at least*** **30 minutes** (60 for **Ibandronate**) [*to minimize esophagus ulceration*].

4) ***If*** ***missed dose***; - ***Weekly dose***; can take it the ***next day***, if ***more than*** **1 day** the ***dose is skipped*** *until* the **next week**.

- ***Monthly dose***; it can be ***taken*** up to **7 days** ***before*** the **next administration**.

5) **Patient** ***should*** **take** **Calcium** and **Vitamin D** (**Calcium** ***should not take at the same time***; at least one hour after bisphosphonates); **Fosamax® Plus** & **Fosavance®**; **Alendronate + Cholecalciferol**.

6) ***Should*** ***not*** be **given** to ***patients with*** **active upper GI disease**.

7) ***Should*** be ***discontinued*** in ***patients who*** **develop** ***any*** **symptoms** of **esophagitis**.

8) ***Delay*** **bisphosphonate therapy** in **dental** ***implant*** or ***extraction*** for a ***few*** **months** ***until*** **healing** of the **jaw** is ***complete***.

9) ***Once-yearly*** ***administration of*** **Zoledronic acid** ***should be*** ***infused*** ***over at least*** **15 minutes** with a **pump** [**Acetaminophen** or **ibuprofen** can be given to ***decrease*** **acute phase reactions**].

** **Dose** ** **For Osteoporosis** **

- **Alendronate**; *For prevention*; 5 mg daily or 35 mg weekly
  - *For treatment*; 10 mg daily or 70 mg tablet (**Fosavance®**; 70 mg tablet + vitamin D 2,800 or 5,600 units), or 75 mL liquid weekly.
- **Risedronate**; 5 mg daily, 35 mg weekly, 75 mg for 2 days monthly, 150 mg monthly
- **Ibandronate**; 150 mg monthly, 3 mg intravenous quarterly (every 3 months).
- **Zoledronic acid**; *For treatment*; 5 mg intravenous infusion yearly.
  - *For treatment*; 5 mg intravenous infusion every 2 year.

Selective Estrogen Receptor Modulators (SERMs)

- **Selective estrogen receptor modulators** (**SERMs**) are a **class of drugs** that *act on* the **estrogen receptor**, *produce* **estrogenic** and **anti-estrogenic effects** ***depending on*** the **specific tissue** (**mixed estrogen agonist/antagonist**; **EAA**).
- **SERMs** are considered to provide the ***beneficial effects*** of **Estrogen** ***without*** the **potentially adverse** ***outcomes***.
- **SERMs** are ***used dependent*** on their **pattern of action** in **various tissues**:

Femarelle® is a ***dietary supplement*** that may act as a **SERM**, it can ***reduce*** the **risk** for **osteoporosis**.

Raloxifene (Evista®)#

Raloxifene is a *selective* estrogen receptor modulator (SERM) *approved for* the *prevention* and *treatment* of osteoporosis in postmenopausal women.

It has *estrogen-like effects* on bone and *estrogen antagonist effects* on breast and endometrium.

- It is *FDA-approved* for *reduction* in risk of invasive breast cancer.
- *Supplemental* Calcium and Vitamin D *should be* added.
- Raloxifene causes some *+ve* lipid effects; *reduces* levels of total cholesterol and LDL.
- *Dose*; 60 mg orally once a day.
- *Common side effects*; hot flashes and leg cramps.
- *FDA black box warning*; *risk* of *venous thromboembolism* and death *due to* stroke.

Pregnancy; Raloxifene is a teratogenic drug (Category X).

- *Contradictions*; lactating women or pregnant women and in women with *active* or *past history* of venous thromboembolic events.

Bazedoxifene (Viviant®)#/Conjugated Estrogens (Premarin®)# OR Bazedoxifene/Conjugated Estrogens (Duavee®)#

- Bazedoxifene is a *3rd generation selective* estrogen receptor modulator; *by Pfizer.*

In 2013, Duavee® (Bazedoxifene/Conjugated Estrogens) *approval for* ***prevention*** (*not treatment*) of postmenopausal osteoporosis.

- Conjugated Estrogens; are *blended equine* estrogens, which may include estrone sulfate, equilin sulfate and equilenin sulfate.

Conjugated Estrogens are *added* to;

- *Reduced risk* of endometrial hyperplasia.
- *Reduced* vasomotor symptoms (hot flashes) of *menopause*.

- *Dose*; Conjugated Estrogens 0.45 mg and Bazedoxifene 20 mg orally *once* a day.
- *FDA black box warning*; *risk* of; *venous thromboembolism*, endometrial/breast cancer and probable dementia.

Pregnancy; Category X.

Calcitonin Hormone

Calcitonin (Miacalcic®)# (Miacalcin®)# (Fortical®)#

- **Calcitonin** is an ***endogenous hormone released from*** the **thyroid gland** when ***serum*** **calcium** is ***elevated***, ***opposing*** the **effects** of **parathyroid hormone (PTH)**.
- It is ***produced*** either by **recombinant DNA technology** or by **chemical peptide synthesis** of **Salmon Calcitonin** (*Salmon fish*).
- **Calcitonin-Salmon**; is ***more potent*** and ***longer lasting*** than **Mammalian Calcitonin**.

Indications; - **Postmenopausal Osteoporosis** (> 5 years of postmenopause); **intranasal** ***preferred than*** **parenteral**.
- ***Acute management*** **hypercalcemia** (*only IM or SC*).
- ***Symptomatic*** **Paget's disease** (*only IM or SC*).

- ***Because*** **efficacy** is ***less than*** the ***other*** **antiresorptive therapies** (*such as* **bisphosphonates**), **Calcitonin** is *reserved as* ***third-line treatment***.
- ***Dose***; In **Postmenopausal Osteoporosis**; - ***SC/IM***; 100 IU every other day.
  - ***Nasal Spray***: 1 spray (200 IU) daily.
- ***N.B.***; In **osteoporosis** ***ensure*** **adequate** **Calcium** and **Vitamin D** **intake**.
- ***Efficacy***; ***Only*** **vertebral fractures** ***decrease*** with ***intranasal*** **calcitonin therapy** (not affect hip).
- ***Pregnancy***; **Category C**.
- ***Warning***; - **Hypersensitivity reactions** (*anaphylaxis*).
  - **Nasal adverse reactions** (*rhinitis*).
  - **Malignancy**.
  - **Risk of hypocalcemia**.

Monoclonal Antibody

Denosumab (Prolia®)# (Xgeva®)#

- **Denosumab** is ***a monoclonal antibody*** with ***affinity*** for **nuclear factor-kappa ligand (RANKL)**.

Indications; - **Prolia®**; **Postmenopausal osteoporosis** (*with high risk of fracture*) *and* **bone loss** (*due to certain medications*).
- **Xgeva®**; **Hypercalcemia** of **malignancy** and **bone metastases**.

- ***Off-label***; **bone destruction** ***caused by*** **rheumatoid arthritis**.
- ***Dose***; 60 mg SC as a single dose, once every 6 months.
- ***N.B.***; ***Ensure*** **adequate** **Calcium** and **Vitamin D** **intake**.
- ***Most common side effects***; **joint** and **muscle pain**, ***increased*** **risk of infections** (*cellulitis*) and **hypocalcemia**, **hypersensitivity allergy reactions**, **osteonecrosis** *of the* **jaw (ONJ)** and **atypical hip fractures**.
- ***Pregnancy***; **Category D**.
- ***Contraindications***; ***Pre-existing*** **hypercalcemia**.

- **Romosozumab** is an ***anti-sclerostin monoclonal antibody*** in development for the treatment of **osteoporosis in postmenopausal women** at ***increased*** **risk of fracture** (*not approved; 5/2017*).

Hormone Replacement Therapy (HRT)

- *Although* **Estrogens** are ***FDA indicated*** for ***prevention*** of **osteoporosis**, they should only be used ***short-term***, because adverse effects associated with estrogen therapy (e.g., risks for breast cancer, myocardial infarction, stroke, and venous thromboembolic events).
- **Hormone replacement therapy (HRT)** [**Estrogen** ***with*** or ***without*** **Progestogen**] is ***not currently*** **recommended** for the ***treatment*** of **osteoporosis**.

Anabolic Therapy

Parathyroid Hormone (PTH)

Teriparatide (Forteo®)#

Teriparatide is a *recombinant form* of human parathyroid hormone (PTH).
- It is the ***only*** available **anabolic agent** (*bone growing*) for the ***treatment of*** **osteoporosis**.
- *Mechanism of action*;
  - ***Endogenous*** PTH ***regulate*** Calcium and Phosphate *metabolism* in **bone** and **kidney**.
  - PTH ***increase*** **serum** Calcium by ***increasing*** **bone resorption** (chronically elevated PTH will deplete bone stores).
  - *However*, ***intermittent*** **exposure** to PTH (once-daily injections of Teriparatide) will ***activate*** **osteoblasts** ***more than*** **osteoclasts**, ***stimulating*** **new bone formation** *leading to* ***increased*** **bone mineral density**.

Teriparatide ***increases*** **bone formation, bone remodeling rate, osteoblast number *and* activity**.

Teriparatide is the ***first*** **drug** that ***stimulates*** **bone formation** (other agents inhibit bone resorption).

Indications; - **Osteoporosis in men (primary** or **hypogonadal osteoporosis)**; *with high risk for fracture.*
- **Osteoporosis in postmenopausal women**: *with high risk for fracture.*
- **Glucocorticoid-induced osteoporosis**; *with high risk for fracture.*

- *N.B.*; Teriparatide ***should be reserved for*** **patients** at ***high risk of fractures*** and those who have ***failed*** or ***cannot*** **tolerate** ***other*** **osteoporosis therapies**.
- *Off-label*; Teriparatide also ***accelerates*** **fracture healing**.
- *N.B.*; ***Ensure*** **adequate** Calcium and Vitamin D **intake** (before treatment, levels of serum Calcium, PTH, and 25(OH) D need to be ***monitored***).

Dose; SC injection 20 mcg once a day in the thigh or abdomen.
- *Pregnancy*; Category C.
- *Contraindications*; - Teriparatide **administration** ***not recommended*** ***more than*** **2 years** (safety and efficacy not been evaluated).
  - ***Pre-existing*** **hypercalcemia**.
  - ***Severe*** **renal impairment**.
  - **Metabolic bone diseases** ***other than*** **primary osteoporosis** (such as **hyperparathyroidism** and **Paget's disease**).

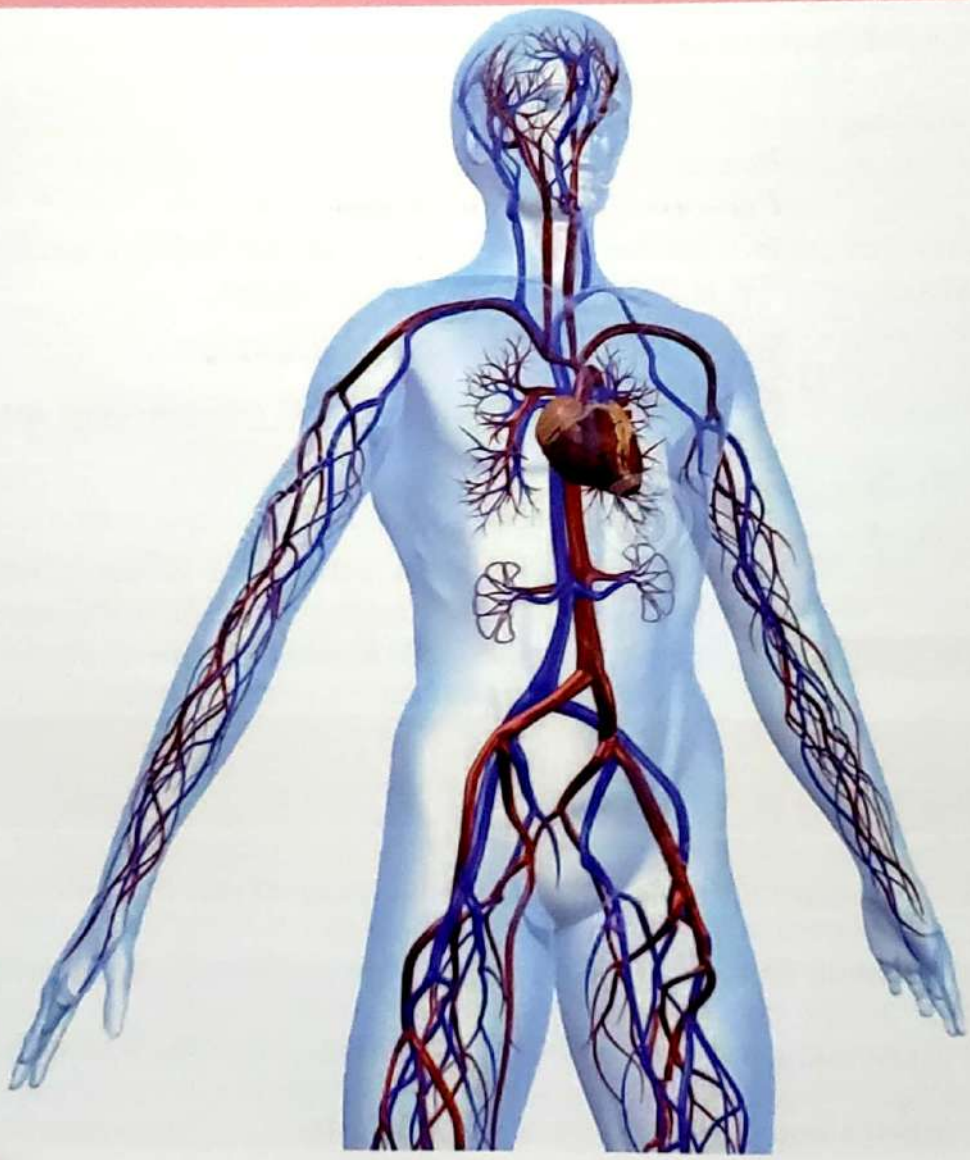
FDA black box warning; Teriparatide has been ***associated with*** an ***increased risk*** of **osteosarcoma** (cancerous tumor in a bone) in **rats**.

Other Agents

Strontium Ranelate (Protelos®)#

- Strontium Ranelate is composed of Ranelic acid and Strontium.
- It ***increases*** **collagen** and **non-collagenic proteins** ***synthesis*** by ***mature*** **osteoblast enriched cells**.
- The effects on **bone formation** were ***confirmed*** by ***enhanced pre-*****osteoblastic cells replication**.
- Strontium Ranelate is ***not approved*** by the **US FDA**, ***but*** in the **United Kingdom** is ***prescribed***.
- *Should be* **taken 2 hours *before*** **food** or **other agents**.

Cardiovascular System (CVS)



Hypertension

➢ Normal Resting Blood Pressure by Age:-

Blood Pressure Value	Male Age (year)			Female Age (year)		
	10-15	20-30	50-60	10-15	20-30	50-60
Systolic blood pressure SBP (mmHg)	100	120	134	84	120	130
Diastolic blood pressure DBP (mmHg)	60	80	84	40	74	84
Mean arterial pressure MAP (mmHg)	73	93	97	55	88	92

BP = Cardiac Output (CO) X Peripheral Vascular Resistance (PVR)

- Cardiac Output (CO): **CO** = Stroke Volume (**SV**) **X** Heart Rate (**HR**)
- Stroke Volume (SV): is the volume of blood pumped from the left ventricle of the heart per beat.
- Heart Rate (HR): is the speed of the heartbeat measured by the number of poundings of the heart per unit of time (typically beats per minute).
  - ***Increase*** **CO** or **PVR**, or **both** ⇨ ***Increase*** BP.
  - ***Decrease*** **CO** or **PVR**, or **both** ⇨ ***Decrease*** BP.

➢ Classification of Hypertension Defined by the American Heart Association:-

Blood Pressure Category	Systolic (mm Hg)	Diastolic (mm Hg)	Follow-up
Normal	< 120	< 80	Recheck once every 2 years.
High-normal (Prehypertension)	120-139	80-89	Recheck once every 1 year.
Stage 1	140-159	90-99	Confirm within 2 months.
Stage 2	≥ 160	≥ 100	Healthcare provider within a month.
Hypertensive Crisis	≥ 180	≥ 110	Emergency care needed

- *N.B.;* There is another classification in 2014 according to Eighth Joint National Committee (JNC 8), which the **prehypertension class** is ***removed***.

➢ Diagnosis of Hypertension:-

- Diagnosis of hypertension ***should be*** based on the **average of two or more readings taken at each of two or more clinical encounters.**
- Patient ***should be*** **seated quietly in chair for at least 5 minutes.**

➢ Uncontrolled Hypertension Effects on the Body:-

Arteries Damage;
- Artery walls thick and stiff (**arteriosclerosis**).
- ***Cause***; angina (chest pain), heart attack, heart failure, kidney failure, stroke, blocked arteries in legs or arms (peripheral artery disease) and eye damage.

Heart Damage;
- Uncontrolled high blood pressure can damage the heart in a number of ways, such as: **coronary artery disease**, **enlarged left heart** (left ventricular hypertrophy) and **heart failure** (heart muscle weakness and work less efficiently).

Kidneys Damage;
- Uncontrolled high blood pressure can injure renal blood vessels and leading **nephropathy**
- ***Cause***, weakens and damages the artery wall, lead to kidney failure.
- Diabetes in addition to high blood pressure can worsen the damage.

Eye Damage;
- *Cause*; **Hypertensive Retinopathy**:
  - Damage in the arterial and arteriolar circulation in response to the high blood pressure.

Brain Damage;
- **Stroke**; due to damaging and weakening brain blood vessels.
- **Dementia**; due to narrowing and blockage of the arteries that supply blood to the brain.

➢ Classification of Hypertension Defined by Causes:-

- **Primary (Essential or Idiopathic) Hypertension**: Majority of cases about 90%
  - No specific medical causes (no identifiable causes).
  - Unknown etiology but multiple factors may contribute to the development of primary hypertension including;
    - Smoking, obesity, stressful lifestyle, high dietary intake of sodium, family history and alcohol intake.
    - Overactive of renin-angiotensin system or sympathetic nervous system.
    - Deficiency in the local synthesis of vasodilating substances (NO, bradykinin and prostacyclin) or excess vasoconstricting substances (angiotensin II and endothelin).
    - Insulin resistance, hyperinsulinemia and obesity, also linked with renin-angiotensin system.
    - Vitamin D deficiency may leads to an increase in renin secretion.
- **Secondary Hypertension**: Few cases about 10%.
  - Most of these are caused by ↘
    - Chronic kidney disease or renovascular disease.
    - Primary aldosteronism (Conn's syndrome) & hypercortisolism (Cushing's syndrome).
    - Pheochromocytoma and hyperthyroidism.
    - Drugs may increase BP include; Corticosteroids, Estrogens, NSAIDs & Amphetamines.

➢ Treatments of Hypertension:-

Lifestyle Modification (Non-pharmacologic treatments)	Medications (Antihypertensive drugs)
- **Dietary Approaches to Stop Hypertension (DASH) eating plan**; *- BP reduced by 8–14 mm Hg.* - **Dietary sodium** (salts) **restriction**: *- BP reduced by 2–8 mm Hg.* - **Weight loss**; Normal (BMI 18.5–24.9 kg/m2) *- BP reduced by 5–20 mm Hg per 10-kg loss.* - **Regular aerobic physical activity**: *- BP reduced by 2–9 mm Hg.* - **Moderate alcohol consumption**: *- BP reduced by 2–4 mm Hg.* - **Smoking cessation.** - **Reduction of environmental stressors.**	- Diuretics. - β-blockers (BBs). - ACE Inhibitors (ACEIs). - Angiotensin Receptor Blockers (ARBs). - Direct Renin Inhibitors. - α-blockers. - Calcium Channel Blockers (CCBs). - Centrally Acting Sympathetic Inhibitors. - Peripherally Acting Sympathetic Inhibitors - Ganglionic Blockers. - Vasodilators. - Natural Antihypertensive Agents.

* **Lifestyle modification *alone*** are **effective for most patients with prehypertension, *but*** is **insufficient alone for patients with hypertension.**

Diuretics

Thiazide Diuretics

Hydrochlorothiazide (Esidrix®)# (Hydretic®)# | **Chlorthalidone** (Thalitone®)

Thiazide diuretics are ***not effective*** in **patients with inadequate kidney function** (estimated glomerular filtration rate less than 30 mL/min/m^2). **Loop diuretics** may be required in these patients.

- *Dose*; **Hydrochlorothiazide**; 25-100 mg/day (single). **Chlorthalidone**; 25-50 mg/day (single).

Uses; **1) Mild and moderate hypertension. 2) Congestive heart failure (CHF). 3) Nephrolithiasis (Idiopathic hypercalciuria). 4) Nephrogenic diabetes insipidus.**

Side effects; **Hypokalemia, metabolic alkalosis, hypercalcaemia, hyperuricemia, hyperlipidemia, hyperglycemia, hyponatremia, hypomagnesaemia, hypersensitivity.**

Contraindications; **Digitalis toxicity, hepatic cirrhosis** (overzealous use), **renal failure, sulfonamide allergy, Gout** and **Diabetes mellitus.**

Drug interactions; **Lithium, Digitalis** and **NSAIDs.**

Thiazide-Like Diuretics (Thiazide Analogues)

Indapamide (Natrilix® SR)# (Hypotense®)

Indapamide is the ***first*** of a ***new class*** of '**antihypertensive/diuretics**'.

It have a **unique mechanism of action**; act by combining **diuretic effects *with*** a **direct vasodilatation** (Ca^{2+} channels blocker) **effect.**

It *used* in **hypertension** and **edema** *due to* **congestive heart failure.**

- *Dose*; 2.5-10 mg/day (*single dose*).
- The drug produces toxicity similar to that of the thiazide diuretics.

Clopamide (Hypoten®)# | **Xipamide** (Epitens®) | **Metolazone** (Zaroxolyn®)#

Clopamide, Xipamide and **Metolazone** are a **thiazide-like diuretic** and works in *similar way* as the **thiazide diuretics.**

Loop Diuretics (High Ceiling)

Loop diuretics are the ***most efficacious*** **diuretic agents currently available.**

Loop diuretics are ***more effective*** in **patients with impaired kidney function.**

Furosemide (Lasix®)# | **Torsemide** (Examide®)# (Torseretic®)#

Bumetanide (Burinex®)# (Edemex®) | **Ethacrynic acid** (Edecrin®)#

Furosemide, Torsemide, Bumetanide are ***sulfonamide*** **loop diuretics.**

Ethacrynic acid, *not a sulfonamide* **diuretics.**

- *Doses*;

Drug	Total daily dose	Relative potency
Furosemide	20-80 mg	1
Torsemide	5-20 mg	3
Bumetanide	0.5-2 mg	40
Ethacrynic acid	50-200 mg	0.7

Uses; **1) Edema. 2) Hypertension. 3) Hyperkalemia. 4) Oliguria** (< 400 ml urine/day); ***only*** **high dose**; **Lasix 500 mg** tab. or **Lasix 250 mg** amp.

Side effects; **Hypokalemia, metabolic alkalosis, ototoxicity, hyperuricemia, hypomagnesaemia, hyponatremia, *severe* dehydration, hyperlipidemia, hyperglycemia** and **hypersensitivity.**

Contraindications; **Digitalis toxicity, hepatic cirrhosis** (overzealous use), **sulfonamide allergy** and **Gout.**

Drug interactions; **Aminoglycosides, Lithium, Digitalis, Warfarin** and **NSAIDs.**

Potassium (K^+) Sparing Diuretics (Low Ceiling)

- **Potassium-sparing diuretics** ***prevent*** **K^+ secretion** by antagonizing the effects of aldosterone in collecting tubules (aldosterone antagonists) ***or*** by inhibition of Na^+ influx through ion channels in the luminal membrane (non-aldosterone antagonists).

Aldosterone Antagonists

Spironolactone (Aldactone®)#	**Eplerenone** (Eplorefix®)#

- **Spironolactone** is a ***synthetic*** **steroid** that acts as a ***competitive*** **antagonist** to **aldosterone** at **mineralocorticoid receptors**, it has a slow ***onset of action*** *requiring* **several days** before ***full*** **therapeutic effect** is achieved.
- **Eplerenone** is a **spironolactone** ***analogue*** with ***much greater*** **selectivity** for the **mineralocorticoid receptors**.
- **Eplerenone** has a ***several*** **hundred-fold** ***less active*** on **androgen** and **progesterone** ***receptors*** *than* **Spironolactone**, therefore, **Eplerenone** has considerably ***fewer*** **adverse effects**.

Uses; **Spironolactone**;

- **Primary hyperaldosteronism (Conn's syndrome)**:
  - ***Usual adult dose***; Initial dose: 100 mg orally once a day. This dosage may be divided into two daily doses, and increased as tolerated every two to three days to a maximum recommended total daily dose of 400 mg.
- **Edema**; **Congestive heart failure (CHF)**, **Cirrhosis** or **Nephrotic syndrome**:
  - ***Usual adult dose for CHF***; 25 mg/day orally.

Essential hypertension; alone *or* in ***combination*** with **thiazide** or **loop diuretics**!!

1) ***Synergistic*** **diuretic effect**. 2) ***Correct*** **hypokalemia**.

Spironolactone 25 or **50 mg** + **HTZ 25** or **50 mg** (**Aldactazide®**)

Spironolactone 50 or **100 mg** + **Furosemide 20** or **50 mg** (**Lasilactone®**)

- ***Usual adult dose for HTN***; 25 to 200 mg/day orally in 1 or 2 divided doses.
- **Hypokalemia**; ***Usual adult dose***; 25 to 200 mg/day orally in 1 or 2 divided doses.
- **Antiandrogen**; **Hirsutism**, **acne** (in women) & **androgenic alopecia**.
  - ***Usual adult dose for Hirsutism***; 50 to 200 mg/day orally in 1 or 2 divided doses.

Side effects; - **Hyperkalemia** and **metabolic acidosis**.

- **Endocrine abnormalities**; **Gynecomastia** and **Impotence**; all have been reported ***only*** with **Spironolactone**.

Contraindications; **anuria** and **renal insufficiency** and **hyperkalemia**.

- ***Drug interactions***; **Other K^+-sparing diuretics, β-blockers, NSAIDs, ACEIs, ARBs, Aliskiren, K^+ supplements** and **diet rich in K^+**.

- **Diuretics** are ***not*** **part** of the ***standard*** **treatment** for **gestational hypertension** and **edema**. *Their application* is ***limited*** to **special indications**.

Hydrochlorothiazide is the ***drug of choice*** (**Category B**).

Furosemide *may be* **used** to ***manage*** **heart/kidney failure** (**Category C**).

Spironolactone *may be* **used** (**Category C**), it may showed ***feminization*** of **male fetuses** or **endocrine** ***dysfunction*** in *both* **male** and **female**.

Non-aldosterone Antagonists (Epithelial sodium channel blockers)

Amiloride (Midamor®)# | **Triamterene** (Dyrenium®)

- **Amiloride** & **Triamterene** are direct inhibitors of Na^+ influx in cortical collecting tubule
Used as **adjunctive treatment** with **thiazide diuretics** or **loop diuretics** in **congestive heart failure** or **hypertension** to;
  1) *Synergistic* **diuretic effect**.
  2) *Correct* **hypokalemia**.
  Amiloride 5 mg + **Hydrochlorothiazide** 50 mg (**Moduretic®**)
  Triamterene 37.5 mg + **Hydrochlorothiazide** 25 mg (**Dyazide®**)
- *Side effects*; - **Hyperkalemia** and **metabolic acidosis**.
  - **Triamterene** may cause **kidney stones** (*due to slightly soluble in urine*).
- *Drug interactions*; **Other K^+-sparing diuretics, β-blockers, NSAIDs, ACEIs, ARBs, Aliskiren, K^+ supplements** and **diet rich in K^+**.
  - **Triamterene** *with* **Indomethacin** has been reported to cause **acute renal failure**.

Carbonic Anhydrase Inhibitors

- By *blocking* **carbonic anhydrase** ⇨ ↓ **$NaHCO_3$** *reabsorption* (block Na/H^+ exchange) & cause **diuresis**. **Carbonic anhydrase inhibitors** are ***now*** **rarely used as diuretics**.
- *Pharmacodynamics*; - **Kidney**; weak self-limiting diuretic.
  - **Eye**; ↓ synthesis of aqueous humour (↓ IOP).
  - **CNS**; antiepileptic effects & ↑ ventilation.

Acetazolamide (Diamox®)# | **Methazolamide** (Neptazane®)

Dichlorphenamide (Daranide®) | **Dorzolamide** (Trusopt®)#

Brinzolamide (Azopt®)#

Uses; - **Diuretics** (***but*** **rarely used as diuretics**).
  - **Glaucoma**; **Acetazolamide** *dose* in **open angle** (**orally** or **IV**: 250 mg 1 to 4 times a day) and **close angle** (250 to 500 mg **IV**, may repeat in 2 to 4 hours to a maximum of 1 gram/day).
  Methazolamide *dose* in open and closed; 50 to 100 mg orally 2 to 3 times daily.
  Dichlorphenamide *dose*; ***initial***; 100mg 2 times daily, ***maintenance***; 25-50mg 1 to 3 times daily.
  Dorzolamide (**Trusopt** 2%) & **Brinzolamide** (**Azopt** 1%) *dose*; 1 drop 3 times daily.
  - **Urinary alkalinization and metabolic alkalosis**.
  - **Acute mountain sickness** (**Altitude sickness**); due to ↑ ventilation.
  - **Adjuvants in the treatment of epilepsy**.
- *Side effects*; **Hyperchloremic metabolic acidosis, hypokalemia & hypersensitivity**.
  - **Phosphaturia** and **hypercalciuria**; *due to* alkalinization of urine.
  - ***CNS***; **drowsiness** and **paresthesia**.

Osmotic Diuretics

Mannitol (Osmitrol®)

- **Mannitol** is classified as a **sugar alcohol**, which is derived from a sugar (mannose) by reduction. Other sugar alcohols include **xylitol** and **sorbitol**. **Mannitol** and **sorbitol** are ***isomers***.
- *Pharmacokinetics*; Mannitol is poorly absorbed by the GIT, when administered orally, it cause osmotic diarrhea rather than diuresis. For systemic effect, mannitol must be given IV.
- *Uses*; **Mannitol** is used clinically in **osmotherapy**;
  - ***Prevention*** and/or ***treatment*** of the **oliguric phase of acute renal failure**.
  - ***Reduction*** of **intracranial pressure** (**ICP**) and ***treatment*** of **cerebral edema**.
  - ***Reduction*** of elevated **intraocular pressure** (**IOP**); when cannot be lowered by other means.
  - ***Promotion*** of **urinary excretion of toxins**.

Antihypertensive Drugs

1) β-Blocker

All β-blockers are useful for *lowering* **blood pressure** in *mild* **to** *moderate* **hypertension**.
In *severe* **hypertension**, β-blockers are especially useful in ***preventing*** the **reflex tachycardia** that often results from ***treatment with*** **direct vasodilators**.
β-blockers have been shown to ***reduce*** **mortality** ***after*** a **myocardial infarction** and some also ***reduce*** **mortality in patients with heart failure**.
β-blockers precautions; **# # # # # # # # PATIENT COUNSELLING # # # # # # # #**

1) **β-blockers** ***must be*** **tapered off gradually**; ***Long-term*** use of **β-blocker** ⇨ ***up-regulation*** of the **β-receptors**. ***Sudden stop*** ⇨ ***increased*** **receptors sensitivity** and can ***worsen*** **angina** or **hypertension**.
2) *Non-selective β-blockers* ***used with caution*** in **insulin-dependent diabetic patients** (***Mask*** **hypoglycemia symptoms**).
3) *Non-selective β-blockers*, are *contraindicated* in patients with **COPD** or **asthma**.
4) **β-blocker** ***not used*** with **non-dihydropyridines Ca^{2+} channel blockers** (**Verapamil** and **Diltiazem**) ***to avoid*** **heart block**.
5) **Carvedilol > Metoprolol Succinate > Bisoprolol** are ***only*** **β-blockers** ***may be used*** in **CHF**.

Propranolol (Inderal®)#	**Nadolol** (Corgard®)#

Propranolol and **Nadolol** are a *non-selective* **β-blocker**
Nadolol is *more potent* than **Propranolol**.
- **Nadolol** has a *very long* **duration of action** with *low* **lipid solubility** than **Propranolol**.
- *Doses*;
  - **Propranolol**: (orally) ***initial***; 80 mg/day. ***Maintenance***; 120-240 mg/day (↑ if needed).
  - **Nadolol**: (orally) ***initial***; 40 mg/day. ***Maintenance***; 40-80 mg/day (↑ if needed)
  - **Propranolol** *other uses* (*non-cardio*); **hyperthyroidism**, **migraine** ***prophylaxis*** & **anxiety**.

Atenolol (Tenormin®)# (Ateno®)	**Bisoprolol** (Concor®)# (Bistol®)
Metoprolol (Lopressor®)#	**Nebivolol** (Nebilet®)# (Nevilob®)
Esmolol (Brevibloc®)#	

They are *selective* **β_1-blockers** (*cardioselective*); be ***advantageous*** in **treating hypertensive patients** who also ***suffer from*** **asthma**, **diabetes** or **peripheral vascular disease**.
Carvedilol > Metoprolol Succinate > Bisoprolol are ***only*** **β-blockers** ***used*** in **Congestive Heart Failure (CHF)**.
Nebivolol ***induce*** *releases of* **nitric oxide** from **endothelial cells** and causes **vasodilation**.
Esmolol is an *ultra-short-acting*, **half-life** (***about*** **10 minutes**). It is ***only available*** IV & it is ***used*** *during* **surgery** or **diagnostic procedures**, *sometimes* for **emergency care**.
- *Doses*;
  - **Metoprolol**: (orally) ***initial***; 100 mg/day. ***Maintenance***; 100-450 mg/day.
  - **Atenolol**: (orally) 50 mg once daily, ***may be increased*** to 100 mg once daily.
  - **Esmolol**: (IV) ***initial***; 500 mcg/kg/min over 1 min, ***Maintenance***; 50 mcg/kg/min for 4 min.
  - **Bisoprolol**: (orally) ***initial***; 5 mg once daily. ***Maintenance***; 5 to 20 mg once daily.
  - **Nebivolol**: (orally) ***initial***; 5 mg once daily. ***Maintenance***: > 40 mg once daily.

Acebutolol (Sectral®) | **Pindolol** (Visken®) | **Celiprolol** (Selectol®)
Oxprenolol (Trasicor®) | **Penbutolol** (Levatol®)

They are **β-blocker** with ***some*** **intrinsic sympathomimetic activity** (**ISA**), **They lower blood pressure** by ***decreasing*** **vascular resistance** and ***depress*** **cardiac output** or **heart rate** less than other β-blockers, ***and this may be particularly beneficial for*** **patients** with **bradyarrhythmias** or **peripheral vascular disease**.

- ***Doses***;
  - **Acebutolol**: (orally) ***initial***: 400 mg once or 200 mg twice. ***Maintenance***: 400 - 800 mg/day.
  - **Pindolol**: (orally) ***initial***: 5 mg twice daily. ***Maintenance***: 10 to 60 mg/day.
  - **Celiprolol**: (orally) ***initial***: 200 mg once daily. ***Maintenance***: 400 mg/day.
  - **Oxprenolol**: (orally) 80-160 mg a day, 2 to 3 doses. ***Maximum daily*** is 320 mg.
  - **Penbutolol**: (orally) ***initial***: 20 mg once daily. ***Maintenance***: 20 to 40 mg once daily.

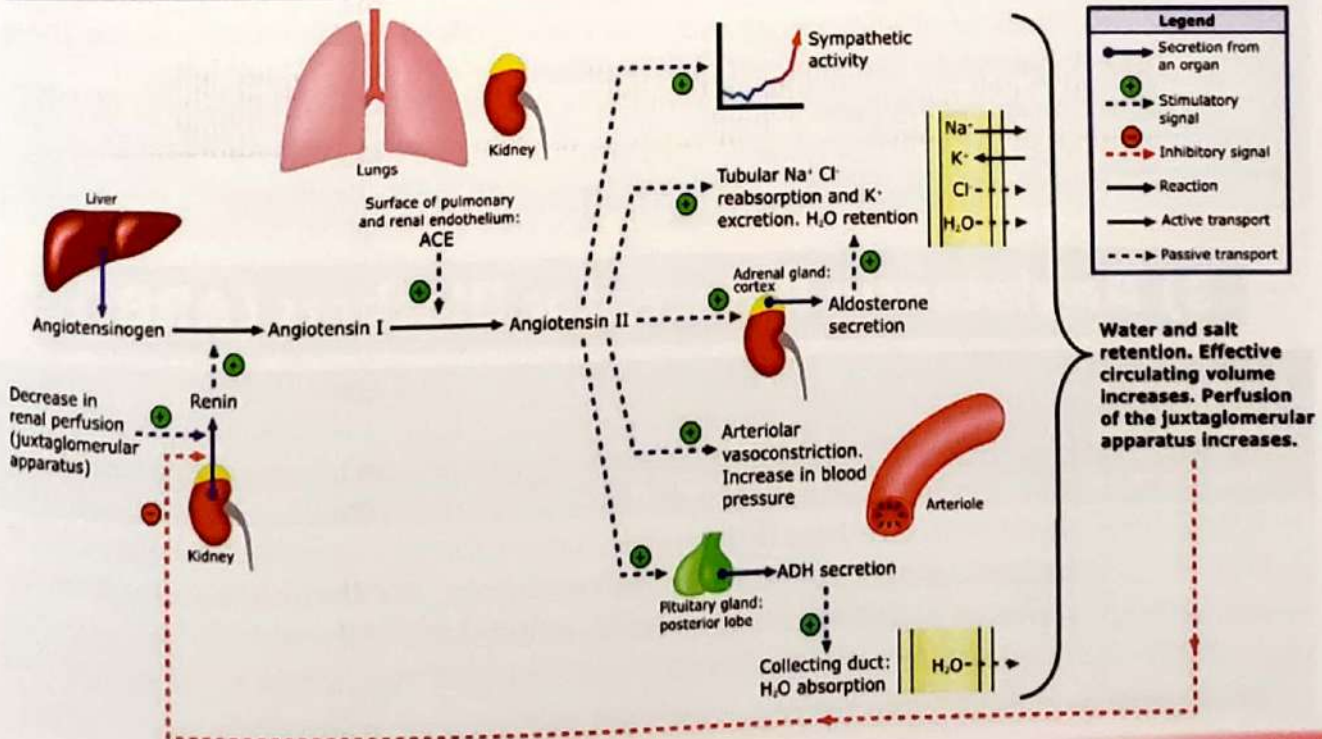
Labetalol (Trandate®) | **Carvedilol** (Dilatrend®)

Labetalol and **Carvedilol** are a ***non-selective*** **β-blocker** and ***selective*** **α_1-blocker**.
Labetalol used in treatment of ***chronic*** or ***acute*** **hypertension** *of* ***pheochromocytoma*** **and** ***hypertensive crisis***.
- **Carvedilol** *reduces* **mortality** in patients with **heart failure** (***protective effect***) and is therefore particularly ***useful*** in patients with ***both*** **heart failure** and **hypertension**.
- ***Doses***;
  - **Labetalol**: (orally) ***initial***: 100 mg twice daily. ***Maintenance***: 200 to 400 mg twice daily.
    (IV) 20-80 mg to treat **hypertensive crisis**.
  - **Carvedilol**: (orally) ***initial***: 6.25 mg twice daily with food. ***Maintenance***: 6.25-25 mg twice

2) Angiotensin-Converting Enzyme Inhibitors (ACEIs)

The **hypotensive activity** of **ACE inhibitors**, ***due to***;
  - ***Blocks*** the **conversion** of **angiotensin I** to **angiotensin II**.
  - ***Inhibits*** the **degradation** of **bradykinin** (vasodilator peptide, **cause** VD via NO release).
- **Cardiac output** and **heart rate** are ***not significantly*** changed.

Renin-angiotensin-aldosterone system



Captopril (Capoten®)#	**Lisinopril** (Zestril®)#	**Enalapril** (Renitec®)#
Fosinopril (Monopril®)#	**Perindopril** (Coversyl®)#	**Ramipril** (Tritace®)#
Benazepril (Cibacen®)	**Cilazapril** (Zapritens®)	**Imidapril** (Tanatril®)#
Zofenopril (Zofecard®)	**Quinapril** (Accupril®)	**Trandolapril** (Mavik®)

ACE inhibitors are easily identifiable by their common suffix, '**-pril**'.
All* ACE inhibitors** are ***orally bioavailable as a **drug** or **prodrug**.
All* ACE inhibitors** are given as **prodrug** to ***improve **oral bioavailability**, *except* **Captopril** and **Lisinopril**, ***so*** *these agents* may be ***preferred*** in **patients *with* severe hepatic impairment**.
Captopril is the ***first* ACE inhibitor**, and has a **shorter duration** of ***action***, and the ***only* sulfur-containing ACE inhibitor**; **sulfonamide allergy**.
Enalapril is an oral ***prodrug*** that is *converted to* **Enalaprilat**.
Enalaprilat is the ***only*** drug in this class **available** ***intravenously***.
Fosinopril is the ***only* ACE inhibitor** that is ***not eliminated*** primarily by the **kidneys** and does ***not require* dose adjustment** in patients with **renal impairment**.
ACE inhibitors *used* alone or in **combination**.
ACE inhibitors are ***first-line drugs*** for **hypertensive patients** *with* **diabetes**, **chronic kidney disease**, and patients at increased risk of **coronary artery disease**.

ACEIs precautions; **####### PATIENT COUNSELLING #######**

1) **Hypotension *may occur* after initial dose.**
2) **Avoid K^+ supplements, diet rich in K^+** and ***other drugs*** *that* **increases K^+ level** in the blood e.g. **ARBs**, **Aliskiren** and **K^+ sparing diuretics**; may cause ***life-threatening* hyperkalemia**.
3) **Dry persistent cough** and **angioedema** (>20%of patients); due to ***increase*** levels of **bradykinin** and **substance P**, this effect **resolves *within* a few days of discontinuation**. Can be treated by (***two studies suggested***);
   - **Iron supplements** (e.g. **Ferrous sulfate**) an ***inhibitor*** of **NO synthase**.
   - **NSAIDs**; (e.g. **Aspirin** 500 mg/day).
4) **Contraindicated *with* pregnancy**; ***increase* risk** of **fetal malformation** (**fetal lung hypoplasia** and **skeletal deformities**).
5) **Other *drug interactions***;
   - ***Increase* serum level** of **Lithium**.
   - **NSAIDs**; ***reduce* hypotensive effects** of **ACE inhibitors**.

3) Angiotensin II Receptor Blockers (ARBs)

Losartan (Cozaar®)#	**Valsartan** (Diovan®)# (Tareg®)#	**Candesartan** (Atacand®)#
Irbesartan (Aprovel®)#	**Eprosartan** (Teveten®)	**Telmisartan** (Micardis®)#
Olmesartan (Erastapex®)	**Fimasartan** (Kanarb®)	**Azilsartan** (Edarbi®)

ARBs *used* alone or in **combination**. **ARBs** have a ***similar benefits*** to those of **ACE inhibitors** in patients with **hypertension, heart failure** and **chronic kidney disease**.
ARBs *more selective blockers* of **angiotensin effect** than **ACE inhibitors**.
ARBs have a ***similar precautions*** to **ACE inhibitors**, but ***less*** in **cough** and **angioedema**.

4) Direct Renin Inhibitors

Aliskiren (Tekturna®)#

- **Aliskiren** is the ***first*** and ***only*** drug **available** in a **class** (FDA approval in 2007).
- It is ***used*** in **treatment of hypertension** (***alone*** or in ***combination***).
- It has **long duration of action**, used ***once daily***.

Aliskiren have a ***similar precautions*** to **ACE inhibitors**, but ***less*** < < < in **cough** and **angioedema**.

5) α-Adrenoceptor Blocking Agents

Prazosin (Minipress®)# | Doxazosin (Cardura®)# | Terazosin (Hytrin®)#

These drugs are ***selective competitive*** α_1 **receptors blockers** and ***used*** **primarily** ***in men*** *with* **concurrent hypertension and benign prostatic hyperplasia (BPH)**.

- ***Doses***;
  - **Prazosin**: (orally) ***initial***: 1 mg 2-3 times daily. ***Maintenance***: 6-15 mg/d in divided doses.
  - **Doxazosin**: (orally) ***initial***: 1 mg once daily. ***Maintenance***: 1-16 mg once daily.
  - **Terazosin**: (orally) ***initial***: 1 mg once daily at bedtime. ***Maintenance***: 1 to 5 mg once daily.

Most common side effects is **first-dose orthostatic hypotension** (***initial syncope attack or first-dose phenomenon***) this include **headache**, **dizziness** and **palpitations** ⇨ *to overcome*; the ***first dose*** must be;

1) **minimized**
2) ***Giving at*** **bed time**.

Phenoxybenzamine (Dibenzyline®) | Phentolamine (Rogitine®)

Tolazoline (Priscoline®)

- **Phenoxybenzamine**, **Phentolamine**, **Tolazoline** are ***non-selective*** **α-adrenoceptor blockers**.
- The drugs are **useful in diagnosis** and **treatment** of ***pheochromocytoma***.

6) Calcium Channel Blockers (CCBs)

There are three classes of CCBs;

1) **Dihydropyridines**; ***mostly***; *selective for* **vascular smooth muscle**.
2) **Phenylalkylamines**; ***mostly***; *selective for* **cardiac muscle**.
3) **Benzothiazepines**; ***intermediate between*** **phenylalkylamines** & **dihydropyridines**.

CCBs are ***useful*** in the **treatment** of **hypertensive patients** who also have **asthma**, **diabetes**, and/or **peripheral vascular disease**.

All CCBs are ***useful*** in the **treatment** of **angina**. In addition, **non-dihydropyridines CCBs** are ***used*** in the **treatment** of **atrial fibrillation**.

Side effects;

- # **Hypotension**; ***Dizziness***, ***headache***, and ***feeling of fatigue*** *with*; **Dihydropyridines**.
- # **Peripheral edema** *with*; **Dihydropyridines**.
- # **First-degree atrioventricular block** and **constipation** *with*; **Verapamil**.
- # **Verapamil** & **Diltiazem** ***should be avoided*** in **patients with heart failure** or **with atrioventricular block**.
- # **Nifedipine** & **other dihydropyridines** may cause **gingival hyperplasia**.

Pregnancy; ***Generally***; **CCBs are commonly used during pregnancy and lactation** to **treat hypertension**, **arrhythmia**, and **preeclampsia**. They have also been ***used*** as **tocolytic agents** to **prevent premature labour** and its complications.

Dihydropyridines

Nifedipine (Adalat®)#	**Amlodipine** (Norvasc®)#	**Felodipine** (Plendil®)#
Isradipine (DynaCirc®)	**Lacidipine** (Lacipil®)	**Nicardipine** (Cardene®)
Lercanidipine (Care dipine®)	**Nitrendipine** (Cardif®)	**Nimodipine** (Nimotop®)

This **CCB class** is *easily identified* by the suffix "**-dipine**".

All dihydropyridines have a *much greater affinity* for **vascular calcium channels** *than* for **calcium channels in the heart**; **Show** *little* **interaction** with other cardiovascular drugs, such as **Digoxin**.

- **Most of these agents** have ***short half-lives*** (3 to 8 hours) following an oral dose. **Sustained-release** (**SR**) preparations are available and permit ***once-daily dosing***. **Amlodipine** has a **very long half-life** and does not require a sustained-release formulation.

- *Indication and dosage*;

Drug	Indication (most common)	Dosage
Nifedipine	Angina, Hypertension, Raynaud's phenomenon	IV; 3-10 mcg/kg. Orally (*not SR*) 20-40 mg 3 times/d.
Amlodipine	Angina, Hypertension	5-10 mg orally once daily
Felodipine	Hypertension	5-10 mg orally once daily
Isradipine	Hypertension	2.5-10 orally twice daily
Lacidipine	Hypertension	2-6 mg orally once daily
Nitrendipine	Hypertension	20 mg orally once or twice daily
Lercanidipine	Angina, Hypertension	20-30 mg once daily at least 15 min before meals
Nicardipine	Angina, Hypertension, Cerebral vasospasm	20-40 mg orally 3 times daily
Nimodipine	Cerebral vasospasm, Subarachnoid Hemorrhage	60 mg orally every 4 hours

Nifedipine may be ***used for*** **migraine prophylaxis** or **premature labor**.

- **Felodipine** *interact with* **grapefruit juice** (block the CYP3A4 enzymes).

- **Nimodipine** and **Nicardipine** can ***pass*** **BBB** and is ***used to*** prevent **cerebral vasospasm**.

Clevidipine (Cleviprex®) is a ***newer agent*** that is ***formulated*** for **IV use only**.

Phenylalkylamines

Verapamil (Isoptin®)#

Verapamil has significant effects on ***both*** **cardiac** and **vascular smooth muscle**.

- It is the ***least effective*** of any **CCBs** on **vascular smooth muscle**.

It is ***used*** to **treat hypertension**, **angina**, **supraventricular tachyarrhythmias**, **migraine prophylaxis** and **cluster headaches prophylaxis**.

- *Adult dose*; Orally (**not SR**) 80-160 mg orally 3 times daily.
  IV 75-150mcg/kg as bolus over at > 2 min.

Benzothiazepines

Diltiazem (Altiazem®)#

- **Diltiazem** affects ***both*** **cardiac** and **vascular smooth muscle**.

It is ***used*** in the **treatment** of **hypertension**, **angina**, and **supraventricular tachyarrhythmias**.

Topical **Diltiazem** as a **2%** cream or ointment effective in **treatment chronic anal fissure**, it ***cause*** **muscle relaxation** and ***improve*** **blood flow** to ***facilitate*** **healing**.

- *Adult dose*; Orally (**not SR**) 30-80 mg orally 4 times daily.
  IV 75-150mcg/kg as bolus over at > 2 min.

7) Centrally Acting Sympathetic Inhibitors

Clonidine (Catapres®)#

Clonidine is an α_2 agonist (*centrally* and *peripherally*) is *used* for **hypertension**.
- *Adult dose*; - **Oral** (Catapres®) ⇨ ***Must be given*** twice a day.
  - *Initial*; 0.1 mg tablet twice daily (morning and bedtime).
  - *Maintenance*; 0.2-0.6 mg per day given in divided doses.
- **Transdermal** (Catapres-TTS®) ⇨ given once every 7 days.
- *Side effects* (*dose-related*); **Dry mouth, drowsiness, dizziness, constipation** and **sedation**.
ACEIs precautions; ######## **PATIENT COUNSELLING**
  - *Clonidine therapy should be gradually tapered off*; Clonidine ***suppresses sympathetic outflow*** resulting in ***lower*** **blood pressure**, but ***sudden*** **discontinuation** can cause ***rebound*** **hypertension** (***life-threating*** **hypertensive crisis**) due to a ***rebound*** in **sympathetic outflow**. (***Treated by*** α_1 and β blockers).

α-Methyldopa (Aldomet®)#

Methyldopa is an α_2 agonist that has *both* ***central*** and ***peripheral*** **effects**.
Used for **management of hypertension in pregnancy** (**FDA pregnancy** ***category*** **B**).
- ***Used with caution*** in **lactating women** (appears in breast milk).
- *Adult dose*;
  - *Initial*; 250 mg orally 2-3 times a day in the first 48 hours.
  - *Maintenance*; 500 mg to 2 g orally divided in 2 to 4 doses, up to a maximum of 3 g/day.
  - *Hypertensive emergency*; 250 to 500 mg IV over 30 to 60 minutes every 6 hours up to a maximum of 1 g every 6 hours or 4 g/day.

Selective Imidazoline Receptors Agonists

Rilmenidine (Hyperium®)	Moxonidine (Cynt®)
- *Used* in **mild to moderate essential hypertension**.	

8) Peripherally Acting Sympathetic Inhibitors

Guanethidine (Ismelin®)

- It acts by ***blocking the release*** of stored **norepinephrine** (NE).
- *Used* in the treatment of ***moderate*** and ***severe*** **hypertension** and **renal hypertension**.
- *Side effects*: **Bradycardia, orthostatic hypotension, failure of ejaculation & nasal congestion**

Reserpine (Hypoten®)#

- Reserpine is a **plant alkaloid** from dried root of ***Rauwolfia serpentina***.
- It acts by irreversibly blocks of monoamine neurotransmitters (norepinephrine, dopamine, and serotonin) from storage vesicles in the adrenergic nerve terminals in all body tissues.
- It has a ***slow onset***, a ***long duration*** of action.
- It is *used* in the treatment of **mild hypertension**.
- *Most common side effects*: diarrhea, hyperacidity, bradycardia and nasal congestion.

9) Ganglionic Blockers (GBs)

Trimethaphan (Arfonad®)	Mecamylamine (Inversine®)
- Mono sulfonium (S^+). - Don't pass BBB. - Ultra short duration of action (10 to 15 min.). - Not given orally (IV).	- Secondary amine. - Pass BBB. - Longer duration of action. - Given orally.

10) Vasodilators

Hydralazine (Apresoline®)

Hydralazine is a ***direct vasodilator***, it **dilates arterioles *but* not veins**.

Uses; - **Severe essential hypertension**.
- ***Commonly* used in combination *with* nitrates** for the **treatment of CHF in self-identified African American populations**.
- **Oral hydralazine** is effective as **monotherapy *or*** as **add-on therapy** to **methyldopa** in the long term **management of chronic hypertension in pregnancy**.

- *Adult dose*; - ***Oral dose***: 10 mg orally 4 times a day for the first 2 to 4 days. ***Increase*** to 25 mg orally 4 times a day for the balance of the first week. ***For the second and subsequent weeks***, increase dosage to 50 mg orally 4 times a day.
- ***Hypertensive emergency***; Usual dose: 20 to 40 mg IV or IM, repeated as necessary (patients with marked renal damage may require a lower dose).

Common side effects; **Headache, nausea, anorexia, palpitation, sweating** and **flushing**. Up to 20% of patients (how slowly acetylate the drug) who receive 400 mg/day or more mainly develop a # **systemic lupus erythematosus syndrome** #.

Minoxidil (Loniten®)

- **Minoxidil** is a ***very efficacious* orally active vasodilator**.
- Like **hydralazine, minoxidil dilates arterioles *but* not veins**.
- ***Because*** of its **greater potential antihypertensive effect, minoxidil *should replace* hydralazine *when* maximal dose of the hydralazine is not effective**.

Uses; - **Oral**; **Treatment of severe hypertension**.
- *Adult dose*; 5 mg as a single daily dose, may be increased to 10, 20 and then to 40 mg. The effective dosage range is usually 10 to 40 mg per day. The maximum recommended dosage is 100 mg/day.

#**Topical** (**Rogaine®**); **Androgenic alopecia** in **males** and **females** and **stabilisation of hair loss** in patients with androgenic alopecia.

- *Most common side effects;* **Tachycardia, angina** and **edema**.
- **Headache, sweating** and **hypertrichosis**.

Sodium Nitroprusside (Nipride®)

- **Sodium Nitroprusside**, is a ***powerful* short acting parenterally vasodilator** that is ***used*** in treating **hypertensive emergencies** as well as **sever heart failure**.
- It is **dilates *both* arterial** and **venous vessels**.
- *Pharmacokinetics*; - ***Duration of action***; 1 - 10 minutes after infusion is stopped.
- ***Dose***; 0.5 mcg/kg/min, maximum dose; 10 mcg/kg/min.
- *Toxicity*; The most serious toxicity is related to accumulation of cyanide and may cause death. Administration of **sodium thiosulfate** (sulfur donor) facilitates cyanide metabolism. **Hydroxocobalamin (vit. B_{12})** combined with cyanide to form the non-toxic cyanocobalamin.

Diazoxide (Proglycem®)

- **Diazoxide** long acting **arteriolar dilator** that is ***used*** to **treat hypertensive emergencies**.
- It is a ***potassium channel activator***, which causes vascular smooth muscle relaxation.
- It is also **inhibits the secretion of insulin** from the pancreas, thus it is ***used*** to **counter hypoglycemia** in disease states such as insulinoma (a tumor producing insulin) or congenital hyperinsulinism.
- ***FDA warning*** (7/2015) pulmonary hypertension has been reported in infants and newborns treated with diazoxide.

Fenoldopam (Corlopam®)

- **Fenoldopam** is a *peripheral* **dopamine D_1 receptors** *agonist*.
- *Routes of administration*: for **continuous IV infusion** only ⇨ due to extensive first-pass metabolism and short half-life elimination (10 minutes).
- *Period of administration*: up to 48 hours in adults - up to 4 hours in pediatric.
- *Mechanism of action*: **rapid-acting vasodilator** ⇨ agonist of peripheral dopamine D_1 receptors ⇨ VD of renal blood vessels ⇨ diuresis.
- *Uses*: **severe hypertension** in **hospitalized patients**.
- *Dose*: initial; 0.1 mcg/kg/min, dose titrated every 15 or 20 min. to a maximum 1.6 mcg/kg/min.
- *Adverse effects*: **Headache, flushing, dizziness, nausea** and **tachycardia**.

11) Natural Antihypertensive Agents

Hibiscus Tea (*Hibiscus sabdariffa*)

- Hibiscus flowers contain **anthocyanins**, which are believed to be the active antihypertensive compounds, acting as **ACE inhibitors**.
- There is **no difference** between drinking hibiscus **cold** *or* **hot**.

Co-Enzyme Q_{10}

- CoQ-10 is a natural antioxidant (is a vitamin-like substance) synthesized by the body, found in many foods & available as a supplement, found in small amounts in meats & seafood.
- CoQ10 may play a role in treating heart and **blood vessel** conditions such as **CHF**, **angina** and **hypertension**.
- CoQ10 may play a role in reducing the number and severity of **migraine headaches**, and improving ***sperm*** **motility** in men.

Statins have ***side effects***, including **muscle** and **joint aches**; taking a **CoQ10** *might* ***reduce*** the **risk** of these **side effects**.

➢ Special Populations:-

- Diuretics
- β-blockers
- ACEIs
- ARBs
- Renin Inhibitors

- α-blockers
- CCBs
- Centrally-acting inhibitors
- Peripherally-acting inhibitors
- Vasodilators

Population or Disease State	Preferred Agents	Avoid Agents
- African Americans and Elderly	Thiazide, CCB	
- Pregnancy	α-Methyldopa, CCB, Labetalol	ACEI, ARB, Aliskiren and >
- Coronary Diseases (Angina & MI)	β-blocker, CCB, ACEI, ARB	
- Asthma and COPD	CCB	β-blockers, ACEI, ARB
- Benign Prostatic Hyperplasia	α-blocker	
- Depression	CCB, ACEI, ARB	Centrally acting inhibitors, β-blockers, Reserpine
- Diabetes Mellitus	CCB, ACEI, ARB	β-blockers
- Gout	CCB, ACEI, ARB	Diuretics
- Heart Failure	ACEI, ARB, β-blocker	
- Hyperlipidemia	CCB, ACEI, ARB	β-blockers, Diuretics
- Migraine	β-blocker, CCB	
- Osteoporosis	Thiazide	Loop diuretics
- Peripheral Vascular Diseases	α-blockers, Dihydropyridines CCB	β-blockers
- Renal Diseases	Loop diuretics	Thiazide diuretics

Antihypotensive Drugs

Lifestyle Modification;

1) **Drink enough amount of water**; to increase blood volume.
2) **Add more salt *in* diet**; to increase blood volume.
3) **Eat healthy diet**; contains all nutrients for good health.
4) **Eat *small*, *low*-carbohydrate meals**; prevent blood pressure from dropping sharply after meals.
5) **Morning dose of caffeine**; as coffee or tablet form can be effective.
6) ***Stand up* gradually**; to reduce the dizziness and lightheadedness.
7) ***Avoid* standing for long periods of time**; to prevent neurally mediated hypotension.
8) **Wear compression stockings**; to reduce the pooling of blood in the legs.

Sympathomimetic Agents

Etilefrine (Effortil®)#

- **Etilefrine** is a cardiac stimulant, stimulation of both α and β adrenergic receptors.

Used for **symptomatic treatment of orthostatic hypotension (OH)**.

- ***Dosage forms***; oral solution (drops), tablets and injection.
- ***Oral solution*** (10 drops = about 5 mg) should be taken with liquid ***before*** **meals**;
  - **Under 2 years**: 2-5 drops three times a day.
  - **2-6 years**: 5-10 drops three times a day.
  - **Over 6 years**: 10-20 drops three times a day.

Midodrine (Gutron®)#

- **Midodrine** is a prodrug that is hydrolysed to **Desglymidodrine**.
- **Desglymidodrine**, is an **α_1-agonist**, ***does not*** stimulate cardiac β-adrenergic receptors.

It is ***used*** orally for **symptomatic treatment of orthostatic hypotension (OH)**.

- ***Dose***; adult, 10 mg orally three times a day. Do not give more frequently than every 3 hours, after the evening meal, or less than 4 hours before bedtime. Because Desglymidodrine is excreted renally, dosing in patients with abnormal renal function should be cautious, it is recommended that treatment of these patients be initiated using 2.5-mg doses.

Heptaminol (Corasore®)#

- **Heptaminol** is a cardiac stimulant drug, it have a positive inotropic action, with a slight peripheral vasoconstrictor properties.

Uses; **hypotension, fainting tendency** and **circulatory collapse**.

- ***Dose***; - **< 12 years**: 4-16 drops (25-100 mg) depending on age, 2-4 times daily, up to 6 times daily if necessary.
  - **< 12 years**: One tablet or 25 drops, (150 mg) 2-4 times daily, up to 6 times daily if necessary.
- ***Pregnancy***; No data available.

Sympathomimetic Agents used in Hypotensive Shock

- **Epinephrine**; ***used in* anaphylactic shock**.
- **Norepinephrine, Dopamine** and **Dobutamine**; ***used in* cardiogenic** and **septic shock**.

Synthetic Mineralocorticoids

Fludrocortisone (Astonin-H®)#

- **Fludrocortisone** (9α-fluorocortisol or 9α-fluorohydrocortisone) is a ***synthetic* corticosteroid** with ***moderate* glucocorticoid potency** and ***much greater* mineralocorticoid potency**.

It is ***used*** primarily to replace the missing aldosterone hormone in **adrenal insufficiency** (Addison's disease), it cause ↑ salt and water retention ⇨ ↑ blood volume ⇨ ↑ CO ⇨ ↑ BP.

- ***Used with caution*** in **diabetes mellitus, CHF, glaucoma, children** and **pregnancy**.
- ***Most common side effects***; ankle edema, hypokalemia, headache and rarely congestive heart failure.
- ***Dose***; 0.05 to 0.1 mg orally/24 hours.

Antianginal Drugs

1) Organic Nitrates

Nitroglycerin (NitromAck®)# | **Isosorbide Mononitrate** (Effox®)#
Isosorbide Dinitrate (Isordil®)# (Dinitra®)# | **Amyl Nitrate**

- *Doses*;
  - *Short Acting* (Acute Attacks):
    - **Nitroglycerin**;
      - IV; 5 mcg/min continuous IV infusion via non-absorptive tubing; increase by 5 mcg/min every 3 to 5 minutes as needed up to 20 mcg/min, then by 10 or 20 mcg/min if needed. N.B; Starting doses of 25 mcg/min or higher have been used with polyvinyl chloride (PVC) tubing.
      - **Lingual Spray**; 1 to 2 sprays (0.4 to 0.8 mg) on or under tongue every 5 minutes as needed, up to 3 sprays in 15 min.
      - **Sublingual Tablet**; 0.3 to 0.6 mg sublingually or in the buccal pouch every 5 min. as needed, up to 3 doses in 15 min.
    - **Isosorbide Dinitrate**;
      - **Sublingual Tablet**; 2.5-5 mg every 2 to 3 hours.
    - **Amyl Nitrite**;
      - **Inhalation**; 0.3 milliliter (1 ampule) taken by inhaling the vapour of amyl nitrite through the nose. Dose may be repeated within 1 to 5 minutes if pain is not relieved.
  - *Long Acting* (Angina Prophylaxis):
    - **Nitroglycerin**;
      - **Extend Release Capsule**; 2.5 to 6 mg orally 3 to 4 times a day.
      - **Topical Ointment**; 1/2 inch or 1.27 cm (7.5 mg) topically on rising in the morning and 1/2 inch (7.5 mg) 6 hours later.
      - **Transdermal Patch**; 0.2 to 0.4 mg/hr., patch applied topically once a day for 12 to 14 hr per day (patch-off 10-12 hr).
    - **Isosorbide Dinitrate**;
      - **Immediate Release**; initial: 5-20 mg orally 8-12hr, maintenance: 10-40 mg orally 8-12hr.
      - **Extended Release**; initial: 40 mg orally, maintenance: 40-80 once or twice daily.
      - **Sublingual Tablet** (***Prophylaxis***): 2.5-5 mg 15 minutes before performing activities likely to cause angina.
    - **Isosorbide Mononitrate**;
      - **Immediate Release**; 20 mg orally twice a day.
      - **Extended Release**; 30 to 60 mg orally once a day in the morning.
- *Side effects*;

Vasodilation Related Side Effects #

- *The major acute adverse effects of organic nitrates are*: **Orthostatic hypotension** (dizziness or syncope), **throbbing headache** (cerebral vasodilation), **reflux tachycardia** & **facial flushing**.

Nitrate Tolerance #

- Avoid Nitrate Tolerance;
  1) **Nitrate holiday** ("**nitrate free period**" or **NFP**) of at least 10 hours and preferably up to 14 hours is recommended to avoid tolerance;
     - *For example;*
       - Regular-release isosorbide dinitrate, which is administered 3-4 times daily, may be scheduled at 7:00 AM, Noon, and 5:00 PM.
       - Isosorbide-5-mononitrate and sustained release preparations of nitroglycerin or isosorbide dinitrate may be given twice daily at 8:00 AM and 3:00 PM, allowing a 10-12 hour nitrate holiday.
       - Removal of nitroglycerin ointment paper and residual ointment at bedtime.
       - A nitroglycerin transdermal patch placed at 8:00 AM may be removed at bedtime.
  2) **Sulfhydryl group donors** like **N-acetylcysteine** (**NAC**) and **L-methionine** have been shown to potentially reduce nitrate tolerance, but they may potentiate the effects of nitrates.
  3) Oral **vitamin C**, **vitamin E** (antioxidants) and **folic acid** may be effective in ameliorating nitrate tolerance.
  4) **Carvedilol** (antioxidant properties) and **Nebivolol** (antioxidant properties and NO-mediated vasodilatory effects) may reduce nitrate tolerance associated with continuous nitrate therapy.
- *Recent study*; ACEIs and ARBs may be effective in nitrate tolerance.

Drug Interaction; **Sildenafil**, **Tadalafil** and **Vardenafil**; *severe* **hypotension**.

2) β-Blockers

- *See previous topic*; Antihypertensive drugs.

3) Calcium Channel Blockers (CCBs)

- *See previous topic*; Antihypertensive drugs.

4) Newer Antianginal Drugs

Ranolazine (Ranexa®)#

It is a *newer antianginal drug* (approved in 2006), classified as Na^+ channel blocker.
- *Uses*; **treatment of chronic angina** and may be used ***alone*** or in ***combination***.
- *Dose*; 500 mg twice daily. ***May*** increase to 1 g daily, based on symptoms (max, 2g/day).
- *Drug interactions*; **Diltiazem**, **Verapamil**, **Erythromycin** and **grapefruit juice** and **Tricyclic antidepressants** (dose; not exceed 500 mg).
- *Most common side effects*; **dizziness**, **headache**, **constipation** and **nausea**.
- It ***can*** **prolong QT interval** and ***should be avoided*** with other drugs that cause QT prolongation.
- *Pregnancy*; **category C.**

Trimetazidine (Vastarel® MR)#

Trimetazidine (**TMZ**) is a **first cytoprotective anti-ischemic agent**.
- **Trimetazidine** has ***no*** **negative inotropic** or **vasodilator properties**.
- *Uses*; ***add-on therapy*** with **stable angina pectoris**.
- *Dose*; 20 mg 3 times a day during meals or 35 mg twice daily during meals.
- *Contraindication*; **Parkinson disease** & ***severe*** **renal impairment** (CrCl < 30ml/min).
- *Most common side effects*; **dizziness**, **headache**, **abdominal pain**, **diarrhea**, **dyspepsia**, **nausea**, **vomiting** and **hypersensitivity reactions**.

Nicorandil (Randil®)#

- **Nicorandil** is a ***new organic nitrate*** ***with*** ***vasodilator properties***.
- **Nicorandil** has the ***dual properties*** of a **nitrate** and **potassium channel activators**.
- *Dose*; 10 mg twice, may increase this dose if necessary, max. dose is 30 mg twice daily.
- *Most common side effects*; headaches, dizziness, flushing and reflex tachycardia.

Ivabradine (Procoralan®)#

- It was approved by the European Medicines Agency (EMA) in 2005 & by FDA in 2015
- It is *indicated for* the **symptomatic treatment of chronic stable angina pectoris** in patients with normal sinus rhythm who cannot take β-blockers or in combination with β-blockers in patients inadequately controlled with an optimal beta-blocker dose.
- It is *also indicated* in **combination *with* beta blockers** in **heart failure** patients with left ventricular ejection fraction lowers than 35% inadequately controlled by β-blockers alone and whose heart rate exceeds 70 beats per minute.
- *Dose*; starting dose 5 mg twice. The maintenance dose usually 7.5 mg twice daily.
- ***If there is no improvement within 3 months***, **Ivabradine** should be discontinued.
- *Most common side effects*; luminous phenomena or phosphenes (seeing light without light actually entering the eye), first-degree AV block, ventricular extrasystoles, dizziness and/or blurred vision.
- *Drug interactions*; **Liver CYP_3A_4 inhibitors.**

Drugs for Heart Failure (HF)

- *Treatment options of* acute decompensated heart failure (**ADHF**) *is different from* treatment options of chronic heart failure (**CHF**).

		ADHF	CHF
1) Angiotensin-Converting Enzyme (ACE) Inhibitors			✓
2) Angiotensin II Receptor Blockers (ARBs)			✓
3) Angiotensin-Receptor Neprilysin Inhibitors (ARNIs)			✓
4) β-Adrenergic Blocking Agents (β-Blockers)			✓
5) Diuretics	A) Loop Diuretics	✓	✓
	B) Thiazide Diuretics	✓	✓
6) Aldosterone Antagonists			✓
7) Vasodilators	A) Hydralazine + Isosorbide Dinitrate		✓
	B) Na^+ Nitroprusside or IV Nitroglycerin	✓	
	C) Nesiritide	✓	
8) Inotropic Agents	A) Cardiac Glycosides		✓
	B) β-Adrenergic Agonists	✓	
	C) Phosphodiesterase III Inhibitors	✓	

- ✓; Drugs which are used.
- ADHF; Acute Decompensated Heart Failure.
- CHF; Chronic Heart Failure.

1) ACE Inhibitors

ACEIs *should be prescribed* to **all patients** *with* **HF*r*EF**, *unless* there is a **contraindication**.
- *Monitoring*; renal function and serum K^+ should be assessed within 1-2 weeks of initiation of therapy, recheck at 1, 3 and 6 months, if the function is normal perform it every 6 months.
- *See previous topic*; **Antihypertensive drugs**.

2) ARBs

ARBs are *recommended* in **patients with HF*r*EF with current or prior symptoms who are unable to take an ACE inhibitor**.
- *See previous topic*; **Antihypertensive drugs**.

3) Angiotensin-Receptor Neprilysin Inhibitors (ARNIs)

Sacubitril/Valsartan (Entresto®)#

#ARNIs are a *new drug combination* of a **neprilysin inhibitor** and an **ARB**.
- First approved by FDA in July 7th, 2015.
- **Entresto®** an oral fixed-dose combination of the ***neprilysin inhibitor*** **Sacubitril** and the ***angiotensin receptor blocker*** (**ARB**) **Valsartan**.

Used in ***conjunction with*** other **heart failure therapies**, *in place of* an **ACE inhibitor** or *other* **ARBs**.
- **Sacubitril** is a ***pro-drug*** that is activated to LBQ657, which inhibits neprilysin enzyme.
- ***The recommended starting dose*** of **Entresto®** is 49/51 mg (Sacubitril/Valsartan) twice-daily. Double the dose of **Entresto®** after 2 to 4 weeks to the target maintenance dose of 97/103 mg (Sacubitril/Valsartan) twice-daily.

4) β-Blockers

Three β-blockers have been shown to be effective in reducing the risk of death in patients with chronic HF*r*EF: **Bisoprolol**, **Carvedilol**, and **Metoprolol Succinate**.
- **β-blockers** ***should be*** **prescribed to all patients *with* HF*r*EF *unless*** they have a contraindication to their use or are intolerant of these drugs.
- *See previous topic*; **Antihypertensive drugs**.

5) Diuretic Agents

Diuretics are ***recommended*** in **patients *with* HF*r*EF *who have evidence of* fluid retention**.
- **Loop diuretics** are ***preferred*** diuretic agents for use in most patients with HF.
- ***Should be*** prescribed to **all patients *with* fluid retention**.
- ***Should be combined with*** an **ACE inhibitor**, **β-blocker** and **aldosterone antagonist**.
- *See previous topic*; **Antihypertensive drugs**.

6) Aldosterone Antagonists

- **Aldosterone antagonists** are ***recommended in patients with***;
  - **Patients with NYHA class II-IV HF and who have LVEF of 35% or less.**
  - **Patients with HF*r*EF after myocardial infarction.**
- ***Should be added*** to **ACE inhibitor**, **β-blocker**.
- ***Monitoring***: **K^+ levels** and **renal function *should be*** rechecked within 2 to 3 days and again at 7 days after initiation of therapy.
- *See previous topic*; **Antihypertensive drugs**.

7) Vasodilators

A) Hydralazine + Isosorbide Dinitrate (*only for* CHF)

The combination of **Hydralazine** and **Isosorbide Dinitrate** (**BiDil®**) are ***recommended in addition to*** **ACE inhibitors + β-blockers to reduce morbidity and mortality for patients self-described as African Americans with HF*r*EF.**
The combination of **Hydralazine** and **Isosorbide Dinitrate** (**BiDil®**); ***may be useful*** in **patients with current or prior symptoms of HF*r*EF who are unable to tolerate an ACEI or an ARB.**
- ***Dosing and administration;***

Initial Dose	Target Dose
37.5 mg hydralazine + 20 mg ISDN 3 times daily	75 mg hydralazine + 40 mg ISDN 3 times daily

B) Na+ Nitroprusside or IV Nitroglycerin (only for ADHF)

- **Sodium Nitroprusside** (Nipride®); *useful for* **patients with ADHF and advanced HF.** *Typical dose*; 0.5-1 mcg/kg/minute IV.
- **IV Nitroglycerin**; is a rapid and short acting organic nitrate, it produces venous vasodilation ***reductions*** in **preload, arterial BP** and ***relief*** **pulmonary congestion** make it particularly *useful for* **patients with ADHF.** *Typical dose*; 25-75 mcg/minute IV, titrated to response.

C) Nesiritide (only for ADHF)

- **Nesiritide** (Natrecor®); *Used in* **patients with ADHF who have dyspnea at rest or with minimal physical activity.**
- *Typical dose*; 0.01 mcg/kg/minute IV, May omit bolus if low systolic blood pressure.

8) Inotropic Agents

A) Cardiac Glycosides

Digoxin (Lanoxin®)#	**Digitoxin** (Unidigin®)	**Ouabain** (Uabanin®)

Digoxin therapy is *indicated* in **patients with severe HF*r*EF after initiation of ACE inhibitor, β-blocker** and **diuretic therapy.**
- *Better results* are obtained in **patients with atrial fibrillation or flutter.**
- *Dose*;
  - **Digoxin**; **0.125 to 0.25 mg daily** or ***every*** **other day**
  - **Monitoring Serum Digoxin Concentration** (SDC); range of 0.5 to 0.9 ng/mL.

Side effects;
- **Major side effect** is **cardiac arrhythmia.**
- ***Early manifestation of toxicity***; **Anorexia, nausea** and **vomiting** and **bradycardia.**
- ***Late manifestation of toxicity***;
  - ***Eye***; **Visual disturbance** (**Chromatopsia** or **Xanthopsia**).
  - ***CVS***; **Arrhythmias.**
  - ***GIT***; **Anorexia, nausea, vomiting** and **diarrhea.**
  - ***CNS***; **Hallucination, convulsions, confusion** and **delusions.**
  - ***Endocrine***; **Gynecomastia** (rare).

Factors that increase digitalis toxicity; **### PATIENT COUNSELLING ###**
- **Drugs increase toxicity** e.g. thiazide and loop diuretic (hypokalemia).
- **Organ dysfunction** e.g. Kidneys (Digoxin) and liver (Digitoxin).
- **Dosing *errors*.**
- **Old age** (>70 years of age).
- **Serum electrolytes disturbances**: hypokalemia, hypomagnesaemia or hypercalcemia.

Digoxin Immune Fab (Ovine) (Digibind®)#

Digoxin Immune Fab (Ovine), is a sterile lyophilized powder of antigen binding fragments (Fab) ***derived from*** specific **antidigoxin antibodies** raised in sheep (Ovine).
Digoxin Immune Fab (Ovine), is ***indicated for*** **treatment of potentially life-threatening digoxin intoxication.**
- *Dose*;
  - A) Skin Testing.
  - B) Dose Calculations;

TABLE : Adult Dose Estimate of DIGIBIND (in # of vials) from Steady-State Serum Digoxin Concentration

	Serum Digoxin Concentration (ng/mL)						
Patient Weight (kg)	1	2	4	8	12	16	20
40	0.5 v	1 v	2 v	3 v	5 v	7 v	8 v
60	0.5 v	1 v	3 v	5 v	7 v	10 v	12 v
70	1 v	2 v	3 v	6 v	9 v	11 v	14 v
80	1 v	2 v	3 v	7 v	10 v	13 v	16 v
100	1 v	2 v	4 v	8 v	12 v	16 v	20 v

v = vials

B) β-Adrenergic Agonists (only for ADHF)

Dopamine (Intropin®)#	Dobutamine (Dobutrex®)#

Dopamine; is a cardiac stimulant drug (**β_1 agonist effect**) ⇨ +ve inotropic. It has renal blood vessels dilatation effect (**D_1 agonist**) ⇨ increase blood flow to the kidneys).

Dobutamine is a ***predominantly* β_1 receptor agonist** ⇨ improve cardiac performance by causing positive inotropic effects with slight peripheral vasodilation.

- **Dobutamine** is ***the most commonly used*** **inotropic agent.**
- **Dobutamine** ***typical dose***; 5 mcg/kg/minute IV.
- ***Both drugs*** must be given by IV infusion and are primarily ***used in*** the **short-term treatment of ADHF** in the hospital setting.

C) Phosphodiesterase III Inhibitors (only for ADHF)

Amrinone (Inocor®)#	Milrinone (Primacor®)#

Both drugs must be given by IV and are primarily ***used in*** the **short-term treatment of ADHF** in the hospital setting.

- ***Dose***; - **Amrinone**; 0.75 mg/kg IV bolus over 2-3 minutes, then 5-10 mcg/kg/min IV.
  - **Milrinone**; 50mcg/kg IV bolus, then 0.375 mcg/kg/min IV.
- ***Side effects***; Arrhythmia, Hypotension and Thrombocytopenia.

Antiarrhythmic Drugs

Class/Ion Affected	Agents	Physiologic Effect	Result on Electrophysiologic Parameters	Clinical Utility
Class I (Na⁺ channel blockers)				
IA (intermediate)	Quinidine Disopyramide Procainamide	↓ Conduction velocity ↑ Refractory period	↑ QRS complex and ↑ QT interval	Atrial and ventricular arrhythmias
IB (fast)	Lidocaine Mexiletine	↓ Conduction velocity ↓ Refractory period	↓ QT interval	Ventricular arrhythmias
IC (slow)	Flecainide Propafenone	↓↓↓ Conduction velocity Ø Refractory period	↑ QRS complex	Supraventricular arrhythmias and ventricular arrhythmias
Class II (β-Blockers)	Metoprolol Esmolol Atenolol	↓ Conduction velocity ↑ Refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias
Class III (K⁺ channel blockers)	Amiodarone Dronedarone Sotalol Dofetilide Ibutilide	Ø Conduction velocity ↑↑↑ Refractory period	↑ QT interval	Atrial and ventricular arrhythmias
Class IV (Ca²⁺ channel blockers)	Diltiazem verapamil	↓ Conduction velocity ↑ Refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias

1) Class I (Sodium Channel Blockers)

A) Class IA

Quinidine (Quinacard®) | **Procainamide** (Pronestyl®) | **Disopyramide** (Norpace®)

- **Quinidine**; **Atrial fibrillation/flutter** and **ventricular tachycardia**.
  - ***Dose***; As Sulfate: 200–400 mg orally every 6 hours.
    As Gluconate (CR): 324 mg orally every 8-12 hours.
- **Procainamide**; **Atrial fibrillation/flutter conversion**: 1 g IV for 30 min; then 2 mg/min.
  - **Ventricular tachycardia conversion**: 20 mg/min IV until 17 mg/kg or arrhythmia is controlled.
  - **Ventricular tachycardia maintenance**: 1-4 mg/min.
    (reduce dose in renal and liver dysfunction)
- **Disopyramide**; **Atrial fibrillation/flutter conversion**: Immediate-release (IR) 200 mg (if <50 kg) or 300 mg (if >50 kg) orally/6 hours.
  - **Atrial fibrillation/flutter maintenance**: IR 150 mg orally every 6 hours or as controlled release (CR) 300 mg orally every 12 hours, dose adjustment if; <50 kg, moderate renal dysfunction or hepatic dysfunction.

Side effects;

- **Quinidine**; ***common side effects***; **nausea**, **vomiting**, **diarrhea** and **Cinchonism** or **Quinism** (**blurred vision**, **tinnitus**, **headache**, **disorientation** and **psychosis**).
- **Procainamide**; ***common side effects***; **hypotension** (IV).
- **Disopyramide**; ***common side effects***; **anticholinergic effects** (**dry mouth**, **urinary retention**, **blurred vision** and **constipation**).
- ***Both*** **Quinidine** and **Disopyramide** should be ***used with*** **caution** with ***potent*** **inhibitors** of **CYP3A4**.

B) Class IB

Lidocaine (LidoPen®) | **Mexiletine** (Mexitil®)

Lidocaine is the ***agent of choice*** for ***termination*** of **ventricular tachycardia** and ***prevention*** of **ventricular fibrillation after acute myocardial infarction**.

- **Mexiletine** is indicated for the ***treatment*** of **ventricular tachycardia**.

Side effects;

- **Lidocaine** has a **wide therapeutic index**, ***common side effects***; CNS effects; nystagmus (early indicator of toxicity), drowsiness, slurred speech, paresthesia, agitation, confusion and convulsions.
- **Mexiletine** has a **narrow therapeutic index** and caution should be used when administering the drug with inhibitors of CYP2D6, ***common side effects***; nausea, vomiting, and dyspepsia.

C) Class IC

Flecainide (Tambocor®) | **Propafenone** (Rythmol®)

- **Flecainide**;
  - **Atrial fibrillation/flutter conversion**; 300 mg orally once.
  - **Atrial fibrillation/flutter maintenance**, **Ventricular tachycardia**, **Wolff-Parkinson-White Syndrome** and **Supraventricular tachycardia**; 50-150 mg orally/12 h.
- **Propafenone**;
  - **Atrial fibrillation/flutter conversion**: 600 mg orally once.
  - **Atrial fibrillation/flutter maintenance**, **Ventricular tachycardia**, **Wolff-Parkinson-White Syndrome**; *Immediate release*: 150-300 mg orally every 8-12 hours.
    - *Extended release*: 225-425 mg orally every 12 hours.
- ***Side effects***; **blurred vision**, **dizziness** and **nausea**.
- **Propafenone**; may cause **bronchospasm**
- ***Both*** **drugs** should be used *with* **caution** with ***potent*** **inhibitors** of **CYP2D6**.

2) Class II (β-blockers)

- Class II are ***useful in treating*** **tachyarrhythmias** caused by increased sympathetic activity.
- They are also ***used for*** **atrial flutter** and **fibrillation** and for **AV nodal reentrant tachycardia**. In addition, β-blockers ***prevent*** **life-threatening ventricular arrhythmias following a myocardial infarction**.
- **Esmolol** is a ***short acting*** **β-blocker** used primarily as an ***antiarrhythmic drug for*** **intraoperative and other acute arrhythmias**.
- **Sotalol** is a ***nonselective*** **β-blocker** that prolongs the action potential ⇨ **class III action**.
- *See previous topic*; **Antihypertensive drugs**.

3) Class III (Potassium-Channel Blockers)

Amiodarone (Cordarone®)#

Structure; **Amiodarone** ***contains*** **iodine** and is related structurally to **Thyroxine**.
Bioavailability; bioavailability = 35-65% (***due to*** variably absorption).
Onset of action; may occur in 2 to 3 days, but more commonly takes 1 to 3 weeks, even with loading doses.
Elimination half-life; is a complex, with a rapid component of 3-10 days (50% of the drug) and a slower component of several weeks.
After discontinuation of the drug; effect are maintained for 1-3 months.
Metabolism; **Amiodarone** is metabolized to **des-ethyl-amiodarone** (DEA) by CYP3A and CYP2C8. Dose should be reduced by up to 50% in substantial liver impairment
Elimination; biliary excretion.
Dosage Guidelines for Amiodarone;

Life-threatening arrhythmia	150-mg IV bolus over 10 minutes (if necessary, bolus may be repeated in 10 to 30 minutes); then 1 mg per minute for 6 hours; then 0.5 mg per minute for 18 hours; then reduce IV dosage or convert to oral dosing when possible.
Ventricular arrhythmia	800 to 1,600 mg per day in divided doses until a total of 10 g has been given; then 200 to 400 mg per day.
Atrial fibrillation	600 to 800 mg per day in divided doses until a total of 10 g has been given (may use higher initial dosage or IV dosing in unstable inpatients); then 200 mg per day.

Toxicity; **Pulmonary fibrosis** 3-17%, **hyperthyroidism** 3%, **hypothyroidism** 30% (**amiodarone-induced thyrotoxicosis**; **AIT**), **neurologic toxicity** 20-40%, **GI upset**, **photosensitivity**, **hepatitis**, **blue-gray skin discoloration** 15%, **heart block** 14%, **hypotension** (IV) and **phlebitis** (IV).

- ***Most common drug interaction***; warfarin, digoxin, statins.
Finally; Keep an eye on **Amiodarone patients**.

Dronedarone (Multaq®)#

Dronedarone is a ***non-iodinated*** **Amiodarone derivative**.
Pharmacokinetics; ***less*** **lipophilic**, has ***lower*** **tissue accumulation** and has a ***shorter*** serum **half-life** than amiodarone.
Side effects; **Dronedarone** has a ***better*** **adverse effect profile** than **Amiodarone** ***but*** **may still cause liver failure**.
Uses; **Dronedarone** is used to maintain sinus rhythm in **atrial fibrillation** or **flutter**, ***but*** it is **less effective** than **Amiodarone**.
- ***Dose***; 400 mg orally 2 times a day with a meal.
- ***FDA Warning***; Dronedarone is ***contraindicated*** in **patients with symptomatic heart failure with recent decompensation requiring hospitalization** or **NYHA class IV heart failure**.
- **Celivarone** is another ***non-iodinated*** **Amiodarone derivative** similar to **Dronedarone** that is currently undergoing clinical trials (Sanofi-Aventis) for the prevention of ventricular recurrence.

Sotalol (Betacor®)#

Sotalol is a *non-selective* competitive β-adrenergic receptor blocker that also exhibits Class III antiarrhythmic properties.
- The *l*-sotalol has β-blocking activity, and *d*-sotalol has class III antiarrhythmic action.
Uses; atrial fibrillation, atrial flutter and ventricular arrhythmias.
- *Dose*; - *Initial*: 80 mg orally 2 times a day, dose *should be* adjusted gradually every 3 days.
  - Dose should be *adjusted* in people with a creatinine clearance rate below 40 mL/min.
- *Side effects*; This drug can cause the typical adverse effects *associated* with β-blockers *but* has a *low rate* of adverse effects *when compared* to other antiarrhythmic agents.

Dofetilide (Tikosyn®)

- Dofetilide is a pure potassium channel blocker, *dose*; 125-500 mcg twice a day.
- *Uses*; It is approved for the maintenance of normal sinus rhythm in patients with atrial fibrillation.
- *Because* of the risk of pro-arrhythmia, treatment with Dofetilide *should be initiated* in hospital *after baseline measurement* of rate corrected QT interval and serum electrolytes.

Ibutilide (Corvert®)

- Ibutilide is a potassium channel blocker *that also have* action on the slow sodium channel (mixed class III and IA action).
- It is *used* for the acute conversion of atrial flutter and atrial fibrillation (more effective in atrial flutter than atrial fibrillation) to normal sinus rhythm.
- *Because* of the risk of pro-arrhythmia, treatment with Ibutilide *should be initiated* in hospital *after baseline measurement* of the rate corrected QT interval (QT c).

Vernakalant (Brinavess®)

- Vernakalant is a multi-ion channel blocker that was *developed for* the treatment of atrial fibrillation (final approval for this purpose is pending).
- Vernakalant does *not change* the QT interval on the ECG.
- *Side effects*; dysgeusia (disturbance of taste), sneezing, paresthesia, cough and hypotension.

4) Class IV (Calcium Channel Blockers)

Verapamil (Isoptin®)# | Diltiazem (Altiazem®)#

- Verapamil shows *greater action* on the heart *than* on vascular smooth muscle, and Diltiazem is *intermediate* in its *actions*.
- *Uses*;
  - Supraventricular tachycardia is the *major arrhythmia* indication for Verapamil.
  - Verapamil can also *reduce* the ventricular rate in atrial fibrillation and flutter.
  - Diltiazem appears to be *similar* in efficacy to Verapamil in the management of supraventricular arrhythmias, including rate control in atrial fibrillation.

5) Miscellaneous Antiarrhythmic Agents

Digoxin (Lanoxin®)#

Digoxin is used to control atrial fibrillation and flutter.
- *Note*: Serum digoxin concentrations of 1-2 ng/mL are desirable for atrial fibrillation or flutter, whereas lower concentrations of 0.5 to 0.8 ng/mL are targeted for systolic heart failure.

Adenosine (Adenocard®)#

IV adenosine is the *drug of choice* for acute supraventricular tachycardia.
- Adenosine has an *extremely* short duration of action (approximately 10 to 15 seconds) due to rapid uptake by erythrocytes and endothelial cells.
- *Dose*; It is usually given in a bolus dose of 6 mg *followed*, if necessary, by a dose of 12 mg.
- *Toxicity*; flushing (20%), chest pain (10%) and hypotension.

Magnesium Sulfate

IV magnesium sulfate *used for* patients with digitalis-induced arrhythmias *who were* hypomagnesaemia, *dose* is 1 g (as sulfate) given IV over 20 min & repeated once if necessary.

Antithrombotic Drugs

Antithrombotics Classification:

1) **Anticoagulants**; limit the ability of the blood to clot.
2) **Thrombolytic *or* Fibrinolytic Drugs**; act to dissolve clots after they have formed.
3) **Antiplatelet Drugs**; limit the migration or aggregation of platelets.

Anticoagulant Drugs

Anticoagulants Classification (Mechanism):

1) **Indirect Thrombin Inhibitors (Heparins).**
2) **Direct Thrombin Inhibitors (DTIs).**
3) **Direct Factor Xa Inhibitors.**
4) **Vitamin K Antagonist (Coumarin Anticoagulants).**

Heparins

Unfractionated Heparin (UFH)

Heparin (Calciparine®) (Cal-heparin®)#

Low Molecular Weight Heparins (LMWHs)

Enoxaparin (Clexane®)# | **Dalteparin** (Fragmin®)# | **Tinzaparin** (Innohep®)#

Must be administrated; **SC** or **IV *only***.
Avoid* IM**; ***cause; irritation, erythema, pain, hematoma or ulceration.
UFH; ***inhibition*** of **thrombin** about 1000-fold ***and* factor Xa**.
LMWHs; One molecules ***bind*** to with **AT-III** ⇨ ***inactivate* factor Xa**.
These agents are used for;
- ***Treatment of* acute venous thromboembolism (DVT** or **PE)**.
- ***Prophylaxis of* postoperative venous thrombosis *in patients* undergoing surgery and those with acute MI.**
- ***Drug of choice for using in* pregnant women.**

- ***Doses***;
  - **UFH**;
    - ***Initial bolus injection***; 80-100 units/kg, followed by;
      Continuous infusion; 15-22 units/kg/h (*monitoring is needed*).
    - ***Prophylaxis***; 5000 units SC every 8–12 h (*monitoring is needed*).
  - **Enoxaparin (Clexane®)**; SC 30 mg twice daily or 40 mg once daily, *alternatively*; 1 mg/kg SC every 12 hours or 1.5 mg/kg once a day.
  - **Dalteparin (Fragmin®)**; 200 units/kg once a day for venous disease or 120 units/kg every 12 hours for acute coronary syndrome.
  - **Tinzaparin (Innohep®)**; 175 units/kg SC once daily.

Monitoring of Heparin Effect; by **Activated Partial Thromboplastin Time (aPTT)**.
Side effects;
1) **Bleeding**; ***Monitoring*** is **required** to minimize bleeding.
   - ***Excessive bleeding*** may be **managed** by **discontinuing** the drug ***or*** by ***treating*** with **protamine sulfate**; - For every **100 units of heparin** remaining in the patient, **1 mg of protamine sulfate** is given **IV infusion** (rate ***should not exceed*** 50 mg in any 10-minute period).
2) **Hypersensitivity Reaction**; chills, fever, urticaria, and anaphylactic shock.
3) **Thrombocytopenia**; **Heparin-induced thrombocytopenia (HIT)**
4) ***Other Side Effects***; - **Osteoporosis** has been observed in patients on long-term therapy.
   - **Hair loss** and **alopecia** have been reported.

Direct Thrombin Inhibitors (DTIs)

Parenteral Direct Thrombin Inhibitors

Bivalirudin (Angiomax®) | **Lepirudin** (Refludan®) | **Desirudin** (Iprivask®)

Uses; - **Bivalirudin** also ***inhibits*** **platelet activation** and has been FDA-approved for use in **percutaneous coronary intervention (PCI)**.
- *Dose*; initial: 0.75 mg/kg *IV bolus*, followed by *continuous infusion*: 1.75 mg/kg/hour over 4 hours, may be continued at 0.2 mg/kg/hour for up to 20 hours, patients should also receive aspirin 300-325 mg/day.

- **Lepirudin** is approved by the FDA for use in **patients with thrombosis related to heparin-induced thrombocytopenia (HIT)**.
- *Dose*; Initial: 0.4 mg/kg *IV slowly* (over 15 to 20 seconds) followed by 0.15 mg/kg/hr IV *continuous infusion* for 2 to 10 days or longer if clinically needed.

- **Desirudin** is approved by the FDA for use for ***prophylaxis*** of **deep vein thrombosis**, ***which may lead to*** **pulmonary embolism**, ***in patients undergoing*** **elective hip replacement surgery**.
- *Dose*; 15 mg SC every 12 hr; initiate 5-15 min before surgery (but after induction of regional block anesthesia) and continue for 9-12 days.

- *Side effects*; ***Like the others***, **bleeding** is the major side effect of these agents.
- Up to 40% of patients who receive long-term infusions of **Lepirudin** develop an **antibody**, which may develop **life-threatening anaphylactic reactions**.

Argatroban (Argatroban®)

Uses; - ***Prophylaxis*** or ***treatment*** of **thrombosis** in **patients with heparin-induced thrombocytopenia (HIT)**.
- ***During*** **percutaneous coronary interventions (PCI)** in **patients who have HIT** or **are at risk for developing it**.

- *Dose*; **Before** administering Argatroban; ***discontinue*** **heparin therapy** and ***obtain*** a **baseline aPTT**. The recommended ***initial dose*** for adult patients without hepatic impairment is **2 mcg/kg/min** as a continuous infusion, ***monitoring is needed*** (aPTT).
- *Side effects*; As with other anticoagulants, the major side effect is **bleeding**.
- *Contraindication*; Patients with hepatic impairment.

Oral Direct Thrombin Inhibitors

Dabigatran Etexilate (Pradaxa®)#

Pharmacokinetics; **Dabigatran Etexilate** is the ***prodrug*** of the active moiety **Dabigatran**.
Oral bioavailability is 3-7%.
Oral bioavailability ***may increase*** by up to **75%** when pellets are ***taken out*** of the **hydroxypropylmethylcellulose (HPMC) capsule**. Therefore, capsules ***should not*** be opened and pellets taken alone.
- The **half-life** of the drug is 12-17 hours.
- **Renal impairment** results in ***prolonged drug clearance*** and may **require dose adjustment** (***should be*** **avoided** in patients with **severe renal impairment**).

Uses; - ***Prevention*** **of stroke in non-valvular atrial fibrillation**.
- ***Prevention*** **of venous thromboembolism (DVT** and **PE)** ***in patients who have undergone*** **hip** ***or*** **knee replacement surgery**.

- *Dose*; - For patients with creatinine clearance (CrCl) **>30 mL/min**; **150 mg** taken orally, ***twice daily***.
- For patients with severe renal impairment (CrCl **15-30 mL/min**); **75 mg** ***twice daily***.
- **No monitoring** is required.

- *Side effects*; The ***primary*** **toxicity** is **bleeding**, ***GI adverse effects*** are common with this drug and may include **dyspepsia**, **abdominal pain**, **esophagitis**, and **GI bleeding**.

- *Drug interactions*; **Ketoconazole**, **Amiodarone**, **Quinidine**, **Clopidogrel** ***increases drug effect***

Dabigatran antidote; **Idarucizumab** (**Praxbind®**) is a monoclonal antibody and the ***first*** **reversal agent** for the **Dabigatran** has been approved by the FDA in October 16, 2015.

Direct Factor Xa Inhibitors

Parenteral Direct Factor Xa Inhibitors

Fondaparinux (Arixtra®)#

Fondaparinux is a ***pentasaccharide anticoagulant*** that is synthetically derived, is a chemically related to ***low molecular weight heparins*** (***LMWHs***).
- ***Pharmacokinetics***; - **SC *administration***. - ***Long*** half-life; 15 hours (once-daily).
Uses; ***Treatment*** or ***prophylaxis*** of **venous thromboembolism** (**DVT** and **PE**).
- ***Dose***; A) ***Treatments***; - Under 50 kg: 5 mg subcutaneously once a day.
- 50 to 100 kg: 7.5 mg subcutaneously once a day.
- Over 100 kg: 10 mg subcutaneously once a day.

B) ***Prophylaxis***; 2.5 mg SC once a day for 5 to 9 days.
- ***Side effects***; Major side effect is **bleeding** (***no antidote***).
- ***Contraindication***; Patients with **severe renal impairment** (CrCl less than 30 mL/min).
FDA warning; **Fondaparinux *should not be* used in the setting of lumbar puncture** or **spinal cord surgery**, ***Due to*** **risk of epidural or spinal hematomas**.

Oral Direct Factor Xa Inhibitors

Rivaroxaban (Xarelto®)# (Andorivaban®)#

Rivaroxaban is the first ***oral selective* factor Xa *inhibitor*** approved by the FDA in 2011.
Bioavailability; - 10 mg dose; 80-100% and is not affected by food.
- 20 mg dose; 66% in the fasted state, with food ↑ the bioavailability.
Uses; - ***Prevention* of stroke in non-valvular atrial fibrillation**.
- ***Dose***; 20 mg orally once a day.
- ***Prophylaxis* of deep vein thrombosis (DVT)** which may lead to **pulmonary embolism (PE)** ***in patients undergoing* knee or hip replacement surgery**.
- ***Dose***;
- ***In* DVT or PE**; ***Initial***: 15 mg orally twice a day for first 21 days of therapy. ***Maintenance***: 20 mg orally once a day for the remaining duration of treatment.
- ***In* DVT or PE recurrence**; 20 mg orally once a day.
- ***In* DVT prophylaxis after hip or knee replacement surgery**;
- ***Initial***: 10 mg orally once a day starting 6 to 10 hours after surgery.
- ***Duration of therapy***: Hip: 35 days - Knee: 12 days.
- ***Side effects***; Major side effect is **bleeding** (***no antidote***).
- ***Contraindication***; **Patients** with **severe renal impairment** (CrCl less than 30 mL/min in DVT and CrCl less than 15 mL/min in non-valvular atrial fibrillation).

Apixaban (Eliquis®)#

Apixaban is an ***oral selective* factor Xa *inhibitor***.
- ***Uses***; - ***Prevention of* stroke in non-valvular atrial fibrillation**.
- ***Dose***; 5 mg taken orally twice daily.
- ***Prophylaxis of* deep vein thrombosis (DVT)** which may lead to **pulmonary embolism (PE)** ***in patients undergoing* knee or hip replacement surgery**.
- ***Dose***; ***Duration of therapy***: Hip: 35 days - Knee: 12 days.
- ***In* DVT or PE**; 10 mg orally twice daily for the first 7 days. After 7 days, the recommended dose is 5 mg taken orally twice daily.
- ***In* DVT or PE recurrence**; 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.
- ***In* DVT prophylaxis after hip or knee replacement surgery**; 2.5 mg taken orally twice daily, taken 12-24h after surgery.
- ***Side effects***; Major side effect is **bleeding** (***no antidote***).
FDA warning; **Apixaban *should not be* used in the setting of lumbar puncture** or **spinal cord surgery**, ***Due to*** **risk of epidural or spinal hematomas**.
- ***Premature* discontinuation** of **Apixaban**, ***increases*** **the risk of thrombotic events**.

Vitamin K Antagonists (Coumarin Anticoagulants)

Warfarin (Coumadin®)# (Marevan®)#

Warfarin *inhibits* **vitamin K epoxide reductase enzyme**, resulting in depletion of the reduced form of vitamin K.

Vitamin K is a *cofactor* for **coagulation factors** II, VII, IX, and X and anticoagulant proteins C and S is ***inhibited***.

Unlike **heparin**, the anticoagulant effects of warfarin are not observed ***immediately after drug administration***;

- ***Peak anticoagulant effect*** may be delayed **72-96 hours** (the time required to deplete the pool of circulating clotting factors).
- ***Treatment initiated*** with **UFH** or **LMWH** for the **first 5-7** days, with an overlap with **Warfarin**. Once therapeutic effects of warfarin have been established, therapy with warfarin is continued for a minimum of 3-6 months.

Uses;

- ***Prophylaxis*** and ***treatment*** of **deep vein thrombosis (DVT)** and its extension, **pulmonary embolism (PE)**.
- ***Prophylaxis*** and ***treatment*** of **thromboembolic complications associated with atrial fibrillation (AF)** ***and/or*** **cardiac valve replacement**.
- ***Reduction*** in the **risk of death**, ***recurrent*** **myocardial infarction (MI)** ***and*** **thromboembolic events** such as **stroke**.
- **Protein C and S deficiency symptoms** (is an inherited disorder causes abnormal blood clotting).
- **Antiphospholipid syndrome** (is an autoimmune, hypercoagulable state caused by antiphospholipid antibodies).

- *Dose*;

- **International Normalized Ratio (INR)**; is the prothrombin time ratio (patient prothrombin time/mean of normal prothrombin time for lab).
- Adjust the warfarin dose to maintain a target INR of 2.5 (INR range, 2.0-3.0) for all treatment durations.
- ***Initial dose***: 2-5 mg orally or IV once a day for 1-2 days, then adjust dose according to results of the INR or prothrombin time (PT).
- ***Maintenance dose***: 2-10 mg orally or IV once a day.

Color-Coded for Safety; Generic warfarin tablets may come in different shapes, but each strength comes in just one color.

- ***For example***, 5 mg tablet; peach/light orange color.

Side effects; **Hemorrhage, Warfarin Necrosis, Osteoporosis** and **Purple Toe Syndrome**.

Pregnancy; **Warfarin** is **teratogenic** and ***should never be*** **used during pregnancy**.

- *Drug interactions*; **numerous drug interactions**.

Fibrinolytic Drugs

Fibrinolytic drugs (**Thrombolytic drug**) rapidly lyse thrombi (***dissolve*** **blood clots**) by catalyzing the formation of plasmin (serine protease) from its precursor plasminogen.

The ***major side effects*** of **these drugs** are **bleeding**.

These drugs are ***contraindicated*** in **pregnancy** and in ***patients with*** **healing wounds**, a *history of* **cerebrovascular accident**, **brain tumor**, **head trauma**, **intracranial bleeding** and **metastatic cancer**.

Streptokinase (SK) (Kabikinase®)#

Streptokinase **is a protein** synthesized by ***streptococci***.

Uses; **acute MI**, **DVT** and **PE**.

- ***Dose***; IV infusion of a loading dose of 250,000 units, followed by 100,000 units/h for 24-72 hours.

Streptokinase has ***high*** **antigenicity**, ***so*** **patients** with ***anti-streptococcal antibodies*** can develop **fever**, **allergic reactions** and **therapeutic resistance**.

- **Streptokinase** is ***rarely*** **used** and is no longer available in many markets.

Urokinase (Angikinase®)#

Urokinase ***also called*** **urokinase-type plasminogen activator** (**uPA**), it is produced ***naturally*** in the body by the kidneys.

- **Therapeutic urokinase** is ***isolated*** from **cultures of human kidney cells** and has ***low*** **antigenicity**.
- ***Uses***; **PE**, **DVT**, **acute MI**, **coronary artery thrombosis** and **arterial thrombosis**.
- ***Dose***; loading; 300,000 units over 10 min. and a maintenance; 300,000 units/h for 12 hours.

Anistreplase (Eminase®)#

Anistreplase is ***also known as*** **anisoylated plasminogen streptokinase activator complex** (**APSAC**).

It is a **complex of** ***purified*** **human plasminogen** ***and*** **bacterial streptokinase**.

- ***Uses***; **acute MI**, now this drug is discontinued in the USA.
- ***Dose***; Single IV injection of 30 units over 2 to 5 min.

Alteplase (Cathflo® Activase®)# | Reteplase (Retavase®)# | Tenecteplase (TNKase®)#

Plasminogen can also be ***activated*** endogenously by **tissue plasminogen activators** (**t-PAs**).

- ***Uses***;
  - **Alteplase**; **Treatment of acute MI**, **massive PE** and **acute ischemic stroke**.
    - ***Dose***; IV infusion (due to very short half-life; 5-30 minutes); 60 mg over the first hour and then 40 mg at a rate of 20 mg/h.
  - **Reteplase**; **Treatment of acute MI** (***off-label used*** in **DVT** and **massive PE**).
    - ***Dose***; Double IV bolus (moderate half-life) injections of 10 units (10+10) each, separated by 30 minutes.
  - **Tenecteplase**; **Treatment of acute MI**.
    - ***Dose***; Single IV bolus (long half-life) of 0.5 mg/kg.
- ***N.B***; **Alteplase** may cause angioedema, and there may be an increased risk of this effect when combined with angiotensin-converting enzyme (ACE) inhibitors.

Antiplatelet Drugs

1) *Inhibit* Prostaglandin Synthesis (Aspirin).
2) *Inhibit* ADP-induced Platelet Aggregation (Clopidogrel, Prasugrel and Ticlopidne).
3) *Block* Glycoprotein IIb/IIIa Receptors (Abciximab, Tirofiban and Eptifibatide).
4) Protease-Activated Receptor-1 (PAR-1) *Antagonists* (Vorapaxar and Atopaxar).
5) *Other* Antiplatelet Drugs (Dipyridamole and Cilostazol).

Thromboxane A_2 Inhibitor

Aspirin (Aspocid®)#

Aspirin ***inhibits*** **synthesis of thromboxane A_2** by ***irreversible acetylation*** of **cyclooxygenase (COX) enzyme.**
Aspirin inhibit platelet function ***within*** **60 min.**
Aspirin is ***used*** in the ***prophylactic treatment*** **of transient cerebral ischemia and thromboembolic stroke**, and ***reduce*** **the incidence of recurrent MI.**
The ***recommended dose***; ranges from **75-325 mg/d.**
Side effects; **GI disturbances**, ↑ bleeding time and may cause bronchospasm in susceptible patients.

P_2Y_{12} Receptor Inhibitors

Clopidogrel (Plavix®)#	**Ticlopidine** (Ticlid®)#
Prasugrel (Effient®)#	**Ticagrelor** (Brilinta®)#

- ***Absorption*** of **Ticlopidine** ↓ **with food** ***but*** **not** with the **other agents.**
Metabolism; by the cytochrome P450 (CYP) system;
Clopidogrel is a **prodrug** that ***requires activation*** via the cytochrome P450 enzyme isoform **CYP2C19.**
Drugs that impair CYP2C19 function, such as **Omeprazole**, should be ***used with caution.***
Uses; **Myocardial infarction, Stroke** and **peripheral arterial disease.**
- ***Doses***; - **Clopidogrel** ***loading dose***; 300-600 mg once, ***followed*** by of 75 mg daily.
- **Prasugrel**; ***loading dose*** 60 mg ***followed*** by 10 mg daily.
- **Ticlopidine**; ***loading dose*** 500 mg ***followed*** by 250 mg twice daily, for
- **Ticagrelor**; ***loading dose*** 180 mg ***followed*** by 90 mg twice daily.

Glycoprotein IIb/IIIa Inhibitors

Abciximab (ReoPro®)# | **Eptifibatide** (Integrilin®)# | **Tirofiban** (Aggrastat®)#

Uses; These agents are **given IV,** ***along with*** **heparin** and **aspirin**, as an **adjunct to PCI** ***for the*** **prevention of cardiac ischemic complications.**
- ***Dose***; - **Abciximab**; 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min. (max 10 mcg/kg) for 12 hr.
- **Eptifibatide**; 180-mcg/kg IV bolus × 2 (10 minutes apart); 2 mcg/kg/min. initiated after first bolus for 18–24 h. {maintenance dose in creatinine clearance < 50 ml/min. = 1 mcg/kg/min.}
- **Tirofiban**; 25-mcg/kg IV bolus over 3 minutes, then 0.15 mcg/kg/minute for 18–24 hr.
- ***Side effects***; The major side effects of these agents is **bleeding,** especially if used with anticoagulants.
- ***N.B***; Oral formulations of IIb/IIIa antagonists are in various stages of development.

Protease-Activated Receptor-1 (PAR-1) Antagonists

Vorapaxar (Zontivity®) | Atopaxar

- **Vorapaxar** is the ***first drug inhibit*** the **protease-activated receptor-1 (PAR-1)**, the primary receptor for thrombin, approved by the FDA in 2014.
- ***Uses***; ***reduce*** **thrombotic cardiovascular events** ***in patients with a history of*** **MI** or ***with*** **peripheral arterial disease**.
- ***Dose***; **2.08 mg** orally ***once-daily***, ***should be*** **used with** daily **Aspirin** ***and/or*** **Clopidogrel** according to their indications or standard of care.
- ***Side effects***; ***increases*** the **risk of bleeding**, including life-threatening and fatal bleeding.

Other Antiplatelet Drugs

Dipyridamole (Persantin®)

- **Dipyridamole** is a **vasodilator** that also ***inhibits*** **platelet function** by ***inhibiting*** **adenosine uptake**.
- ***Uses***; Dipyridamole by itself has ***little*** or ***no*** **beneficial effect**. ***Therefore***;
  - ***Used*** in **combination** ***primarily*** **with aspirin to prevent cerebrovascular ischemia** ⇨ **Aggrenox®** (aspirin/extended-release Dipyridamole capsules).
  - ***Used*** in **combination** ***with*** **warfarin** ***for*** **primary prophylaxis of thromboemboli** ***in patients with*** **prosthetic heart valves**.
- ***Side effects***; Headache and can lead to orthostatic hypotension (especially if administered IV).

Cilostazol (Pletal®)#

- **Cilostazol** is a ***newer*** **phosphodiesterase type III** ***inhibitor*** that ***promotes*** **vasodilation** (↑ cAMP) and ***inhibition*** of **platelet aggregation**.
- **Cilostazol** is ***extensively metabolized*** in the liver by the CYP3A4, 2C19 and 1A2 isoenzymes.
- ***Uses***; It is approved to ***reduce*** **the symptoms of intermittent claudication**.
- ***Side effects***; **Headache**, **GI side effects** (diarrhea, abnormal stools, dyspepsia, and abdominal pain) and **palpitation**.
- ***FDA warning***; **Cilostazol** is ***contraindicated*** in **patients with congestive heart failure**.
- ***Drug interactions***; **Itraconazole**, **Erythromycin**, **Ketoconazole**, **Diltiazem**, **Omeprazole** and **Grapefruit juice**.

Antihemorrhagic Agents

Vitamin K (konakion®)# (Amri-K®)#

Vitamins K_1 and **K_2** is a ***fat-soluble*** require bile salts for absorption from the intestinal tract.
Vitamin K_1 is ***available clinically*** in **oral** and **parenteral *forms***.
- ***Onset of effect*** is delayed for **6 hours** but the ***effect is complete*** by **24 hours**.
- ***Administration***; orally, SC, IM and IV.
- ***FDA warning***; IV administration of vitamin K_1 ***should be*** **very slowly**, not exceeding 1 mg/minute, **Severe hypersensitivity reactions**, including **anaphylactic reactions** and **deaths**.
Uses; ***Treating*** **bleeding problems** caused by low vitamin K blood levels or decreased vitamin K activity, It may also be used to **treat or prevent certain bleeding problems in newborns**.
- ***Dosage Guidelines***;

Newborns prophylaxis	0.5 - 1 mg IM within 1 hour of birth
Newborns treatment	1 mg SC or IM
Usually adult dose	2.5 mg - 10 mg
Prothrombin deficiency due to warfarin	up to 25 mg
Prothrombin deficiency due to other causes	2.5 mg - 25 mg

Aminocaproic Acid (Amicar®) | Tranexamic Acid (Kapron®)# (Cyklokapron®)

Aminocaproic acid or **Tranexamic acid** are ***antifibrinolytic drugs***.
- ***Both agents*** are **synthetic**, **orally active** and **excreted in the urine**.
Uses; - **Adjunctive therapy in haemophilia** (is a group of hereditary genetic disorders that impair the body's ability to control blood clotting).
- **Bleeding from fibrinolytic therapy**.
- **Prophylaxis for re-bleeding from intracranial aneurysms**.
- **Postsurgical GI bleeding**, **post-prostatectomy bleeding** and **bladder hemorrhage**.
- **Tranexamic acid**; ***used as first-line*** **nonhormonal treatment of dysfunctional uterine bleeding (heavy menstrual bleeding or menorrhagia)**, ***dose***; 650 mg three times daily for five days during menses.

- ***Dose***;
  - **Aminocaproic acid**; ***For acute bleeding syndromes***; 5 g during the first hour of treatment, followed by a continuing rate 1 g per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.
  - **Tranexamic acid**; short-term use (2-8 days) ***in patients with haemophilia*** to reduce/prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction; **10 mg/kg IV 3 to 4 times daily**.
- ***Side effects***; Risk of intravascular thrombosis, hypotension, myopathy, abdominal discomfort, diarrhea, and nasal stuffiness.

Ethamsylate or Etamsylate (Dicynone®)#

Ethamsylate is a ***synthetic antihaemorrhagic*** and ***angioprotective drug*** acting on the ***first step*** of haemostasis (endothelium-platelet interaction).
- ***Uses***; - ***Prevention*** and ***treatment*** of **pre- or postsurgical capillary haemorrhages**.
  - ***Prophylaxis*** and ***control*** of **blood loss from small blood vessels**.
  - ***Control*** **heavy menstrual periods** or those who suffer from **excessive bleeding due to an intrauterine contraceptive device**.
- ***Dose***; - ***Before surgery***; 500-1000 mg, ***followed*** by 500 mg every 4-6 hours.
  - ***Usual adult dose***; 500 mg 3-4 times daily.
  - ***Usual children dose***; 250 mg 3-4 times daily.
- ***Side effects***; GIT disturbance, nausea, headache, skin rash.

Plasma Fractions

Dried Factor VIII Fraction (8Y®)

- It is a ***concentrate*** of **Factor VIII** and **von Willebrand Factor** (VWF) ***prepared from*** **blood plasma** from screened donors and then heat-treated.
- ***Uses***; IV injection, to ***prevent*** & ***treat*** **bleeding in patients with haemophilia A** (an inherited shortage of Factor VIII in the blood) or von Willebrand disease (VWD).
- ***Dose***; 10-50 IU/kg body weight, doses may be repeated at intervals of 8, 12 or 24 hours, as required.
- ***Warning***; Because this product is made from human blood, it may carry a **risk of transmitting infectious agents** and may cause **hypersensitivity** or **allergic reactions**.

Factor IX Complex (BEBULIN®)

- **BEBULIN®** is a nano-filtered and vapour heated is a purified, sterile, freeze-dried concentrate of the **coagulation factor IX** (Christmas factor) as well as **Factor II** and **Factor X** and ***low amounts*** of **Factor VII**. In addition, the product contains ***small amounts*** of **heparin**.
- ***Uses***; ***prevention*** and ***control*** of **bleeding episodes in adult patients with haemophilia B** (congenital Factor IX deficiency or Christmas disease).
- ***Dose***; (IV only) ***Minor bleeding***; 25-35 IU/kg once. ***Moderate***; 50-65 IU/kg every 24 hours twice or until adequate wound healing. ***Major***; 75-90 IU/kg every 24 hours 3-4 times or until adequate wound healing.
- ***Warning***; **Hypersensitivity** or **allergic reactions** ***may occurs***.

Anti-Inhibitor Coagulant Complex Heat Treated (Autoplex®)

- **Autoplex®** is a sterile product prepared from pooled human plasma.
- The product is standardized by its ***ability*** to **correct the clotting time** of **Factor VIII deficient plasma** or Factor VIII deficient plasma which contains ***inhibitors*** to **Factor VIII**.
- ***Uses***; ***only*** in **patients with inhibitors to Factor VIII** ***who are bleeding or undergo surgery***.
- ***Dose***; (IV only) 25-100 Hyland Factor VIII Correctional Units/kg of body weight, depending upon the severity of hemorrhage. If no hemostatic improvement is observed approximately 6 hours following the initial administration, the dosage should be repeated.
- ***Warning***; **hypersensitivity** or **allergic reactions**.

Anti-Inhibitor Coagulant Complex (FEIBA-^{NF}®)

- **FEIBA** (**F**actor **E**ight **I**nhibitor **B**ypass **A**ctivity); is a nano-filtered and vapour heated, is a freeze-dried sterile human plasma fraction with **Factor VIII inhibitor bypassing activity**.
- It contains Factors II, IX, and X, mainly non-activated and Factor VII mainly in the activated form. The product contains Factor VIII inhibitor bypassing activity and Prothrombin Complex Factors.
- ***Uses***; ***Control*** of **spontaneous bleeding episodes** ***or to cover*** **surgical interventions** in **haemophilia A and haemophilia B patients with inhibitors**.
- ***Dose***; (IV infusion) 50-100 Units of FEIBA^{NF}/kg/day is recommended.
- ***Warning***; **Hypersensitivity** or **thromboembolic event** or **risk of transmitting infectious agents**.

Recombinant Human Coagulation Factor VIIa (rFVIIa) (NovoSeven®)

- **NovoSeven®** is structurally similar to human plasma-derived Factor VIIa.
- ***Uses***; ***Control*** **bleeding episodes** and to ***prevent*** **excessive bleeding during surgery** in people;
  - **Inhibitors to clotting factors VIII** or **IX**.
  - **Congenital FVII deficiency**.
  - **Glanzmann's Thrombasthenia**.
- ***Dose***; 35-120 micrograms/kg (usually 90 micrograms/kg) given every two hours by bolus infusion until hemostasis is achieved, or until the treatment has been judged to be inadequate.
- ***Warning***; **thromboembolic event** ***may occurs***.

Cryoprecipitate (CRYO)

- The ***main constituents*** of **Cryoprecipitate** are **Factors VIII** and **XIII**, **von Willebrand Factor** and **Fibrinogen**.
- ***Uses***; **Haemophilia**, **von Willebrand disease** & **hypofibrinogenaemia** (low fibrinogen levels).
- ***Dose***; 1 U/5kg patient weight repeat if needed.
- ***Warning***; **Hypersensitivity** or **allergic reactions** or **risk of transmitting infectious agents**.

Antihyperlipidemic Agents

➢ Plasma Cholesterol Levels:-

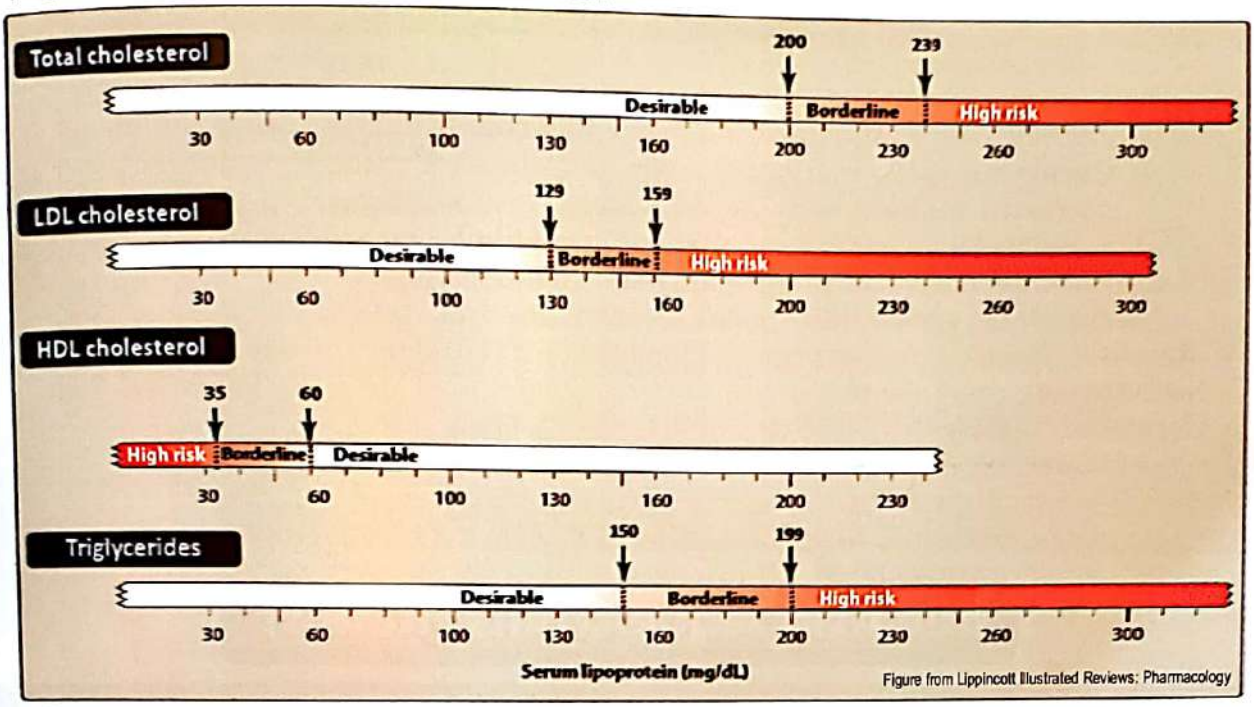


Figure from Lippincott Illustrated Reviews: Pharmacology

- Classes of Hyperlipidemia Medications:
  - HMG-CoA Reductase Inhibitors (Statins).
  - Niacin (Nicotinic acid or Vitamin B3).
  - Cholesterol Absorption Inhibitors (Ezetimibe).
  - Bile Acid Sequestrants (Resins).
  - Fibric Acid Derivatives (Fibrates).
  - Omega-3 Fatty Acids.

HMG-CoA Reductase Inhibitors (Statins)

Atorvastatin (Lipitor®)# (Ator®)#	Rosuvastatin (Crestor®)# (Crestolip®)#
Fluvastatin (Lescol® XL)	Simvastatin (Zocor®)#
Pravastatin (Lipostat®)	Pitavastatin (Lipidalon®) | Lovastatin (Lipdip®)

Pitavastatin, Rosuvastatin and Atorvastatin are the *most potent LDL cholesterol lowering statins, followed by* Simvastatin and Pravastatin *then* Lovastatin and Fluvastatin.

Statins are useful alone or with Resins, Niacin or Ezetimibe in **reducing levels of LDL.**

Atoreza®; Atorvastatin + Ezetimibe # Inegy®; Simvastatin + Ezetimibe

Women with **hyperlipidemia** who are **pregnant, lactating** or likely to **become pregnant** *should not be* given these agents.

- Because **cholesterol synthesis** ***occurs predominantly*** **at night,** Statins ***except*** Atorvastatin and Rosuvastatin ***should be given*** **in the evening** if a single daily dose is used.

Dose

- *Intensity of Statin Doses*;

High Intensity	Moderate Intensity	Lower Intensity
When taken daily, will lower LDL an average of ≥ 50%	When taken daily, will lower LDL an average of 30% to < 50%	When taken daily, will lower LDL an average of < 30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg twice/d Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Side effects; "FDA Warning"
  # Hepatic;
    - *Elevated* liver enzymes up to 3 times normal *in* some patients.
    - *Monitoring*; liver function test; at 1–2 months, and then every 6–12 months (if stable).
  # Muscle;
    - The *most common statin side effect* is muscle pain (10-15%).
    - *Rare reactions* statins can cause myopathy (inflammation of the muscles).
    - *Very rarely*, statins can cause life-threatening muscle damage *called* rhabdomyolysis.
    # # Coenzyme Q10 (is a cofactor for mitochondrial energy production) levels are decreased in statin use, CoQ10 supplements are sometimes used to treat statin-associated myopathy. *Dose*; **100-240 mg/daily** *for up to* 2.5 years.
    - **Fibrates**: *Increase* **risk of myopathy** and **rhabdomyolysis**.
    - **Niacin**: Doses greater than 1 g/day *increase* **the risk**.
  - **Digestive; nausea, gas, diarrhea** or **constipation** *after taking a statin*.
  - **Neurological; cognitive impairment (memory loss)** from statin use for several years.
  - **Hormonal; *slightly* increased risk of diabetes** (2-17%).
- *Pregnancy*; Category X.
- *Contraindications*; **liver disease, pregnancy** and **lactating women**.
- *Drug interaction*; ***numerous* drug interaction**; CYP3A4 and CYP2C9.

Bile Acid Sequestrants (Resins)

Cholestyramine (Questran®)# | **Colesevelam** (Cholestagel®) | **Colestipol** (Colestid®)

They are *anion-exchange resins* that bind negatively charged bile acids and bile salts in the small intestine; **not absorbed** and **not metabolically altered** *by the* **intestine**.
Cholestyramine can also **relieve pruritus** caused by biliary stasis.
- *Dose*; **Cholestyramine** are available as granular preparations;
  - ***Initial dose***; 4 g orally once or twice a day.
  - ***Gradual increase*** to ***maintenance dose***; 20 g/d is recommended.
  - ***Total dosages*** of 30–32 g/d may be needed for maximum effect.
  - The usual ***dosage for a child*** is 10-20 g/d.
  - Granular are mixed with juice/water & allowed to hydrate for 1 min.

Side effects;
  - **GI disturbances**;
    - Such as; **Constipation, nausea** and **flatulence**.
    - Usually ***relieved by*** **increasing dietary fiber** or **mixing psyllium seed** with the resin.
  - **Malabsorption of fat-soluble vitamins** (A, D, E and K) ***may occur***.
    - ***Not*** **used with pregnant** women ***due to*** vitamin deficiencies that may affect the fetus.
- *Drug interaction*; ***decrease*** **absorption** of ***certain*** **drugs**.
- *Contraindications*; These agents may raise triglyceride levels and are contraindicated in **patients with significant hypertriglyceridemia** (≥400 mg/dL).

Niacin (Nicotinic Acid or Vitamin B3)

Niacin (Niaspan®)# (Nicotipan®)#

- **Niacin** or **Nicotinic acid** (***not*** **Niacinamide**); is a **Vitamin B_3**, it is primarily ***used*** to treat **hypercholesterolemia** and **pellagra** (niacin deficiency).
- **Niacin** is ***administered*** **orally**.
- *Dose*; - ***Intermediate Release***; *Initial*: 100 mg orally 3 times a day, with or after meals. *Maintenance*: 1 to 2 g orally 3 times a day, with or after meals (Max. dose 6 g/day).
  - ***Extended Release*** (Niaspan®); *Initial*: 500 mg orally once a day at bedtime. *Maximum* dose is 2 g/day.
  - ***Sustained Release*** (Slo-Niacin®); *Initial*: 250-750 mg orally once a day morning or evening.

Skin Benefits of Niacin and Niacin Derivatives

- **Acne**; Topical 4% nicotinamide gel was as effective as 1% clindamycin gel in the treatment of moderate inflammatory acne vulgaris.
- **Lip Plumper**; Niacin is applied topically as a lip plumper, due to its vasodilation effect. The vasodilator effect on lips are slightly swollen and redder, making them appear "full-blooming" which is typically desired.
- **Moisturizing Effects**; Nicotinamide 2% cream more effective than petrolatum, the same ingredient in Vaseline, at boosting hydration levels in the patient's dry skin.
- **Rosacea Improvement**; Nicotinamide moisturizer provided substantial improvements in rosacea symptoms.
- **Possible Skin Cancer Prevention**; Oral (500 mg) nicotinamide prevent the progression of premalignant actinic keratoses to malignant squamous cell cancers.
- **Reduce Wrinkles**; Topical nicotinamide provided reductions in fine lines and wrinkles.
- **Skin Whitening**; Topical nicotinamide provided reductions hyperpigmented spots.

Side effects;

1) **Niacin Flush** (**Facial Flushing**);
   - ***Due to prostaglandin mediated vasodilation effect.***
   - > **78%** of **patients** and ***usually resolved*** **after 2 weeks** of continued therapy.
   - Flushing usually ***lasts for*** about **15** to **30 minutes.**
   - **Flushing** can be ***minimized by***;

 # # # # # # # # PATIENT COUNSELLING # # # # # # # #

1) ***Taking*** **Aspirin 325 mg** or **Ibuprofen 200 mg 30-60 minutes** ***before*** **Niacin.**
2) Use of an ***extended release*** **formulation.**
3) ***Gradual*** **dosage titration** (over 2 to 3 months).
4) ***Taking*** **Niacin** ***during*** or ***within*** **30 min.** ***after*** **meals.**
5) ***Taking*** **Niacin** at **bedtime** *with* **food** and ***avoiding*** **hot beverages, spicy foods** and **hot showers** ***around*** the **time of administration.**

2) **Upper GI Distress**; Some patients experience **nausea** and **dyspepsia** (**indigestion**).
3) **Hepatic**; ***Reversible elevations*** in **liver enzymes**; ***monitor***; every 6-12 weeks & then yearly
4) **Metabolic**; **Hyperuricemia**, **Allopurinol** can be given with niacin if needed.
   - **Hyperglycemia**, especially in obese patients, but this is usually reversible.
5) **Other**; ***Rarely***, niacin is associated with **arrhythmias.**

- ***Contraindications***; **Liver disease, severe gout** and **active peptic ulcer.**
- ***Pregnancy***; **Category C**, but not recommended.

Lactation; **Niacin** is ***excreted*** in **human milk**, may cause ***serious*** **adverse reactions** in **infants.**

Fibric Acid Derivatives (Fibrates)

Fenofibrate (Lipanthyl®)#	**Gemfibrozil** (Lopid®)#

- It is a ***pro-drug*** of the active chemical moiety **Fenofibric acid.**

Lipanthyl® Supra; is a ***film-coated*** **tablet** of ***micronized*** **Fenofibrate** and is **supra-bioavailable** (***larger*** **bioavailability**).

They are ***useful*** in ***severe*** **hypertriglyceridemia.**

They are ***useful*** in **hypertriglyceridemia** *in which* **VLDL** ***predominate.***

They also may be of ***benefit*** in ***treating*** the **hypertriglyceridemia** that ***results from treatment with*** **viral protease inhibitors.**

- ***Dose***;
  - **Fenofibrate**; is available in several formulations with several dose range and is sold under several brand names; The initial dose of tablets ranges from 40- 160 mg per day.
  - **Gemfibrozil**; 600 mg orally twice a day, 30 minutes before meal.

Side effects; **Mild GI disturbances, Gallstones, Myositis** (**Muscle inflammation;** have been reported in ***patients taking*** **Gemfibrozil** and **Statins** ***together***) and ***elevated*** **liver enzymes.**

- ***Pregnancy***; **category C.**
- ***Contraindications***: **Severe renal/hepatic disease** and **gallbladder disease.**

Cholesterol Absorption Inhibitors

Ezetimibe (Ezetrol®)

Ezetimibe is *synergistic* with **Statins**, *so* it is often *used* as an;
Adjunct to statin therapy. # **Statin-intolerant patients**.
- *Dose*; - Dosage range of 5-20 mg/d. - Usually single daily dose; 10 mg/d.

Omega-3 Fatty Acids

Omega-3 Fatty Acids (Lovaza®)# (Vascepa®)# (Epanova®)#

- **Omega-3 Fatty Acids**; (ω-3 fatty acids) are **essential fatty acids**, **polyunsaturated fatty acids** (**PUFAs**) with a double bond (C=C) at the third carbon atom from the end of the carbon chain.
- **Essential fatty acids** *inhibit* **VLDL** and **triglyceride** *synthesis* in liver (unknown mechanism).
- The *three types* of **omega-3 fatty acids** involved *in* **human** physiology are **α-linolenic acid** (**ALA**) (found in plant oils), **Eicosapentaenoic acid** (**EPA**) and **Docosahexaenoic acid** (**DHA**) (both commonly found in marine oils).
- *Efficacy* (**DHA** and **EPA**) Lovaza®; *Lowers* TG, may *raise* in LDL-C.
  - **Icosapent ethyl** (Vascepa®); is a form of EPA, unlike other fish oil supplements, does not significantly raise LDL-C and lowers TG by 33%.

Uses; **hypertriglyceridemia** as an **adjunct** *to* **diet** in **adults** with **TG conc.** of ≥ **500 mg/dL**.
- *Dose*; - **DHA** and **EPA** (Lovaza®); 4 g/day as a single dose or in two divided doses.
  - **Icosapent ethyl** (Vascepa®); 2 g twice daily with food.
- *Side effects*; **GI effects** (abdominal pain, nausea and diarrhea) and **fishy aftertaste**.
  - **Risk of bleeding** especially in patients who are taking anticoagulant or antiplatelet drugs (*due to* it inhibit platelet aggregation).
- *N.B*; - **Omega-6 fatty acids**; are essential fatty acids (polyunsaturated fat).
  - **Omega-9 fatty acids**; are monounsaturated fats.
  - **Omega-3-6-9 fatty acids** play specific roles in overall health;
    # *Prevent*; **coronary heart disease**, **stroke** and **diabetes**.
    # *Promote*; **healthy nerve activity** and **cell development**.
    # *Maintain* a **healthy immune system**.
- **Omega-3-Carboxylic Acid** (Epanova®);
  - *Efficacy*; *Lowers* TG, may *raise* HDL-C by 5% and may *raise* LDL-C by 25%.
  - *Uses*; *treat* **hypertriglyceridemia** as an **adjunct** *to* **diet** with **TG conc.** of ≥ **500 mg/dL**.
  - *Side effects*: *Diarrhea*.
  - *Dose*; 2 g or 4 g once daily.

Others

Red Yeast Rice (Cholestin®) (Statosan®)=

- **Red Yeast Rice** is *made from* yeast grown on rice. It is a bright reddish purple colour; *One of these* **ingredient** *is*, **Monacolin K**, has the same structure as the drugs **Lovastatin**.
- *Dose*; *for high cholesterol*; 1,200-2,400 mg of red yeast powder 1-2 times daily for up to 12 weeks.
- *Side effects*: *elevated* **liver enzymes** and **GI symptoms**.

Garlic (Tomex®)=

- The results of research on garlic have been **mixed**, but it *may help* lower blood pressure, reduce blood cholesterol levels, and slow the progress of atherosclerosis. Some evidence suggests that taking garlic supplements can slightly lower blood cholesterol levels.

Drugs for Varicose Veins

- **Lifestyle Modification**; ######## PATIENT COUNSELLING ########
  1) **Elevating the legs**; it is important to raise the legs up above the level of the heart to get the maximum effect & to do this for about a half-hour each time & during sleep.
  2) ***W*eight reduction** and ***W*alking**.
  3) ***Eat*** a **healthy diet** high in fiber and low in fat and salt can help.
  4) ***Avoid*** **long period time** *of* **traveling**.
  5) ***Avoid*** **chronic constipation**, **urinary retention** or **cough**.
  6) ***Avoid*** **wearing tight girdles** or **belts**.
  7) ***Avoid*** **alcohol**.

Compression Therapy; ***Wear*** **compression stockings** (*such as* **Venosan®** - **Duomed®**); put them in the morning before walking and before the veins become more swollen and remove them at night before going to bed. If a person tries them and experiences worsening pain, especially after walking, remove them and see a health care professional.

Venoactive Drugs

- **Venoactive drugs** (**VADs**) are a heterogenic group of drugs that has **vasoprotective effects**.
- ***They can be classified in 4 major categories***;
  1) **Benzopyrones**:
     A) **α-benzopyrones**; **Coumarin**.
     B) **δ-benzopyrones**; **Diosmin**, **Micronized purified flavonoid fraction** (**MPFF**), and **Rutosides** (**Rutin**, **Troxerutin** and **Hydroxyethylrutosides**).
  2) **Saponins**; **Horse chestnut seed extract** (**Aescin** or **Escin**) and ***Ruscus*** **extracts**.
  3) **Other Plant Extracts**; ***Ginkgo biloba***, ***Centella asiatica***, ***Hamamelis*** and **Grape seeds** contain flavonoids, such as **anthocyanins** and **proanthocyanidins**.
  4) **Synthetics Drugs**; **Calcium Dobesilate**, **Naftazone** and **Benzarone**.

Micronized Purified Flavonoid Fraction (MPFF) (Daflon®)#

- **Diosmin** and **Hesperidin** are a flavonoid, indicated for *relief* ***symptoms*** **venous insufficiency**.
- **Daflon®** formulation contain; 90% **Micronized Diosmin** + 10% **Hesperidin**.
- ***Flavonoid fractions mechanism of action*** (**Diosmin** and **Hesperidin**);
  1) **Veins**; prolongs the vasoconstrictor effect of norepinephrine on the vein wall; ↑ venous tone ⇨ ↓ venous capacitance ⇨ ↑ venous return and ↓ venous hyper-pressure.
  2) **Lymphatic System**; improves lymphatic drainage by ↑ frequency and intensity of lymphatic contractions and by ↑ total number of functional lymphatic capillaries.
  3) **Microcirculation**; reduces capillary hyper-permeability and ↑ capillary resistance by protecting the microcirculation from damaging processes.
  4) **Other**; reduces the expression of endothelial adhesion molecules and inhibits the adhesion, migration, and activation of leukocytes at the capillary level ⇨ reduction in the release of inflammatory mediators, principally oxygen free radicals and prostaglandins.
- ***Uses***; 1) ***Symptoms of*** **chronic venous insufficiency** (**CVI**);
  - ***Dose***; 500 mg 2 times daily (morning and evening) *OR* 1000 mg once daily (morning) during meals at least 6 months.
  2) ***Symptoms related to*** **venous insufficiency of the hemorrhoidal plexus**.
  - ***Dose***; ***In acute hemorrhoidal crisis***; 6 tablets 500 mg (or 3 tablets 1000 mg) per day for the first 4 days and then 4 tablets 500 mg (or 2 tablets 1000 mg) a day for 3 days and then 2 tablets 500 mg (or 1 tablets 1000 mg) a day for at least 3 months.
  3) ***Symptoms of*** **pre/post-operative saphenectomy** (remove large varicose veins);
  - ***Dose***; 500 mg 2 times daily (morning and evening) *OR* 1000 mg once daily (morning) during meals at least 4 weeks.

4) ***Symptoms of* postoperative hemorrhoidectomy** (surgery to remove hemorrhoids):
- ***Dose***; 6 tablets 500 mg (or 3 tablets 1000 mg) per day for 3 days and then 4 tablets 500 mg (or 2 tablets 1000 mg) a day for 4 days and then 2 tablets 500 mg (or 1 tablets 1000 mg) a day for at least 1 week.

5) **Chronic pelvic pain *associated with* pelvic congestion syndrome**;
- ***Dose***; 500 mg 2 times daily (morning and evening) *OR* 1000 mg once daily (morning) during meals at least 4 to 6 months.

- ***Side effects***; Diarrhea, dyspepsia, nausea and vomiting.
- **Daflon®**; is considered to be ***safe*** during **pregnancy** and **breastfeeding**.

Rutin (Ruta-C®)#

- **Rutosides** such as **Rutin** are herbal remedy which have been shown to ***reduce*** swelling and skin changes in other conditions affecting the veins such as in **chronic venous insufficiency (CVI)**.
- Rutin is an **antioxidant**, **anti-inflammatory**, **antithrombotic**, **cytoprotective** and **vasoprotective**.
- **Vitamin C *increases* rutin effects** and has a ***positive* effect** on **lipids metabolism**.
- The greatest benefits of rutin are in ***treating* varicose veins** and **hemorrhoids**.
- ***Dose***; 500 mg of rutin per day.

Aescin or Escin (Reparil®)#

- **Aescin** or **Escin** is a mixture of saponins with **anti-inflammatory**, **vasoconstrictor** and **vasoprotective** effects.
- ***Effect***; Antiedematous and anti-inflammatory effect.
- ***Uses***; Oral horse chestnut seed extract (**Aescin**) is effective in the short-term treatment of mild to moderate long-term **venous insufficiency**.
- **Aescin** 20-120 mg is available in tablet form and topical gels containing aescin 2% are available.
- ***Dose*** of **Reparil®** tablets; 20-40 mg 3 times daily with a little fluid after meals.
- Most commonly ***side effects***; nausea and stomach discomfort.

Oligomeric Proanthocyanidin Complex (OPC) (Gervital®) (Grapexon®)

- **OPC** are ***effective*** against; **Venous insufficiency** (**varicose veins**), **atherosclerosis**, **night vision** and **attention deficit hyperactivity disorder** (**ADHD**).
- Usual adult ***dose*** in **varicose veins**; 150 mg daily.

Calcium Dobesilate (Doxium®)#

- **Calcium Dobesilate** is a calcium salt of **Dobesilic acid**.
- It is commonly ***used*** in the treatment of **diabetic retinopathy** and **chronic venous insufficiency**.
- It acts on the capillary walls by regulating its impaired physiological functions of resistance and permeability, it reduces plasma and blood hyper-viscosity.
- ***Usual adult dose***; 500-1000 mg once or twice a day with the main meals.

Other Agents

Pentoxifylline (Trental®)#

Pentoxifylline is a **methyl-xanthine** *derivative* that ***inhibits* phosphodiesterase** enzyme and ***affects* blood rheology**.
- It improves blood flow by increasing erythrocyte and leukocyte flexibility. It also inhibits platelet aggregation.
- ***Mechanism of action***; It inhibits erythrocyte phosphodiesterase, resulting in an increase in erythrocyte cAMP activity ⇨ erythrocyte membrane becomes more resistant to deformity. Along with erythrocyte activity, it also decreases blood viscosity by reducing plasma fibrinogen concentrations and increasing fibrinolytic activity. It is also a non-selective adenosine receptor antagonist.
- It is ***used*** in the treatment of **peripheral vascular diseases** and in the **management of cerebrovascular insufficiency**.
- It is ***used*** in **intermittent claudication** due to chronic occlusive arterial disease of limbs.
- It is ***also effective*** in **venous ulcer** with compression therapy.
- ***Dose***; 400 mg orally 3 times a day.

Drugs for Hemorroides

Lifestyle with Home Remedies;

Patient Counselling # #

Topical treatments; apply an **OTC hemorrhoid cream** or **suppository** containing **hydrocortisone** or use pads containing witch-hazel (astringent plant extract) or a numbing agent such as **Preparation H®** cream, suppository, totables or wipes.

Sitz bath; by soaking anal area in plain warm water 10 to 15 min. two to three times a day.

Keep the anal area clean; by shower daily. Avoid soap, it may aggravate the problem. Avoid alcohol based or perfumed wipes.

Don't use dry toilet paper; keep the anal area clean after a bowel movement and use moist towelettes or wet toilet paper that doesn't contain perfume or alcohol.

Apply cold; apply ice packs or cold compresses on the anus to relieve swelling.

Take oral pain relievers; such as short-term use of NSAIDs.

Medications

Topical (or **suppository**) **corticosteroids**; relieve inflammation and itching (should not be used for more than 2 weeks, because they can thin the skin).

Topical zinc oxide, **petroleum jelly**, **cocoa butter**, **hard fat**, **mineral oil** or **shark liver oil**; can prevent further injury and reduce itching by forming a barrier over hemorrhoids.

Topical local anesthetic; can help some people, especially those who have painful external hemorrhoids.

Topical Nitroglycerine and **Diltiazem**; also have been used to relieve symptoms associated with anal sphincter spasm.

Topical vasoconstrictor (**Phenylephrine**) or **astringent** (**Witch-hazel**); reduce pain associated with hemorrhoids by contract swollen veins.

 # Preparation H® #

- Preparation H® was originally developed since 1935. The H simply for "Hemorrhoid".
- Preparation H® which became one of the world's best-selling hemorrhoid treatments.
- The product is sold and manufactured by Pfizer since 2009.
- It is available in several formulation such as; cream, suppository, totables or wipes.
- It contains medications such as that are discussed above.

- **Oral Venoactive Drugs** such as **MPFF** (**Daflon®**).
- **Oral NSAIDs**; relieve pain (should not be used for more than 1 week).

Procedures

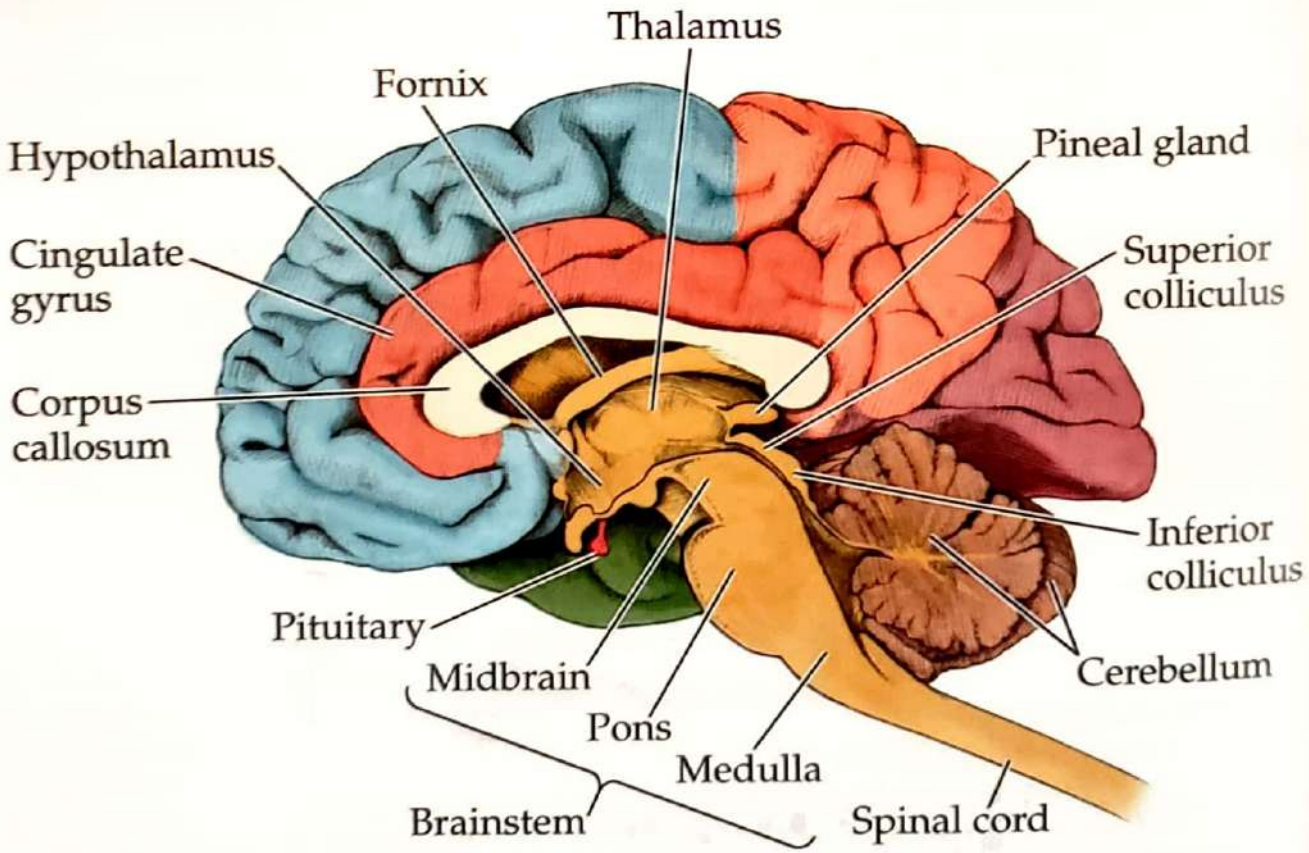
A) Office-based Procedures;

1) **Rubber Band Ligation** (RBL).
2) **Sclerotherapy** and **Cryotherapy**.
3) **Coagulation** (**infrared**, **laser** or **bipolar**).

2) Surgical Procedures;

1) **Excisional Hemorrhoidectomy**.
2) **Stapled Hemorrhoidectomy** (SH).
3) **Transanal Hemorrhoidal Dearterialization** (THD).

Central Nervous System (CNS)



Sedative-Hypnotic Drugs

I) Benzodiazepines (BDZs)

➢ **Classification and examples:-**

Long-acting (> 24 hrs. half-life)		
Diazepam (Valium®)#	**Clonazepam** (Rivotril®)#	**Clorazepate** (Tranxene®)
Quazepam (Doral®)	**Flurazepam** (Dalmane®)	**Clobazam** (Frisium®)
Intermediate-acting (12-24 hrs. half-life)		
Bromazepam (Calmepam®)	**Lorazepam** (Ativan®)	**Estazolam** (ProSom®)
Chlordiazepoxide (librium®)	**Temazepam** (Restoril®)#	
Short-acting (< 12 hrs. half-life)		
Alprazolam (Xanax®)#	**Midazolam** (Dormicum®)#	**Oxazepam** (Comedormir®)
Triazolam (Halcion®)		

** *All* **benzodiazepines** are **sedating** (*anxiolytic*), *but* only *five* benzodiazepines are FDA approved as **sedative-hypnotics** *because* they are rapidly absorbed and produce CNS sedation more quickly;

5 BDZs Hypnotics

- ***Long-acting***; **Quazepam** and **Flurazepam**.
- ***Intermediate-acting***; **Temazepam** and **Estazolam**.
- ***Short-acting***; **Triazolam**.

BDZs Mechanism of Action; 1) **BDZs** ***potentiate*** the **action** *of* **GABA** by binding to BDZs sites (BZ_1 or BZ_2) on $GABA_A$ receptors ⇨ ***increasing*** their **affinity** *for* **GABA**. 2) This ***results*** in an ***increased*** **opening** of Cl^- **channels** and ***enhanced*** **hyperpolarization** ⇨ sedative effect.

All **BDZs** ***exhibit*** *five* ***therapeutic*** **properties**;

1) **Anxiolytic** (*also known as* **minor tranquilizers**); ***At low doses***.
2) **Hypnotic**; ***At high doses*** have hypnotic effects.
3) **Amnesic Actions** (*memory loss*); ***All*** **BDZs** cause ***temporary*** **impairment of memory**.
4) **Anticonvulsant**; ***Several*** **BDZs** have **anticonvulsant activity**.
5) **Muscle Relaxant**; ***At high doses***, ***several*** **BDZs** ***relax*** the ***spastic*** **skeletal muscle**.

Uses;

1) **Anxiety Disorders**; *The most commonly prescribed*; **Clonazepam**, **Chlordiazepoxide**, **Lorazepam**, **Diazepam** and **Alprazolam**.
2) **Sleep Disorders**; *The most commonly prescribed BDZs as sedative-hypnotics*; **Quazepam**, **Flurazepam**, **Temazepam**, **Estazolam** and **Triazolam**; ***newer hypnotics***; **Zolpidem**, **Zaleplon** and **Eszopiclone** ***more*** **preferred**.
   - People with **problems** in *sleep initiation*; most likely benefit from an agent with a quick onset.
   - People with **problems** in *sleep maintenance*; most likely benefit from an agent with a longer half-life.
3) **Adjuncts to Anesthesia**; ***shorter-acting agents*** (**Midazolam**) are often ***used to*** **facilitate amnesia** in anxiety-provoking procedures, such as endoscopy, dental procedures and angioplasty. **Diazepam**, **Lorazepam** & **Midazolam** are used ***IV*** in **anesthesia**.
4) **Seizures**; In a **hospital emergencies**; **IV** **Clonazepam** (*stronger*), **Lorazepam** (*longer*) and **Diazepam** (*faster*) are ***first-choices***. **Clobazam** is ***widely used*** by ***specialist*** **epilepsy clinics** ***worldwide***, while **Clonazepam** is ***most*** **popular**.
5) **Alcohol Withdrawal Syndrome**; **Chlordiazepoxide** (*most commonly*), **Clorazepate**, **Diazepam**, **Lorazepam**, and **Oxazepam** are the ***preferred choice*** to ***reduce*** the **risk** of **withdrawal-related seizures**.
6) **Muscle Spasms**; **Diazepam** is ***useful*** in the treatment of skeletal muscle spasms.

Side effects:
  # *Next day* **drowsiness** and **confusion** (***most common side effects***);
    - ***Most*** common with ***long-acting as*** **Diazepam** & **Flurazepam**.
  # ***Next day*** **sedation, ataxia** and **impair driving**; ***Most*** common in elderly.
  # ***Cognitive Impairment*** (**Anterograde Amnesia**);
    - ***All*** BDZs with ***long-term*** **use** appear to ***impair ability*** to learn new information and may also impair memory storage and recall.
  # **Hypotension & Respiratory Depression**;
    - **IV** BDZs can be associated with cardiac and/or respiratory arrest.
  # **Rebound Insomnia**;
    - Can occur when the drug is discontinued abruptly and usually lasts for 1-2 days It is most common after the use of short acting agents (*most common with*; **Triazolam**).
  # **Tolerance, Dependence** and **Abuse**;

 # # # # Tolerance # # # #

  # It is occurs when used for more than **1-2 weeks**.
  # It is ***associated with*** a decrease in **GABA receptor density**.
  # ***Cross-tolerance*** exists between the **BDZs** and **Ethanol**.
  # **Triazolam** often shows a ***rapid development*** of tolerance.

 # # # # Dependence and Abuse # # # #

  # Dependence occurs within weeks to months of continued use.
  # ***Abrupt*** **cessation** can ***lead to withdrawal symptoms***; **Confusion, anxiety, agitation, restlessness, insomnia, tension** and (*rarely*) **seizures**.
  # ***Short-acting*** **BDZs**, such as **Triazolam**, more abrupt and ***severe*** **withdrawal reactions**.

- ***Notes***; - ***Pregnancy***; **Sedative-hypnotics** may ***increase*** the **risk** of **fetal malformations**.
  - **Alcohol** & *other* **CNS depressants** ↑ sedative–hypnotic effects of BDZs.
  - ***Most*** **sedative-hypnotics** ***used with caution*** in patients with **renal** or **hepatic disease**.
  - **BDZs** should be ***avoided*** in patients with acute **closed-angle glaucoma**.
  - **Flumazenil** (BDZs antagonist) used in BDZs overdoses.

Flumazenil (Anexate®)#

Flumazenil ***rapidly reverses*** the **effects of BDZs** by ***competitive*** **inhibition** at the BDZs **binding site** on the **$GABA_A$ receptor**.
It is primarily ***used*** to treat **benzodiazepine overdoses**.
The drug is available for **IV** **administration** ***only***.
Onset is ***rapid*** (within 1-2 min.), ***but*** the ***duration*** is ***short***, with a half-life of about 1 hour, so, ***frequent administration*** may be **necessary** to ***maintain*** **reversal** of a **long-acting BDZs**.
Dose; 0.2 mg IV one time over 30 seconds ⇨ if no response after 30 seconds ⇨ repeated 0.5 mg every minute (maximum 3 mg/hr).

- ***Common side effects***; dizziness, nausea, vomiting and agitation.

Non-Benzodiazepines

Zolpidem (Stilnox®)# (Zodium®)#	**Zaleplon** (Siesta®)# (Sleep-aid®)#
Eszopiclone (Lunesta®)# (Night Calm®)#	**Zopiclone** (Hypnor®)#

They are an ***oral*** **non-benzodiazepine hypnotics**, are also known as **Z-drugs**.
Eszopiclone is the active ***dextrorotatory*** stereoisomer of **Zopiclone**
Compared with BDZs; ***More*** selective as hypnotics agent, ***Lower*** risk of tolerance and withdrawal, ***No*** significantly alter the various **sleep stages**, ***No*** **anticonvulsant** or **muscle-relaxing** properties, ***No*** **respiratory depressant** effect.

- **Zolpidem** is available as an IR, CR, sublingual tablet (**Edluar®**) and sublingual spray (**Zolpimist®**), the FDA has ***reduced*** the **dosing** to ***limit*** **next day impairment**.
- **Zaleplon** is indicated only for short-term treatment of insomnia (*duration*; 3 h.).

Uses; **insomnia treatment**;
  - **Zaleplon** is ***indicated only*** for **short-term treatment of insomnia**.
  - **Zolpidem** (SR) and **Eszopiclone** can be used for **chronic insomnia**.

#***Side Effects***; **Nightmares, agitation, anterograde amnesia, headache** & **daytime drowsiness**.

- This drugs are classified as a Schedule IV controlled substance by federal U.S. drug policy.

II) Barbiturates

Barbiturates, were be used as **anxiolytic-hypnotic** ***in the past***, but **today** they have been ***largely replaced*** by the **benzodiazepines**, ***because***;

BDZs are

1) High therapeutic index.
2) More selective.
3) Mild physical dependence and tolerance.
4) Little cardiovascular and respiratory depression.
5) Not significantly enzyme inducer.
6) Available of specific antidote (Flumazenil).

➢ **Classification and *examples*:-**

Long-acting		
Phenobarbital or Phenobarbitone (Luminal®)#		
Intermediate-short-acting		
Secobarbital (Seconal®)#	**Amobarbital** (Amytal®)#	**Butalbital** (Fioricet®)
Ultra-short-acting		
Thiopental (Pentothal®)#		

- Phenobarbital has a **duration of action** ***greater than*** a **day (1-2 days)**.
- Secobarbital, Amobarbital & Butalbital have a **duration of action** ***less than*** a **day (3-8 hr)**.
- Thiopental ***acts within*** **seconds** and has a ***duration of action*** of about **20 min**.

Pharmacological Action;

1) **CNS Depression**;
   - ***At low doses***; **Sedation**. - ***At normal doses***; **Anxiolytic** and **anticonvulsant effects**.
   - ***At higher doses***; **Hypnosis**, ***followed by*** **anesthesia** and finally **coma** and **death**.
2) **CVS Depression**;
   - ***At low doses***; Minimal effects. - ***At higher doses***; **Hypotension**.
3) **Respiratory Depression**;
   - ***Lethal doses***; **Respiratory depression** and **death**.
   - ***The Lethal Injection***; Sodium Thiopental, as an **anesthetic** agent (unconscious in less than 30 seconds) and *facilitate* **respiratory depression**.
4) **Liver Microsomal Enzyme Inducers**; most notably CYP2C9, CYP2C19 and CYP3A4.

Uses;

1) **Anesthesia**; Thiopental have been used IV to **induce anesthesia**.
2) **Sedative-hypnotic**; ***now*** **rarely** (or not) used.
3) **Seizures**; Phenobarbital has ***specific*** **anticonvulsant activity** (**tonic-clonic seizures**), ***first-line choice*** of **neonatal seizures**

- Fioricet®; Butalbital is ***commonly*** **used** in ***combination with*** Acetaminophen and Caffeine or Aspirin and Caffeine as a sedative to assist in the management of **tension-headache** or **migraine headache**.

Side effects; - **Drowsiness**, **confusion** and **impaired concentration** (most common).
- ***CNS depressant effects*** of **barbiturates** ***synergize*** with ***other*** **CNS depressants**.
- **Hypersensitivity**: facial edema and skin rash (1 to 2%).
- **Death** may also result from overdose (CV and respiratory depression).
- ***Withdrawal Symptoms***; withdrawal is ***much more severe*** than that associated with opiates and ***can result*** in **death**. ***Abrupt cessation*** of barbiturates after chronic administration may cause tremors, anxiety, nausea, vomiting, seizures and cardiac arrest. ***Treatment of phenobarbital overdose*** is **supportive** (***no*** **antidote available**).
- **Tolerance**, **psychological** & **physical dependence** may occur with continued use.

- ***Drug Interactions***; such as phenytoin, oral contraceptives and most oral anticoagulants.
- **Barbiturates** ***contraindicated*** in **pregnancy**, it can depress the fetus.

III) Other Agents

Non-Barbiturates

Chloral Hydrate (Chloral®)#

Chloral Hydrate is a non-barbiturate sedative-hypnotic.
- **Hypnotic effects** of chloral hydrate due to its ***active metabolite*** Trichloroethanol.
Onset of Action; 30-60 minutes.
Uses; - **Short-term insomnia**, it is also still used as a ***sedative prior*** to EEG.
- **Prevention of alcohol withdrawal symptoms**.
- **Relieve anxiety *due to* certain procedures** (minor medical or dental).
- *Dose*; **Adult**; 500 mg to 1 g 15 to 30 min before bedtime [every 6 h, if needed (max, 2 g/day)].
Child; 50 mg/ kg of body weight.
- ***Most Common Side Effects***; **Ataxia**; **dizziness**, **rashes** and **gastric discomfort**.

Serotonin Agonists

Buspirone (Buspar®)#

Buspirone is a *selective* 5-HT_{1A} agonist, which is an antianxiety agent.
It is primarily *used* to treat **generalized anxiety disorder (GAD)**;
- *Contraindication*: should ***not*** be used with **MAOIs** may cause **serotonin syndrome**.
- ***Most common side effects***: dizziness, nausea, headache, nervousness, and excitement.
- ***Usual* adult *dose***: - ***Initial***: 5 mg 3 times a day. - ***Maintenance***: 20 to 60 mg/day in divided doses.
- Buspirone has *no* potential for **abuse** and *no* evidence of dependence or withdrawal effects.

Melatonin Agonists

Ramelteon (Rozerem®)#

Ramelteon is *first* in a **new class** of sleep agents that ***selective*** agonist at the MT_1 and MT_2 subtypes of **melatonin receptors**. - *Duration of Action*; 2-5 hours.
- *Metabolism*; primarily by CYP 1A2, ***but*** affect by 2C9 and 3A4 inducers or inhibitors.
Used; ***long term*** for **chronic insomnia**, *particularly* in **sleep initiation**.
- *Dose*; 8 mg orally within 30 minutes of going to bed. (Maximum dose: 8 mg per day).
- *Common Side Effects*; dizziness, fatigue, somnolence and may also increase prolactin levels.
- *To date*; it has *minimal* potential for abuse, *no* evidence of dependence or withdrawal effects.

Orexin Antagonists

Suvorexant (Belsomra®)#

Suvorexant is a *selective*, dual orexin receptor antagonist (OX_1 and OX_2).
- It was approved by the FDA on 2014 and became available in US in February 2015.
Uses; **Insomnia**, ***characterized by*** difficulties with **sleep initiation** and/or **sleep maintenance**.
- It is *metabolized* by CYP 3A4 (affect by 3A4 inducers or inhibitors).
- This drug is *classified as* a Schedule IV controlled substance by federal U.S. drug policy.

Antihistamines

Doxylamine (Donormyl®)#

OTC *First* **generation antihistamines** with ***sedating properties***, such as Doxylamine and Diphenhydramine are effective in ***treating*** **mild types** of **situational insomnia**, ***but not*** as effective as BDZs or non-BDZs. - *Side effects*; **anticholinergic effects**.

Antidepressants

Doxepin (Silenor®)#

Management of insomnia, *particularly* in **patients *with* difficulty sleep maintenance**.

Herbal Agents

Valerian Extracts (Dormival®)# | **Kava-Kava** | ***Humulus lupulus* (hops) extract**

Antidepressant Drugs

I) Tricyclic Antidepressants (TCAs)

Tertiary Amines		
Imipramine (Tofranil®)#	**Amitriptyline** (Tryptizol®)#	**Clomipramine** (Anafranil®)#
Trimipramine (Surmontil®)#	**Doxepin** (Silenor®)#	
Secondary Amines		
Desipramine (Norpramin®)	**Nortriptyline** (Pamelor®)	**Protriptyline** (Vivactil®)
Tetracyclic Antidepressant		
Maprotiline (ludiomil®)	**Amoxapine** (Amokisan®)	

Tricyclic antidepressants (TCAs) were the *first* **antidepressants available**.
- Also in the **1950s** the ***first*** **tricyclic antidepressants** (Imipramine) were discovered.
They are *used for* **depression**, but they have *several* **off-label uses** such as treatment for **pain syndromes, migraine prophylaxis** and **anxiety disorders**.
- They are *effective*, *but* **adverse effects** have *limited* **their use**.
- The TCAs were the ***dominant*** class of antidepressants ***until*** the introduction of **Selective Serotonin Reuptake Inhibitors** (SSRIs) in the **1980s** and **1990s**.
- **TCAs** have ***long*** **half-lives**; most are *dosed* **once daily** at **night** ***because*** **sedating effects**.
TCAs have a *narrow* **therapeutic index** (five- to six-fold the maximal daily dose of **imipramine** can be lethal), ***increasing*** their probability for **toxicity**, *monitoring* **serum concentration** during therapy ***may needed***.
Mechanism; **TCAs** ***inhibits*** **neuronal reuptake** of **NE** and **5-HT** into ***presynaptic*** nerve terminal ⇨ ***increase*** **concentration** of **monoamine** in **synaptic cleft**.
- **TCAs** ***elevate*** **mood**, ***improve*** **mental alertness** and ***increase*** **physical activity**.
- The ***onset*** of the **mood elevation** is **slow**, requiring **2 weeks** or **longer**.
- ***After*** a **therapeutic response**, the **dosage** can be ***gradually*** **reduced** to ***improve*** **tolerability**, unless **relapse** occurs.
Uses; - **Management of moderate** to **severe depression**.
- **Panic disorder**.
- **Imipramine** has been used to ***control*** **bed-wetting** in **children** ***older than*** **6 years** of age; but now, it has ***largely*** been *replaced by* **Desmopressin** (***vasopressin analogue***).
- **Amitriptyline**, have been used to help ***prevent*** **migraine headache**.
- **Doxepin**; *low doses* of doxepin can be used to ***treat*** **insomnia**.
- **Clomipramine**, has been used to ***delay ejaculation*** in **premature ejaculation**; but now, it has largely been replaced by **SSRIs**.
- ***Several*** **TCAs**, including **Amitriptyline, Nortriptyline, Desipramine**, and **Imipramine**, have been studied for ***treatment*** of **neuropathic pain**.

Side effects;
- **Muscarinic Receptors Blocking Side Effects** (**Atropine *like action***).
- **α-adrenergic Receptors Blocking Side Effects**; **Orthostatic hypotension**.
- **Histaminic (H_1) Receptors Blocking Side Effects**; **Sedation**.
- **Serotonergic Receptors Blocking Side Effects**; **Weight gain** and **sexual dysfunction**.
- **Quinidine Like Effects** (**Sodium Channel Blockers**); **life-threatening arrhythmias**.

Drug interactions; **Warfarin, Aspirin, LME inhibitors** or **inducers, Clonidine, Quinidine, MAOIs** and **SSRIs**.
- *Contraindications*; **Benign prostatic hyperplasia, urinary tension, glaucoma** and **epilepsy**.
- **Life-threatening arrhythmias of TCAs** *are treated by*; **Sodium bicarbonate**.
The **US FDA** requires ***all*** **antidepressants**, to carry a **black box warning** with a generic warning about a ***possible*** **suicide risk**.

II) Selective Serotonin Reuptake Inhibitors (SSRIs)

- *Advantage*; **SSRIs** have *little blocking* activity at **muscarinic**, **α-adrenergic**, and **histaminic H_1 receptors**. *Therefore*, **common side effects** *associated with* **TCAs**, are *not commonly* seen with the **SSRIs**. **SSRIs** have *largely replaced* **TCAs** and as the *drugs of choice* in **depression**.
- The **FDA** has *approved* **six SSRIs** for the treatment of **depression**:

Fluoxetine (Prozac®)#	**Sertraline** (Lustral®)#	**Paroxetine** (Seroxat®)#
Fluvoxamine (Faverin®)#	**Citalopram** (Cipram®)#	**Escitalopram** (Cipralex®)#

Escitalopram is the *pure* **S-enantiomer** of Citalopram.
Fluvoxamine is *indicated only* for **obsessive-compulsive disorder (OCD)** but is an **antidepressant**.
- *All* **SSRIs** are *well* **absorbed** after *oral* **administration**.
- **Food** has *little* **effect** on absorption (*except*, Sertraline; ↑ **absorption**).
Fluoxetine *differs* from the *other* **SSRIs**; It having a *much* **longer half-life**, *due to* it **active metabolite** Norfluoxetine, The *elimination* **half-life** of Norfluoxetine is about *three* **times** longer than **fluoxetine**. Fluoxetine has to be *discontinued* **4 weeks** or **longer** *before* an **MAOI** can be administered to *decrease* the **risk** of **serotonin syndrome**.

	Half-life	Active metabolite	Usual dose (mg/day)	Maximal daily dose (mg)
Fluoxetine	1-4 days	**Norfluoxetine**	20-60	80
Sertraline	26 hours	No	50-200	200
Paroxetine	21 hours	No	10-60	50-60
Fluvoxamine	15 hours	No	50-300	300
Citalopram	32 hours	No	20-40	40
Escitalopram	27-32 hours	No	10-20	20

Extended formulations: Fluoxetine **90 mg** (Durazac®) can be taken *once* **weekly**.
Escitalopram is *S-isomer* of Citalopram; **10mg** Escitalopram is as *effective as* **20 mg** Citalopram.
- *Metabolism* by **cytochrome P450** enzymes;
  - Fluoxetine and Paroxetine are potent inhibitors of the CYP2D6.
  - Fluvoxamine is an inhibitor of CYP3A4.
  - Citalopram, Escitalopram & Sertraline; modest CYP interactions.

- The *efficacy* of **SSRIs** is **equal** for **treatment** of **depression**.
- *Onset* & *duration*; **SSRIs** (*Other* **Antidepressants**), typically take at *least* **2 weeks** to *produce* **significant improvement** in **mood** and *maximum* benefit may require up to **12 weeks** or more.
Uses; - **Depression**; All SSRIs *except* Fluvoxamine (*but* it is effective).
  - **Generalized Anxiety Disorder (GAD)**; All SSRIs *except* Fluvoxamine.
  - **Obsessive Compulsive Disorder**; All SSRIs.
  - **Eating Disorders** (**Bulimia Nervosa**); *only*, Fluoxetine.
  - **Stroke Recovery** All SSRIs *except* Fluvoxamine.
  - **Premature Ejaculation**. All SSRIs (*include*; Dapoxetine) *except* Fluvoxamine.
Side effects; **SSRIs** are considered to have *fewer* or *less* **severe adverse effects** than the **TCAs** and **MAOIs**, *but not without* **adverse effects**.
  - *In general*; **side effects of SSRI**; **GI side effects** (nausea, vomiting and diarrhea), **headache**, **anxiety**, **agitation**, **fatigue**, **sexual dysfunction**, **changes in weight** and **sleep disturbances**.

Sexual Dysfunction; may include *loss* of **libido** and *delayed* **ejaculation**.

  - *Treatment of SSRI-induced sexual dysfunction*;
    1) *Adding* Bupropion, or
    2) *Lowering* the dose of the **SSRI**, or
    3) *Adding* an agent such as Sildenafil or Cyproheptadine, or
    4) *Changing* to a drug less likely to cause this problem.

Citalopram **40 mg** *increase* the **risk** of **QT interval** *prolongation*.

Serotonin Syndrome; ######## PATIENT COUNSELLING

- Because these drugs have *potent* **serotonergic activity**, **combinations** with *other drugs* **affecting serotonin** can *lead to* **serotonin syndrome**.
- *Other drug* **examples**; **MAOIs**, **TCAs**, **SNRIs**, **Dextromethorphan**, **Meperidine**, **Sympathomimetics**, **Triptans** and **Lithium**.

Serotonin syndrome *includes*;

1) **Neuromuscular hyperactivity**; Muscle rigidity, tremors & incoordination.
2) **Altered mental status**; Agitation, confusion and hypomania.
3) **Autonomic instability**; Hyperthermia and diaphoresis.

Treatments; - *Discontinuing* the **offending agent**.

Supportive treatments *such as* **cooling blankets** and **respiratory assistance** and *providing* **Clonazepam** *for* **seizures** and **Nifedipine** *for* **hypertension**.

Withdrawal Symptoms; ######## PATIENT COUNSELLING

Sudden **discontinuation** of **short half-life SSRIs** such as **Paroxetine** and **Sertraline** is associated with a ***discontinuation syndrome*** in some patients ***characterized by***;

- Dizziness, malaise, and flu-like symptoms, agitation and irritability, nervousness and changes in sleep pattern.

- *Symptoms* ***beginning*** 1 or 2 days after stopping the drug and persisting for 1 wk or longer.
- ***So*** a ***gradual dose reduction*** (e.g., over 2-4 weeks) may be indicated.
- **Fluoxetine** has the lowest risk of causing an SSRI withdrawal syndrome.

- ***Pregnancy***; ***Most*** **antidepressants** are **category C** (**Paroxetine** is a **category D**).
- ***Children***; Antidepressants should be used cautiously in children.
  - **Fluoxetine**, **Sertraline** and **Fluvoxamine** are ***approved for*** use in ***children*** to treat **obsessive-compulsive disorder**.
  - **Fluoxetine** and **Escitalopram** are ***approved*** to treat ***childhood*** **depression**.

III) Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

- **SNRIs** ***inhibit*** the **reuptake** of **serotonin** and **norepinephrine** into the presynaptic neuron.

SNRIs, ***may be*** **effective** in **depression** in ***patients in whom*** **SSRIs** are ***ineffective***.

SNRIs, ***may be*** **effective** in **depression** is often ***accompanied*** by ***chronic*** **painful symptoms**, such as **backache** and **muscle aches** (This pain is, in part, modulated by serotonin and norepinephrine pathways in the CNS).

Both **SNRIs** and **TCAs**, are **effective** in ***relieving*** **pain** ***associated with*** **diabetic peripheral neuropathy**, **postherpetic neuralgia**, **fibromyalgia** and **low back pain**.

The **SNRIs** have ***relatively fewer*** **CYP450 interactions** ***than*** the **SSRIs**.

All the **SNRIs** may ***produce*** **serotonin syndrome**.

SNRIs ***may produce*** a **withdrawal syndrome** ***if*** treatment is ***abruptly*** **stopped**.

Both **Duloxetine** and **Venlafaxine** have been ***associated*** with ***higher rates*** of **suicide** compared with **SSRIs**. The ***risk of*** **suicide** with **SNRIs** is ***still lower*** than with **TCAs**.

Venlafaxine (Effexor®)#	Desvenlafaxine (Pristiq®)#

Venlafaxine is a ***potent inhibitor*** of **serotonin** reuptake and at ***medium*** to ***higher*** **doses**, is an ***inhibitor*** of **norepinephrine** reuptake (at doses less than 150 mg/day, it has primarily a serotonin effect).

Desvenlafaxine is the active metabolite of **Venlafaxine**.

- **Venlafaxine** is a ***substrate*** but ***not*** an **inhibitor** of CYP2D6.
- **Desvenlafaxine** is a ***minor*** **substrate** for CYP3A4.
- ***Dose***;
  - **Venlafaxine** 75-375 mg/d.
  - **Desvenlafaxine** 50-200 mg/d.
- ***Side effects***; ***similar*** to that of the **SSRIs** (GI effects are common), they are ***can*** cause ***increases*** in blood pressure, which are ***usually*** **mild** and not clinically significant ***unless*** the patient already has **hypertension** that is ***not well*** **controlled**.

Duloxetine (Cymbalta®)# (Cymbatex®)#

Duloxetine is an *inhibitor* of **serotonin** and **norepinephrine** reuptake at *all doses*.
- It is a ***moderate inhibitor*** of CYP2D6.
It is *indicated for* the **treatment** of:
1) Major Depressive Disorder. **2) Generalized Anxiety Disorder.**
3) Diabetic Peripheral Neuropathy. **4) Fibromyalgia.**
5) Chronic Musculoskeletal Pain *caused by* chronic lower back pain or **osteoarthritis pain.**
- *Dose*; 40-120 mg/d.
- *Side effects*; ***similar*** to that of the **SSRI**, ***increase*** **blood pressure, tachycardia** (*monitor* blood pressure), **dry mouth** and **constipation.**
- Duloxetine can *cause* **liver toxicity** *and should not* be **used in patients** with **hepatic insufficiency** and ***severe*** **renal impairment.**

Levomilnacipran (Fetzima®)#

- It is ***primarily*** *metabolized* by CYP3A4.
It is *indicated* for the ***treatment*** of **major depressive disorder** in adults. It is ***not approved*** for the **management of fibromyalgia.**
- *Dose*; 40-120 mg/day.
- *Side effects*; ***similar*** to that of the **SSRI**, ***increase*** **blood pressure, tachycardia** (*monitor* blood pressure) and **constipation.**

IV) Norepinephrine Reuptake Inhibitors (NRIs)

Reboxetine (Edronax®)#

NRIs ***are commonly*** used in the treatment of conditions like **ADHD** and **narcolepsy** due to their ***psychostimulant effects*** and in **obesity** due to their ***appetite suppressant effects***. They are also frequently used as ***antidepressants*** for the treatment of **major depressive disorder, anxiety** and **panic disorder.**
- NRIs ***may produce*** a **withdrawal syndrome** ***if*** treatment is ***abruptly*** **stopped.**
- Reboxetine is primarily *metabolized* by the CYP3A4 isozyme.
Reboxetine is indicated for the ***treatment*** of **depression.**
- ***Most common*** **side effects** of **Reboxetine**; insomnia, nausea, sweating, dry mouth and constipation.
- *Contraindications*; **Reboxetine** is ***contraindicated*** in **narrow-angle glaucoma, cardiovascular disease, epilepsy, bipolar disorder, patients *concomitantly*** on **MAOIs.**
N.B.; **Atomoxetine** (Strattera®) is another norepinephrine reuptake inhibitor ***approved*** for the **treatment** of **attention deficit hyperactivity disorder** (**ADHD**).

V) Atypical Antidepressants

Each drug in this category has a **unique mechanism** of action.

Bupropion (Wellbutrin®)#

Bupropion is a *weak* **norepinephrine-dopamine** *reuptake* **inhibitor** (**NDRI**), the ***exact*** **mechanism** of action remains **unknown.**
It is *indicated* for;

- **Major depressive disorder** and **seasonal affective disorder.**
- **Smoking cessation**; it ***reduces*** the **severity** of **nicotine withdrawal symptoms,** but ***somewhat less*** **effective** than **Varenicline** (**Chantix®**).
- **Sexual dysfunction**; it is the ***drug of choice*** for the ***treatment*** of **SSRI-induced sexual dysfunction.**
- **Attention Deficit Hyperactivity Disorder** (**ADHD**); not very common to use it.
- **Obesity**; FDA approves **Bupropion/Naltrexone** (**Contrave®**).

- *Dose*; **200-450mg/day** (in 2 or 3 divided doses).
- ***Most common*** **side effects**; ***increased*** **risk of seizures, insomnia, anxiety, irritability, headache**, and ***decreased*** **appetite.**

Warning; **Bupropion** ***should not be*** **prescribed** to individuals with **epilepsy** or other conditions that ***lower*** the **seizure threshold**.

- The ***risk*** of **seizures** can be ***minimized*** by the following: **# # # Patient Counselling # # #**
  1) ***Avoid*** use in **susceptible patients** (history of seizure disorder and eating disorders).
  2) ***Do not*** give ***more than*** **150 mg/dose** or **450 mg/day**.
  3) ***Avoid*** **dosage titration** any ***more frequently*** *than* ***every*** **3 days**.

Mirtazapine (Remeron®)#

- Mirtazapine ***has*** a ***complex*** **pharmacology** ***mechanisms***.
- ***Not*** cause ***antimuscarinic*** **side effects** like **TCAs**, or interfere with ***sexual function*** like **SSRIs**.
It is ***used*** ***primarily*** in the **treatment** of **depression**. It is also ***off-label*** ***used*** as an **anxiolytic**, **hypnotic** and **appetite stimulant**.
- Mirtazapine may be an ***advantage*** in **depressed patients** ***having*** **difficulty sleeping**.
- ***Dose***; 15-45/day.
- ***Common*** **side effects**; ***Marked*** **sedation**, ***increased*** **appetite**, **weight gain** and **constipation**.
- Mirtazapine and **other antidepressants** may ***cause*** a **withdrawal syndrome**.

Trazodone (Trittico®)# | Nefazodone (Serzone®)#

Trazodone ***causes*** ***marked*** **sedation**, **priapism** and **orthostatic hypotension**.
Trazodone in ***low doses*** is commonly ***used*** *off-label* for the **management of insomnia**.
- Nefazodone ***unlike*** Trazodone, it causes ***minimal effects*** on **sexual function** and is ***less likely*** to cause **orthostatic hypotension**.
- Nefazodone has been ***associated*** with a ***risk*** for **hepatotoxicity**.
- ***Dose***; - Trazodone 150-300 mg/d. - Nefazodone 300-500 mg/d.

Vilazodone (Viibryd®)

- Vilazodone is a **serotonin** ***reuptake*** **inhibitor** and a **5-HT$_{1A}$** ***partial*** **agonist**.
- It was approved by the U.S. FDA for ***treatment*** **major depressive disorder** in 2011.
- ***Dose***; ***initial dose***; 10 mg/day with food. ***Maintenance dose***; 20-40 mg/d with food.
- ***Side effect***; similar to the **SSRIs**, including a ***risk*** for **withdrawal syndrome**.

Vortioxetine (Brintellix®)#

- It is ***metabolized*** by CYP2D6. - It is ***used*** for ***treatment*** **major depressive disorder**.
- ***Dose***; ***initial dose***; 10 mg/day. ***Maximum dose***; 20mg/d.
- ***Most common*** **side effects**; **Nausea**, **vomiting** and **constipation**.

VI) Monoamine Oxidase Inhibitors (MAOIs)

Non-selective (MAO-A & MAO-B) Inhibitors (*Irreversible*)

Phenelzine (Nardil®) | **Isocarboxazid** (Marplan®) | **Tranylcypromine** (Parnate®)

Selective MAO-A Inhibitors (*Reversible*)

Moclobemide (Aurorix®)

- The use of **MAOIs** ***with*** **other antidepressants** is ***contraindicated***.
Drug Switching; - ***From*** **another antidepressant** ***to*** an **MAOI**; Wait for 2 weeks after the antidepressant is discontinued before initiating the MAOI (***except*** for **Fluoxetine**, waiting for 5-6 weeks).
- ***From*** an **MAOI** ***to*** **another antidepressant**; Wait for 2 weeks.
- ***Side effects***; ***Severe*** and ***unpredictable***, due to **drug-food** and **drug-drug interactions**. ***Most common***; **drowsiness**, **hypotension**, **blurred vision**, **dry mouth** & **constipation**.

 # # # Drug-Food Interaction (Cheese Reaction) # # #

- **Tyramine**, ***found*** in **foods**, such as **aged** (or **rip**) **cheeses**, **meats**, **chicken liver**, **pickled** or **smoked fish** and **red wines**.
- **Tyramine** acts as **catecholamine** ***releasing agent*** & **normally** ***inactivated*** by **MAO** in the **gut**.
- **Patients** ***taking*** **MAOI** are ***unable*** to **degrade tyramine** obtained from the diet ⇨ ***release*** of **large amounts of catecholamines** from nerve terminals ⇨ **hypertensive crisis** (headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures and stroke).

Lithium Therapy

Lithium (Li^+) Carbonate (Prianil®)#

Lithium was the *first* mood-stabilizing medication *approved* by the FDA in the 1970s for treatment of **mood disorders**.

- **Lithium** has been used for the *treatment* of **mania** for *over* **60 years**, yet the *exact* **mechanisms** remain *unclear*.
- **Lithium salts** are *used acutely* and *prophylactically* for **managing bipolar patients**.
- **Lithium** is *effective* in **treating 60-80%** of **patients** *exhibiting* **mania** and **hypomania**.

Pharmacokinetics;

Absorption	- Complete absorption within 6-8 hours. - Peak plasma levels in 30 minutes to 2 hours.
Therapeutic index	- The therapeutic index of lithium is extremely low.
Distribution	- Initial volume of distribution is 0.5 L/kg, rising to 0.7-0.9 L/kg. - No protein binding.
Metabolism	- Non
Excretion	- More than 95% urinary and any renal impairment delays it. - Half-life is 20–24 hours.
Plasma conc.	- 0.6-1.4 mEq/L.
Dose	- 0.5 mEq/kg/d in divided doses (600-900 mg/day).

- *Dose*;
  1) **Pre-lithium workup**; patient confirm the following; a complete blood cell count, electrolytes, renal function, thyroid function tests, urinalysis, electrocardiogram (ECG) and pregnancy test for women.
  2) **Dosing**; ***Initial***; **600-900 mg/day** in ***divided doses*** and then ***titrated*** *according to* **response** and **tolerability**.
  3) **Monitoring**; **Li^+ serum concentrations *must be* monitored**.
     - ***Serum concentrations***; **0.8-1.2 mEq/L** in ***acute mania*** & **0.6-1.0 mEq/L** in ***maintenance***.
     - These measurements are taken **10-12 hours *after*** the **last dose**.
     - ***Initial determination*** serum concentrations ***should be*** obtained about **5 days *after*** the start **of treatment** (at which time steady-state conditions should have been attained).
     - ***After dose changing***; serum concentration obtained 3 days after dosage changes.
     - ***Perform*** **renal function tests**, **thyroid function tests**, and a **urinalysis *every* 6-12 months**.

Side effects;

* *Neuromuscular*; **Tremor** is one of the most common side effects. **Lithium-induced tremor** can be ***treated*** with **Propranolol** (or **Atenolol**) or **reduce dose**.

* *CNS*; **Confusion** and **Agitation**; ***treated*** by **reduce dose**.

- *GIT*; **Nausea**, **Vomiting** and **Diarrhea**; ***treated*** by **reduce dose** or **extended-release**.

* **Hypothyroidism**; ***treated*** by ***discontinue*** **Li^+** or ***give*** **levothyroxine**.

* *Kidney*; **Polydipsia** and **Polyuria**; ***due to*** loss of responsiveness to antidiuretic hormone (nephrogenic diabetes insipidus). ***Treated by***; **reduce dose** or use of **Amiloride** or *single bedtime low dose of* **Thiazide** or **NSAIDs** (block Li^+ uptake by kidney tubules). **Nephrotoxicity** may occur during ***long-term*** **lithium therapy**.

- *Pregnancy*; **Teratogenicity**; ***Avoid*** during **first trimester**, if possible.

* *Others*;

- *CVS*: **Arrhythmia** and **Hypotension** may occur.
- *Dermatologic*: **Rash**, **Alopecia** and exacerbation of **Psoriasis**.
- **Edema** and **Weight gain**.

- *Drug Interactions*; **Thiazides**, **NSAIDs**, **Aminophylline**, **Theophylline** and **ACEIs**.

Stimulants (Psychostimulants)

Stimulants (Psychostimulants)

Stimulants are the ***first-line therapy*** and probably the ***most effective*** **treatment** ***for*** **Attention Deficit Hyperactivity Disorder (ADHD)**
Stimulants are ***preferred*** to **other medications** ***because*** stimulants have a **rapid onset of action** and **long record of safety** and **efficacy**.
All stimulants have ***similar efficacy*** ***but differ*** by **dosing**, **duration of action**, and **adverse effect** profiles in individual patients.
Stimulants may cause ***significant*** **insomnia** ***if taken*** at **night**.
Most common **adverse effects** of stimulants include **appetite suppression** and **weight loss**, **headaches** and **mood effects** (depression, irritability).
Stimulant medications do ***enhance*** **mental executive** ***functions*** for those with **ADHD**.
Most commonly **stimulants** ***for*** **ADHD** are **phenethylamines**: Amphetamine (Adderall®), Methylphenidate (Ritalin®), Dexmethylphenidate (Focalin®), Dextroamphetamine (Dexedrine®), Dextromethamphetamine (Desoxyn®) & Lisdexamfetamine (Vyvanse®).

Amphetamine (Adderall®)#

Amphetamine is a ***potent CNS stimulant***, marked ***stimulant effects*** on mood and alertness and a ***depressant effect*** on appetite. It is has a **mood-elevating** (***euphoria***) **effect**.
Uses; - **Attention Deficit Hyperactivity Disorder** (ADHD)
- **Narcolepsy** (*chronic sleep disorder*).
Off-label: **Performance-enhancing**, **Improve work performance**, **Depression** and **Obesity**.
Side effects; ☛ ***Cardiovascular***; Palpitations and increase blood pressure.
☛ ***CNS***; Insomnia, anxiety, confusion, hallucination and tremor.
☛ ***Other***; Weight loss, painful urination, headache, nausea, vomiting, abdominal cramps and diarrhea or constipation.
FDA Warning; #### **AMPHETAMINES-RELATED DEATH**
- *Administration of* **amphetamines** for ***prolonged periods*** of time may lead to ***drug dependence***, and, therefore, this must be avoided.
- ***Misuse*** of **amphetamines** may cause ***sudden*** **death** and ***serious*** **cardiovascular events** (**heart attack** and **heart stroke**).

Dextroamphetamine (Dexedrine®) | Lisdexamfetamine (Vyvanse®)

Dextroamphetamine is the ***more active*** *enantiomer* of the **Amphetamine** molecule.
Lisdexamfetamine is a ***prodrug*** that is converted to active component **Dextroamphetamine**.

Methamphetamine (Desoxyn®)

Methamphetamine also known as "***speed***".
- It is like amphetamine ***but***; much stronger, act quicker, and can be considered more addicting.
Uses: ***approved by the FDA for treating*** ☛
- **Attention Deficit Hyperactivity Disorder** (ADHD).
- **Exogenous obesity**: obesity originating from factors outside the patient's control.
Off-Label: **Increase sexual desire**, **lift the mood**, **increase energy**, **depression** & **narcolepsy**.

Methylphenidate (Ritalin®)#

- **Methylphenidate** is an amphetamine derivatives with ***less*** **side effects**.
- **Addiction** and **psychological dependence** are ***rare*** with methylphenidate.
It is presently one of the ***most prescribed*** medications in **ADHD**.
It is also effective in the treatment of **narcolepsy**.
Off-label: **Depression** and **performance-enhancing**.

Modafinil (Provigil®)# (Bravamax®)#

Modafinil is a *wakefulness-promoting agent*.
Uses: **sleep disorders**; **narcolepsy, obstructive sleep apnea (OSA)** and **shift work disorder (SWD)**. In the US military, it has been used on certain Air Force missions as a "**go pill**".
- *Dose*; 200 mg orally once a day in the morning or 1 hour before start of the work shift.

Fenethylline (Captagon®)#

Fenethylline is a *prodrug*, it is metabolized to form two drugs amphetamine and theophylline.
Most of the **amphetamines** abused in **Saudi Arabia** and ***other*** **Arab countries** come in the form of **Captagon tablets**.

Non-Stimulants

Atomoxetine (Strattera®)#

Atomoxetine is a norepinephrine reuptake inhibitor approved for the ***treatment*** of **attention deficit hyperactivity disorder (ADHD)**.
It has become a *second-line* and, in ***some cases***, ***first-line*** treatment in **children** and **adults** ***with*** **ADHD** ***because*** of its efficacy.
- The ***initial*** **therapeutic effects** usually take **2-4 weeks** to ***become*** **apparent**.
- It can be ***abruptly*** **stopped** ***without significant*** **withdrawal effects**.
- *Dose*; ranges from 40mg/day to 100mg/day given in 1-2 divided doses
- *Side effects*; Insomnia, dry mouth, cough, decreased appetite, upset stomach, nausea or vomiting, dizziness, drowsiness, problems urinating, irritability, constipation, skin rash, itching, increased menstrual cramps, increase blood pressure and sexual side effects including impotence, loss libido or trouble having an orgasm.
- *Drug interactions*; **CYP2D6 inhibitors** ***such as*** Bupropion or Fluoxetine ⇨ ↑ plasma atomoxetine levels (Atomoxetine is a substrate for **CYP2D6**) and **MAOIs**.

Clonidine (Kapvay®)#

Clonidine is a ***centrally acting*** α_2-adrenergic agonist used as **antihypertensive agent**.
In **2010 US FDA** has *approved* Kapvay® (Clonidine Hydrochloride) ***extended-release*** for the ***treatment*** of **ADHD** as ***monotherapy*** and as ***adjunctive therapy*** to **stimulant medications**, for paediatric patients aged 6-17 years. It was later approved for adults.
- *Dose*; should be ***initiated with*** **one 0.1 mg** tablet at **bedtime**, ***if*** **dose** ***equal*** or ***higher than*** **0.2 mg/day**, **doses** should be taken **twice** a day (max. dose; 0.4mg/day).
- *Most common side effects* and *precautions*;
  - **Hypotension** and **bradycardia**; dose-related decreases in blood pressure and heart rate.
  - **Sedation** and **somnolence**.
  - **Rebound hypertension**; in ***abrupt discontinuation***.
- Warning; ***Sudden*** **deaths** have been ***reported*** in **children** taking Clonidine with Methylphenidate at **bedtime**.

Guanfacine (Intuniv®)#

Guanfacine ***like*** Clonidine, is a ***centrally acting*** α_2-adrenergic agonist, used in the ***treatment*** of **ADHD** and **hypertension**.
Like Clonidine, in **2010 US FDA** has *approved* Intuniv® (Guanfacine Hydrochloride) ***extended-release*** for the ***treatment*** of **ADHD** as ***monotherapy*** and as ***adjunctive therapy*** to **stimulant medications**, for paediatric patients aged 6-17 years.
- *Dose*; should be ***initiated with*** 1 mg/day once and adjust in increments of no more than 1 mg/week. Target dose range (0.05 - 0.12 mg/kg/day). ***Dosage adjustments*** are recommended with concomitant use of ***strong*** **CYP3A4 inhibitors**.
- *Most common side effects* and *precautions*; same as Clonidine.

Antipsychotic Drugs

The **antipsychotic drugs** (*also called* neuroleptics or major tranquilizers) are **used** *primarily* to treat **schizophrenia**, but they are ***also effective*** in **other psychotic** and **manic states**.

- **Antipsychotic drugs** are ***not*** **curative** and ***do not eliminate*** **chronic thought disorders**, but they often ***decrease*** the **intensity of hallucinations** and **delusions**.

The **antipsychotic drugs** are ***divided into*** first generation and second generation agents.

First-generation antipsychotics, ***known as*** typical antipsychotics, while **second-generation antipsychotics**, ***known as*** atypical antipsychotics.

The first-generation drugs are ***further classified as*** "low potency" or "high potency".

- ***This*** **classification** ***does not indicate*** **clinical effectiveness** of the drugs, ***but*** rather specifies ***affinity*** for the **dopamine D_2 receptor**, which, in turn, may ***influence*** the **adverse effect** of drug.

First-Generation Antipsychotics; FGAs (Typical)

Low Potency

Fewer extrapyramidal symptoms; (EPS), *but more* H_1, α_1 and muscarinic *blocking effects*.

Phenothiazines	
Chlorpromazine (CPZ) (Neurazine®)#	**Thioridazine** (Mellaril®)

High Potency

More extrapyramidal symptoms (EPS), *but less* H_1, α_1 and muscarinic *blocking effects*.

Phenothiazines	
Fluphenazine (Modecate®)#	**Perphenazine** (Trilafon®)
Mesoridazine (Serentil®)	**Trifluoperazine** (Stelazine®)
Prochlorperazine (Compazine®)#	**Promethazine** (Phenergan®)#
Butyrophenones	
Haloperidol (Haldol®)#	**Droperidol** (Inapsine®)
Others	
Loxapine (loxitane®)	**Zuclopenthixol** (Clopixol®)#
Pimozide (Orap®)	**Thiothixene** (Navane®)
	Flupenthixol (Fluanxol®)

Second-Generation Antipsychotics; SGAs (Atypical)

Lower incidence of **EPS** and have ***little*** or ***no*** have effect on H_1, α_1 and **muscarinic** receptor than the first-generation agents, they are ***associated with*** a ***higher risk*** of **metabolic side effects**, such as **diabetes**, **hypercholesterolemia** and **weight gain**.

Second-generation agents are ***generally*** used as ***first-line therapy*** for **schizophrenia** to ***minimize*** the ***risk of*** EPS ***associated*** with the first-generation agents.

The second-generation drugs appear to owe their unique activity to ***blockade*** of ***both*** **serotonin** and **dopamine** and **other receptors**.

Clozapine (Clozaril®)#	**Aripiprazole** (Abilify®)#	**Olanzapine** (Zyprexa®)#
Paliperidone (Invega®)#	**Quetiapine** (Seroquel®)#	**Risperidone** (Risperdal®)#
Lurasidone (Latuda®)#	**Iloperidone** (Fanapt®)#	**Ziprasidone** (Zeldox®)#
Asenapine (Saphris®)#	**Sertindole** (Serdolect®)#	**Sulpiride** (Dogmatil®)#

Only Ziprasidone and Paliperidone; ***increased*** **absorption** ***with*** **food**.
Haloperidol can be ***given*** **IM** (**IV** has been linked to toxicity and ***should not be given***).
All of **first-generation** and ***most*** of the **second-generation** ***block*** **D_2 dopamine receptors**.
Most of **second-generation** **agents** ***inhibit*** **5-HT receptors**, ***particularly*** **5-HT_{2A}** receptors
Long acting parenteral (**IM**) **formulations** (***only for*** **chronic therapy** in patients who have ***trouble*** **adhering** to **oral therapy**);
- **Depot forms** (***long-acting forms***) of Haloperidol, Fluphenazine, Zuclopenthixol and Risperidone are ***available***, providing ***sustained*** **concentrations** for about **1 month** ***for*** Haloperidol and **2-3 weeks** for Fluphenazine, Zuclopenthixol and Risperidone (***only for chronic therapy***).
- Paliperidone Palmitate (Invega® Sustenna) (*FDA approved 5/2015*); It is a **3-month** ***extended-release*** **injectable suspension**.
- Olanzapine Palmitate; ***once monthly***, it is also available.
- Aripiprazole Monohydrate (Abilify® Maintena); ***once monthly***, also available.

- Asenapine (Saphris®); is ***available*** in a **sublingual formulation**; 5-10 mg twice daily.

Uses;

A) Psychiatric Indications;
- **Schizophrenia**; is the ***primary*** **indication** for **antipsychotic agents**.
- **Psychotic bipolar disorder (BP-I)**, **psychotic depression** and **treatment-resistant depression**; Chlorpromazine, Aripiprazole, Olanzapine, Quetiapine, Risperidone & Ziprasidone are ***approved*** by the FDA for **treatment** of the **manic phase** of **bipolar disorder**.
- **Schizoaffective disorders**; characteristics of both **schizophrenia** and **affective disorders** (**depression**, **bipolar disorder** & **anxiety disorder**).
- **Tourette's syndrome** and ***disturbed behavior*** in patients with **Alzheimer's disease**.

B) Non-psychiatric Indications;
- **Prevention of nausea and vomiting**; ***most*** of ***older*** **typical antipsychotic drugs** (***except*** Thioridazine) have a ***strong*** **antiemetic effect**, Prochlorperazine used as antiemetic.
- **Neuroleptanalgesia in medical procedure**; Droperidol (typical antipsychotic) is **used** in ***combination*** with Fentanyl (opioid) in **neuroleptanalgesia**.

- ***Doses***;

Most Common	Minim Effective Dose (mg)	Usual Daily Doses (mg)
Chlorpromazine	100	100-1000
Fluphenazine	2	2-60
Haloperidol	2	2-60
Clozapine	50	300-600
Aripiprazole	10	10-30
Olanzapine	5	10-30
Quetiapine	150	150-800
Risperidone	4	4-16
Ziprasidone	40	80-160

Side effects;

A) *Serious Side Effects*;

1) **Extrapyramidal Side Effects (EPSE)**; ***drug-induced*** **movement disorders**; **Dystonia**, **Akathisia**, **Pseudoparkinsonism** and **Tardive Dyskinesia** (**Clozapine** has ***not been associated*** with **tardive dyskinesia**).
2) **Neuroleptic Malignant Syndrome (NMS)**; **agitation**, **confusion**, **consciousness disturbance**, **fever**, **tachycardia**, ***unstable*** **blood pressure** and **sweating**.

B) *General Side Effects*;

1) **Sedation and drowsiness**; ***Due to*** **antihistaminic effects**, ***usually*** during the **first few weeks** of treatment, ***particularly*** with **Chlorpromazine**, **Olanzapine**, **Quetiapine** & **Clozapine**.
2) **Antimuscarinic**; ***Particularly***; **Thioridazine**, **Chlorpromazine**, **Clozapine** and **Olanzapine** may produce blurred vision, dry mouth (except **Clozapine**), urinary retention and constipation.
3) **Orthostatic Hypotension and light-headedness**; ***Due to*** **block α_1 receptors**.
4) **Hyperprolactinemia**;
   - ***In female***; Menstrual disturbance (**amenorrhea**) & **galactorrhea**.
   - ***In male***; **Gynecomastia** and **impotence** (erectile dysfunction).
5) **Sexual Dysfunction**:
   - ***Erectile problems*** occur in 23-54% of men.
   - ***Loss*** of **libido** may occur in **men** and **women**.
6) **Weight Gain**;
   - This occurs in up to 40% of patients, with ***low-potency agents*** having ***higher*** **risk**.
   - Weight gain may occur because of ***actions*** at **histamine** or **serotonin receptors**.
7) **Risk of Venous thromboembolism (VTE)**.

C) *Specific Side Effects for Typical Antipsychotics*;

- ***Low-potency agents*** (**Thioridazine** and **Chlorpromazine**) can cause **pigmentary** ***deposits*** on the **retina** and **corneal opacity**.
- ***Many*** of the **typical agents** (**Thioridazine**, **Pimozide**, and ***IV*** **Haloperidol**) can cause ***serious*** **ECG changes** (e.g., **QT interval** ***prolongation***), these changes can ***lead to*** **arrhythmias** and **death**.

D) **Clozapine *Serious Side Effects***:

1) **Agranulocytosis**; ***risk*** of **serious** or **fatal infections**.
   - It is occurs ***about*** **1-2%** and is ***highest*** during the ***first*** **4-6 months of therapy**.
   - It is ***contraindicated*** if the white blood cell count is ***less than*** 3500 cells/mm^3.
   - Patients ***must be*** **enrolled** in a **Clozaril registry program**, which ***monitors*** **neutrophil** and **white blood cell** ***counts***.
2) ***Black box warnings***; **seizures** (at higher doses) and **myocarditis**, **orthostatic hypotension** and **respiratory arrest**.

FDA Warning;

- ***Most*** **of antipsychotics** *may* ***lower*** the **seizure threshold** and ***should be*** **used** ***cautiously*** in **patients** with **seizure disorders** or **those** with an ***increased*** **risk for seizures**, such as **withdrawal from alcohol**.
- ***Most*** **of antipsychotics** also carry the **black box warning** of ***increased risk*** for **mortality** when used in **elderly patients *with* dementia related psychosis**.

Drugs for Neurodegenerative Diseases

Antiparkinsonian Drugs

I) Levodopa (L-dopa)

Levodopa/Carbidopa (Sinemet®)# (Parcopa®)

Dopamine *can't* be **given** in the **treatment** of **PD** as it *doesn't* **penetrate** the **BBB**.
Dopa is the **amino acid** *precursor* of Dopamine.
Levodopa (L-dopa) is the *levorotatory stereoisomer* of dopa.
Levodopa is *metabolized* to Dopamine by the *dopa-decarboxylase* **enzyme**.
> **95%** of Levodopa is *metabolized* **outside** the **brain** by **peripheral** *dopa-decarboxylase*.
Only about **1-3%** of Levodopa *enters* the **brain**.
Levodopa is *combined* with **peripheral** *dopa-decarboxylase* **inhibitors** (**DDCI**); Carbidopa and Benserazide (doesn't cross BBB) ⇨ ***Prevents some*** of the **peripheral conversion** of Levodopa to Dopamine ⇨ ***increase*** **brain level** of Levodopa.
Dose; - **75** mg/day of Carbidopa is *usually* ***inhibit*** **peripheral decarboxylase activity**.
- *Formulation* of Carbidopa/Levodopa (Sinemet®; 25/100, 50/200); available as orally **disintegrating tablet**, that ***disintegrates*** in the **mouth** and is **swallowed** ***with the*** **saliva**.
- It ***should be*** taken **30-60 minutes** ***before*** **meals**.

Formulations;
1) **Standard Formulation** (**SF**): **initial dose**, 25 mg/100 mg 1 tablet orally three times daily, and ***gradually increased*** (**dose titration**)..
2) **Controlled-release** (**CR**) **Formulation**: 1 tablet orally two or three times daily.
- N.B.; If patient need conversion from SF to CR, see guidelines for conversion.
3) **Combination** (Stalevo®); Levodopa, Carbidopa and Entacapone.

Side effects;
A) Acute Side Effects (Levodopa/Carbidopa);
1) GIT Effects; Nausea and vomiting; **< 20%** and can **tolerate** in higher doses.
2) CVS Effects; Orthostatic hypotension and cardiac arrhythmias; **< 10%**.
3) CNS Effects; Depression, insomnia, agitation & hallucinations; **< 10%**.

B) Long-term Side Effects (Levodopa/Carbidopa)*;
1) Response Fluctuations;
a) Wearing-off phenomenon or end-of-dose akinesia (**timing of doses**);
- ***Characterized by***; ***Return*** of Parkinson **symptoms** ***before*** the **next dose**.
- ***Treatments***; ***adding*** a **dopamine agonist** or **MAO-B inhibitor**, or **COMT inhibitor** or ***increasing*** the **frequency/dose** of **levodopa**.

b) On-off phenomenon (***unrelated*** to the **timing of doses**);
- ***Characterized by***;
  - Off; Off-periods of ***marked*** **akinesia**.
  - On; On-periods of ***improved*** **mobility**.
  - ***Treatments***; ***adding*** Entacapone, Rasagiline, Pramipexole, Ropinirole, Apomorphine & Selegiline or ***redistributing*** **dietary protein**.

2) Dyskinesia;
- Is a ***drug-induced*** **involuntary movements** including **chorea** & **dystonia**.
- **Treatments**; ***decrease*** Levodopa **dose** or ***adding*** Amantadine (***antidyskinetic***).

N.B; A **drug holiday** (discontinuance of the drug for 3-21 days) may temporarily improve responsiveness to levodopa but is usually little help.

- *Drug interactions*;
A) If Levodopa **used alone**; Pyridoxine (Vitamin B_6) and MAO-A inhibitors.
B) Levodopa/Carbidopa; Antihypertensive agents, TCAs, D_2 antagonists and Iron.

- *Contraindications*; - **Closed-angle glaucoma**.
- **Cardiac arrhythmia** & **peptic ulcer** patients must be managed carefully.
- **Suspicious, undiagnosed skin lesions** or a history of **melanoma** patients.

II) Dopamine Receptor Agonists

Ergot Derivatives

Bromocriptine (Parlodel®)#

Bromocriptine is an *ergot* (*ergoline*) *derivative*, is a **dopamine agonist** that is used in the *treatment* of **Parkinson's disease, Hyperprolactinaemia** and **Neuroleptic Malignant Syndrome** (NMS).

- The ***older*** **ergot derivatives** (Bromocriptine and Pergolide) have been ***widely*** used to treat **Parkinson's disease *in the* past** ***but*** are **now *rarely* used**.
- *Dose* for **parkinsonism**; **5-40 mg/day**.
- *Side Effects*; **Hallucinations, confusion, delirium, nausea & orthostatic hypotension.**
  - ***Potential*** to cause **pulmonary** and **retroperitoneal fibrosis.**
- ***Used with caution*** in patients with history of **myocardial infarction** or **peripheral vascular disease**.

Non-ergot Derivatives

Apomorphine (Apokyn®)#	**Pramipexole** (Mirapex®)#
Ropinirole (Requip®)#	**Rotigotine** (Neupro®)#

- They are *non-ergot* **dopamine agonists**; *approved for* the *treatment* of **Parkinson's**.

Pharmacokinetics;
- Pramipexole & Ropinirole are ***available*** **orally** in ***extended-release*** formulations.
- Apomorphine is ***available*** **injectable** formulation.
- Rotigotine is ***available in*** **transdermal** formulation (***once-daily***).

Indications; - Apomorphine is ***used for*** **acute management** of the **hypomobility "off" phenomenon** in ***advanced*** **Parkinson's disease**.
- Pramipexole, Ropinirole and Rotigotine used for **Parkinson's disease** and **Restless Legs Syndrome** (RLS).

Side Effects; **Hallucinations, confusion, delirium, nausea & orthostatic hypotension**
- ***Unlike*** the **ergot derivatives**, these agents do ***not exacerbate*** **peripheral vascular disorders** or **cause fibrosis**.

Notes; - Apomorphine *drug interaction*; **5-HT3 antagonist antiemetics** (e.g., **Ondansetron, Dolasetron, Granisetron**); risk of severe hypotension.
- Apomorphine *contraindications*; sulfite sensitivity/allergy patients.

III) Monoamine Oxidase-B (MAO-B) Inhibitors

Selegiline (Eldepryl®)	**Rasagiline** (Azilect®)

Formulations; - Selegiline; **tablets, orally dissolving tablets** and **patches**. The patches (Emsam®) are FDA approved ***only for*** **depression**.
- Rasagiline; ***once daily*** **tablets**.

Dose; - Selegiline; - **Tablets**; 5 mg orally twice daily (morning and noon).
- **Disintegrating tablets**; 1.25-2.5 mg/day.
- Rasagiline; 0.5-1 mg/day orally.

- Selegiline is ***metabolized to*** **amphetamine-like substances**, may produce insomnia if the drug is administered at night, (Rasagiline is not metabolized to an amphetamine-like substance).
- Selegiline may **administered *with*** Levodopa, it ***enhances*** the **actions** of Levodopa and substantially ***reduces*** the **required dose**.
- *Common Side Effects*; Nausea, hallucinations and orthostatic hypotension (**insomnia *only with*** Selegiline).
- *Drug Interactions*;
  - Selegiline; ***with*** Meperidine ⇨ ***increase risk*** of **serotonin syndrome**.
  - Rasagiline; ***with*** Tramadol, Methadone, Dextromethorphan, Sympathomimetics, Fluoxetine, or Fluvoxamine ⇨ ***increase risk*** of **serotonin syndrome**.
  - Ciprofloxacin ↑ Rasagiline **concentration** (through **CYP1A2 *inhibition***).

IV) Catechol-O-Methyltransferase (COMT) Inhibitors

Tolcapone (Tasmar®)	Entacapone (Comtan®)

- Tolcapone has both **central & peripheral** *effects*, whereas the effect of Entacapone is **peripheral**.

Tolcapone is *severely* **widely restricted** *because* of **hepatotoxicity** (Entacapone has *largely replaced* Tolcapone).

COMT inhibitors *reduce* the **symptoms** of **fluctuations response** in *patients* used Levodopa/Carbidopa.

- ***Side effects***; **Dyskinesia, nausea, diarrhea, urine discoloration (orange)** and **hallucinations**.

Stalevo®; ***Consists of*** a ***combination*** of Levodopa/Carbidopa/Entacapone. It is available in ***three*** **strengths**:

Stalevo® 50 (50/12.5/200 mg)
Stalevo® 100 (100/25/200 mg)
Stalevo® 150 (150/37.5/200 mg)

V) Other Agents

Anticholinergic Agents

Benztropine (Cogentin®)#	Trihexyphenidyl (Parkinol®)	Biperiden (Akineton®)#
Procyclidine (Kemadrin®)	Orphenadrine (Norflex®)#	

- **Anticholinergic drugs** were the ***first*** **pharmacological agents** used in the ***treatment*** of **Parkinson's disease** (Orphenadrine is the first agents used in 1940s).
- **These agents** may ***improve*** **tremor & rigidity** ***but*** have ***little effect*** on **bradykinesia**.
- ***Dose***;
  - Trihexyphenidyl; ***initial dose*** 0.5 mg orally twice daily, ***maintenance*** 6- 10 mg/day.
  - Benztropine; ***initial dose*** 0.5 mg orally twice daily, ***maintenance*** 1-6 mg/day.
  - Biperiden; **2 mg** orally 3 to 4 times a day.
  - Orphenadrine is a ***derivative*** of the ***first-generation*** **antihistamine** Diphenhydramine and has effects to ***block*** **muscarinic receptors**, ***now rarely*** **used in Parkinson's disease** (it is particularly toxic in overdose), ***but*** **used** in ***acute*** **painful musculoskeletal conditions**.
- ***Common Side Effects***; **Confusion, dry mouth, dry eyes, urinary retention** and **constipation**.

Other Agent

Amantadine (Symmetrel®)# (PK-Merz®)#

Amantadine is an **antiviral agent**, was ***by chance*** found to have ***Antiparkinsonism properties***.

It has ***symptomatic*** **benefits** and may ***reduce*** **dyskinesia** caused by Levodopa or **dopamine agonists**.

- ***Dose***; 100 mg orally 2-3 times daily (***caution*** in **renal dysfunction**).
- ***Side effects***; **Dizziness, insomnia,** livedo reticularis**, nausea** and **nightmares**.

Drugs for Alzheimer's Disease

I) Cholinesterase Inhibitors

Tacrine | **Donepezil** (Aricept®)#
Rivastigmine (Exelon®)# | **Galantamine** (Reminyl®)#

- The *inhibition* of **acetylcholinesterase** (**AChE**) *within* the **CNS** will *improve* **cholinergic transmission**, at least at those neurons that are still functioning.

Tacrine was the ***first*** to ***become*** **available**, it has been ***replaced*** because of its **hepatotoxicity**.

Donepezil, **Galantamine** and **Rivastigmine** are ***reversible*** **AChE inhibitors** ***approved for*** the **treatment of mild to moderate Alzheimer's disease**.

- **All of them** have ***some*** **selectivity** for **AChE** in the **CNS**, as ***compared to*** the **periphery**.

Only **Donepezil** is ***approved for*** **treatment of advanced Alzheimer's disease**.

Rivastigmine is the ***only*** **AChE inhibitor** ***available*** as a **transdermal** ***formulation*** and the **only agent** ***approved for*** the **management of dementia associated with Parkinson's disease**.

- **All of them** ***except*** **Rivastigmine** are substrates for **CYP450**; ***potential*** **drug interactions**.

- ***Doses***; - **Donepezil**; - For ***mild*** **to** ***moderate*** **AD**; 5-10 mg once daily.
  - For ***moderate*** **to** ***severe*** **AD**; 10 or 23 mg once daily.
- **Rivastigmine**; - **Tab.**; 1.5 mg orally twice daily, with a maximum dose of 12 mg/day.
  - **Transdermal patches**;
    - **Initial**; **4.6 mg/24 hours**, dose increased slowly (minimum 4 weeks) to **9.5 mg/24 hours** (***maximum effective*** dose of **13.3 mg/24 hours**).
    - * **Transdermal patch 13.3 mg/24 h** is ***approved*** for **all stages** of AD, ***including severe***.
- **Galantamine**; - **Immediate-release** ***formulation***; 4 mg twice daily (initial).
  - **Extended-release** ***formulation***; 8 mg once daily (initial).
  - ***Maintenance dose*** after dose titration is 16-24 mg/day.

- ***Side effects***; **nausea**, **diarrhea**, **vomiting**, **anorexia**, **tremors**, **bradycardia** & **muscle cramps**.

II) N-Methyl-D-Aspartate Antagonists

Memantine (Ebixa®)#

- ***Overstimulation*** of **glutamate receptors**, ***particularly*** of the **NMDA type**, may ***result*** in **excitotoxic effects** on **neurons** and is ***suggested as*** a **mechanism** ***for*** **neurodegenerative** or **apoptotic** (programmed cell death) **processes** via Ca^{2+} ***release*** **mechanism**.

Memantine is an **NMDA receptor** ***antagonist*** ***first used*** as an **anti-influenza** ***agent***, it indicated for **moderate to severe Alzheimer's disease** and in **dementia with Lewy bodies**.

- It acts by ***blocking*** the **NMDA receptor** and ***limiting*** Ca^{2+} **influx** into the **neuron**.

- ***Dose***; - ***Immediate-release***; 5 mg once daily, can titrated to a maximum dose of 20 mg/day.
  - ***Extended-release***; 7 mg once daily, can titrated to a maximum dose of 28 mg/day.

- ***Common side effects***; **Confusion**, **dizziness**, **drowsiness**, **headache**, **insomnia** and **agitation**.

Nutritional Supplement

Caprylidene (Axona®)#

- **Axona** is a **medical food** used as a dietary management of the impairment of metabolic processes associated with **mild to moderate Alzheimer's disease**.
- **Axona** has ***not*** been **approved** by the **US FDA** for **Alzheimer's disease**.

Drugs for Multiple Sclerosis

I) Disease-Modifying Therapies (DMTs)

Beta Interferons

Interferon β-1a (Avonex®)# (Rebif®)# | **Interferon β-1b** (Betaseron®)# (Extavia®)#

Peginterferon β-1a (Plegridy®)#

The *first medication approved by* the **FDA** for **MS**, in **1993**, was **Interferon beta-1b**.
Peginterferon β-1a; is an **Interferon beta-1a** ***conjugated to*** a **polyethylene glycol** to ***decrease*** **frequency of injections** (every 2 weeks), it is ***approved by*** in **2014** for **MS**.
Most common side effects; **Skin reactions** (at the injection site, more common in SC injection), **flulike symptoms** (fever, muscle aches, fatigue and headaches, usually disappear after 3 months and can be treated with NSAIDs such as **Ibuprofen**), **leukopenia** (*reduce* white blood cells count) and ***affect*** **liver function**.
Neutralizing antibodies (**NAbs**); The ***development of*** **neutralizing antibodies** is a ***major problem*** in **multiple sclerosis patients** ***treated with*** **Interferon-beta** that can ***reduce*** **drug effectiveness**.

Non-Beta Interferons

Glatiramer Acetate (Copaxone®)#

Approved for the ***reduction*** of the **frequency of relapses** in ***patients with*** **MS**.
- ***Most common side effects***; **Skin reactions** (at the injection site), **flulike symptoms**, **flushing**, **chest tightness**, **palpitations**, **anxiety** and **shortness of breath**.

Dimethyl Fumarate (DMF) (Tecfidera®)#

- **Dimethyl Fumarate** is the methyl ester of fumaric acid.
- It have **immunomodulatory properties** ***without significant*** **immunosuppression** to ***reduce*** **relapse rate** and ***increased*** **time** to **progression** of **disability** in **MS**.
- ***Dose***; 120 mg orally twice daily, then increased to the maintenance dose of 240 mg twice daily.
- ***Most common side effects***; **Skin flushing**, **GIT effects** (abdominal pain, diarrhea and nausea) and **lymphocytopenia** (risk of infections).

Fingolimod (Gilenya®)#

It is the ***first oral disease-modifying drug*** ***approved by*** the **FDA** in **2010** to ***reduce*** **relapses** & ***delay*** **disability progression** in ***patients with*** **relapsing forms** of **MS**.
It is ***derived from*** **Myriocin**, a metabolite of the fungus *Isaria sinclairii*, the **treatment cost** is ***very expensive*** (**GILENYA®** 0.5mg 28 cap.; 15,807 Egyptian pound).
- ***Dose***; **0.5 mg** ***once*** a **day**.
Side effects; **# # # # # # # PATIENT COUNSELLING # # # # # # #**
  # **Bradycardia**; ECG monitoring is recommended within 6 months.
  # **First-** and **second-degree atrioventricular block**.
  # **Hypertension**; Blood pressure monitoring during treatment.
  # **Lymphocytopenia**; Risk of infections; herpes virus infection, CBC monitoring.
  # **Macular edema** (edema in the macula of the retina); Ophthalmologic examination is needed before and 3-4 months after drug therapy.
  # **Respiratory effects**; decrease FEV_1 and diffusion lung capacity for carbon monoxide.
  # **Liver effects**; Elevations of liver enzymes.

- *Contraindications*; ######## **PATIENT COUNSELLING** ########
  - *Patients with* **myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure** or **second-** or **third-degree atrioventricular block.**
- *Pregnancy*; ***Avoid*** **(Category C)** ***during*** **treatment** & for **2 months** ***after*** **treatment.**
- ***Avoid*** **live attenuated vaccines** (vaccines less effective during and 2 months after drug treatment).

Teriflunomide (Aubagio®)#

Teriflunomide is the ***active metabolite*** of **Leflunomide.**
Leflunomide (**Arava®**) is a **DMARD** ***used in*** **rheumatoid arthritis.**
Teriflunomide was ***approved by*** the **FDA** in **2012** for the ***treatment of patients with*** **relapsing forms of MS**, the **treatment cost** is ***very expensive*** (price *higher than* **GILENYA®**).
- *Half life*; ***Long*** **half-life** (8-19 days); ***about*** 3 months to reach steady-state concentrations; ***about*** 8 months to eliminate drug and may take up to 2 years.
- *Dose*; 7 mg or 14 mg once daily.
- *Most common side effects*; **Hepatotoxicity, Teratogenic *effect*, GI *effects*** **(diarrhea** and **nausea), dermatologic *effects*** **(alopecia** and **rash), Hypertension, Neutropenia** and **lymphopenia** (***risk of infection***, ***particularly*** **TB infections**).
- ***If women*** **planning** to be **pregnant**, she ***must be*** **discontinue the drug** and ***insure*** the **plasma concentrations** of **Teriflunomide** less than 0.02 mg/L.
- **FDA black box warning**; ***risk of*** **hepatotoxicity** and **teratogenicity** **(category X).**

Natalizumab (Tysabri®)#

Natalizumab is a ***humanized*** **monoclonal antibody** ***against*** the **α-4 subunit of integrin molecules**, ***used*** in the ***treatment of*** **multiple sclerosis** and **Crohn's disease.**
- *Indication in MS* as a ***monotherapy*** for the treatment of **patients** ***with*** **relapsing forms of MS.**
- *Dose in MS*; **300 mg** ***IV infusion*** *over* **1 hour** *every* **4 weeks**, the **treatment cost** is ***very expensive*** (price *higher than* previous drugs).
- **Side effects/Precautions**;
  - **Progressive Multifocal Leukoencephalopathy**; **PML** (viral CNS infection, John Cunningham virus; JCV); rapidly progressive and usually results in death or permanent disability. The ***risk of PML***; **1)** history of previous immunosuppression. **2)** Long duration of **Natalizumab** treatment, beyond 2 years. **3)** JC virus antibody positivity.
  - ***Common side effects***; **hypersensitivity reactions** (low risk of anaphylaxis), **fatigue, headache** and **nausea.**
  - **Antibodies formation** to **Natalizumab** (9-10%), *associated with* ***increased*** **relapses** and **hypersensitivity reactions.**

Mitoxantrone (Novantrone®)#

- **Mitoxantrone** is an ***antineoplastic agent.***
Indication in MS; In ***secondary*** **progressive** or **relapsing-remitting MS.**
- *Dose in MS*; 12 mg/m^2 IV infusion every 3 months (max. lifetime dose: 140 mg/m^2).
- *Because* of the ***potential for*** **toxicity**, **Mitoxantrone** is ***used only*** patients with ***advancing*** **MS** who's ***other therapies*** have **failed.**
- *Toxicity*; **Cardiotoxicity** (risk for heart failure, ECG monitoring must be performed) and **leukemia.**
- *Pregnancy*; ***Avoid*** **pregnancy (Category D).**
- *Precautions*; **laboratory tests** (CBC, bilirubin, liver enzymes, alkaline phosphatase and pregnancy test) ***must be*** **performed** ***before*** **each infusion.**

Alemtuzumab (Lemtrada®)#

- Alemtuzumab is a ***recombinant*** **monoclonal antibody** ***against*** **lymphocyte antigen** (CD52), it is used in the ***treatment*** of certain types of **lymphocytic leukemia**.

In 2014, **FDA approved** Alemtuzumab (Lemtrada®) for the ***treatment of*** **relapsing forms of MS**.

Indication in MS; ***Patients with*** **relapsing forms** of **MS**, ***generally*** who have had an ***inadequate*** **response** to **2** or **more** ***other*** **medications**.

- ***Dose in MS***; it is administered as ***2 separate*** **courses** (the **treatment cost** is ***very expensive***);
  - **First treatment course**: 12 mg/day IV infusion on 5 consecutive days (60 mg total dose).
  - **Second treatment course**: 12 mg/day IV infusion on 3 consecutive days (36 mg total dose) given 12 months after the first treatment course.
- **Risk Evaluation Mitigation Strategy (REMS) program**; the drug ***must be*** **registered** in a **REMS monitoring program**, ***because of*** the **risk of autoimmunity** (serious, sometimes fatal; such as immune thrombocytopenia), **infusion reactions** (such as anaphylaxis) and **malignancies** (increased risk of malignancies, including thyroid cancer and melanoma).

II) Symptomatic Therapies

Fatigue

Amantadine (PK-Merz®), **Methylphenidate** (Ritalin®) and **Fluoxetine** (Prozac®).

Pain

Tricyclic antidepressants; are ***first-line drugs*** for **primary pain**.

Anticonvulsants; **Carbamazepine**, **Phenytoin** & **Gabapentin** as ***second-line agents***.

NSAIDs or **other analgesics** can be used in secondary pain.

Spasticity (Muscle tone caused by brain or spinal problems)

First line; **Baclofen** (Lioresal®) and **Tizanidine** (Sirdalud®); *skeletal muscle relaxant*

Second line; **Dantrolene** (Dantrium®), direct muscle relaxant, **Diazepam** (Valium®).

Third line; ***Intrathecal*** **Baclofen**.

Focal spasticity; **Botulinum toxin** (Botox®).

Walking Impairment

Dalfampridine (Ampyra®)

It is the ***only*** **medication** ***approved by*** the **FDA** in 2010 for ***improvement of*** **walking** in **patients** with **multiple sclerosis**.

- ***Dose***; 10 mg orally twice daily.
- ***Most common side effects***; **seizures**, **urinary tract infections** and **insomnia**.
- ***Warnings/Precautions***; **Anaphylaxis**, **Seizures** (dose-dependent) & **urinary tract infection**.

Pseudobulbar Affect (PBA); Emotional Mismatch

Dextromethorphan/Quinidine (Nuedexta®)

Dextromethorphan; is a cough suppressant drug, **Quinidine**; is an antiarrhythmic drug.

Nuedexta® contain **20 mg** **Dextromethorphan Hydrobromide** and **10 mg** **Quinidine Sulfate**.

Antiepileptic Drugs

➢ Classification of Seizures:-

A) Focal-Onset Seizures

* Is a seizure, which the **electrical disturbances** is ***focused*** in just **one part** of the **brain**.

1) Simple Focal Seizures

* ***Affect only*** a **small region** *of the* **brain**.
* **Preserved consciousness.**

2) Complex Focal Seizures

* ***Usually*** **start** in a **small area**, then ***quickly*** involve **other areas** of the brain.
* **Some alteration** or **impairment of consciousness.**
- ***Typically last*** **30 sec.** to **2 min.**, ***but*** may feel tired for several hours after attack.
- **Motor behaviour aura** ***called*** **automatisms** (such as finger rubbing, lip smacking, chewing or swallowing or sleepwalking).
- The ***abnormal*** **electrical activity** might ***spread to*** cause a **secondary generalized seizures.**

3) Secondarily Generalized Seizures

- ***Often*** **begin** with an **aura** (warning sign) ⇨ ***then into*** a **generalized tonic-clonic convulsion.**

B) Generalized-Onset Seizures

* Is a seizure, which the **electrical disturbances** found in the **whole** or a **larger portion** of brain.
* ***Impair*** in **consciousness.**

1) Generalized Tonic-clonic Seizures

* The ***old term*** is **grand mal** [grahn-mahl] **seizures** (*from the French* "**great illness**").
* ***Typically*** **last 1-3 minutes.**
- A **tonic-clonic seizure** ***comprises*** **two main phases;**
  * **Tonic phase** (*comes first and short*); ***Quick*** **loss of consciousness** ⇨ ***falls*** to the **floor** ⇨ ***suddenly*** **muscles tension** (**stiffness**); body flexion and extremities pulled towards the body (***may*** **cry out** *due to* **air** is ***forced from*** the **lungs** and ***may*** **turn blue** in **face**).
  * **Clonic phase**; The **arms** and *usually* the **legs** begin to **jerk** ***rapidly*** and **rhythmically** (**rhythmic** ***jerking***) ⇨ after a ***few minutes***, the **jerking** ***slows*** and **stops.**

2) Absence Seizures

* The ***old term*** is **petit mal** [PET-ee-mahl] **seizures** (*from the French* "**little illness**").
* ***Typically*** begin during **childhood** and ***may persist*** into **adulthood** (***more common*** in **children**).
* ***Short period*** of **impaired consciousness.**
* ***Typically*** **last 10-30 seconds.**
* ***Attack***; *Generally*, ***short period*** of **impaired consciousness** (***only*** **clinical symptom**).
* **Attacks** *may occur* ***up to*** **hundreds** of **times** a **day.**

3) Myoclonic Seizures

* **Myoclonic** [MY-o-KLON-ik] **seizures** are a ***brief*** of **sporadic shock-like jerking** of a **muscles.**
* **Patient** *usually* **awake** and ***able to*** **think** ***clearly.***
* **Jerking movements** ***occurs in*** the **upper** or **lower extremities**, or ***may occur*** in **entire body.**
- They occur in a variety of epilepsy syndromes that have different characteristics

4) Atonic Seizures

* ***Characterized by*** a ***brief loss*** of **muscle tone** and ***falls*** to the **ground** (*known as* **drop attacks**).
- They begin in childhood and may persist into adulthood.

5) Tonic Seizures

* ***Only*** **tonic phase** of a **tonic-clonic seizure**; ***sudden stiffening movements.***

6) Clonic Seizures

* ***Only*** **clonic phase** of a **tonic-clonic seizure**; ***rhythmic jerking muscle movements.***

C) Status Epilepticus (SE)

* **Status Epilepticus** (**SE**) *new definition*; is ***any seizure*** that **lasts** ***more than*** **5 minutes** or ***more than*** **1 seizure** ***within*** a **5 minutes** period ***without returning to*** **normal** ***between*** **them.**

➢ General Mechanism of Action of Antiepileptic Drugs:-

Blocking voltage-gated channels (Na^+ or Ca^{2+}).
Enhancing inhibitory γ-aminobutyric acid (GABA).
Interfering with excitatory glutamate transmission.

- *N.B.*; Antiepileptic drugs *suppress* seizures *but* do not "*cure*" or "*prevent*" epilepsy.
- Antiepileptic Drugs *Brief History*; In the mid-**1800s**, the first effective anti-seizure medication, **Potassium Bromide**, was introduced. The ***first modern*** treatment, **Phenobarbital**, was developed in **1912**, with **Phenytoin** coming into use in **1938**.

➢ Antiepileptic Drugs:-

Antiepileptic Drugs (AEDs)

I) Sodium Channel Blockers

Hydantoins
- **Phenytoin** (Dilantin®)
- **Fosphenytoin** (Cerebyx®)
- **Ethotoin** (Peganone®)
- **Mephenytoin** (Mesantoin®)

Carboxamides
- **Carbamazepine** (Tegretol®)
- **Oxcarbazepine** (Trileptal®)
- **Eslicarbazepine Acetate** (Aptiom®)

Other Sodium Channel Blockers
- **Lamotrigine** (Lamictal®)
- **Zonisamide** (Zonegran®)
- **Lacosamide** (Vimpat®)
- **Rufinamide** (Banzel®)

II) GABA Enhancing Agents

Barbiturates
- **Phenobarbital** (Luminal®)
- **Primidone** (Mysoline®)

Benzodiazepines
- **Clonazepam** (Rivotril®)
- **Clobazam** (Frisium®)
- **Lorazepam** (Ativan®)
- **Diazepam** (Valium®)

Valproates
- **Valproic Acid** (Depakene®)
- **Sodium Valproate** (Depakine®)
- **Divalproex Sodium** (Depakote®)

Other GABA Enhancing Agents
- **Vigabatrin** (Sabril®)
- **Tiagabine** (Gabitril®)

III) GABA Analogs

- **Gabapentin** (Neurontin®)
- **Pregabalin** (Lyrica®)

IV) Multiple or Other Mechanisms of Action

Felbamate (Felbatol®)	**Topiramate** (Topamax®)	**Perampanel** (Fycompa®)
Ethosuximide (Zarontin®)	**Levetiracetam** (Keppra®)	**Brivaracetam** (Briviact®)
Ezogabine (Potiga®)	**Stiripentol** (Diacomit®)	**Acetazolamide** (Diamox®)

I) Sodium Channel Blockers

Hydantoins

Phenytoin (Dilantin®)# (Epanutin®)#

- *Routes of administration*; **Oral** (cap, chew tab or susp), **Rectal** and **IV** (IM not recommended).
* **Phenytoin** is an *inducer* of the **CYP3A4** and **CYP2C19** families.
# *Indications*; **Focal** (or **partial**), **generalized tonic-clonic seizures** and **status epilepticus**.
- *Dose*; **Orally** 200mg - 500mg daily divided into 1 or 2 doses. **IV**; 10-15 mg/kg at 25-50 mg/min.
Side effects;
  * *Dose-related side effects*; **Nystagmus**, **Diplopia**, **ataxia** & **drowsiness**.
  * *Non-dose-related side effects* (*chronic*); **Gingival hyperplasia**, **hirsutism**, **acne**, **rash**, **hepatotoxicity** and **coarsening of facial features** (change in normal facial features).
  - *Chronic use* may associated with *decrease* **bone mineral density** (*vitamin D metabolism abnormality*) and **megaloblastic anemia**.
  - *IV infusion side effects*; **phlebitis** and **hypotension** (*with rapid infusion*).
Pregnancy **category D**;
  - **Fetal Hydantoin Syndrome**; **Cleft lip or palate**, **congenital heart disease**, **slowing of growth** and **mental deficiency**.
  - **Life-threatening fetus bleeding**; decrease vitamin K-dependent clotting factors.
- *Drug interactions*; **CYP3A4 *inhibitors* or *inducers***.
- *N.B.*; **Phenytoin** (Healosol® spray) in **wound healing**; **evidence *suggests*** that **topical phenytoin** is ***useful*** in **wound healing** in people with **chronic skin wounds**.

Fosphenytoin (Cerebyx®)

- **Fosphenytoin** is a *prodrug* that is ***rapidly converted to*** **Phenytoin** within minutes.
* *Advantages over phenytoin*;
1) **IM dosing** and ***more safely*** **IV dosing**.
2) **Phlebitis** is *minimized*.
3) **Infusion rate 3 times** *faster* (150 mg/min).
4) ***Can*** **deliver** in **normal saline** or **5% dextrose**.
- *Dose*; 15-20 mg/kg at 100-150 mg/min (1.5 mg of **Fosphenytoin** = 1 mg of **Phenytoin**).
- *Indications*; ***most commonly*** **used in status epilepticus**.
- *Side effects*: **Hypotension**, **perianal itching** and *other side effects* of **Phenytoin**.

Ethotoin (Peganone®)

- *Indications*; **used in patients** who are ***hypersensitive*** to **Phenytoin**, ***but*** **less effective**.
- *Side effects*; ***less severe*** than **Phenytoin** (***lacks of*** **gingival hyperplasia** and **hirsutism**).

Mephenytoin (Mesantoin®)

- It is ***metabolized to*** **Nirvanol**; is ***quite*** **toxic**. **Mephenytoin** is ***no*** **longer available**.

Carboxamides

Carbamazepine (Tegretol®)# (Carbatrol®)

Carbamazepine (**CBZ**) is a ***major most popular first-line antiepileptic drug for*** **focal seizures** and **generalized tonic-clonic seizures**.
Carbamazepine is ***closely related to*** **Imipramine** and it is a **tricyclic compound** ***effective*** in ***treatment*** **bipolar depression**, the ***value*** in the **treatment of** ***epilepsy*** was ***discovered*** by **chance**.
- *Mechanism of action*; like **Phenytoin**, ***blocks*** **voltage-gated sodium channels**.
- *Pharmacokinetics*; **Absorbed** ***slowly*** after **oral administration** and **varies** ***widely*** **among patients**, *but* ***complete*** **absorption** apparently ***occurs in*** **all**.
  * **Carbamazepine** is an *inducer* of the **CYP1A2**, **CYP2C**, and **CYP3A**.
- *Formulations*; **Tegretol®**; **Chewable tablets** 100 mg, 200 mg, **Suspension** 100 mg/5 mL and **Suppositories** 125mg, 250mg. **Tegretol®** CR or XR; **Extended-release tablets** 100 mg, 200 mg & 400 mg (twice). - *Dose*; 800 mg - 1200 mg divided into 2 or 4 doses.
- *N.B.*; **Tegretol®** CR or XR, ***must be*** **swallowed whole** and ***never*** **crushed** or **chewed**, while **Carbatrol®** extended-release capsules ***can be*** **opened** and ***sprinkled on*** **food**.

Indications; **Focal, generalized tonic-clonic seizures, trigeminal neuralgia & bipolar disorder.**
* It is *not effective* for **absence seizures** or **myoclonic seizures** (*may increase seizures*).
# *Side effects*;
* *Dose-related side effects*;
- **Diplopia, ataxia, drowsiness** and **mild GI upsets.**
- **Hyponatremia** due to an antidiuretic hormone (ADH)-like effect.
* *Non-dose-related side effects*; **Aplastic anemia, thrombocytopenia** and **leukopenia.**
* *Idiosyncratic side effects*; **skin rash** and **hepatic dysfunction.**
# FDA Warning; Hypersensitivity Reactions, HLA-B*1502 and HLA-A*3101 Alleles
- *Drug interactions*; CYP3A4 *inhibitors or inducers.*

Oxcarbazepine (Trileptal®)# (Oxtellar® XR)#

Oxcarbazepine (OXC) is a *prodrug* that is ***rapidly reduced*** to the **active monohydroxy** (**MHD**) **metabolite derivatives** (***R*-licarbazepine** and ***S*-licarbazepine**).
Formulations; - Trileptal®; tablets 150 mg, 300 mg, 600 mg and suspension 60 mg/ml.
- Oxtellar® XR; extended-release tablets 150 mg, 300 mg, 600 mg.
- *Dose*; 600 mg - 2400 mg daily divided into 2 or 3 doses.
Indications; ***Approved*** as ***monotherapy*** or ***adjunctive therapy*** in ***patients with* partial seizures.**
Off-label; **Bipolar disorder, diabetic neuropathy** and **trigeminal neuralgia.**
- **Oxcarbazepine** and **MHD** are **CYP3A4 & CYP3A5** ***inducers***, (***less potent than* Carbamazepine**).
- *Side effects*;
* **Hyponatremia** ***more common*** *than* with **Carbamazepine** (***increased with* dose & age**).
- **Hematologic** ***side effects less common*** *than* with **Carbamazepine.**
- **Hypersensitivity** ***less common*** *than* with **Carbamazepine** (25-30% of patients with hypersensitivity to Carbamazepine will have hypersensitivity to Oxcarbazepine).
- *Drug interactions*; CYP3A4 *inhibitors or inducers.*

Eslicarbazepine Acetate (Aptiom®)

Eslicarbazepine (ESL) Acetate is a *prodrug* that is ***converted to*** the **active metabolite Eslicarbazepine** (***S*-licarbazepine**). ***S*-licarbazepine** is ***active metabolite*** of **Oxcarbazepine.**
- *Indications*; **Eslicarbazepine** is ***similar to* Oxcarbazepine**. The ***possible advantage*** of **Eslicarbazepine** is ***linear pharmacokinetics*** and *dose* is **once daily**.
- *Formulations*; Aptiom®; tablets 200 mg, 400 mg, 600 mg, 800 mg.
- *Side effects*; **Dizziness, somnolence, nausea, headache** and **diplopia** (**Hypersensitivity** and **hyponatremia** are ***less common***).

Other Sodium Channel Blockers

Lamotrigine (Lamictal®)#

- It is ***metabolized predominantly*** by **glucuronic acid** ***conjugation.***
Formulations; - Lamictal® tablets; 25 mg, 100 mg, 150 mg, 200 mg.
- Lamictal® XR; 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg.
- Lamictal® Chewable/dispersible tablets; 2 mg, 5 mg, 25 mg.
- Lamictal® Disintegrating tablets; 25 mg, 50 mg, 100 mg, 200 mg.
Indications; ***Monotherapy*** or ***adjunctive therapy*** in **partial, generalized, absence, myoclonic seizures, Lennox-Gastaut syndrome** ***associated seizures*** and **bipolar disorder.**
Off-label; **Peripheral neuropathy, trigeminal neuralgia, cluster headaches, migraines** and ***many* psychiatric disorders.**
* *Side effects* (*FDA warning*); ***Risk of* skin rash** (**Stevens-Johnson syndrome** and **toxic epidermal necrolysis**), which may be ***life-threatening* reaction.**
* *N.B.*; * **Estrogen** (in *oral contraceptives*) ***increase* Lamotrigine clearance**, so ***twice*** the **amount** of **Lamotrigine** ***may be* necessary.**
* **Valproic acid** ***decreases* Lamotrigine metabolism** and ***dose adjustment*** is **required.**

Zonisamide (Zonegran®)

Zonisamide is a *sulfonamide anticonvulsant* with *weak* **carbonic anhydrase inhibitor** *effect*.
- *Indications*; *Approved by* **FDA** *for* used as *adjunctive therapy* in *patients with* **focal seizures**.
- *Dose*; 100 mg - 600 mg/d in adults and 4 mg to 12 mg/d in children.
- *Side effects*; **Drowsiness**, **cognitive impairment** and **skin rashes** (*sulfa allergies*).
* *N.B.*; *Concomitant use* of Zonisamide and *other* **carbonic anhydrase inhibitors** such as Topiramate and Acetazolamide, *increase* the potential for **metabolic acidosis**.

Lacosamide (Vimpat®)

- *Indications*; *Approved* as *monotherapy* and as *adjunctive therapy* for **adolescents 17 years** and **older** with **partial-onset seizures**.
- *Side effects*; **Dizziness**, **ataxia**, **vomiting** and **diplopia**.
- *Warning*; **Suicidal ideation**, **arrhythmia** and **hypersensitivity reactions**.

Rufinamide (Banzel®)

- *Pharmacokinetics*; **Absorption** *increased by* **food**.
- *Indications*; It was *approved by* the **US FDA** in **2008** as *adjunctive treatment* of *seizures associated* with **Lennox-Gastaut syndrome**.
- *Side effects*; **Somnolence**, **vomiting**, **fatigue**, **diarrhea** and **QT interval** *shortening*.

II) GABA Enhancing Agents

Barbiturates

Phenobarbital (Luminal®)#

Currently, its **use** is *limited because* of its **adverse effects**.
Phenobarbital is a *powerful* **inducer** of the **hepatic microsomal enzymes** (Enzyme Inducing Antiepileptic Drugs; EIAEDs *such as* Phenytoin, Carbamazepine and Phenobarbital.
- *Indications*; *Usually in* **status epilepticus** (*emergency*), *when* **other agents** *fail*.

Primidone (Mysoline®)

- Primidone (Desoxyphenobarbital) is *metabolized* to Phenobarbital (*major*) and Phenylethylmalonamide, *all three compounds* are **active anticonvulsants**.
- *Indications*; **Partial** and **generalized tonic-clonic seizures**,
- *History*; Primidone was once a *primary* **anticonvulsant** in the treatment of **partial** and **generalized seizures** and was the *treatment of choice*, *especially* when *combined with* Phenytoin, *but* in early **1980s**, Carbamazepine had *surpassed* Primidone *popularity*.

Benzodiazepines (BDZs)

Clonazepam (Rivotril®)#	**Clobazam** (Frisium®)#
Lorazepam (Ativan®)#	**Diazepam** (Valium®)#

- *Most commonly used*; Clonazepam (stronger), Lorazepam (longer) and Diazepam (faster).
- Clobazam is *widely used* by **specialist epilepsy clinics** *worldwide*.
- Clonazepam is *most* **popular**.
- *Indications*; *Usually used as* **adjunctive**, **short-term therapy** (*emergency*).

Valproates (VPAs)

Valproic Acid (Depakene®)#	**Sodium Valproate** (Depakine®)
Divalproex Sodium (Depakote®)	

- Valproates was *first made* in **1882** and came into *medical use* in **1960s**.
- Valproic Acid is a *fatty carboxylic acids*.
Divalproex Sodium is a *combination* of Sodium Valproate *and* Valproic Acid that is *converted to* Valproate when it reaches the **GIT**, *All* of this **forms** are *equivalent* in **efficacy**.
Formulations; **Valproates** are *available* in **multiple-salt dosage forms** and *extended-release* **formulations** (Depakine® Chrono).

Indications; **Valproates** are ***very effective against*** **absence seizures, myoclonic seizures** and **tonic-clonic seizures**. *Dose*; 1000 mg - 2000 mg daily divided into 1 or 2 doses.
- *Other uses*; **Bipolar disorder** and **migraine prophylaxis**.
- *Most common side effects*; **Nausea, vomiting** and **drowsiness**.
FDA Warning; **Fatal hepatotoxicity** (liver enzyme monitoring is needed within the first 6 months), **Severe birth defects** (Spina bifida and lower intelligence quotient; IQ), **fatal pancreatitis** and **suicidal ideation**.
- *Drug interactions*; **Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine** and **Primidone**.

Other GABA Enhancing Agents

Vigabatrin (Sabril®)#

Indications; **Partial seizures** and **infantile spasms** (*rare epileptic disorder in infants*).
- *Dose*; 2000-3000 mg/d divided into 1-2 doses, **infant**; 50-150 mg/kg/day in 2 divided doses.
Side effects; **drowsiness, dizziness, blurred vision** and **weight gain**.
FDA Warning; Vision loss (*long-term therapy*) from mild to severe in 30% or more of patients.

Tiagabine (Gabitril®)#

Indications; *approved by* FDA; ***adjunctive treatment*** for **partial seizures** in **ages 12 *and* up**.
Off-label; **Anxiety disorders** and **neuropathic pain**.
- *Side effects*; **Dizziness, paresthesia, nervousness, tremor** and **depressed mood**.

III) GABA Analogs

Gabapentin (Neurontin®)#

Gabapentin is an *analog* (*analogue*) *of* **GABA**, it was *developed to* have a **structure** ***similar*** to that of **GABA**; however, *in fact*, **little** or **no action** on the **GABA receptor** or ***enhance*** **GABA actions**, it was originally ***approved by*** the U.S. FDA in **1993**, for use as an ***adjunctive treatment*** for **partial seizures** in **adults**.
Gabapentin has *anticonvulsant*, and *anxiolytic effects*.
- *Pharmacokinetics*; **Absorption** is ***nonlinear***, ***not*** **metabolized** and **eliminated unchanged** ***renally*** (dose adjustments in renal dysfunction).
Indications; ***adjunctive treatment*** for **focal-onset seizures** and **postherpetic neuralgia** (neuropathic pain following shingles; herpes zoster virus).
- *Dose*; 900 mg - 3600 mg daily divided into 3 doses.
Another formulations; - **Gabapentin** (Gralise®) ***extended-release*** **tablets** 300 and 600 mg, ***indicated only*** for **postherpetic neuralgia *not* epilepsy**.
- **Gabapentin Enacarbil** (Horizant®) ***extended-release*** **tablets** 300 and 600 mg, is a ***prodrug*** for **Gabapentin** and is ***indicated for*** **postherpetic neuralgia** and **restless legs syndrome**, ***not*** **epilepsy**.
- *Side effects*; **Dizziness, fatigue, drowsiness, ataxia, nystagmus** and **tremor**.
- *Drug interactions*; ***Negligible***.

Pregabalin (Lyrica®)#

Pregabalin is a ***structural*** ***analogue of*** **GABA**, has ***analgesic***, ***anticonvulsant*** and *anxiolytic effects*, it was ***approved by*** the U.S. FDA in **2004**.
Pregabalin (Lyrica®) is ***one*** of the **top 10** ***most seller*** **drugs** ($3.4 billion in 2015).
- *Pharmacokinetics*; like **Gabapentin**, ***not*** **metabolized** and **eliminated** ***renally*** (dose adjustments in renal dysfunction).
Indications; ***adjunctive treatment*** for **focal-onset seizures, diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia** & **neuropathic pain** ***associated with*** **spinal cord injury**.
- *Dose*; 300 mg daily divided into 2-3 doses.
- *Side effects*; **Drowsiness, blurred vision, weight gain** and **peripheral edema**.
N.B.; **Pregabalin** is ***classified as*** **Schedule V controlled substance** in **US**, ***abrupt discontinuation***, may cause ***withdrawal symptoms***; **insomnia, nausea, headache** & **diarrhea**.

IV) Multiple or Other Mechanisms of Action

Felbamate (Felbatol®)#

- Felbamate is a *potent anticonvulsant*, *very effective against* multiple seizure types.
Indications; It is reserved for use in refractory epilepsies (*particularly* Lennox-Gastaut syndrome) *because of* the *risk of* aplastic anemia and hepatic failure.

Topiramate (Topamax®)#

- Topiramate is a *fructose derivative*, *was developed as* an antidiabetic drug, *but* it was found to have *very potent anticonvulsant effects*.
- *Pharmacokinetics*; *Not* metabolized and eliminated unchanged *renally*.
Indications; Partial & generalized tonic-clonic seizures, Lennox-Gastaut syndrome, migraine prophylaxis, *in 2012*, it was approved in *combination with* Phentermine for weight loss.
- *Side effects*; Somnolence, paresthesia, cognitive slowing, confusion, weight loss, renal stones, glaucoma, oligohidrosis (*decreased sweating*) and hyperthermia.

Perampanel (Fycompa®)

- *Pharmacokinetics*; *Long* half-life (*once-daily*),
- *Indications*; *In 2012*, US FDA *approved* Perampanel as *adjunctive treatment* for partial-onset seizures; *in 2015* as *adjunctive treatment* for primary generalized tonic-clonic seizures.
- *Side effects*; Dizziness, *aggressive behaviour* (irritability, aggression, anger, anxiety), drowsiness and headache.
- *Warning*; *Serious* or *possibly* life-threatening mental, mood or behaviour problems, Perampanel is designated as a Schedule III controlled *substance*.

Ethosuximide (Zarontin®)

Ethosuximide is a *succinimide anticonvulsant*, it was introduced in 1960s.
Mechanism of action; *blocking* T-type Ca^{2+} channels receptors.
Indications; *Only* effective in *treating* absence seizures.
- *Side effects*; Gastric distress, nausea and vomiting.

Levetiracetam (Keppra®)#

- Levetiracetam is an *S*-enantiomer of Etiracetam, it is a Piracetam *analog*.
* *Pharmacokinetics*; *Not* metabolized & eliminated unchanged *renally* (*No* drug interactions)
- *Indications*; *Adjunctive* for focal, myoclonic, and primary generalized tonic-clonic seizures.
- *Off-label*; Status epilepticus (*parenteral formulation*).
- *Side effects*; Somnolence, asthenia, ataxia and dizziness.

Brivaracetam (Briviact®)

- It *was approved* in February 19th, 2016 as *adjunctive treatment* of partial-onset seizures.

Ezogabine or Retigabine (Potiga®)

- Ezogabine is a *unique anticonvulsant* (*novel mechanism*), it *was approved* in 2011.
- *Mechanism of action*; Potassium channel *opener*.
- *Indications*; *Adjunctive* for partial-onset seizures. - *Dose*; 600-1200 mg/d divided into 3 doses.
- *Off-label*; Tinnitus.
- *Side effects*; Urinary retention, QT interval *prolongation*, blue skin discoloration and retinal abnormalities.
- *N.B.*; Ezogabine is *classified as* Schedule V controlled substance.

Stiripentol (Diacomit®)

- *Indications*; *With* Clobazam and Valproate in the *adjunctive therapy* of *refractory* generalized tonic-clonic seizures in patients *with* severe myoclonic epilepsy of infancy (SMEI, Dravet's syndrome). *Dose*; 50mg/kg/day divided into 2-3 doses.
- *Side effects*; Nausea, vomiting, aggression and ataxia *due to* Stiripentol (*potent inhibitor* of CYP3A4, CYP1A2 and CYP2C19) *increase* concentrations of Clobazam and Valproate.

Medication Selection for Various Seizure Types:-

- *Colour Guide*;

First-line drug
Second-line drug
May be used
Adjunctive treatment
Only when benefits outweigh risks

Table from American College of Clinical Pharmacy (ACCP) Updates in Therapeutics 2015

- **Newly diagnosed epilepsy**; First line drug ⇨ If seizures persist ⇨ Second line drug ⇨ If seizures persist ⇨ Adjunctive therapy ⇨ If seizures persist ⇨ Vagal nerve stimulation

Headache Managements

	Migraine	Tension Headache	Cluster Headache
			
Pain	Pulsating or Throbbing	Pressing or Tightening	Sharp or Stabbing
Pain Intensity	Moderate to Severe	Mild to Moderate	Severe to Very severe
Duration	4 hours to 3 days	30 min. to several days	15-180 minutes
Location	Unilateral or Bilateral	Bilateral	Unilateral, eye focused
Aura	With or Without	Without	Without
Nausea/Vomiting	Very common	No	No
Photophobia or Phonophobia	Very common	No more than one	No (running nose and tears are common)

Migraine

➢ Symptoms and Signs:-

- **Typical symptoms** of **migraine** ***include the following***: (TV-~~ON~~-SD)

Throbbing (Pulsating) Pain	- Pain with each beat of the heart, with moderate to severe.
Visual Disturbances "Aura"	- Visual disturbances are considered a common warning sign of classical migraine (migraine with aura; MWA, *see next*).
One Sided Head Pain	- Most of patients feels; one-sided head pain (unilateral). - *Some* of patient feels; pain on both sides, in their neck, or at the front or back of their head (bilateral).
Nausea or Vomiting	- Nausea (80%) and vomiting (50%) are very common.
Sensitivity to Light and Sound	- Sensitivity or aversion to light and sound is one of the most common signs of migraine.
Dizziness	- Dizziness is common.

➢ Migraine Triggers:-

Hormonal	Lifestyle	Foods
Menstruation Pregnancy Menopause	Smoking Emotional stress Sleep disturbances Not eating or skipping meals	Caffeine Chocolate Alcohol (Red wine) Aspartame (sweetener) Aged cheese (tyramine food) Monosodium glutamate (MSG) Ice cream (*ice not cream*) Smoked fish and meats Processed meat Citrus fruits Onions, Nuts Avocados, Tomatoes,
Environmental	**Medications**	
Bright, flash or fluorescent light Strong odour (perfumes) Weather changes	Oral contraceptives Vasodilators	

➢ **Managements:-**

Acute Attack Treatment

Triptans

Sumatriptan (Imitrex®)#	**Zolmitriptan** (Zomig®)#	**Rizatriptan** (Maxalt®)
Naratriptan (Amerge®)#	**Eletriptan** (Relpax®)#	**Almotriptan** (Axert®)
Frovatriptan (Frova®)		

- They are ***selective* agonists** for **5-HT$_{1B}$** and **5-HT$_{1D}$** receptors.
Triptans are a family of tryptamine-based drugs, introduced in the 1990s for the ***treatment*** of **migraines** and **cluster headaches**.
All of these agents available in **oral preparation**, **Sumatriptan** available in **nasal**, **SC** and **rectal** ***preparation***, **Zolmitriptan** available in **nasal** ***preparation***, **Zolmitriptan** and **Rizatriptan** are available in an **oral disintegrating tablet**.
There is also a ***combination preparation*** of **triptan/nonsteroidal anti-inflammatory (NSAIDs)**; **Sumatriptan/Naproxen** (**Treximet®**), ***indicated for*** the ***acute treatment*** of **migraine with** or **without aura**, and more ***effective*** in **menstrual migraine**.
- ***Contraindication***; Patients with **coronary artery disease**, **stroke**, **uncontrolled hypertension**, **peripheral vascular disease** & **pregnancy** (**Category C**; when benefits outweigh the risks).
- **Serotonin syndrome**; **Triptans** with **SSRIs**, **MAOIs**, or other **antidepressant drugs** (**TCAs**).
- ***Dose***; - ***General Principles***; # # # # # # # **PATIENT COUNSELLING** # # # # # # #
  - * **One dose** for **early/mild headache**.
  - * ***May be*** **repeated** ***after*** **two hours**.
  - * **Do not use** ***more than*** **two doses** within a **24-hours**.
  - * **Do not use** ***more than*** **2-3 days** ***weekly***.
  - * **NSAIDs**, **opioids** & **antiemetics** ***may*** be **used** ***with*** **triptans**.
  - * **Ergot alkaloids** ***cannot*** be **taken** on the **same day** ***with*** **triptans**.

Triptans	Dosage Forms	Maximum Daily Dose
Sumatriptan (Imitrex®)	Tablets; 25 mg, 50 mg, 100 mg	200
	SC injection; 4 mg, 6 mg	12
	Intranasal; 5 mg, 20 mg	40
Zolmitriptan (Zomig®)	Tablets 2.5 mg, 5 mg	10
	Disintegrating tab.; 2.5 mg, 5 mg	10
	Intranasal 2.5 mg, 5 mg	10
Rizatriptan (Maxalt®)	Tablets; 5 mg, 10 mg	30
	Disintegrating tab.; 5 mg, 10 mg	30
Naratriptan (Amerge®)	Tablets; 1 mg, 2.5 mg	5
Eletriptan (Relpax®)	Tablets; 20 mg, 40 mg	80
Almotriptan (Axert®)	Tablets; 6.25 mg, 12.5 mg	25
Frovatriptan (Frova®)	Tablets; 2.5 mg	7.5
Sumatriptan/Naproxen (Treximet®)	Tablets; 85 mg/500 mg	170/1000

Ergot Alkaloids

Ergotamine (Ergomar®)#	**Dihydroergotamine** (D.H.E. 45®)# (Migranal®)#

- Used in ***acute treatment*** of **migraine** (***should be*** considered for **patients** with **nausea** or **vomiting**).
- **Ergotamine**, it is often ***combined with*** **Caffeine** to ***facilitate*** **absorption** of **ergot alkaloids**.
- **Dihydroergotamine** has ***non*-oral administration routes** (SC, IV and intranasal).

- *Dose*; - Ergotamine (Ergomar®); **Initial dose**: **2 mg** under the tongue, ***may be*** **repeated** ***after*** **30 minute** (**must** ***not exceed*** **3 tablets** per day; **6 mg**), **total weekly dose**; **10 mg**.
  - Dihydroergotamine (D.H.E. 45®) (Migranal®);
    - *Intranasal*; **1 spray** (0.5 mg) into each nostril (**1 mg**), ***may be*** **repeated** ***after*** **15 minutes** (**must** ***not exceed*** **2 mg** per day), the total **weekly dose**; 8 sprays (**4 mg**).
    - *IV/IM/SC*; **1 mg** after the ***first symptom***, ***may be*** **repeated** ***after*** **1 hour** (**must** ***not exceed*** **3 mg** per day), the ***total*** **weekly dose**; **6 mg**.
- *Contraindication*; Patients with **coronary artery disease**, **stroke**, **uncontrolled hypertension**, **peripheral vascular disease** & **pregnancy** (Category X).
- *Drug interactions*; with **potent CYP3A4 inhibitors**, ***elevates*** the **serum levels** of Ergotamine, increase ***risk for*** **vasospasm**; **cerebral ischemia** and/or **ischemia** *of the* **extremities**.

Analgesics

- Non-Steroidal Anti-Inflammatory; NSAIDs (Simple Analgesics);
  - # For ***only*** ***moderate*** **migraine attacks** ***not associated with*** **vomiting** or **severe nausea**, **NSAIDs** (*include* Paracetamol) or **combination analgesics** are ***first choice agents*** because they are ***effective***, ***less expensive***, and ***less side effects*** than triptans or ergots.
  - # When ***moderate*** **attacks** are ***associated with*** **severe nausea** or **vomiting**, an **oral** or **rectal antiemetic drug** can be **used in** ***conjunction with*** **NSAIDs**.
- Opioid Analgesics; **Opioids** and Barbiturates ***should not be used*** for the ***treatment*** of moderate to severe **migraine**, ***except*** as a **last resort**, due to their ***potential for*** **tolerance** and **dependence**.

Antiemetics

- IV Metoclopramide, and IV or IM Chlorpromazine and Prochlorperazine can be ***used as*** **monotherapy** for **acute migraine headache**, act as **antiemetics** ***mainly*** because they are dopamine antagonists. In addition, they are ***effective*** for ***reducing*** **migraine headache pain**.
- Oral **antiemetics** ***should not be considered as*** **monotherapy** in **acute migraine**, **used in** ***adjunctive therapy*** (Metoclopramide) with **NSAIDs** to ***decrease*** **nausea** and **vomiting**.

Other Agents

- Isometheptene; is a ***sympathomimetic amine*** sometimes ***used in*** **combination** in the **treatment of migraines** due to its ***vasoconstricting properties***.

Combinations

- *Common Combination Egyptian Brands*;
  - # Migracid®; Paracetamol + Metoclopramide.
  - # Amigraine®; Ergotamine 1mg + Caffeine 100mg + Metamizole (or Analgin *like NSAIDs*) 300mg.
  - # Metograine®; Ergotamine 1mg + Paracetamol 325mg + Caffeine 100mg + Metoclopramide 5mg.
  - # Migrainil®; Ergotamine 1mg + Meprobamate (*like Barbiturates*) 150mg + Metamizole 200 mg + Pentobarbital 10 mg + Caffeine 50mg.
- *Common Combination World Brands*;
  - # Tylenol® No.3; Acetaminophen 300mg (*Paracetamol name in USA*) + Codeine 15, 30, 60mg.
  - # Midrin®; Acetaminophen 325mg + Isometheptene 65mg + Dichloralphenazone 100mg.
  - # Fiorinal®; Butalbital (*Barbiturates*) 50mg + Aspirin 325mg + Caffeine 40mg.
  - # Excedrin® Migraine; Acetaminophen 250mg + Aspirin 250mg + Caffeine 65mg.

Status Migrainosus

Status Migrainosus: **Attack** of **migraine**, with **headache phase** ***lasting more than*** **72 hours** ***despite treatment***. **Headache-free intervals** of ***less than*** **4 hours**.

- Patients need to be ***hospitalized*** for a short period and may need to be treated with ***intravenous*** Valproate or Dihydroergotamine or Corticosteroids for a **few days**.

Migraine Prophylaxis

*** High efficacy
** Low efficacy
* Limited efficacy

A) **Antihypertensives**; **Beta Blockers** (Propranolol*** and Timolol***), **Calcium Channel Blockers** (Verapamil** and Flunarizine***), **Centrally Acting Agents** (Clonidine**) **ACEIs** (Lisinopril*), **Angiotensin-Receptor Blockers** (Candesartan*).
B) **Antiepileptics**; Valproate***, Topiramate***, Lamotrigine**, Gabapentin*, Oxcarbazepine*.
C) **Antidepressants**; **TCAs** (Amitriptyline***, Nortriptyline***, Doxepin*** Protriptyline***), **SSRIs** (Paroxetine*, Fluoxetine* and Sertraline*).
D) **Serotonin Antagonists**; Methysergide***, Pizotifen*** and Cyproheptadine**.
E) **Botulinum Toxin**; *Clostridium botulinum* **toxin type A** *** (Botox®) *Approved.*
F) **Devices**; **TENS** (Transcutaneous Electrical Nerve Stimulation) **device***** (Cefaly® device), *Approved.*

Tension-type Headache (TTH)

Acute Attack Treatment

A) **Simple Analgesics**; *such as* Aspirin, Ibuprofen, and Paracetamol.
B) **Analgesic/combinations**; are ***widely used***.

Prophylaxis Medications

- **Tricyclic Antidepressants**; Amitriptyline and Nortriptyline are the most commonly used.
- **Evidence** is ***insufficient*** for use; **SSRIs**, Propranolol & *Clostridium botulinum* **toxin type A**.

Cluster Headache (CH)

Acute Attack Treatment

A) **Oxygen**; **100%** via ***non-rebreather*** **face mask** at 12 to 15 L per minute for 15 to 20 minutes, ***relieves*** **pain** in **50-85%** of **patients**.
B) **Triptans**; **SC** and ***intranasal*** Sumatriptan and ***intranasal*** Zolmitriptan are **effective**. **Oral formulations** usually ***do not act quickly enough***, ***but*** **oral** Zolmitriptan showed ***efficacy*** in **one trial**.
C) **Intranasal Lidocaine**; **20-60 mg** as a **nasal drop** or **spray** (1 mL of 10% solution applied bilaterally with a cotton swab for five minutes).
D) Octreotide (**Somatostatin** ***analogues***; **growth hormone** ***inhibitor***), 100 mcg SC have been used.

Prophylaxis Medications

A) **Verapamil**; 240 mg orally per day, in single or divided doses.
B) **Steroids**; oral Prednisone 50-80 mg/d, tapered gradually 10-12 days or sub-occipital injection of Betamethasone (used until other drug take effect).
C) **Antiepileptics**; Valproate and Topiramate are effective.
D) **Melatonin** is effective.

General Anesthetics

Inhalation Anesthetics

Nitrous Oxide (N_2O)

It is an **oxide of nitrogen**, ***commonly known as*** **laughing gas**, **nitrous**, **nitro** or **NOS**.
- It is a ***non***-**irritating** ***potent*** **analgesic** ***but*** a ***weak*** **general anesthetic**, if **used** ***alone*** *cannot* **produce surgical anesthesia**, ***but*** it is ***commonly combined*** with *other* ***more*** **potent anesthetic**.
It is ***used*** in **surgery** and **dentistry** for its **anaesthetic** and **analgesic effects**. It is known as **"laughing gas"** ***due to*** the **euphoric effects** of inhaling.
Nitrous oxide is ***poorly*** **soluble** in **blood** and **other tissues**, allowing it to ***move very*** **rapidly** **in** (***induction***) and **out** (***recovery***) of the ***body***.
- ***Concentrations***; in ***general anesthesia***, **30 %** to **70 %** in ***combination*** with **oxygen**.
Safety; **Nitrous oxide** ***does not*** ***depress*** **respiration** and ***does not*** ***produce*** **muscle relaxation**, ***little*** or ***no*** ***effect*** on **CVS** or **cerebral blood flow**, ***last*** **hepatotoxic** ***effect***.
- ***Side effects***; **Hallucination**, ***Postoperative*** **nausea** and **vomiting**.
- ***Prolonged*** **exposure** may cause **megaloblastic anemia**.

Halothane (Fluothane®)#

- **Halothane** is ***halogenated hydrocarbon***.
It is produce; ***rapid*** **induction**, ***quick*** **recovery**, ***not*** ***adequate*** **analgesia** (usually co-administered with **Nitrous oxide**, **opioids**, or **local anesthetics**) and ***not*** ***sufficient*** **muscle relaxation** (**neuromuscular backers** *may be required*, **dose** ***must be adjusted***, due to **Halothane** ***markedly*** ***augments*** the **non-depolarizing neuromuscular blocking effects**).
- ***Metabolism***; **oxidation** to **tissue-toxic hydrocarbons** (e.g. **Trifluoroethanol**) & **Bromide ion**.
Uses; ***induction*** and ***maintenance*** of **general anesthesia**.
Halothane and **Sevoflurane** ***agents of choice*** in ***patients with*** **airway problems** (***not have*** **pungent odour** to ***stimulate*** **respiratory reflexes**).
* **Hepatotoxicity** (**Halothane Hepatitis**); **Liver damage**, from ***mild*** **hepatitis** to **hepatic necrosis**.
* **Malignant Hyperthermia**; **Halothane** with **Succinylcholine** (***neuromuscular blocker***).
- ***Due to*** **side effects**; **Halothane** has been ***replaced*** in ***most*** **countries** by **newer agents** such as **Sevoflurane**, **Isoflurane** and **Desflurane**.

Isoflurane (Forane®)#

Isoflurane is a ***structural isomer*** of **Enflurane** (**Ethrane®**), **Enflurane** ***no*** **longer use** *due to* ***depression*** of **myocardial contractility**, ***higher*** **metabolism** (***high*** **toxic metabolites**, ***potentially*** **nephrotoxic**) and ***lower*** **seizures threshold**.
- ***Little*** **metabolism** (***less*** **toxic metabolites**), ***no*** or ***little*** **hepatotoxicity**.

N.B.; **Hepatic metabolism rank** for **inhaled anesthetics** is; **Halothane** > **Enflurane** > **Sevoflurane** > **Isoflurane** > **Desflurane** > **Nitrous oxide**.

Cardiac arrhythmias or ***dose-dependent*** **hypotension** ***may occur*** (*Other* ***newer*** **inhaled anesthetics** **Desflurane** and **Sevoflurane** are considerably ***less*** **arrhythmogenic**).
- It has a **pungent odour** and ***stimulates*** **respiratory reflexes** (breath holding, salivation, coughing and laryngospasm or bronchospasm), so ***not*** **used** in for **inhalation induction**.
- ***Used*** for ***maintenance*** of **general anesthesia**.
- ***Concern***; Use of **Isoflurane** and **Ketamine** in ***together*** in **infants** or **young children**, may ***increase*** **risk** of **neurodegeneration**.
- ***Now***; **Isoflurane** is ***being*** **replaced** ***with*** **Sevoflurane** and **Desflurane**.

Desflurane (Suprane®)#

- It is ***very*** **rapid onset** and **recovery** due to ***low*** **blood solubility**.

Like **Isoflurane**, it has a **pungent odour**, ***used*** for ***maintenance*** of **general anesthesia**, ***but*** due to ***high*** **cost** may ***precludes*** its **use**.

- ***Metabolism***; is ***minimal*** and **tissue toxicity** is ***rare***.

Sevoflurane (Sevorane®)#

- It has ***low*** **pungency**, ***used*** for ***induction*** and ***maintenance*** of **general anesthesia** in **adult** ***and*** **paediatric**.
- It has a ***rapid*** **onset** and **recovery** due to ***low*** **blood solubility**.
- ***Metabolism*** of **Sevoflurane** may ***generate*** **toxic metabolites** that are ***potentially*** **nephrotoxic**.

- ***N.B.***; - **Isoflurane**, **Desflurane** and **Sevoflurane** are a ***trigger*** of **malignant hyperthermia**.
  - **Mutagenicity**, **teratogenicity**, **reproductive effects** and **carcinogenicity** are a **chronic toxicity** for **inhalation anesthetics**, ***increase*** in **operating room personnel** who were exposed to trace concentrations of anesthetic agents.
  - **Methoxyflurane** is ***another*** **halogenated anesthetic** has ***not been*** **hepatotoxicity** *reported* after administration, *However*, **fluoride** ***release*** *from* **prolonged use** of **Methoxyflurane** has caused ***renal insufficiency***.

Intravenous Anesthetics

Barbiturates

Thiopental (Pentothal®)	Methohexital (Brevital®)

- ***This agents*** have been ***largely replaced*** as **induction anesthetics** by **Propofol**.
- It is a ***potent*** **anesthetic** **but** a ***weak*** **analgesic**.
- **Thiopental** ***induce*** **anesthesia** ***within*** **30-60 seconds** ***after*** **IV injection**.
- ***All*** **barbiturates** are ***potent*** **cardiac** and **respiratory depressant**, *These agents* have been ***largely replaced*** as **induction anesthetics** by **Propofol**.

Benzodiazepines

Midazolam (Dormicum®)#	Lorazepam (Ativan®)#

Diazepam (Valium®)#

- **Benzodiazepines** (*still commonly used*); **Midazolam** (*short*), **Lorazepam** (*intermediate*) and **Diazepam** (*long*) are ***commonly*** used in **Preanesthetic medications** with **anesthetics**.
- Their ***most*** **desired effects** are **anxiolytic** and **providing amnesia**.
- ***All*** **benzodiazepines** are ***minimal*** **cardiac** and **respiratory depressant**.

Intravenous Anesthetics

Propofol (Diprivan®)#

Propofol is a ***short-acting*** **IV anesthetic** (***potent*** **anesthetic** but a ***weak*** **analgesic**) ***used for*** ***induction*** and ***maintenance*** of **anesthesia**.

It is ***widely*** **used** and has ***replaced*** **Thiopental** as the ***first choice*** for ***induction*** of **anesthesia**.

Formulation; ***Poor*** **solubility** in **water**, it is formulated as an **emulsion** (10% soybean oil, 2.25% glycerol and 1.2% lecithin{egg phospholipid}), it has been ***referred to*** as **milk of amnesia** ***because*** of the **milk-like appearance** (it is ***contraindicated*** in patients with allergies to **eggs** or **soy products**).

- ***Not used*** after **8 hours** of **vial opening** (*bacterial growth*).

- *Pharmacokinetics*; - *Onset*: **30-40 seconds** *after administration*.
  - *Duration*; **5-10 minutes**.
  - *Metabolism*; *Rapidly* **metabolized** in the **liver**.
- *Excretion*; *inactive* **water soluble metabolites** are **excreted** *renally*.
- **Propofol** *produces*;
  - *Decrease* **blood pressure**.
  - *Minimal* **respiratory depressant**.

Sub-anesthetic **doses** of **Propofol** can be *used* to *treat* **postoperative nausea** and **vomiting**.

- The **respiratory depressant** of **Propofol** are *increased if* **given** with *other* **respiratory depressants (benzodiazepines)**, Michael Jackson was died of acute **Propofol** & **benzodiazepine** intoxication at home.

Fospropofol (**Lusedra**®) is a *water-soluble prodrug* of **Propofol**, *approved* in **2008** as a **sedating agent** for *use* during **Monitored Anesthesia Care (MAC)**.

Etomidate (Amidate®)#

Etomidate is a *short-acting* **IV anesthetic**, *used for induction* of **anesthesia**.

- **Etomidate** *not* has **analgesic effects**.
- *Formulation*; it is *poorly* **soluble** in **water** and is *formulated in* a **propylene glycol** *solution*.
- *Pharmacokinetics*; - *Onset*; **30-60 seconds** *after administration*.
  - *Duration*; *depends* on **redistribution** to inactive tissue sites.
  - *Metabolism*; *Primarily* by **ester hydrolysis**.
  - *Excretion*; *Inactive* **metabolites** are excreted in **urine** (78%) & **bile** (22%)

It has *little* or *no* **effect** on the **heart** and **circulation**, it is **used** *especially* in **patients** *with* **cardiovascular dysfunction**.

- *Side effects*; *decrease* **plasma cortisol** & **aldosterone** (*increased with prolonged infusion*).
- *Combination* of **Etomidate** with **opioids** and/or **benzodiazepines**, may exacerbate **Etomidate-related adrenal insufficiency**.

Ketamine (Ketalar®)#

It *induces* **dissociative anesthesia** (**trance-like state**); **analgesia-amnesia state** in which the **patient's eyes** *remain* **open**, but is *dissociated from* the **environment**, is **immobile** and *does not respond* to **pain**.

- *Pharmacokinetics*; - *Routes*; **IV**, **IM**, **oral**, & **topical routes**.
  - *Onset*; **IV**; *within* a **minute**, **IM**; 5-15 min, **Oral**; 30 min.
  - *Duration*; *More* **prolonged** (*depend on elimination*).
  - *Metabolism*; In the **liver** by **CYP450 system**.
  - *Excretion*; In urine.
- It *has* **effect** on the **heart** and **circulation** (*increase* **blood pressure** and **CO**).
- It is *not* produce **respiratory depression**, and *may* cause **bronchodilation**, It *increase* **cerebrospinal fluid** *pressure*.

It is *beneficial* in **patients** *with* **hypovolemic** or **cardiogenic shock** and **asthmatic**.

Side effects; **Psychic disturbances** (**unpleasant dreams**, **delirium** and **hallucinations**).

- **Ketamine** may be *used* **illicitly**, "**ecstasy drug**" it causes a *dream-like* **state** and **hallucinations**.

Dexmedetomidine (Precedex®)#

- It is an **α_2 receptor** *agonist*. It has **sedative**, **analgesic**, **sympatholytic** and **anxiolytic effects**.
- It is *not* produce **respiratory depression**, *moderate decrease* in **blood pressure** & **heart rate**.

Droperidol/Fentanyl (Innovar®)#

- **Droperidol** (antipsychotic) in *combination* with **Fentanyl** (opioid) usually provide **amnesia** and **analgesia**, and has been *used* to *produce* **neuroleptanalgesia** and **neuroleptanesthesia**.
- *Side effects*; **Hypotension**, **QT interval** *prolongation*, and **extrapyramidal syndrome**.

Local Anesthetics (LAs)

Esters

Cocaine

- It is the *first* used in **1884** and *strong* **stimulant** *mostly used* **illegal drug** *globally*.
- **Cocaine** *inhibits* **reuptake** of **serotonin**, **norepinephrine** and **dopamine**.
- **Cocaine** has since been *largely replaced* in **medicine** by *synthetic* **local anesthetics**.

Benzocaine

- **Benzocaine** is the *first* **synthetic** derivative of **Cocaine**, was developed in **1890**.
It is *found* in many **OTC anesthetic products** *used mainly* for **oral ulcers**.
The **topical use** of *higher concentration* of **Benzocaine** may *cause* **Methemoglobinemia**, this *side effect* is **most common** in **children** *under* **2 years**.

Procaine (Novocain®)#

- **Procaine** was *first synthesized* in **1905**. *To this day*, **Procaine** is *used less frequently*.
Procaine and *many* **other local anesthetics** are *used* *mainly* in *combination* with **Epinephrine** (*vasoconstrictor*), *to*; 1) *Reduce* bleeding.
2) *Increases* duration and quality of anesthesia (decrease absorption).
3) *Decrease* amount of drug from reaching systemic circulation.

Tetracaine (Pontocaine®)#

It is *mainly used topically* in **ophthalmology** (topical local anesthetic for the eyes).

Chloroprocaine (Nesacaine®)#

Rapidly **metabolized** and *placental* **transfer** is *limited*, so, it is *used*, for **epidural anesthesia**.

Amides

Lidocaine (Xylocaine®)# (Lignocaine®)#

- **Lidocaine** *used* **systemic** as an **antiarrhythmic drug** (Class Ib) and **locally** as **local anesthetic**.
Like **Chloroprocaine**, *sometimes used* for **epidural anesthesia**.
Like **Tetracaine**, *can* be *used topically* in **ophthalmology**.
Inhaled **Lidocaine** can be *used* as an **antitussive** (*reduce cough reflex*).
- **Lidocaine** is *available* in *multiple* **formulations** and *most widely* **used**.

Mepivacaine (Mepecaine®)#

- **Mepivacaine** is a **local anesthetic** with *rapid* **onset** and *medium* **duration of action**.
- It *may used* for **epidural anesthesia** (*poor choice*).

Bupivacaine (Marcaine®)#

It is a **local anesthetic** *used* for **epidural anesthesia**, *but* it has *markedly* **cardiotoxic**.
- **Levobupivacaine** (**Chirocaine®**) is the *S-enantiomer* of **Bupivacaine**, *with less* **cardiotoxic**, *less* **potent** and *longer* **duration** than the racemic mixture.

Ropivacaine (Naropin®)#

- **Ropivacaine** was developed after **Bupivacaine**, was *with less* **cardiotoxic**.
It is also a *popular choice* for **nerve block anaesthesia** and **epidural anesthesia**.

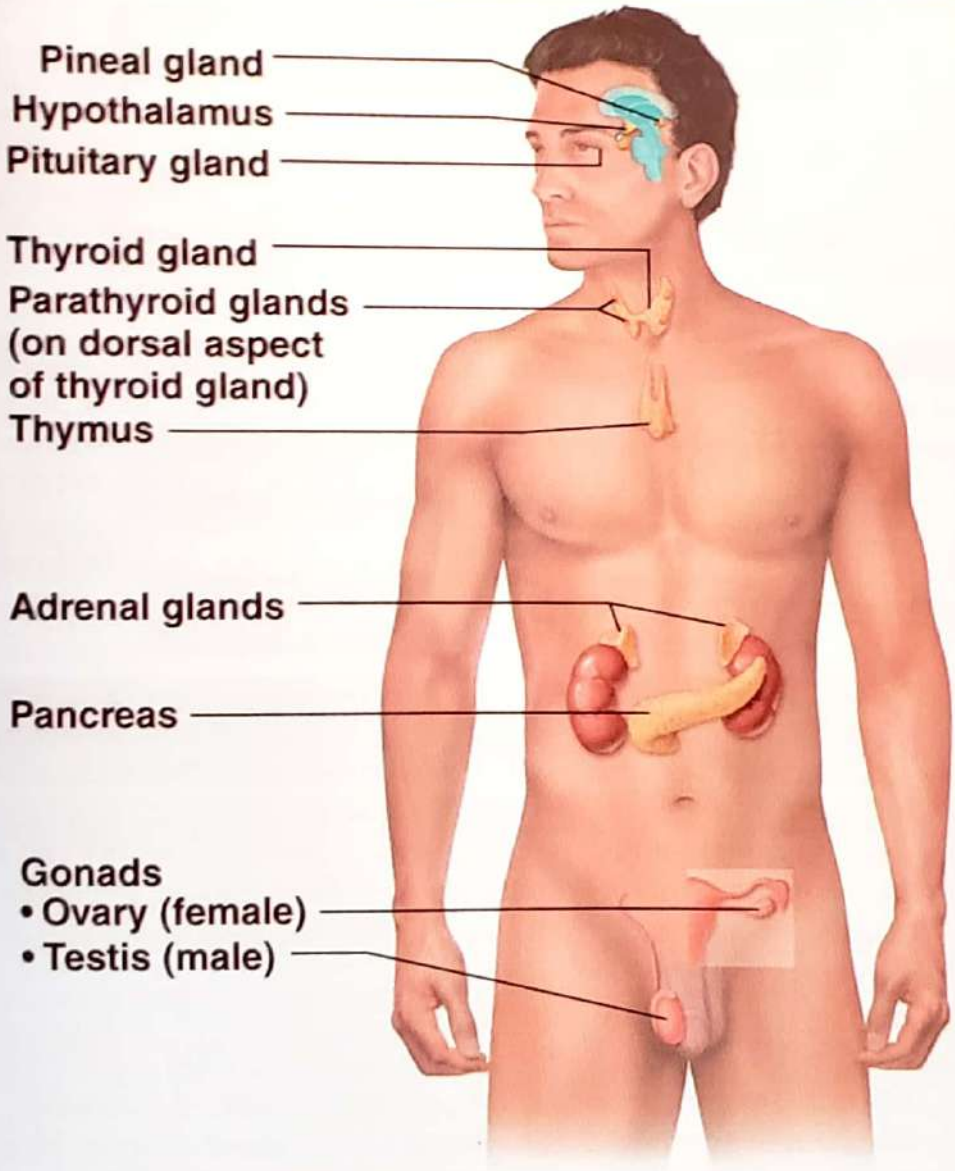
Articaine (Septocaine®)

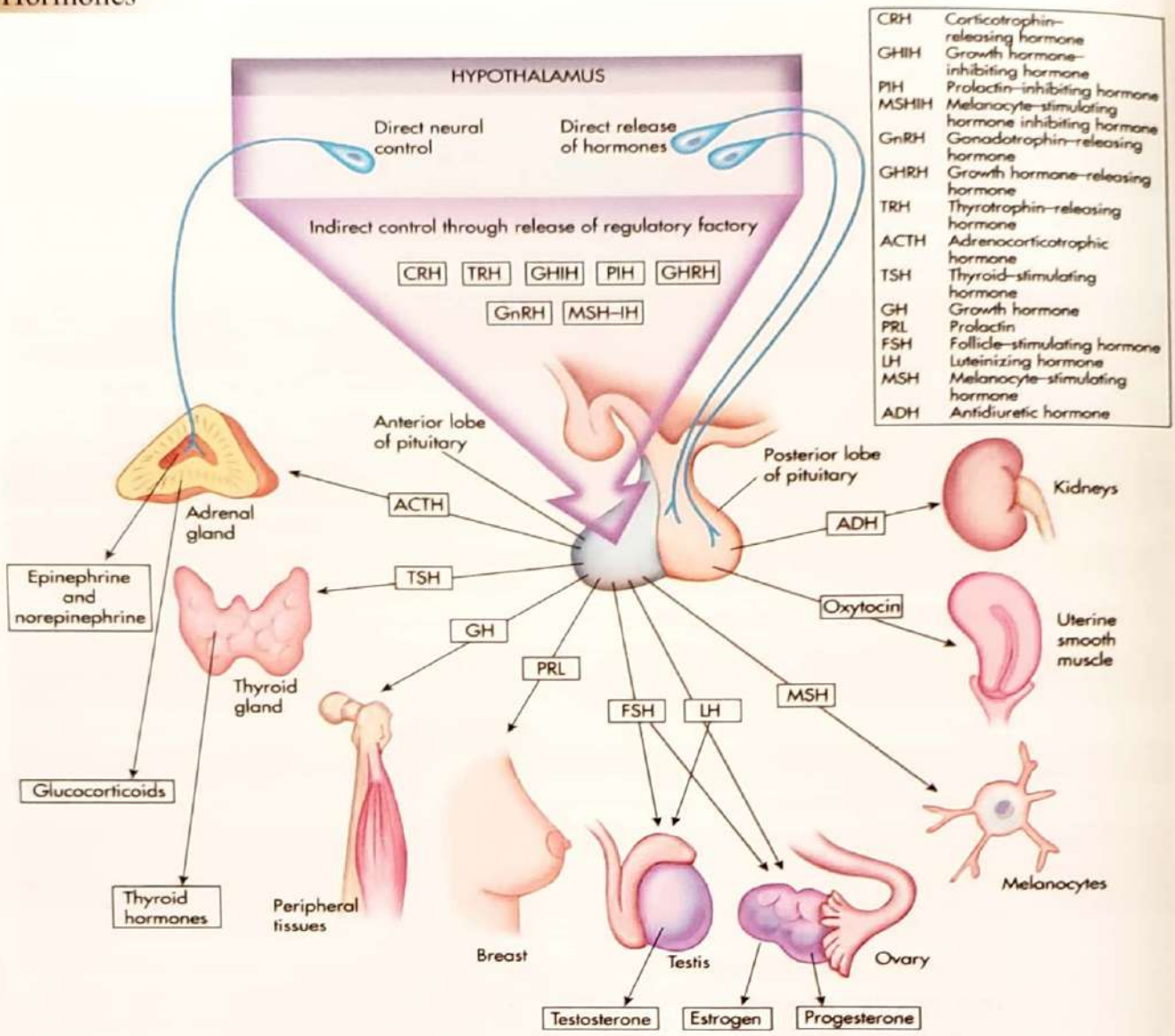
- It was *approved* as a **dental anesthetic** in 2000. Available in a *combination* with **Epinephrine**.
- **Articaine** is the *best choice* of **local anesthetic** in *modern* **dentistry**.
- *Characteristics over than other* **local anesthetics**; *low* **lipid solubility**, *high* **plasma protein binding**, *fast* **metabolization**, *fast* **elimination** and *low* **blood level**.

Prilocaine

- **Prilocaine** also *combined with* **Lidocaine** as a *topical* **preparation** for **dermal anesthesia**.
EMLA® (**E**utectic **M**ixture of **L**ocal **A**nesthetics); **Lidocaine** and **Prilocaine** are **solid bases**, when mixed in equal quantities, they form a **eutectic mixture**, that is the **melting point** of the **mixture** is *lower than* the **melting points** of the **individual components**.

Hormones





CRH	Corticotrophin-releasing hormone
GHIH	Growth hormone-inhibiting hormone
PIH	Prolactin-inhibiting hormone
MSHIH	Melanocyte-stimulating hormone inhibiting hormone
GnRH	Gonadotrophin-releasing hormone
GHRH	Growth hormone-releasing hormone
TRH	Thyrotrophin-releasing hormone
ACTH	Adrenocorticotrophic hormone
TSH	Thyroid-stimulating hormone
GH	Growth hormone
PRL	Prolactin
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
MSH	Melanocyte-stimulating hormone
ADH	Antidiuretic hormone

Pituitary Hormones

Growth Hormone (GH)

Somatotropin

Somatropin (Humatrope®)# (Genotropin®)# (Norditropin®)# (Somatotropin®)#

A ***recombinant form*** of **GH** or **somatotropin**; called **Somatropin**.

- **Growth hormone ↑ protein synthesis, cell division ⇨ *Increase* number and size of cell ⇨ ↑ *size* of tissue and organs; *growth of* linear bone, skeletal muscle, and organs.**

Uses; **GH Deficiency, Short-bowel Syndrome** and **HIV-associated Wasting** or **Cachexia**.

Off-label; **Performance enhancement in athletes**.

Dose; **0.2-0.3 mg/day** (0.6–0.9 IU) **SC *initially***.

Administration; **SC** or **IM**, but ***not all* products** are *approved for* **IM** *administration*.

Side effects; **Headache, nausea, vomiting, fatigue, muscle pain**, or **weakness**.

Precautions; ***Disease-related concerns*, diabetes, pituitary gland disorder, hypothyroidism, *history of* head injury** or **brain tumor**, ***history of* childhood brain cancer**.

Somatostatin

Octreotide (Sandostatin®)# | Lanreotide (Somatuline®)

Somatostatin is *potent inhibitor* of growth hormone, glucagon, insulin and TSH.
Uses; acromegaly, carcinoid tumors and vasoactive intestinal peptide tumors.
Octreotide (Sandostatin®) (greater potency & longer duration) is *off-label* used;
- Esophageal variceal bleeding.
- AIDS-Related Diarrhea.
- Chemotherapy-Related Diarrhea.
- Chylothorax.
- GI or Pancreatic Fistula.
- Ileostomy-Related Diarrhea.
- Dumping Syndrome.
- Neuroendocrine Tumors.

- *Dose*; Octreotide (Acromegaly); 50 mcg 2 or 3 times daily.
Lanreotide (Acromegaly); 90-120 mg; deep SC; every 4 weeks for 3 months.

Growth Hormone Receptor Antagonist

Pegvisomant (Somavert®)

Uses; Acromegaly in *patients who* have *inadequate response* to surgery or radiation therapy.
Dose; - *Initial*: 40 mg SC.
- *Maintenance*: 10-30 mg by SC daily.

Prolactin Hormone (PRL)

Prolactin *responsible for* milk *secretion* and *inhibit* ovulation in female.
Hyperprolactinemia;
- *In* female; Galactorrhea, amenorrhea, and *decrease* libido.
- *In* male; Gynecomastia, impotence, infertility and *decrease* libido.

- Dopamine (Prolactin-inhibiting hormone) ⇨ *Inhibit* Prolactin *release*.

Bromocriptine (Lactodel®)#

Bromocriptine is an *ergot* (*ergoline*) *derivative*, is a dopamine agonist that is used in the *treatment* of Parkinson's disease, Hyperprolactinaemia and Neuroleptic Malignant Syndrome (NMS).
- *Dose* for Hyperprolactinaemia;
- *Initial*: 1.25 mg to 2.5 mg orally daily.
- *Titration*: Add 2.5 mg orally, as tolerated, to the treatment dosage every 2 to 7 days.
- *Maintenance*: 2.5 mg to 15 mg orally daily.
- *Side Effects*; Hallucinations, confusion, delirium, nausea and orthostatic hypotension.
- *Potential* to cause pulmonary and retroperitoneal fibrosis.
- *Used with caution* in patients with history of myocardial infarction or peripheral vascular disease.

Cabergoline (Dostinex®)#

Cabergoline is a *long-acting* dopamine agonist with a *high affinity* for D_2 receptors.
Uses; Hyperprolactinaemia.
Dose;
- *Prevent* lactation; 1 mg (2 tablets) on the first day *after* delivery.
- *Stop* lactation *after* breast-feed; 0.25 mg (1/2 tablet) *every* 12 hours *for* two days.
- *Reduce* prolactin levels in *other* conditions; 0.5 mg/week *spread out* over a week (e.g. 1/2 tablet on Monday and the other 1/2 of the tablet on Thursday).

- *Pregnancy*: Category B.
- *Side effects*; drowsiness, nausea, headache, dizziness, vertigo and GI disturbance.

Adrenocorticotropic Hormone (ACTH)

- Adrenocorticotropic hormone (ACTH), also known as Corticotropin.
- ACTH *stimulates* secretion of glucocorticoid *hormones* from **adrenal cortex cells**.

Cosyntropin or Tetracosactide Acetate or Tetracosactide (Synacthen®)#

- Cosyntropin use as *diagnostic agent* in **adrenocortical insufficiency** (ACTH stimulation test) differentiating between primary adrenal insufficiency (Addison's disease which adrenal glands do not produce sufficient glucocorticoids and mineralocorticoids) and secondary adrenal insufficiency (caused by the inadequate secretion of ACTH by the pituitary); Primary adrenal insufficiency cannot be stimulated by ACTH where a secondary adrenal insufficiency will respond to adequate stimulation with ACTH.
- *Dose*; 0.25 to 0.75 mg IM or IV over 2 minutes.
- Can be used in short-term therapy in conditions for which glucocorticoids are usually used.

Repository Corticotropin Injection (HP Acthar® Gel)#

- HP Acthar® Gel; is a ***highly*** **purified** Adrenocorticotropic hormone (ACTH).
- *Uses*; **Infantile spasms, multiple sclerosis, rheumatic disorder, inflammatory dermatologic diseases, inflammatory ophthalmic diseases, symptomatic sarcoidosis and edematous state.**

Thyroid-Stimulating Hormone (TSH)

- Thyroid-Stimulating Hormone (TSH); Also known as Thyrotropin.
- TSH *stimulates* the thyroid gland to *produce* Thyroxine (T_4) and Triiodothyronine (T_3); T_3 ***four*** **times** ***more*** **potent than** T_4.

Thyrotropin alfa (Thyrogen®)

- *Uses*; as **adjunctive diagnostic tool** for ***serum*** Thyroglobulin (Tg) ***testing*** *with* or *without* **radioiodine imaging** to ***differentiated*** **thyroid cancer**.
- Thyroglobulin (Tg) is a ***protein*** *produced by* the **thyroid**.
- Tg used by ***thyroid gland*** to *produce* the **thyroid hormones** T_4 & T_3.
- Tg ***levels*** in the **blood** can be used as a ***tumor marker*** for *certain kinds* of **thyroid cancer** because Tg is ***not*** *produced by* **medullary** or **anaplastic thyroid carcinoma**.

Gonadotropins

All **gonadotropin preparations** are ***pregnancy*** **category X** ***should be avoid*** *after* **pregnancy**.

	Luteinizing Hormone (LH)	Follicle-stimulating Hormone (FSH)
Female	- ***Induces*** **ovulation**. - ***Development*** of the **corpus luteum** to *produce* Progesterone.	- ***Stimulates*** the **growth** of ***immature*** **ovarian follicles** in the **ovary** *to produce* Estrogen.
Male	- ***Stimulate*** **Leydig cells (interstitial cells)** of the **testis** *to* ***produce*** Testosterone.	- ***Stimulate*** **spermatogenesis**.

FSH Preparations

Derived from the **urine** of **menopausal women**

Urofollitropin (Fertinex®)# (Fostimon®)# (Metrodin®)#

Recombinant preparations (More pure and more easily administered, but they are more expensive)

Follitropin Alfa (Gonal-F®)# (Epigonal®)#

Follitropin Beta (Puregon®)#

Urofollitropin is a preparation of ***highly purified*** Follicle-stimulating hormone (FSH) ***extracted from*** the **urine** of **postmenopausal women**. ***Follitropins*** *stimulate* **ovarian follicular growth** in **women** who do not have *primary* **ovarian failure**.

- FSH is ***required for*** *normal* **follicular growth, maturation, gonadal steroid production**, and **spermatogenesis**.

Uses; - **Assisted Reproductive Technology (ART)**; such as **In Vitro Fertilization (IVF)**.
- **Ovulation induction**: in women received **GnRH** ***agonist*** or ***antagonist*** for pituitary suppression.

- *Dose*; **75-300 IU per day** SC.

LH Preparations

Lutropin Alfa (Luveris®)

- Lutropin alfa is a *recombinant* luteinizing hormone (LH).

Uses; *Infertility* in **women** with *profound* **luteinizing hormone (LH)** *deficiency* (<1.2 units/L); to be used in *combination with* Follitropin alfa.

Other Preparations

Human Menopausal Gonadotropins (hMG) or Menotropin (Pergonal®)# (Menogon®)# (Merional®)# (Menopur®)#

- hMG are *obtained from* the **urine** of **menopausal women** and *contains* FSH and LH.
- hMG also *indicated* in *combination* with Human Chorionic Gonadotropins (hCG).

Uses; - **Assisted Reproductive Technology (ART)**; such as **In Vitro Fertilization (IVF)**.
- *Infertility* in **women** and **men**.

Dose; IM or SC **75-150 IU** of FSH + **75-150 IU** of LH *once* a **day**.

- *Side effects*; **Severe ovarian hyperstimulation syndrome (OHSS)** and **multiple births**.

Human Chorionic Gonadotropins (hCG) (Pregnyl®)# (Choriomon®)# (Epifasi®)#

- hCG *produced by* **human placenta** and *excreted into* the **urine**.

Uses;- **Prepubertal cryptorchidism**; *induce* **testicular descent**.
- **Hypogonadotropic hypogonadism** (*secondary to* a pituitary deficiency) in **males**.
- *Induction* of **ovulation** and **pregnancy**.

- *Dose*; IM *only* **500-1000 units** *3 times* a **week**.
- *Side effects*; **Headache, irritability, restlessness, depression, fatigue, gynecomastia** and **pain** at the *site of* **injection**.

GnRH Agonists (GnRH Analogues)

Leuprolide (Lupron®)	**Buserelin** (Suprefact®)	**Deslorelin** (Ovuplant®)
Histrelin (Vantas®)	**Goserelin** (Zoladex®)#	**Nafarelin** (Synarel®)
Triptorelin (Decapeptyl®)#		

- *Initial* **increase** in FSH and LH *secretion* → *sustained* **stimulation** of **GnRH receptors** → **hypogonadal effect** (*decrease* FSH and LH); *due to down-regulation*.

Uses; **prostate cancer, breast cancer, endometriosis, uterine fibroids** and **early puberty**.

Triptorelin (Decapeptyl®); *widely used* in *preparation for* **In Vitro Fertilization (IVF)**; *prevention* of **LH release** and **ovulation**;

Dose; Decapeptyl® **0.5 mg SC** *once* a day for **7 days**. *From the* **8th day** on, Decapeptyl® **0.1 mg SC** *once* a day.

GnRH Receptor Antagonists

Cetrorelix (Cetrotide®)#	**Ganirelix** (Orgalutran®)#
Abarelix (Plenaxis®)#	**Degarelix** (Firmagon®)#

Uses; **Prostate cancer** and **fertility treatment** in *preparation for* **In Vitro Fertilization (IVF)**.

Antidiuretic Hormone (ADH)

Desmopressin (Minirin®)#

- Desmopressin is a *synthetic* **replacement** for antidiuretic hormone (ADH) or vasopressin, the **hormone** that *reduces* **urine** *production during* **sleep**.

Desmopressin is the *first-line treatment* for **enuresis** in **children** *older than* **5 years**.

Dose; in **Nocturnal enuresis**.
Minirin®; **Regular tablets**; 0.2 mg one hour before bedtime, if needed after 10 to 14 days, the dose may be increased by 0.2 mg to a maximum dose of 0.6 mg.
Minirin®-melt; **Oral melt tablets**; 120 µg sublingual are given 30 to 60 minutes before bedtime; if needed after 10 to 14 days, the dose may be increased by 120 µg to a maximum dose of 360 µg.

Uses; **Nocturnal enuresis, coagulation disorders** and **central diabetes insipidus**.

- *Side effects*; **Nausea, headaches, flushing, hyponatremia** and **seizures**.

Oxytocin

The word oxytocin was *derived from* Greek "**oxys**" and "**tokos**" *meaning* "quick birth".

Function;

A) **During sexual intercourse**;

- *In males*; *Contraction* of the **smooth muscles** in **vas deferens** to *ejaculate* the **semen**.
- *In females*; *Contraction* of the **myometrium** *followed by* **relaxation** to *decrease* **intrauterine pressure** to *facilitate* **transport** of **semen** *into* the **uterus** *after* **intercourse**.

B) **During labour**; *Contraction* of the **uterus** to *facilitate* **delivery**.

C) **During lactation** (*Suckling*); *Contraction* of **myoepithelial cells**, *causing* **milk** to be *ejected into* the **ducts**.

Oxytocin (Syntocinon®)#

Uses; 1) *induction* of **labor** *during* the *third stage* of **labor**.

2) *Control* **postpartum bleeding** or **hemorrhage**; 1 mL (10 units) **IM** or 10-40 units **IV infusion**.

Warning; *during induction* of **labor**; Syntocinon® *must be administered only* by the **IV infusion** and *with adequate* **medical supervision** in a **hospital**.

Oxytocin Analogues

Carbetocin (Pabal®)	Demoxytocin (Sandopart®)

- Is a *synthetic analogue* of Oxytocin (*Longer duration*).
- *Uses*; *Control* **postpartum bleeding** or **hemorrhage**, particularly following **Cesarean section**.

Oxytocin Antagonist

Atosiban (Tractocile®)

- *Tocolytics drugs* (*anti-contraction* **medications**) used in **premature labor**.

Thyroid and Antithyroid Drugs

Effects of Thyroid hormones

Effect on cell metabolism	**Mitochondria**	- ↑ **size** and **number** of **mitochondria** → *leading to* → ↑ **ATP formation**.
	Cell membrane	- ↑ *activity* of Na^+/K^+ **ATPase enzyme** → ↑ Na^+ and K^+ *transport* → *energy* **consumption**.
Effect on body metabolism	**Carbohydrate**	- *Stimulate all* **carbohydrate** *metabolism*: - ↑ **Insulin secretion**. - ↑ **Glucose uptake by the cell**. - ↑ **Glycolysis**. - ↑ **Gluconeogenesis**.
	Lipid	- *Stimulate all* **fat metabolism**: - ↑ **Lipolysis**.
	Protein	- **Thyroid hormone** are *anabolic hormone*: - *Increase* **protein synthesis** *all over* the **body**.
	Plasma lipids	- *Increases* **basal metabolic** *rate* ↓ *plasma* **cholesterol**. - ↑ **LDL receptor** in *liver*. - *Increase* **secretion** of **cholesterol** in **bile** & **stool**

Thyroid Drugs

Levothyroxine (Eltroxin®)# (Euthyrox®)#

- Levothyroxine (L-thyroxine or T_4) is a *synthetic form* of the **thyroid hormone**; Thyroxin.
Bioavailability: **64%** (*non*-fasting); **79-81%** (*fasting*); ***absorption increased*** by **fasting**.
- *Uses*; **Hypothyroidism** and **Myxedema**.
- *Dose* for ***mild hypothyroidism***; **1.7 mcg/kg** or 100-125 mcg/day orally not to exceed 300 mcg/day; need *monitoring* every 6-8Week.
Most common side effects; **Tachycardia, sweating, anxiety, tremors, muscle weakness, weight loss, menstrual irregularity** >>>>>
FDA warning; **Thyroid hormones**, *either* ***alone*** or ***with*** *other* **therapeutic agents**, ***should*** **NOT** be used for the ***treatment of*** **obesity** or for **weight loss**.
Pregnancy; **MUST *be* used** if ***hypothyroidism found***; need *monitoring* every 6-8Week.
TSH test are ***recommended*** *before* **planning for pregnancy**.
Drug interactions;
  - **Heparin** and **oral anticoagulant** (↑ effect of anticoagulant).
  - **Cholestyramine** (↓ absorption of ***Levothyroxine***).
  - **Iron, calcium supplement, antacids** (↓ absorption of **Levothyroxine**).
  - **Sucralfate** (↓ absorption of **Levothyroxine**).

Liothyronine (Cytomel®)

- **Liothyronine** is a *synthetic form* of ***natural*** T_3 **hormone**; T_3 **4 times** ***more potent*** **than** T_4.
Uses; **Hypothyroidism** and **Myxedema**.

Liotrix (Thyrolar®)

- **Liotrix** is a ***mixture*** of T_4 and T_3 *made* ***synthetically***.
  - **Thyrolar® 1/4**; 3.1 mcg T_3 - 12.5 mcg T_4
  - **Thyrolar® 1/2**; 6.25 mcg T_3 - 25 mcg T_4
  - **Thyrolar® 1**; 12.5 mcg T_3 - 50 mcg T_4
  - **Thyrolar® 2**; 25 mcg T_3 - 100 mcg T_4
  - **Thyrolar® 3**; 37.5 mcg T_3 - 150 mcg T_4
- *Uses*; **Hypothyroidism**.

Tiratricol (Triacana®)

- **Tiratricol** (TRIAC or triiodothyroacetic acid) is a **thyroid hormone** ***analogue***.
- **Tiratricol** is used as a ***dietary supplement*** for *thyroid problems including* **thyroid cancer**.
- It is also used for ***increasing*** **metabolic rate** for **weight loss,** and **reducing cellulite**.

Antithyroid Drugs

Propylthiouracil (PTU) (Thyrocil®)#	**Methylthiouracil** (Thimecil®)
Benzylthiouracil (BTU) (Basdene®)	
Carbimazole (Neo-Mercazole®)#	**Methimazole** (Tapazole®)

- ***Absorbed*** **orally**.
- ***Distributed*** **all over the body** (***concentrated*** in **thyroid gland**), ***pass*** **BBB** and **placental** (↓ **fetal thyroid gland**).
- **Carbimazole** is ***prodrug metabolized to*** **Methimazole** (***active metabolites***).
- ***Excreted in*** **urine** and **milk**.
- *Uses*; ***Mild*** **hyperthyroidism**.
- *Side effects*; - **Agranulocytosis**: ***high risk*** of **sore throat infection**; ***monitoring*** is *required*.
  - **Allergy, liver** and **kidney damage, joint pain, GIT disturbance**.
  - **Carbimazole** ***induce*** **acute cholestatic jaundice**.

Adrenocortical Hormones

- Adrenal cortex *formed of* 3 zones:
  1) Zona glomerulosa (Outermost layer); Mineralocorticoids (Aldosterone)
  2) Zona fasciculata (Middle); Glucocorticoids (corticosterone and Cortisol)
  3) Zona reticularis (Innermost); Androgens (dehydroepiandrosterone (DHEA), androstenedione and *small amount* of estrogen).

Mineralocorticoids

- Mineralocorticoids are a *class of* **steroid hormones** *characterized by* their ***influence on*** **salt** and **water** ***balances***.
- Mineralocorticoids;
  - Aldosterone; Very potent (90% of all Mineralocorticoid activity).
  - Deoxycorticosterone; 1/50 of aldosterone activity.
  - Corticosterone; Slight mineralocorticoid activity.
  - Cortisol; Very slight mineralocorticoid activity.
- Glucocorticoids (glucose + cortex); derives from its ***role in*** the ***regulation of*** the **metabolism** of **glucose**, *its synthesis* in the **adrenal cortex**.

Fludrocortisone (Astonin-H®)#

Fludrocortisone (9α-fluorocortisol or 9α-fluorohydrocortisone) is a ***synthetic*** **corticosteroid** with ***moderate*** **glucocorticoid potency** and much ***greater*** **mineralocorticoid potency**.

Uses; ***primarily*** to replace the missing aldosterone hormone in various forms of adrenal insufficiency such as **Addison's disease** and **salt wasting**.

- *Dose*; 0.05-0.1 mg orally/24 hours.

Glucocorticoids (Systemic)

	Relative Potency	K^+/Na^+ Effect	Dose (orally)
Short Acting (<12 hours)			
Cortisol (Hydrocortisone) (Solu-Cortef®)#	1	++	300 mg/day
Cortisone (Cortone Acetate®)	0.8	++	25-300 mg/day
Intermediate Acting (12-36 hours)			
Prednisone (Hostacortin®)#	3.5	+	5-60 mg/day
Prednisolone (Hostacortin-H®)#	4	+	5-60 mg/day
Triamcinolone (Kenacort-A®)#	5	0	8-12 mg/day
Methyl-Prednisolone (Solu-Medrol®)#	5	0	4-24 mg/day
Long Acting (>48 hours)			
Betamethasone (Diprofos®)#	25	0	0.6-7.2 mg/day
Dexamethasone (Dexamethasone®)#	30	0	0.75-9 mg mg/day

Action of Glucocorticoids

(Uses/Side effects/Precautions)

1) ***Effect on metabolism***;
   - A) **Carbohydrates Metabolism**: (**Hyperglycemic** and **Diabetogenic**)
     - # Stimulate Gluconeogenesis in the liver;
       - - ↑ Amino acids uptake by the hepatic cell.
       - - ↑ Activity of enzyme that convert amino acid to glucose.
     - # ↓ Insulin sensitivity of muscle and adipose tissue (***Anti-insulin***);
       - - ↓ Affinity of insulin receptor to insulin.
       - - ↓ Glucose transports from the cell membrane to inside the cell.
   - B) **Protein Metabolism**: (**Catabolic effect**)
     - # ↓ Protein synthesis & ↑ protein catabolism.
     - # ↑ Plasma amino acid level.
     - # ↓ Amino acid transport into extrahepatic cells.
     - # ↑ Increase conversion of amino acids into urea.
   - C) **Fat Metabolism**: (**Lipolytic** and **Ketogenic**)
     - # Lipolysis ⇨ ↑ Free fatty acids in the blood.
     - # Redistribution of fat depot in the facio-cervical-trunk region ⇨ **Moon face** & **Buffalo hump** and in the abdomen ⇨ **Purple Striae** (*stretch mark*).
2) ***Effect on muscle***;
   - # ***Skeletal muscle*** ⇨ ↑ Contraction (due to ↑ ACh release).
   - # ***Cardiac muscle*** ⇨ ↑ Contraction (due stimulation Na^+/K^+ ATPase & β receptor).
3) ***Effect on CVS***; (**Hypertension**)
   - # **Na^+ & water retention** and ↓ capillary permeability.
   - # Potentiate VC *effect* of NE and Angiotensin II.
4) ***Effect on blood cells***;
   - # ↑ Number of neutrophils, RBCs & Platelet.
   - # ↓ Number of eosinophils & T-Lymphocytes.
5) ***Effect on Kidney***;
   - # ↑ Glomerular filtration rate (GFR).
   - # ↑ Uric acid excretion.
6) ***Effect on bone***;
   - # Cortisol inhibits bone formation:
     - - ↓ Formation of osteoblast.
     - - ↓ Absorption of Ca^{2+} & phosphate from intestine (Anti-Vit. D).
   - # Excess cortisol lead to high ↑ in bone resorption ⇨ **Osteoporosis**.
7) ***Effect on Connective tissue***;
   - # Cortisol inhibits collagen synthesis ⇨ **Thinning of skin** (easy rupture)
   - # ↓ Proliferation of fibroblasts.
8) **Effect on GIT**; ↑ HCl secretion leads to **peptic ulcer**.
9) **Fetal lung**; # **Promoting maturation of fetal lung** and ***production*** of the **surfactants** *necessary for* ***extra*** **uterine lung function**; **SURVANTA®** (**Beractant**) ***intratracheal*** **pulmonary surfactants**, **used** *for* **Respiratory Distress Syndrome (RDS) (hyaline membrane disease)** in ***premature*** **infants**.
10) **CNS**; CNS stimulation & Psychological disturbance.

11) **Anti-inflammatory effect**;
- # Suppress the activity of phospholipase A2 ⇨ blocks the release of arachidonic acid the precursor of the prostaglandins and leukotrienes.
- # Suppress cyclooxygenase (COX) activity ⇨ ↓ prostaglandins synthesis.
- # ↓ Synthesis of other inflammatory mediator e.g. Tumor necrosis factor-α (TNF- α) and Interleukins (IL-1, IL-6 and IL-8).
- # Stabilization of intracellular lysosomal membrane ⇨ ↓ cell death.
- # ↓ Migration of leukocyte to site of inflammation.
- # ↓ Capillary permeability ⇨ ↓ inflammatory edema.

12) **Anti-allergic effect**;
- # ↓ Antibody formation.
- # ↓ Antibody/Antigen reaction.
- # Mast cell stabilizer ⇨ ↓ release of Histamine.
- # ↓ Tissue response to allergic mediators.

13) **Immunosuppressant effect**;
- # Inhibit synthesis and action of T-cell and B-cell lymphocytes.

14) **Response to stress**;
- # Unfavourable stress such as acute trauma, major surgery, sever infection or emotional stress ⇨ ↑ CRH ⇨ ↑ ACTH ⇨ ↑ Cortisol.

15) **Anti-Shock effect**;
- # Hypervolemia effect (Na^+ & water retention).
- # Hyperglycemia effect & Potentiate Sympathetic action.

16) **Withdrawal**;
- # Withdrawal from these drugs can be a serious problem.

- **Methylprednisolone Dosepak®: 4 mg/tab.**
  - **Day 1**: 24 mg orally (8 mg before breakfast; 4 mg after lunch; 4 mg after dinner; 8 mg at bedtime).
  - **Day 2**: 20 mg orally (4 mg before breakfast; 4 mg after lunch; 4 mg after dinner; 8 mg at bedtime).
  - **Day 3**: 16 mg orally (4 mg before breakfast; 4 mg after lunch; 4 mg after dinner; 4 mg at bedtime).
  - **Day 4**: 12 mg orally (4 mg before breakfast; 4 mg after lunch; 4 mg at bedtime).
  - **Day 5**: 8 mg orally (4 mg before breakfast; 4 mg at bedtime).
  - **Day 6**: 4 mg orally (4 mg before breakfast).

Precautions and PATIENT COUNSELLING

1) **Sudden withdrawal *should be* avoided**.
2) **Corticosteroids regimen *should be gradually* decreased**.
3) ***Consider* use *dosing* *during*** the **maximal adrenal cortex activity *time* (2 to 8 AM)**, to ***avoid* suppress *endogenous* corticosteroids *secretions***; the **BEST TIME** *between* **6-8 AM**.
4) ***Intake of* high protein diet** to *prevent* **muscle wasting**.
5) ***Intake of* high Calcium *supplementation*** to *prevent* **osteoporosis**.
6) ***Intake of* high vitamin B & vitamin D *supplementation*** due to deficiency by long therapy.
7) ***Intake of fresh* orange, banana juice** or **K^+ *supplementation*** or **oral rehydration therapy** to ***correct* hypokalemia**.
8) ***Protect* stomach** by ***using* corticosteroids *after* meal** or ***using* H_2 blockers** or **PPIs**.
9) **MONITORING**; ***signs for* infection, blood pressure, blood glucose, growth** (length) *in children* and **weight**.

Insulin and Antidiabetic Drugs

- **Insulin** is *synthesized in* **β-cells** of **pancreatic islets** of **Langerhans** as a ***single chain*** **Proinsulin**; **Insulin + C peptide** (***Single chain*** **31 amino acid**).

Regulation of insulin secretion;

1) **High glucose level in the blood** ⇨ ↑ secretion of insulin.
2) **Some amino acid e.g. Arginine and Lysine** ⇨ ↑ secretion of insulin.
2) **GIT hormones** (Secretin, Gastrin, cholecystokinin (CCK), **glucagon-like peptide-1 (GLP-1)** and **Gastric inhibitory polypeptide (GIP)** ⇨ ↑ secretion of insulin.
3) **Systemic hormone:**
   - Glucagon, GH & Thyroid hormones ⇨ ↑ secretion of insulin.
   - Somatostatin ⇨ Slight ↓ secretion of insulin.
4) **Autonomic nervous system:**
   - α_2 ⇨ ↓ secretion of insulin.
   - β_2 ⇨ ↑ secretion of insulin.
   - ACh (Muscarinic) ⇨ ↑ secretion of insulin.
5) **Drugs** (e.g. Sulfonylurea ⇨ ↑ secretion of insulin).

Major Glucose Transporters (GLUT)		
GLUT 1	- All tissues especially: red cells and brain.	Transport across BBB
GLUT 2	- **β cells of pancreas**, Liver, Kidney & Gut.	Regulation of insulin release
GLUT 3	- **Neurons** and placenta.	Uptake into neurons
GLUT 4	- **Muscle and adipose tissue**.	Insulin-mediated uptake of glucose
GLUT 5	- Gut and kidney.	Absorption of fructose

☞ N.B: Neurons do not require insulin to absorb glucose (GLUT 3).

Action of Insulin	
Carbohydrates	- **In hypoglycemia** ⇨ insulin facilitate glucose uptake by adipose tissue and skeletal muscle (GLUT 4). - ↑ Activity of Glucokinase activity ⇨ ↑ Glycolysis. - ↑ Activity of Glycogen synthase ⇨ ↑ Glycogenesis.
Lipids	- ↑ Storage of fat in adipose tissue (Lipogenesis). - ↓ Lipolysis. - ↓ **Ketone bodies formation.** - **Ketone bodies** ⇨ Three different water-soluble biochemicals that are produced as by-products when fatty acids are broken down for energy in the liver. (endogenous ketone bodies are Acetone, Acetoacetic acid, and Beta-hydroxybutyric acid)
Proteins	- ↑ Amino acid uptake by skeletal muscle and ↓ protein catabolism (anabolic action). - ↑ Gene expression (↑ mRNA)
Growth	- Direct effect ⇨ Stimulate synthesis of cartilage & bone ☞ ↑ Growth. - Indirect effect ⇨ ↑ Insulin like growth factor 1 (IGF-1) ☞ ↑ Growth.

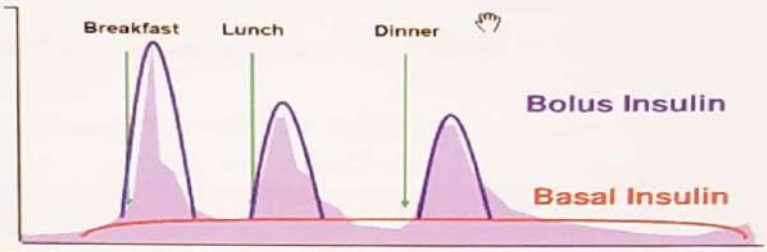
Insulin Resistance

1) *Abnormal* **insulin molecules**.
2) ***Defect*** in **conversion** *from* **Proinsulin** to **Insulin**.
3) ***Increased*** **counter regulatory hormones**.
4) **Anti-insulin** ***antibody***.
5) **Insulin receptor** ***abnormality***.
6) ***Defect*** at the **post-receptor level** (e.g. **Glucose transporter**).

Basal and Bolus Insulin

Basal insulin; is the **insulin** *normally* ***supplied by*** the **pancreas** and is ***present*** 24 hours a day, whether or not the person eats.

Bolus insulin is the ***extra amounts*** of **insulin** ***supplied by*** the **pancreas** in ***response*** to **glucose taken** in *through* **food** (The amount of bolus insulin produced ***depends on*** the **amount of meal**).



Disturbance of Insulin hormone

A) Hypersecretion (Hypoglycemia)

Causes	- ***Over dose*** of **insulin** in **diabetics** (or **taken dose** ***without*** **food**). - **Insulinoma** (Tumor of pancreas ⇨ Secretion). - Symptomatic **hypoglycemia** due to various causes.
Symptoms	- **Palpitation**, **sweating**, **nervousness**, **hanger** and **confusion** (due to ↓ blood glucose). - ***At very low*** **plasma glucose level** ⇨ **Coma** and **convulsion**.
Treatment	- **IV glucose**. - *Administration of* **glucagon**.

B) Hyposecretion (Hyperglycemia) - Diabetes Mellitus (DM)

Classical Symptoms; **Polyuria** (***Frequent*** **urination**), **Polydipsia** (***Increased*** **thirst**) and **Polyphagia** (***Increased*** **hunger**).

Types; - **Type 1 DM** (**insulin-dependent diabetes mellitus - IDDM**).
- **Type 2 DM** (**Non-insulin-dependent diabetes mellitus - NIDDM**).

Type 1 DM (Insulin Deficiency)

Causes;
- ***Mainly*** **autoimmune destruction** of ***insulin-producing*** **beta cells** of the **pancreas**.
- ***Usually*** **young age**.

Risk Factors;
1) **Genetics**.
2) **Dietary factors**; ***early*** **exposure to cow's milk** (*before* **6 months of age**).
3) **Race**; more common in whites than in other races.
4) **Geography**; such as **Finland** and **Sweden**, have higher rates of type 1 diabetes.

Type 2 DM (Insulin Resistance)

Causes;

- ***Mainly decrease*** **tissue sensitivity** to **insulin**.
- ***Usually after*** the **age** of **40 years**.

Risk Factors;

1) **Over Weight** (more fatty tissue more resistant to insulin).
2) **Inactivity**.
3) **Family history**
4) **Race** (including blacks, Hispanics, American Indians and Asians are higher risk).
5) **Age** (Risk increases in older).
6) **Gestational diabetes**; during pregnancy.
7) **Polycystic ovary syndrome**.
8) ***High*** **blood pressure**.
9) ***Abnormal*** **cholesterol levels**.
10) ***High levels*** **of triglycerides**.

Complication of Diabetes

1) **Neuropathy** (***Nerve damage***).
2) **Nephropathy** (***Kidney damage***).
3) **Retinopathy** (***Eye damage***).
4) **Other complication:** Foot damage (leg amputation), Skin problems (bacterial & fungal infections), Osteoporosis, Alzheimer's disease (Type 2 diabetes may increase the risk) & Cancer

Diagnosis

1) **Glycated hemoglobin (A1C) test**:
   - The higher blood glucose levels, the more hemoglobin attached with glucose.
   - Determine the average blood sugar level for the past two to three months.
   - ***Normal value***: 4.7 - 6.5 %
2) **Fasting blood sugar test**:
   - ***Normal value***: 70 - 110 mg/dl
   - ***Pre-diabetes*** ⇨ 110 - 126 mg/dl
   - ***Diabetes*** ⇨ Over 126 mg/dl
3) **Random blood sugar test**:
   - ***Normal value***: 70 - 140 mg/dl
   - ***Pre-diabetes*** ⇨ 140 - 200 mg/dl
   - ***Diabetes*** ⇨ Over 200 mg/dl
4) **Oral glucose tolerance test**:

☞ **N.B:**

Renal Threshold of Glucose (RTG) :

- When the blood glucose level exceeds about 160 – 180 mg/dl, the proximal tubule becomes overwhelmed and begins to excrete glucose in the urine.

Treatment

- **Life style modification:** Healthy eating and Physical activity

Medications	**Type I**	- Insulin therapy. - Pancreas transplantation.
	Type II	- Oral anti-diabetic medications. - Some people also need insulin therapy.
	Gestational	- Insulin therapy only.

Insulin Preparations (Insulin Therapy)

Preparation	Species source
A) Short acting insulins 1) Regular Novolin R 2) Regular Humulin R	**Human**
B) Rapid acting insulins 1) Insulin Aspart 2) Insulin Lispro 3) Insulin Glulisine	**Human analogue**
C) Intermediate acting insulins 1) NPH Novolin 2) NPH Humulin	**Human**
D) Premixed insulins 1) Novolin 70 NPH/30 Regular 2) Humulin 70 NPH/30 Regular	**Human**
E) Long acting insulins 1) Insulin Glargine (Lantus®) 2) Insulin Detemir (Levemir®)	**Human analogue**

A) Short Acting Insulins (Natural insulin)

Soluble Insulin or Regular Insulin (Humulin® R)# (Actrapid®)#	
Chemistry	- Crystalline zinc insulin that is now made by rDNA techniques.
Pharmacokinetics	- *Onset of action*: 30 minutes - *Peak* : 2.5 hours - *Duration* : 5-8 hours
Uses	- Used to control the high blood sugar level that typically occurs after meals (**Bolus only**). - Regular insulin is **only** type of insulin can use **IV** in **emergency** (Due to water solubility).
Time of Administration	- Best if administered **30 minutes before** a meal. - If used ⇨ ☝ You **must eat** (To avoid hypoglycemia).
Role	- Cover insulin need for meals eaten within 30-60 minutes (**Bolus**).
Dose	- Multiple injections/day

B) Rapid Acting Insulins (Insulin analogue)

	Insulin Asprat (NovoRapid®)#	**Insulin Lispro** (Humalog®)#	**Insulin Glulisine** (Apidra®)#
Onset	12-18 min	15-30 min	12-30 min
Peak	1-3 hrs	0.5-2.5 hrs	1.6-2.8 hrs
Duration	3-5 hrs	2-4 hrs	3-4 hrs

Time of Administration	☛ Rapid acting insulins are taken **just before** or **with** a meal. - Act ***very quickly*** (hypoglycemia occur if not eat).
Role	- Covers insulin needs for meals eaten at the same time (**Bolus**).
Dose	- Multiple injections/day

C) Intermediate Acting Insulins (Neutral Protamine Hagedorn –NPH or Isophane)

Insulin NPH (Insulatard®)# (Humulin® N)#

Chemistry	- This is a suspension (**Cloudy/milky**) of crystalline zinc insulin combined with the positively charged polypeptide protamine.
History	- In 1936, Hagedorn and B. Norman Jensen discovered that the effects of injected insulin could be prolonged by the addition of protamine.
Pharmacokinetics	- ***Onset of action***: 1-2 hours - ***Peak*** : 4-12 hours - ***Duration*** : 14-24 hours
Uses	- NPH insulins are often taken in conjunction with a short acting insulin ⇨ Premixed.
Role	☞ **Half** day **basal** insulin coverage.
Dose	- 2 doses (before breakfast and the evening meal).

Principles of Insulin Therapy

1) Two injections daily:
- Using a mixture of short and intermediate-acting insulins before breakfast and the main evening meal.

2) Three injections daily:
- Using a mixture of short and intermediate acting insulins before breakfast.
- Short-acting insulin alone before an afternoon snack.
- Intermediate-acting insulin in the evening meal.

3) Basal-bolus regimen of short-acting insulin 20–30 min before main meals **and** intermediate or long-acting insulin at bedtime.

D) Premixed Insulins

(Mixtard® 70/30)# (Humulin® 70/30)#	- 70 % **NPH** + 30 % **Regular**
(Mixtard® 50/50)#	- 50 % **NPH** + 50 % **Regular**
(Novomix® Flexpen)#	- 70 % **Protamine Aspart** + 30 % **Aspart**
(Humalog® Mix 75/25)#	- 75 % **Protamine Lispro** + 25 % **Lispro**
(Humalog® Mix 50/50)#	- 50 % **Protamine Lispro** + 50 % **Lispro**

- ***Dose***; These products are generally taken twice a day before meal time.

E) Long Acting Insulins (Insulin Analogue) (Basal insulin)

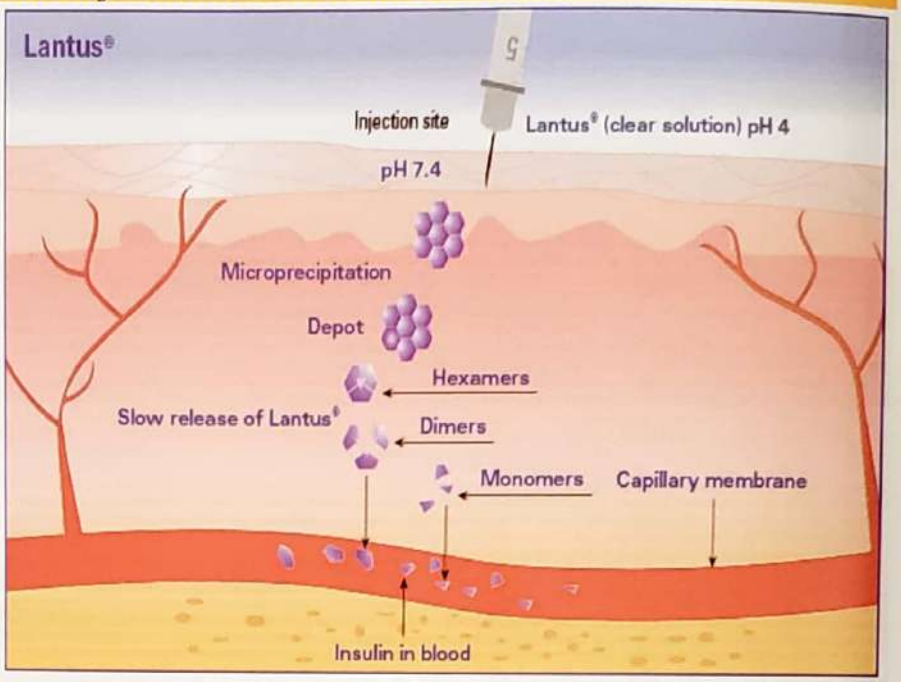
Insulin Glargine (Lantus®)#

- Is a ***long-acting*** **basal insulin analogue**.

Pharmacokinetics	- ***Onset of action***: 1-1.5 hours - ***Peak*** : **No Peak** - ***Duration*** : 20-24 hours - Glargine must not be diluted or mixed with other insulin or solution in the **same syringe**.
Role	☞ **Full** day **basal** insulin coverage.

Mechanism of Lantus® *sustained release*

- The amino acid asparagine at position A21 is replaced by glycine, and two arginines are added to the C-terminus of the B-chain. These changes shift the isoelectric point, producing a solution that is completely soluble at a pH of 4.
- When injected into the subcutaneous tissue, the acidic solution is neutralized (pH 7.4).
- This leads to the formation of microprecipitates, which small amounts of Lantus® are slowly released.
- The slow dissolution of free hexamers results in the lack of a peak and longer duration of action.



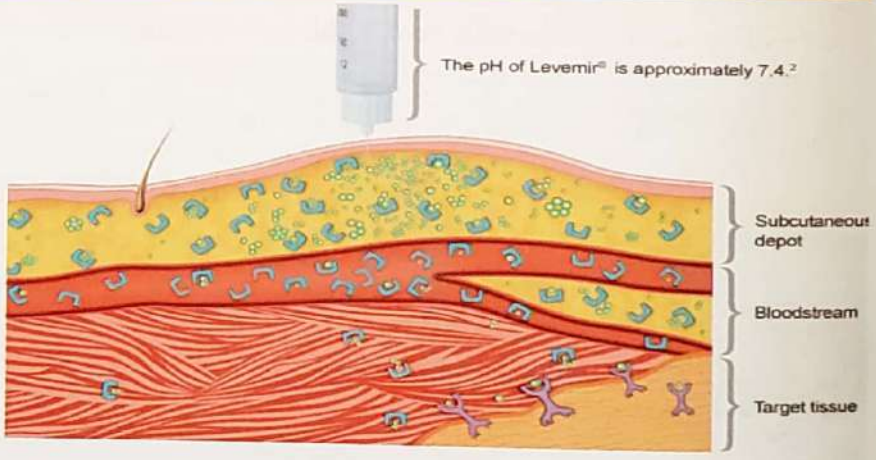
Insulin Detemir (Levemir®)#

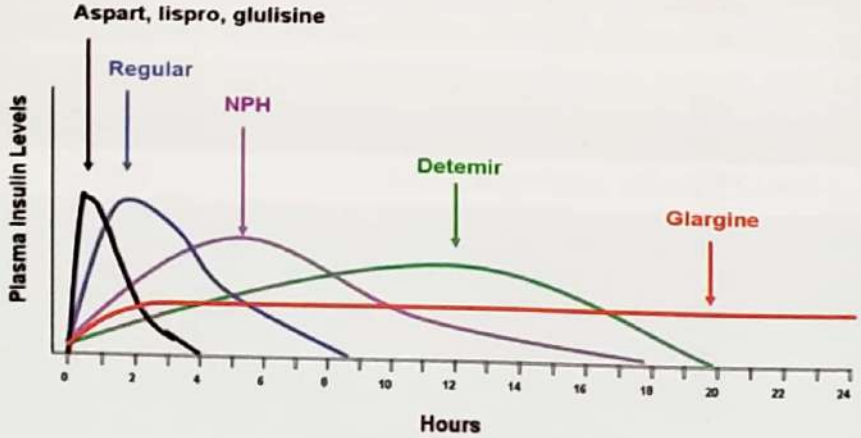
- Is a long-acting **basal** insulin analogue.

Pharmacokinetics	- *Onset*: 1-2 hours - *Peak* : 6-8 hours - *Duration* : Up to 24 hours
Role	☞ Full day basal insulin coverage.

Mechanism of Levemir® *sustained release*

- Insulin Detemir does not form microprecipitates or crystals when injected.
- It is an insulin analogue in which a fatty acid (Myristic acid) is bound to the lysine amino acid at position B29.
- It is quickly absorbed after which it binds to albumin in the blood through its fatty acid at position B29 → slowly dissociates from this complex.





Antidiabetic (Hypoglycemic) Drugs

A) Insulin Secretagogues;
1) Sulfonylureas
2) Meglitinides "Glinides"
3) GLP-1 agonists
4) DPP-4 inhibitors "Gliptins"

B) Sensitizers;
1) Biguanides
2) TZDs/"glitazones" (PPAR)
3) Dual PPAR agonists

C) Other; 1) Alpha-glucosidase inhibitors 2) Amylin analogue 2) SGLT2 inhibitors

Insulin Secretagogues

1) Sulfonylureas

First Generation

Tolazamide (Tolinase®)	**Acetohexamide** (Dymelor®)	**Carbutamide** (Glucidoral®)
Chlorpropamide (Diabinese®)	**Tolbutamide** (Orinase®)	

Second Generation

Gliclazide (Diamicron®)#	**Glimepiride** (Amaryl®)#	**Glipizide** (Minidiab®)
Gliquidone (Glurenorm®)	**Glibornuride** (Glutril®)	**Glisoxepide**
Glibenclamide or **Glyburide** (Daonil®)#	**Glyclopyramide** (Deamelin-S®)	

Second-generation; *good* pharmacokinetic profile, *more* prescribed and *more* available.
Dose (*Second-generation*); *usually* once daily *with* breakfast or *first main* meal of the day.
Combination; *usually combined with* Metformin *such as* Glucovsnce®; Glibenclamide + Metformin.
Main Side effects; Hypoglycemia and Weight gain.
Dose reduction; in renal impairment, *risk of* hypoglycemia.

2) Meglitinides "Glinides"

Repaglinide (NovoNorm®)#	**Nateglinide** (Starlix®)	**Mitiglinide** (Glufast®)

- *Metabolized* by CYP3A4; drug interactions.
NovoNorm® *available as* tablets (white: 0.5 mg; yellow: 1 mg; peach: 2 mg), *dose*; 15 minutes *before each* main meal; 1*2 or 1*3 or 1*4; *maximum daily dose*: 16 mg per day.
- *Main Side effects*; Hypoglycemia and Weight gain.

3) Glucagon-like Peptide-1 (GLP-1) Agonists "Incretin Mimetics"

- *Incretins*; Are a group of gastrointestinal hormones {glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP)} *increase* insulin *release* and also *inhibit* glucagon *release*.

Exenatide (Byetta®)#	**Liraglutide** (Victoza®)#	**Lixisenatide** (Lyxumia®)#
Albiglutide (Eperzan®)	**Taspoglutide**	

- They are a glucagon-like peptide-1 agonist (GLP-1 *agonist*). # *Administration*; SC *only*.
Common side effects; Injection-site nodule and reactions, nausea, vomiting & diarrhea.
Block box warning; *increased* incidence *of* medullary thyroid carcinoma (MTC), *serum* Calcitonin or thyroid ultrasound *monitoring are needed.*
Exenatide (Byetta®); 5 µg/dose SC injectable pen *and* 10 µg/dose SC injectable pen
- *Dose*; 5 µg *twice* a day for 30 days may *increase to* 10 µg *twice* a day; *within* 1 hour *before* morning and evening meal # #.
Liraglutide (Victoza® 18mg/3mL); *approved for* Diabetes Mellitus, Type 2.
- *Dose*; 0.6 mg *once* daily for one week (only to decrease GI side effects and does not provide glycemic control) then *increase* to 1.2 mg *once* daily.
Liraglutide (Saxenda® 18mg/3mL); *approved for* Obesity; BMI of ≥ 30 or ≥27.
- *Dose* 0.6 mg *once* daily for one week; *increase by* 0.6 mg *daily* at weekly *intervals* to a *target dose* of 3 mg *once* daily.
Lixisenatide (Lyxumia®) (Adlyxin®); 10 mcg *once* daily for 14 days, *then* increase dose to 20 mcg *once* daily.

4) Dipeptidyl Peptidase-4 (DPP-4) Inhibitors "Gliptins"

Sitagliptin (Januvia®)#	**Vildagliptin** (Galvus®)#	**Saxagliptin** (Onglyza®)#
Linagliptin (Tradjenta®)	**Gemigliptin** (Zemiglo®)	**Alogliptin** (Nesina®)

- ***DPP-4 inhibitors*** is to ***increase*** **Incretin** ***levels*** (**GLP-1** and **GIP**); which ***inhibit*** **glucagon** ***release*** and ***increases*** **insulin** ***secretion***.

Administration; **Orally**.

Common side effects; **Nasopharyngitis, headache, nausea, heart failure, hypersensitivity,** and **osteoarthritis**.

Sitagliptin (**Januvia®** 25, 50, 100 mg)# - **Vildagliptin** (**Galvus®**50 mg); ***twice*** *with* **meals**.

Sitagliptin + **Metformin** (**Janumet®** 50/500, 50/850, 50/1000 mg); ***twice*** **daily** *with* **meals**.

Sitagliptin + **Metformin** (**Janumet® XR** 50/1000 ^{XR} mg); ***once*** **daily** *with* **meals**.

Vildagliptin + **Metformin** (**Galvus® Met** 50/500, 50/850, 50/1000 mg); ***twice*** *with* **meals**.

Saxagliptin (**Onglyza®** 2.5, 5 mg) ***once*** **daily**.

Saxagliptin + **Metformin** (**Kombiglyze®** 2.5/1000^{XR} mg, 5/1000^{XR} mg); ***once*** **daily**.

Sensitizers

1) Biguanides

Metformin (Glucophage®)#

The ***only currently*** available biguanide.

Metformin is the ***most widely*** and ***first*** **line agent** in **type 2 DM**.

All **type 2 DM** ***must be*** *treated with* **Metformin** *if* ***not tolerated*** or ***contraindicated***.

Metformin *act by* ***decrease*** **insulin resistance**.

Uses; **Type 2 DM** (***First line therapy***) and **Pre-diabetes**.

Off-Label:

- **Gestational diabetes** (*safe as* **insulin**); ***recommended***; **Category B**.
- **Polycystic ovary syndrome** (**PCOS**); ***recommended***
- **Weight loss**; ***not yet*** ***recommended***.
- ***Reduce risk*** of **some cancers** e.g. **pancreatic cancer**.
- ***helps to reduce*** **LDL cholesterol** and **triglyceride levels**.

Dose; *prescribed as* ***maximum*** **tolerated dose** (***until*** **GI side effects** *occur* but ***not more*** *than* **2500 mg/day**), ***start gradually***, **sustained release** (**XR**) ***formulations*** has ***low risk*** for **GI side effects**.

Side effects; **GI upset**; **diarrhea, cramps, nausea, vomiting** and **flatulence**; > 20 of patients.

FDA Warning; **Lactic acidosis** is a ***rare***, but ***potentially*** **severe**.

2) Thiazolidinedione (TZDs) "Glitazones"

Rosiglitazone (Avandia®)#	**Pioglitazone** (Actos®)#

They are ***act by*** ***lowers*** **glucose** by ***improving*** **target cell** ***response*** to **insulin** *without* ***increasing*** **pancreatic cell** ***secretion*** (activates nuclear peroxisome proliferator-activated receptor gamma).

FDA Warning; **Congestive heart failure** ***risk***.

Thiazolidinedione ***should be*** **used** ***only*** by people who ***can't control*** their **diabetes** ***other*** **ways**.

Rosiglitazone (**Avandia®**); 4 mg/day or divided every 12 hours, If inadequate response after 8-12 weeks, may increase dose to 8 mg/day or divided every 12 hours.

Rosiglitazone + **Metformin** (**Avandia® Met**).

Pioglitazone (**Actos®**); **15 mg** or **30 mg** ***orally*** **once** a **day**.

3) Dual PPAR agonists "Glitazar"

Saroglitazar (Lipaglyn®)

- In June 2013, **Saroglitazar** was the ***first*** **glitazar** to be approved for clinical use.
- It is approved for use in **India** (Currently available for sale in India only).

Other

1) Alpha-glucosidase inhibitor

Acarbose (Glucobay®)# | **Miglitol** (Glyset®) | **Voglibose** (Voglib®)

- They act by ***delaying*** the **digestion** of **carbohydrates** by ***inhibit*** **Alpha-glucosidase enzyme** (This enzyme is responsible for the hydrolysis of oligosaccharides to glucose and other sugars).

Uses; **type 2 DM** ***along with*** **diet** and **exercise**.

- **Acarbose** (Glucobay®); 25-100 mg orally 3 times a day.

2) Amylin Analogue

Pramlintide (Symlin®)

- is a new adjunct for diabetes and has been approved for use by Type I and Type II diabetics who use insulin ⇨ to allow patients to use less insulin and ↓ postprandial hyperglycemia.

3) Sodium/glucose Co-transporter-2 (SGLT2) Inhibitors

Dapagliflozin (Forxiga®)# | **Canagliflozin** (Invokana®)#

Empagliflozin (Jardiance®)#

- They act ***inhibits*** **SGLT2**, which is ***responsible for*** at least **90%** of the **glucose** ***reabsorption*** in the **kidney**, ***blocking*** this **transporter** causes **blood glucose** to be ***eliminated*** *through the* **urine**.

CONTRAINDICATIONS; **eGFR <30 mL/min/1.73 m²**.

Side effects; - **Renal impairment** (>10%)
- **Urinary tract infection** and **increased urination** (<10%)
- **Female genital mycotic (Fungal) infections** (<10% with **Dapagliflozin**, >10% with **Canagliflozin**)

- **Dapagliflozin** (Forxiga® **5mg** or **10mg**); **5 mg/day** ***with*** or ***without*** **food**, may **increase** to **10 mg** if **GFR ≥60 mL/min/1.73 m²**.
- **Canagliflozin** (Invokana® **100mg** or **300mg**); **100 mg/day** ***before*** the **first meal** of the **day**, may **increase** to **300 mg** if **GFR ≥60 mL/min/1.73 m²**.
- **Empagliflozin** (Jardiance® **10mg** or **25mg**); **10 mg/day** in the ***morning*** ***with*** or ***without*** **food**, may **increase** to **25 mg** if ***needed*** and ***tolerated***.

Empagliflozin (Jardiance®) *Also* ***indicated to*** **reduce the risk of cardiovascular death** in ***adults*** with **type 2 diabetes mellitus** and **cardiovascular disease**.

4) Bile Acid Sequestrant

Colesevelam (Welchol®)

- Used as ***adjunctive therapy*** to **improve glycemic control** in adults with **type 2 DM**.
- It lowers the HbA_{1c} about 0.5% and LDL by 15% or more.

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Gonadal Hormones

Testosterone

Preparations of Testosterone

Testosterone Undecanoate (Andriol®)#	**Methyltestosterone** (Testred®)
Fluoxymesterone (Halotestin®)	**Testosterone Enanthate** (Cidoteston®)#
Mesterolone (Cidoviron®)#	**Testosterone Cypionate** (Depo-Testosterone®)#

Anabolic Steroids

Nandrolone (Deca-Durabolin®)#

Uses *of* Testosterone #

Androgen replacement therapy; in **male** ***with*** **Hypogonadism** (*delayed puberty*).
Anabolic abuse *in* **sports**; ***exogenous*** **Testosterone** also causes ***suppression*** of **spermatogenesis** and can lead to **infertility**; **Post Cycle Therapy (PCT)** ***must be*** **used** and **semen analysis** ***must be*** **monitoring**.
Improve performance *in* **athlete**; can be ***detected*** **in urine**.
Osteoporosis.
Alone or *with* **estrogen** in **menopausal women**.
Aplastic anemia.

Side effects *of* Testosterone#

Risk of **prostate cancer**.
Masculinization in **female** (**hirsutism**, **acne** and ***deepening*** **voice**).
Suppression of **spermatogenesis** and can ***lead to*** **infertility** in male.
Na^+ & **water** ***retention***.

Post Cycle Therapy (PCT) *medications* #

Human Chorionic Gonadotropins (**hCG**) (**Pregnyl®**).
Exemestane (**Aromasin®**) # **Tamoxifen** (**Nolvadex®**) # **Clomiphene** (**Clomid®**)

Androgen Receptor Antagonist (Antiandrogen)

Cyproterone acetate (Diane 35®)#	**Flutamide** (Eulexin®)#
Bicalutamide (Casodex®)#	**Nilutamide** (Nilandron®)#

Cyproterone acetate (**Diane 35®**); for **prostate cancer**, **precocious puberty**, ***androgen-dependent*** **skin and hair conditions**, **PCOS** and **Hypersexuality**.

Spironolactone (Aldactone®)#

Other inhibitors

Finasteride (Proscar®)#	**Dutasteride** (Avodart®)#

- They are ***5α-reductase inhibitors***.

Alfatradiol (Pantostin®)

- It is a ***5α-reductase inhibitor*** used topically for the treatment of **androgenic alopecia** (hair loss) in **men** and **women**.

Abiraterone (Zytiga®)

- It is a ***steroid synthesis inhibitor***. ***Approved*** for **prostate cancer**.

Gossypol

- In the 1970s, the Chinese government began researching the use of gossypol (cottonseed oil) as **male oral contraceptive**.

Estrogens

Natural estrogens	- Estrone (E1), Estradiol (E2), Estriol (E3) & Estetrol (E4) - E2 ⇨ *Major* & *most* potent. – E3 ⇨ *Less* potent.

Preparations of Estrogens

A) Natural Estradiol

Estradiol (Estraderm®)#	- Transdermal patch in HRT.
Estradiol Benzoate (Agofollin®)#	- IM injection
Estradiol Valerate (Delestrogen®)#	- IM injection
Conjugated Estrogens (Premarin®)#	- Isolated from mare urine (pregnant mare urine) - It is available in oral, IV, and topical (vaginal).
Estradiol Hemihydrate (Fem 7®)#	- It is more hydrated (highly insoluble in water).

B) Semisynthetic Estrogens

Ethinyl Estradiol (Ethinyl Estradiol®)	- Ethinyl Estradiol (EE); *most effective* oral estrogens.
Mestranol	- EE *prodrug*; used in **oral contraceptives**.

C) Synthetic Estrogens (Non-steroidal)

Diethylstilbestrol (DES)	- It is available in oral and parenteral.

Uses *of* Estrogen #

Hormone replacement therapy;
  # *Menopausal syndrome* (**Osteoporosis** & **Vaginal atrophy**).
  # *Under developed* **female secondary sex characters**.
Alone or ***with*** **Progesterone** as **contraceptives**.
Dysmenorrhea and **Amenorrhea**.
Prostate cancer in *male*.
Hirsutism.

Side effects *of* Estrogen #

Na^+ and **water** *retention*.
Swelling of the **ankles** and **legs**.
Enlargement or **tenderness** of the **breasts**.
Weight gain.
Hypertension.
Nausea & **Headache**.
Risk of **breast** and **endometrium cancer**.
Risk of **thromboembolic events** & **myocardial infarction**.

Contraindication *of* Estrogen #

Estrogen-dependent neoplasms (***carcinoma*** in **breast** or **endometrium**).
Undiagnosed genital bleeding.
Liver disease.
History of **thromboembolic disorder**.

Selective Estrogen Receptor Modulators (SERMs)

Clomiphene (Clomid®)#

Clomiphene *induced* **ovulation** in **infertility** in **women**.
- *Act by* ***increase*** **production** of **gonadotropins** (**FSH** & **LH**) by ***inhibiting*** **negative feedback** of **estrogen** on the **hypothalamus** (***block*** **estrogen receptor** in **hypothalamus**).

Dose; - **1 tab.** (**50 mg**) ***daily for*** **5 days**, ***starting from*** the **5th day** of **woman's cycle**.
- ***If no ovulation*** ⇨ *given* **100 mg** ***daily for*** **5 days** *at the* ***next*** **cycle**.

Side effects; *Reversible* **ovarian enlargement** and **vasomotor flushing** (>10%).
Warning; ***Risk of*** **ovarian enlargement** & **ovarian hyperstimulation syndrome**.

Tamoxifen (Nolvadex®)#

Tamoxifen is SERM *used* in *treatment* or *prevention* of **breast cancer**.
- *Act by* ***competitively*** **binds to estrogen receptors** on **breast tissue** → ***inhibits*** **estrogen effects**.
- *Dose*; **20-40 mg/day** in **two** ***divided*** **doses**.
Off-label; **Ovulation induction**; **5-40 mg** ***every*** **12 hrs** for **4 days**; **3rd–7th** of a **woman's cycle**.
- *Side effects*; **Hot flashes, vaginal discharge, amenorrhea** and **menstrual changes**.

Raloxifene (Evista®)#

Raloxifene ***approved for prevention*** and ***treatment*** of **osteoporosis in postmenopausal women** and ***reduction*** in **risk** of **invasive breast cancer**.
- Raloxifene causes some *positive* **lipid effects**; ***reduces*** **levels** of **total cholesterol** and **low density lipoprotein (LDL) cholesterol**.
- *Dose*; 60 mg orally once a day.
- *Common side effects*; **hot flashes** and **leg cramps**.
- *FDA black box warning*; ***risk*** of ***venous thromboembolism*** and **death** *due to* **stroke**.

Progesterone

Progesterone Preparations

A) First Generation Progestins

Norethisterone (Norethindrone) (Ortho-Novum®)#

Norethisterone (Norethindrone) Acetate (Micronor®)#

Ethynodiol Diacetate (Metrodiol®)#

- These compounds *known as* 19-Nortestosterone ***derivatives***.
- Norethindrone was the ***first*** **orally** *highly active* **progestin** to be ***synthesized***.
Norethisterone; *Low* **progestational** ***activity***, *slight* **estrogenic** ***activity*** & *more* **androgenic** ***activity***.
Ethynodiol Diacetate; *Medium* **progestational** ***activity***, It has *minor* **estrogenic effects** and *little* **androgenic** ***activity***.

B) Second Generation Progestins

Norgestrel (Ovrette®)#

- Norgestrel is a ***mixture of*** both Dextronorgestrel (inactive) and Levonorgestrel (active).

Levonorgestrel (Microlut®)#

Is the ***most*** **widely prescribed** contraceptive **progestin** *worldwide*.
- It has ***high*** **progestational** and **androgenic effects**.
Used ***in*** **birth control** has also been ***FDA approved*** for **emergency contraception**.

C) Third-generation Progestins

Desogestrel (Marvelon®) | **Norgestimate** (Cilest®)#

Gestodene (Minulet®)#

High **progestational** ***selectivity***, *minimizing* or *no* **androgenic effects** and **estrogenic** ***activity***.
Less **negative impact** on **glucose** and **lipid metabolism, weight gain, acne**, and *other* **side effects** typical of ***older*** **progestins**.

D) Other Progestins

Medroxyprogesterone Acetate (Depo-Provera®)#

- *Long acting* **contraceptive** drug that is injected ***every*** **3 months**.

Drospirenone + Ethinyl Estradiol (Yasmin®)#

- Drospirenone (1,2-dihydrospirorenone) ***differs from*** other **synthetic progestins** ☞ It has *potent* **mineralocorticoid antagonist** ⇨ ***Counteracts*** Na^+ & **water** ***retention*** *caused by* the **estrogen**, and has also ***mild*** **androgen** ***antagonist*** **activity**.

Uses *of* Progesterone #

1) *Alone* or *with* Estrogen in contraception.
2) *Maintain* pregnancy;- *Preparing* the endometrium for implantation.
   - *Inhibit* uterine contraction.
   - *Decrease* myometrium sensitivity to Oxytocin.
3) *Dysfunctional* uterine bleeding.
4) Dysmenorrhea.
5) Endometriosis.

Side effects *of* Progesterone #

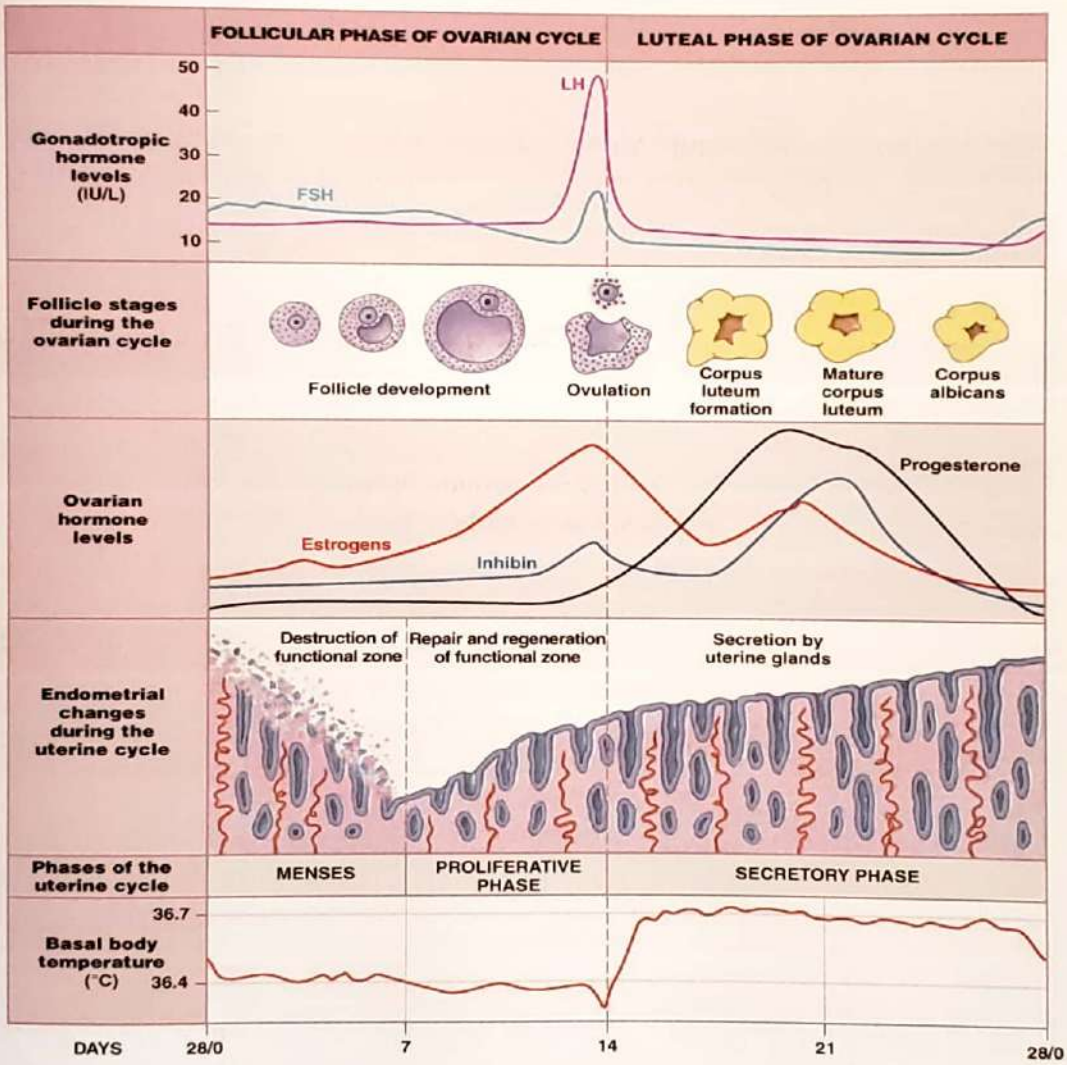
Headache, depression, weight gain, and *changes* in libido.
19-Nortestosterone *derivatives*, have androgenic activity and can *increase* the ratio of LDL to HDL cholesterol and *cause* acne and hirsutism.
Injectable medroxyprogesterone acetate has been *associated with risk* of osteoporosis.

Selective Progesterone Receptor Modulator (SPRM)

Mifepristone (Mifeprex®)#

It is a *powerful* glucocorticoid receptor antagonist; used in Cushing's Syndrome.
Used in medical abortion & emergency contraceptive.

Contraceptive Methods



The key events in the ovarian and uterine cycles

➢ Contraceptive Methods:

I- **Hormonal contraceptives.**
II- **Vaginal Spermicides.**
III- **Barrier contraceptives.**
IV- **Intrauterine devices.**
V- **Sterilization methods.**
VI- **Natural Methods.**
VII- **Emergency contraceptives.**

I- Hormonal Contraceptives

I) Oral Contraceptives (Oral Pills)

A) Combination Oral Contraceptives (COCs)

Monophasic (Fixed Combination)	Biphasic Combination	Triphasic Combination
Containing a fixed ration of Estrogen and Progestin given daily for 21 days, beginning on day 5 of the menstrual cycle	Containing a fixed dose of Estrogen (days 1-21) Containing a different dose of Progestin (days 1- 10) lower than (days 11 -21)	Containing 3 different doses gradual Estrogen increase and/or some pills may also increase the dose of Progestin.
1) High dose of E & P Primovlar® Ethinyl Estradiol 0.05 mg Norgestrel 0.5 mg	Necon® **Light yellow tablet** (10 tab) Norethindrone 0.5 mg Ethinyl Estradiol 0.035 mg	Triocept® **6 Tablets** Levonorgestrel 0.05 mg Ethinyl Estradiol 0.03 mg
2) Low dose of E & P Microvlar® - Microcept® Ethinyl Estradiol 0.03 mg Norgestrel 0.15 mg	**Dark yellow tablet** (11 tab) Norethindrone 1 mg Ethinyl Estradiol 0.035 mg	**5 Tablets** Levonorgestrel 0.075 mg Ethinyl Estradiol 0.04 mg
3) Low dose of E & high dose of P Loestrin® Ethinyl Estradiol 0.03 mg Norethisterone 1.5 mg		**10 Tablets** Levonorgestrel 0.125 mg Ethinyl Estradiol 0.03 mg

B) The Mini-Pill (Progestin Only Pill -POP)

Microlut® - Micronor® - Exluton®

- Progestin ***only*** is given for **28 days *continuously***.
- It is ***less* effective** than COCs, ***especially*** if **one** or **more tablets** are ***missed***.
- ***Good choice*** in **women** are *unable to* take Estrogen (*due to estrogen related side effect*).

C) Sequential Method

- *Start by* Estrogen **alone** for **14-16 days**, then ***combination of*** Estrogen & Progestin for **5-6 days**; ***success*** about 98-99%.

D) Emergency Contraceptive (Post-Coital or Morning After Pills)

1- Progestin-only method

Levonorgestrel (Contraplan II® - 0.75 mg)#

- The pills containing ***high dose*** of Levonorgestrel **0.75 mg**.
- This pill typically ***works up*** to **72 hours *after* intercourse** by using **2 tablets (1.5 mg)**.

2- Yuzpe Regimen

Estrogen + Progesterone

- Taken as ***two doses*** at a **12-hour interval**; large doses of ***both*** Estrogen and Progestin.
- Each dose can vary from 2 to 5 pills depending on the brand of medication being used.
- The ***standard regime*** is **2 tablets** each with **0.05 mg** Ethinyl Estradiol and **0.25 mg** Levonorgestrel, to be repeated 12 hours later; ***works up*** to **72 hours *after* intercourse**.

3- Selective Progesterone Receptor Modulator (SPRM)

Ulipristal Acetate (EllaOne®)# - (Ella®)#

- Ulipristal acetate is a *selective progesterone receptor modulator* (SPRM).
- Ulipristal acetate **30 mg tablet** is *used* **within 120 hours** (5 days) *after* **intercourse**.

Mifepristone (Mifeprex®)#

- Mifepristone is a *selective progesterone receptor modulator* (SPRM).
- *Used* in **medical abortion** & **emergency contraceptive**.
- *Now*; Mifepristone with Misoprostol *widely used* in **abortion**; **Do not get involved**!

2) Injection Contraceptives

Depot Medroxyprogesterone Acetate (DMPA) (Depo-Provera®)#

- Depo-Provera® *contains* DMPA **150 mg**, a *derivative of* Progesterone.
- *Given by* **deep IM injection** *every* **3 months**.

Norethisterone Enanthate (Noricept®)#

- Norethisterone Enanthate **200 mg**, a *derivative of* Progesterone.
- *Given by* **deep IM injection** *every* **2 months**.

Norethisterone Acetate + Estradiol Valerate (Mesigyna®)#

- *Monthly* **Contraceptive Injection**
- *Contains* Norethisterone Acetate **50mg** + Estradiol Valerate **5mg**.
- *Given by* **deep IM injection** *every* **1 months**.

3) Contraceptive Implants

- Progestin ***filled*** **rods** or **capsules** that are ***inserted*** *under* the **skin**.

First Generation (6 Rods System)

Norplant® System

- filled by **36 mg** of Levonorgestrel. ***Implanted*** **sub-dermally** in the **upper arm**, *for* **5 years**

Second Generation (2 Rods System)

Jadelle®

- Each containing **75 mg** of Levonorgestrel. **Sub-dermally** in the **upper arm**.
- ***Effective*** for **3 years**.

1 Rods system

Nexplanon® - Implanon®

- It is contains **68 mg** of Etonogestrel (Progestin). **Sub-dermally** in the **upper arm**.
- ***Effective*** for **3 years**.

4) Vaginal ring

NuvaRing®

- It is **contains** slowly releases Estrogens and/or Progestins. ***Remove*** the **ring 3 weeks** *after* **insertion** on the **same day** of the **week** it was inserted at about the ***same time*** of **day**.

5) Contraceptive Patch

Ortho Evra®

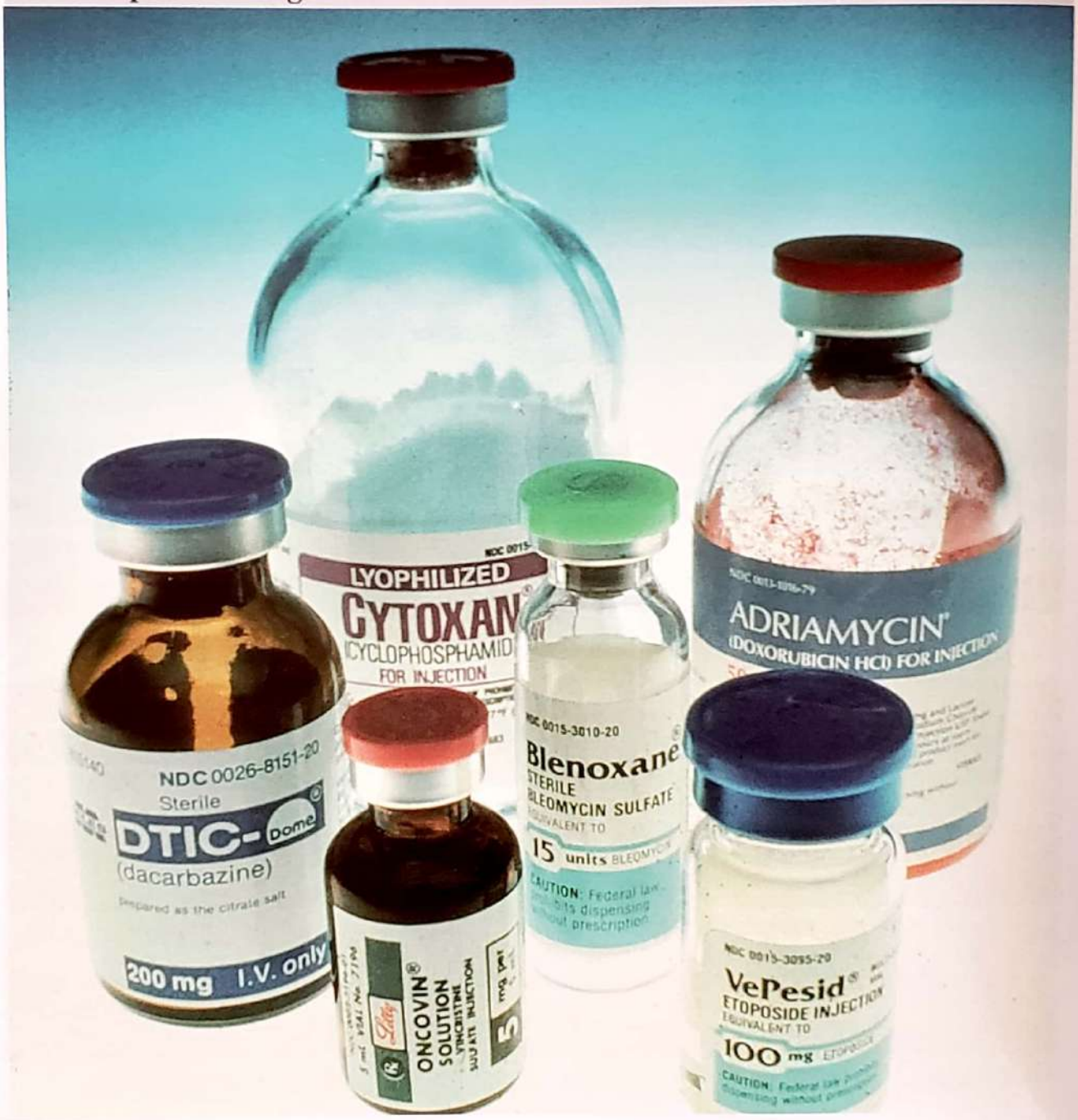
- It is a **transdermal patch** *contains* Estrogens and Progestins *applied to* the **skin** ***once*** a **week** for **3 weeks**, and then stop using for **1 weeks** (patch-free week); Like a period.

6- Hormonal Intrauterine Device

Mirena® - Skyla®

It is a small 'T'-shaped device, containing Levonorgestrel; ***effective up to*** **5 years**.

Miscellaneous Agents



Cancer Chemotherapy

Anti-Neoplastic (Anti-Cancer) Drugs:-

Anti-Cancer Drugs

Cytotoxic Drugs

I) Antimetabolites

Folic
- *Methotrexate
- *Pemetrexed (Alimta®)
- *Pralatrexate (Folotyn®)

Purine
- #6-Mercaptopurine (Purinethol®)
- #Fludarabine (Fludara®)
- #Cladribine (Leustatin®)

Pyrimidin
- *5-Fluorouracil (Adrucil®)
- *Capecitabine (Xeloda®)
- *Floxuridine (FUDR®)

Cytidine
- #Azacitidine (Vidaza®)
- #Cytarabine (Ara-C®)
- #Gemcitabine (Gemzar®)

II) Alkylating Agents

Nitrogen Mustard
- #Mechlorethamine (Mustargen®)
- #Cyclophosphamide (Cytoxan®)
- #Ifosfamide (Ifex®)
- #Chlorambucil (Leukeran®)
- #Melphalan (Alkeran®)
- #Bendamustine (Treanda®)

Nitrosoureas
- *Carmustine (BiCNU®)
- *Lomustine (CeeNu®)
- *Streptozocin (Zanosar®)

Alkyl Sulfonates
- #Busulfan (Myleran®)

Triazines
- *Procarbazine (Natulan®)
- *Dacarbazine (Dtic-Dome®)
- *Temozolomide (Temodal®)

Platinum
- #Cisplatin (Platinol®)
- #Carboplatin (Paraplatin®)
- #Oxaliplatin (Eloxatin®)

III) Cytotoxic Antibiotics

Anthracyclines
- *Daunorubicin (Cerubidine®)
- *Doxorubicin (Adriamycin®)
- *Epirubicin (Ellence®)
- *Idarubicin (Idamycin®)
- *Mitoxantrone (Novantrone®)

Others
- #Bleomycin (Blenoxane®)
- #Mitomycin (Mutamycin®)
- #Dactinomycin (Cosmegen®)

IV) Microtubule Inhibitors

Vinca Alkaloids
- Vincristine (Oncovin®)
- Vinblastine (Velban®)
- Vinorelbine (Navelbine®)

Taxanes
- Paclitaxel (Taxol®)
- Docetaxel (Taxotere®)
- Cabazitaxel (Jevtana®)

V) Endocrine Therapy

- *Prednisone (Hostacortin®)

SERM
- #Estrogens
- *Tamoxifen (Nolvadex®)
- *Fulvestrant (Faslodex®)
- *Raloxifene (Evista®)

Aromatase Inhibitors
- #Anastrozole (Arimidex®)
- #Letrozole (Femara®)
- #Exemestane (Aromasin®)
- *Megestrol Acetate (Megace®)

GnRH Analoges
- #Leuprorelin (Lupron®)
- #Goserelin (Zoladex®)
- #Triptorelin (Trelstar®)

Antiandrogens
- *Flutamide (Eulexin®)
- *Nilutamide (Anandron®)
- *Bicalutamide (Casodex®)

VI) Monoclonal Antibodies

- Rituximab (Rituxan®)
- Trastuzumab (Herceptin®)
- Pertuzumab (Perjeta®)
- Bevacizumab (Avastin®)
- Cetuximab (Erbitux®)
- Panitumumab (Vectibix®)
- *Others*

VII) Tyrosine Kinase Inhibitor

- Imatinib (Gleevec®) (Glivec®)
- Nilotinib (Tasigna®)
- Dasatinib (Sprycel®)
- Erlotinib (Tarceva®)
- Sorafenib (Nexavar®)
- Sunitinib (Sutent®)
- Lapatinib (Tykerb®)

VIII) Topoisomerase Inhibitors

- *Etoposide (Toposar®) *Teniposide (Vumon®)
- #Topotecan (Hycamtin®) #Irinotecan (Campto®)

IX) Others

- -Interferons -L-Asparaginase (Kidrolase®)
- -Procarbazine (Matulane®) -Abiraterone (Zytiga®)
- -Enzalutamide (Xtandi®)

Antimetabolites, Alkylating Agents, Cytotoxic Antibiotics and Microtubule Inhibitors are Cytotoxic drugs.

Cytotoxic drugs can *prevent* the *rapid* growth and division of cancer cells. They can also affect the *growth* of *other* quick dividing cells in the body, like hair follicles and the lining of digestive system.

Cytotoxic drugs also *affects* normal cells *undergoing rapid* proliferation; for example; cells of buccal mucosa, bone marrow, GI mucosa, and hair follicles.

Common side effects: severe vomiting (*controlled by* antiemetic drugs), stomatitis, bone marrow suppression and alopecia.

Specific toxicities;

- Bladder toxicity *with* Cyclophosphamide.
- Cardiotoxicity *with* Doxorubicin.
- Pulmonary fibrosis *with* Bleomycin.

- *Most* chemotherapeutic agents have a narrow therapeutic index.

I) Antimetabolites

Antimetabolite is a *substances* structurally similar to *normal* compounds that exist *within* the cell. They *generally interfere with* the availability of *normal* purine or pyrimidine nucleotide, and *inhibit* synthesis of DNA or RNA.

Folic Acid Analogues

Methotrexate	Pemetrexed (Alimta®)	Pralatrexate (Folotyn®)

Methotrexate (MTX), Pemetrexed and Pralatrexate are *antifolate agents*.

Indications; MTX, *usually* used in combination with other drugs, in acute lymphocytic leukemia, Burkitt's lymphoma in *children*, breast cancer, bladder cancer, and head and neck carcinomas.

Low-dose MTX is *effective as* a single agent *against* certain inflammatory diseases.

Side effects; - *Most common*; Mucosal ulceration (mucositis) and nausea.

- *Other side*; leukopenia, anemia, stomatitis, GI ulcerations and alopecia (*due to inhibiting cellular proliferation*), halitosis (bad breath odour).
- *Dose-related side effects*; hepatotoxicity.
- *Rare side effects*; acute pneumonitis and kidney failure.

- *Monitoring*; Liver enzyme tests, CBC, and monitoring *for* signs of infection.

MTX *should be given with* Folinic acid (leucovorin®) 24 hours *after each* weekly dose or by the use of *daily* Folic acid (not in the same day; *off-days*), although this may *decrease* the efficacy of Methotrexate by *about* 10%, ***but*** this *reduces severity* of adverse effects.

- Pemetrexed and Pralatrexate *should be given with* Folic acid and Vitamin B_{12} *supplements* to *reduce* hematologic and GI toxicities.
- *Drug Interactions*; NSAIDs, penicillins, cephalosporins, aminoglycosides, proton-pump inhibitors and valproates are *increase* plasma concentrations of MTX.

Purine Analogues

6-Mercaptopurine (Purinethol®)# | Fludarabine (Fludara®) | Cladribine (Leustatin®)

- 6-Mercaptopurine (6-MP) was the ***first*** of the ***thiopurine analogs*** found to be ***effective*** in **cancer therapy**.
- Azathioprine, an ***immunosuppressant***, exerts its ***cytotoxic effects*** after ***conversion to*** 6-MP via ***metabolism***.
- ***Indications***;
  - 6-MP ***used*** *primarily* in **acute lymphatic** (***lymphocytic***, ***lymphoblastic***) **leukemia**.
  - Fludarabine ***used*** *primarily* in ***low-grade*** **non-Hodgkin's lymphoma** and **chronic lymphocytic leukemia (CLL)**.
  - Cladribine is ***effective against*** **hairy cell leukemia**, **chronic lymphocytic leukemia (CLL)**, and **non-Hodgkin lymphoma**.
- Fludarabine ***increase risk*** for ***opportunistic infections***, including **fungi**, **herpes**, and *Pneumocystis jiroveci* **pneumonia (PCP)**; **Patients** ***should receive*** **PCP prophylaxis** with Co-Trimoxazole at least **3** ***times*** a **week**, and this ***should continue*** for ***up to*** **1 year** *after* **stopping** Fludarabine ***therapy***.
- Other Purine Analogues;
  - 6-Thioguanine or Thioguanine or Tioguanine (Lanvis®); used to ***treat*** **acute myeloid leukemia (AML)** and **acute lymphocytic leukemia (ALL)**; ***not recommended*** for **maintenance therapy** due to the ***high*** **risk** of **liver toxicity** *associated with* **vascular endothelial damage**.
  - Pentostatin or Deoxycoformycin (Nipent®); Used as ***single-agent*** for ***alpha-interferon-refractory*** **hairy cell leukemia**.

Pyrimidine Analogues

5-Fluorouracil (Adrucil®)#

- 5-Fluorouracil (5-FU) is **used** *primarily* in **solid tumors** (*for example*; **colorectal**, **breast**, **ovarian**, **pancreatic** and **gastric carcinomas**).
- ***Because*** of its **severe toxicity** to the **GI tract**, 5-FU is ***given*** **IV** or, in the case of **skin cancer** used ***topically***.

Capecitabine (Xeloda®)#

- Capecitabine is an **oral** ***prodrug*** (*non-toxic*), which is ***enzymatically*** *converted to* 5-Fluorouracil *inside* the **tumor**.

It is ***used*** in the *treatment* of **colorectal** and *metastatic* **breast cancer**.

- The ***main toxicities*** include **diarrhea** and **hand-foot syndrome** (**Chemotherapy-induced acral erythema**).

Floxuridine (FUDR®)

- Floxuridine or 5-fluorodeoxyuridine is an **oral** ***prodrug***, which is *converted to* 5-FU.
- Floxuridine is ***used*** *primarily* in the ***treatment of*** **colorectal cancer**.

Cytidine Analogues

Azacitidine (Vidaza®)

Azacitidine is ***used*** for the *treatment* of **myelodysplastic syndromes (MDS)** and **acute myeloid leukemia (AML)**.

Cytarabine (Ara-C®)#

- Cytarabine is *used* for the *treatment* of **acute nonlymphocytic (myelogenous) leukemia (AML)**. It can cause **neurotoxicity** in ***high doses***.

Gemcitabine (Gemzar®)#

- Gemcitabine is ***indicated*** as **first-line treatment** for **advanced pancreatic cancer** but is ***now*** **widely used** to treat a broad range of malignancies; ***including*** **non-small cell lung cancer, bladder cancer, ovarian cancer, soft tissue sarcoma** and **non-Hodgkin's lymphoma**.
- Gemcitabine is ***commonly*** **used** ***off-label*** to treat **cholangiocarcinoma** and other **biliary tract cancers**.

II) Alkylating Agents

- Alkylating agents ***exert*** their **cytotoxic effects** by **covalently** ***binding*** to **nucleophilic groups** on ***various cell*** **constituents**.
- **Alkylation** of **DNA** ***within*** the **nucleus** probably represent the **major interactions** that lead to **cell death**. However, these drugs react chemically with sulfhydryl, amino, hydroxyl, carboxyl, and phosphate groups of other cellular nucleophiles as well.
- Alkylating agents are used in ***combination*** with **other agents** to treat a **wide variety** of **lymphatic** and **solid cancers**.

Nitrogen Mustard

- Nitrogen mustards are cytotoxic chemotherapy agents that are a derivative of mustard gas.

Mechlorethamine or Mustine (Mustargen®)

- It used in ***combination*** to treat **Hodgkin's & non-Hodgkin's lymphoma**.

Cyclophosphamide (Cytoxan®)# (Neosar®)# (Endoxan®)# | Ifosfamide (Ifex®)#

- Cyclophosphamide is **one** of the ***most widely*** used **alkylating agents** used in ***combination*** to treat a ***wide variety*** of **lymphatic** and **solid cancers**; such as **lymphoma, multiple myeloma, leukemia, ovarian cancer, breast cancer, small cell lung cancer, neuroblastoma** and **sarcoma**.
- Cyclophosphamide is available in **oral** or **IV**, whereas Ifosfamide is **IV** ***only***.

Cyclophosphamide and Ifosfamide can cause **hemorrhagic cystitis**, which can ***lead to*** **bladder fibrosis**.

Chlorambucil (Leukeran®)#

- Chlorambucil, is used to treat **chronic lymphocytic leukemia (CLL), Hodgkin lymphoma**, and **non-Hodgkin lymphoma**.
- It is given **orally** **1 hour** ***before*** or **2 hours** ***after*** **meals** (***empty*** **stomach**).
- Chlorambucil has been ***largely replaced*** by Fludarabine (Fludara®) as **first-line treatment** in **younger patients**.

Melphalan (Alkeran®)#

- Melphalan ***used*** to **treat** **multiple myeloma** (plasma cell cancer) and **ovarian cancer**.
- It is given **IV** or **orally** (***empty*** **stomach**).

Bendamustine (Treanda®)

- Bendamustine, is used to treat **chronic lymphocytic leukemia (CLL), multiple myeloma**, and **non-Hodgkin's lymphoma**. It is given **IV**.

Nitrosoureas

- Nitrosoureas are *highly* lipid-soluble and are able to *cross* the blood-brain barrier, making them effective in the ***treatment*** of brain tumors.

Carmustine (BiCNU®)# | **Lomustine** (CeeNu®)# | **Streptozocin** (Zanosar®)

- **Carmustine** is **used** to ***treat*** *certain types* of **brain tumors**, **Hodgkin's disease** and **non-Hodgkin's lymphomas**; **IV** and also ***available as*** an **implantable brain wafer**.
- **Lomustine** are **used** in **brain tumors**; **orally** on ***empty*** **stomach** (no food or drink for 2 hours after to decrease incidence of nausea).
- **Streptozocin** is **used** to ***treat*** **islet cell cancer** *of the* **pancreas**.

Alkyl Sulfonates

Busulfan (Myleran®)#

- **Busulfan** is **used** in ***combination with*** **Cyclophosphamide** in **bone marrow transplantation**, *especially in* **chronic myelogenous leukemia** (**CML**).

Toxicity; **Interstitial Pulmonary Fibrosis (Busulfan Lung)** **hyperpigmentation**, **seizures**, **veno-occlusive disease**; **VOD** (hepatic) and **wasting syndrome**.

- *Antiepileptic agent* used as ***prophylaxis*** against **Busulfan-induced seizures**.

Triazines

Procarbazine (Natulan®)

- It is **used** to treat **Hodgkin's** and **non-Hodgkin's lymphoma** and **brain tumors**.

Dacarbazine (Dtic-Dome®)

- **Dacarbazine** is **used** to as a ***single agent*** in **metastatic malignant melanoma**.
- It is **used** in ***combination*** in **Hodgkin's disease** and **soft tissue sarcomas**.
- **Dacarbazine** is ***considered to*** be *highly* **emetogenic** (**antiemetic agents** are used as **pre-medicated**).

Temozolomide (Temodal®)#

- **Temozolomide** is **used** to as *first-line* treatment for **glioblastoma multiforme** (**GBM**) and a *second-line* (after **Nitrosourea** and **Procarbazine**) treatment for **anaplastic astrocytoma** (*types of brain tumors*).

Platinum Salts

Cisplatin (Platinol®)#

Cisplatin was the ***first*** **member** of the ***platinum complex***, but ***because*** of its **severe toxicity** (**Nephrotoxicity**, **Neurotoxicity** & **Ototoxicity**); **Carboplatin** and **Oxaliplatin** was ***developed***.

- It is **used** in **solid tumors** (testicular cancer, ovarian cancer, breast cancer, bladder cancer, head and neck cancer, cervical cancer, lung cancer, mesothelioma, esophageal cancer, brain tumors and neuroblastoma).

Carboplatin (Paraplatin®)#

Carboplatin is **used** to ***treat*** **ovarian cancer**, **lung cancer**, **head** and **neck cancer** and **brain cancer**.

Toxicity; *rarely* **Nephrotoxicity**, **Neurotoxicity** and **Ototoxicity** and **Hepatotoxicity**.

Oxaliplatin (Eloxatin®)#

Oxaliplatin is **used** to ***treat*** **colorectal cancer** in ***combination with*** **Fluorouracil** and **Folinic acid** (**Leucovorin**).

Toxicity; **peripheral neuropathy**.

III) Cytotoxic Antibiotics

- The **Cytotoxic antibiotics** owe their ***cytotoxic action*** primarily to their **interactions** *with* **DNA**, leading to ***disruption*** of **DNA function**.
- **Cytotoxic antibiotics** ***inhibit*** **topoisomerases** (I and II) and ***produce*** **free radicals** also ***play*** a **major role** in their **cytotoxic effect**.

Anthracyclines

Anthracyclines are used to ***treat*** **various cancers** and ***most important*** and ***widely*** used **anticancer drugs** (**Doxorubicin**; one of the ***most important*** anticancer drugs).

The ***main side effects*** of **Anthracyclines** is ***irreversible***, **dose-dependent CARDIOTOXICITY** (due to **free radical** ***formation and other mechanisms***); ***more common*** with **Daunorubicin** and **Doxorubicin** ***than*** with **Idarubicin** and **Epirubicin**.

- **Dexrazoxane** is a ***cardio-protective agent*** (chelates iron and thus reduces the number of metal ions complexed with anthracycline and, consequently, decrease the formation of superoxide radicals) has been used to ***protect*** the **heart** ***against*** the **cardiotoxic** of **Anthracyclines**.
- ***All*** **Anthracyclines** must be ***administered*** **IV** (*due to* ***inactivated*** in the **GI tract**).

Daunorubicin (Cerubidine®)#

- **Daunorubicin** or **Daunomycin** is the ***first*** **Anthracycline** ***discovered***.
- It is **used** to ***treat*** **acute leukemias**.
- In ***contrast to*** **Doxorubicin**, its ***efficacy*** of **Daunorubicin** in **solid tumors** is ***limited***.

Doxorubicin (Adriamycin®) (Adriblastina®)#

Daunorubicin is one of the ***most important*** **anticancer drugs** in ***clinical practice***.

- It is **used** to ***treat*** **leukemias** and **Hodgkin's** and **non-Hodgkin's lymphoma** and **cancers** of **bladder**, **breast**, **stomach**, **lung**, **ovaries**, **thyroid**, **soft tissue sarcoma**, **multiple myeloma**, **testicle**, **liver** and **others**.

Doxorubicin Liposomal (**Doxil®**); is a **polyethylene glycol** ***coated*** **liposome-*encapsulated*** *form* of **Doxorubicin** **used** to treat **AIDS-related Kaposi's sarcoma**, **breast cancer**, **ovarian cancer**, and **other solid tumors**.

- **Doxorubicin Liposomal** is ***less*** **cardiotoxic** *than* the ***usual*** **formulation**.
- ***Commonly used*** **Doxorubicin-Containing Regimens**;

Regimen	Agents	Uses
AC	Adriamycin (Doxorubicin) + Cyclophosphamide	Breast cancer
TAC	Taxotere + Adriamycin + Cyclophosphamide	Breast cancer
ABVD	Adriamycin + Bleomycin + Vinblastine + Dacarbazine	Hodgkin's lymphoma
BEACOPP	Bleomycin + Etoposide + Adriamycin + Cyclophosphamide + Oncovin (Vincristine) + Procarbazine + Prednisone	Hodgkin's lymphoma
CHOP	Cyclophosphamide + Hydroxydaunorubicin + Oncovin + Prednisone	non-Hodgkin's lymphoma
FAC	5-Fluorouracil + Adriamycin + Cyclophosphamide	Breast cancer

Idarubicin (Idamycin®)#

- **Idarubicin** is a ***semisynthetic*** **anthracycline** ***analog*** of **Daunorubicin** used in ***combination with*** **Cytarabine** as a ***first line*** treatment of **acute myeloid leukemia**.

Epirubicin (Ellence®)#

- **Epirubicin** is an ***anthracycline analog*** *approved for* **node-positive breast cancer**.

Mitoxantrone (Novantrone®)#

- Mitoxantrone is an *anthracene compound* whose *structure resembles* the anthracycline ring.
- It is used to *treat advanced, hormone-refractory* prostate cancer and *low-grade* non-Hodgkin's lymphoma.
- It is also used in breast cancer and in acute myeloid leukemias.

Others

Bleomycin (Blenoxane®)#

- It is *primarily* used in the *treatment of* testicular cancer, ovarian cancer and Hodgkin's disease.
- Bleomycin *inactivation*; is *low rate* in lung and is *absent* in skin (enzyme deficiency);
  - # Skin toxicity; Hypertrophic skin changes and hyperpigmentation of the hands.
  - # Pulmonary toxicity; Pneumonitis with cough, dyspnea and pulmonary fibrosis.

The pulmonary fibrosis that is caused by Bleomycin is referred as; Bleomycin lung.

Mitomycin (Mutamycin®)#

- It is used in the *treatment of* cancer of the stomach or pancreas.
- Also used in *treatment* of anal, bladder, breast, cervical, colorectal, head and neck, and non-small cell lung cancer.

Mitomycin *increase* risk of **Hemolytic Uremic Syndrome (HUS)**; hemolytic anemia, *low* platelet count and *permanent* kidney failure.

Dactinomycin or Actinomycin D (Cosmegen®)

- Actinomycin D was the *first antibiotic shown to* have anti-cancer activity.
- It is used in Wilms' tumor (cancer of the kidneys that typically occurs in children), Ewing's sarcoma, Gestational trophoblastic neoplasm, Metastatic testicular tumors, rhabdomyosarcoma, trophoblastic neoplasm and *certain types* of ovarian cancer.
- It is *also* used as a radio-sensitizer (*increase* the radio-sensitivity of tumor cells).

IV) Microtubule Inhibitors

- Mitotic spindle; is an intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells.
- The mitotic spindle *consists of* chromatin and microtubules composed of the protein tubulin.
- The mitotic spindle is *essential for* eukaryotic cell division.

Vinca Alkaloids

- Vinca alkaloids are a set of *anti-mitotic* and *anti-microtubule* alkaloid agents originally derived from the periwinkle plant *Vinca rosea* and other vinca plants.

The *main side effects* of Vinca alkaloids is;

- # **NEUROTOXICITY** (peripheral neuropathy, autonomic nervous system dysfunction with orthostatic hypotension, urinary retention, and paralytic ileus or constipation, cranial nerve palsies, ataxia, seizures and coma); Vincristine > Vinblastine > Vinorelbine
- # Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH); too much antidiuretic hormone and hyponatremia impaired water excretion.

Vincristine (VX) (Oncovin®)#

- It is used in the *treatment of* **acute leukemia, Hodgkin's** and **non- Hodgkin's lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, Wilms' tumor, multiple myeloma, chronic leukemias, thyroid cancer, brain tumors.**
- **Doses *must be* modified** in patients with **impaired hepatic function, biliary obstruction** or in **Vincristine-*related* peripheral neuropathy.**

The **liposome *encapsulation*-Vincristine** (Marqibo®) ***enhances* efficacy** and ***decreasing*** the **neurotoxicity.**

Vinblastine (VBL) (Velban®)#

- It is used in *treatment of* **Hodgkin lymphoma, non-Hodgkin's lymphoma, testicular, Kaposi's sarcoma, breast** and **lung cancer.**

Vinorelbine (VRB) (Navelbine®)#

- It is used in *treatment of* **non-small cell lung cancer, breast cancer & ovarian cancer.**

Taxanes

- **Taxanes** is a ***plant alkaloids*** *derived from* Pacific yew (*Taxus brevifolia*) and European yew (*Taxus baccata*).

Toxicity; hypersensitivity reactions and **neurotoxicity (peripheral neuropathy).**

Paclitaxel (Taxol®)#

- **Paclitaxel** was the ***first member*** of the **taxane family.**

Paclitaxel has ***significant activity*** in a **broad range** of **solid tumors; ovarian,** *advanced (metastatic)* **breast, lung, head** and **neck, esophageal, prostate,** and **bladder cancers** and **AIDS-*related* Kaposi's sarcoma.**

Premedication *with* **Dexamethasone, Diphenhydramine** and an **H_2 blocker** to ***decrease* hypersensitivity reactions** to **Paclitaxel.**

Albumin-bound* Paclitaxel** (Abraxane®) ***form is also ***available*** and used in **metastatic breast cancer, lung cancer** and **pancreatic cancer.**

Abraxane® is ***not associated*** with **hypersensitivity reactions** and **neurotoxicity *more readily* reversible** than **Paclitaxel.**

Docetaxel (Taxotere®)#

- **Docetaxel** is a ***semisynthetic* taxane used** in ***advanced* breast cancer, lung cancer, neck cancer, gastric cancer, ovarian cancer** and **bladder cancer.**

Cabazitaxel (Jevtana®)

- **Cabazitaxel** was approved by FDA for the treatment of ***hormone-refractory* prostate cancer** in **2010.**

Other

Ixabepilone (Ixempra®)

- **Ixabepilone** is **used** in ***aggressive metastatic*** or ***locally advanced* breast cancer.**

➢ Natural product cancer chemotherapy drugs:

Enzyme	Bacteria	Plant			
Asparaginase	Daunorubicin Doxorubicin Bleomycin Mitomycin	Paclitaxel Docetaxel	Vincristine Vinblastine Vinorelbine	Topotecan Irinotecan	Etoposide Teniposide

V) Endocrine Therapy

- A hormone-sensitive cancer or hormone-dependent cancer; is a ***type of cancer*** that is ***dependent on*** a hormone *for* growth.
- ***Examples***; breast cancer, which is ***dependent*** on estrogens *like* Estradiol, and prostate cancer, which is ***dependent*** on androgens *like* Testosterone.

Glucocorticoids

- Glucocorticoids interfere with the ***concentration***, ***distribution*** and ***function*** of leukocytes.
- Glucocorticoids ***prominently*** used in the ***treatment*** of blood cancers.

Prednisone (Hostacortin®)#

- Prednisone is ***primarily*** employed to ***induce*** **remission** in *patients with* **acute lymphocytic leukemia** and both **Hodgkin** and **non-Hodgkin lymphomas** and ***other*** **blood cancers**.
- Prednisone can be ***found*** in ***several*** **combination chemotherapy regimens**.
- Prednisone also ***helps*** to ***decrease*** **nausea** as well as ***promote*** an **appetite**.

Estrogens

- Estrogens, *such as* Ethinyl Estradiol, had been used in the ***treatment of*** **prostatic cancer**. *However*, they have been ***largely replaced*** by the GnRH analogs.

Antiestrogens

Selective Estrogen Receptor Modulator (SERM)

Tamoxifen (Nolvadex®)#

Tamoxifen is used for ***first-line therapy*** in the *treatment of* both ***early*** and ***advanced*** **estrogen receptor–positive breast cancer**; ***orally***.
- Tamoxifen is used to ***prevent*** **estrogen-related gynecomastia**.
- Tamoxifen has the ***potential*** to cause **endometrial cancer**.
Side effects; **hot flashes**, **nausea**, **vomiting**, **skin rash**, **vaginal bleeding** and **discharge** (*due to* estrogenic activity), joint pain and **thromboembolism**.

Fulvestrant (Faslodex®)#

- Fulvestrant is used in **estrogen receptor–positive breast cancer**; IM.

Raloxifene (Evista®)#

- Raloxifene is used in **osteoporosis** in ***postmenopausal*** **women** and to ***reduce*** **risk** of ***invasive*** **breast cancer**; ***orally***.
- ***Side effects***; ***like*** Tamoxifen.

Aromatase Inhibitors

Aromatase is the ***enzyme*** that ***synthesizes*** Estrogen, which ***converts*** Androgens into Estrogens by a *process called* Aromatization.

Anastrozole (Arimidex®)#

- Anastrozole and Letrozole are non-steroidal ***reversible competitive inhibitor***.
- They are used *in* ***hormone-dependent*** **breast cancer**.
- They are used *to* ***prevent*** **estrogen-related gynecomastia**.

Letrozole (Femara®)#

- Letrozole has been used *for* **ovarian stimulation**.
Side effects; **hot flashes**, **joint pain** & **osteoporosis** (Bisphosphonates are *prescribed*)

Exemestane (Aromasin®)#

- Exemestane is a steroidal, ***irreversible inhibitor*** of Aromatase.
- Exemestane is used *in* ***hormone-dependent*** **breast cancer**.

Progestins

Megestrol Acetate (MGA) (Megace®)

- MGA is *used* in **breast** and **endometrial cancer** and as an **appetite stimulant**.

GnRH Analogue

- They are a drug used to *suppress* production of the **sex hormones** (Testosterone and Estrogen), particularly in the *treatment* of **breast** and **prostate cancer**.

Leuprorelin or Leuprolide (Lupron®)#

Goserelin (Zoladex®)# | Triptorelin (Trelstar®)#

- They are **used** to *treat* ***hormone-sensitive*** **cancers** of the **breast** and **prostate**.
- **Leuprolide** is available as - Sustained-release intradermal implant
  - SC depot injection
  - IM depot injection
- **Goserelin acetate** is a SC implant.
- **Triptorelin pamoate** is injected IM.

Antiandrogens

Flutamide (Eulexin®)# | Nilutamide (Anandron®)# | Bicalutamide (Casodex®)#

- **Flutamide**, **Nilutamide** and **Bicalutamide** are *synthetic*, ***non-steroidal*** **antiandrogens** **used** in the *treatment of* **prostate cancer**.

 # Most common side effects; **Gynecomastia** and **breast tenderness**.

- **Flutamide** and **Bicalutamide** ***rarely*** cause **hepatotoxicity**.
- **Nilutamide** can *cause* **visual problems** and **interstitial pneumonitis**.

VI) Monoclonal Antibodies

- **Monoclonal antibody** therapy is a form of ***immunotherapy*** that uses **monoclonal antibodies** (**mAb**) to bind ***mono-specifically*** to *certain* **cells** or **proteins**.
- **Monoclonal antibodies** are ***directed*** at **specific targets** and often have ***fewer*** **adverse effects**.

Rituximab (Rituxan®)#

- **Rituximab** was the ***first*** **monoclonal antibody** to be approved for cancer.
- It is **used** *for* **non-Hodgkin's lymphoma**, **chronic lymphocytic leukemia** and **rheumatoid arthritis**.

 # Severe side effects; *Severe* **infusion** *reactions* (**fatal**) and **tumor lysis syndrome**.

Trastuzumab (Herceptin®)#

- **Trastuzumab** **used** in **breast cancer**.

 # Severe side effects; **heart failure** (*worsened with* **Anthracyclines**) & **allergic reactions**.

Pertuzumab (Perjeta®)#

- **Pertuzumab** used in ***combination*** with **Trastuzumab** and **Docetaxel** for the treatment of ***metastatic*** **HER2-positive breast cancer**.

Bevacizumab (Avastin®)#

- **Bevacizumab** used as ***first-line*** in **metastatic colorectal cancer**.
- It is *also* **used** in **lung cancer**, **glioblastoma**, and **renal-cell carcinoma**.
- It is *also* **used** for ***age-related*** **macular degeneration** (injection into the eye).

 # Severe side effects; **hypertension** and ***heightened*** **risk** of **bleeding**.

Cetuximab (Erbitux®)#	Panitumumab (Vectibix®)#

- Cetuximab and Panitumumab are an epidermal growth factor receptor (*EGFR*) *inhibitor* used for in *metastatic* colorectal cancer,
- Cetuximab also used in *metastatic* non-small cell lung cancer & head & neck cancer

Others	
Ramucirumab (Cyramza®)#	Gastric cancer
Pembrolizumab (Keytruda®)#	Metastatic melanoma
Olaratumab (Lartruvo®)#	Soft tissue sarcoma
Ofatumumab (Arzerra®)	Chronic lymphocytic leukemia
Obinutuzumab (Gazyva®)#	Chronic lymphocytic leukemia
Nivolumab (Opdivo®)	Metastatic squamous non-small cell lung carcinoma and metastatic melanoma
Necitumumab (Portrazza®)	Metastatic squamous non-small cell lung carcinoma
Ipilimumab (Yervoy®)	Metastatic melanoma
Ibritumomab (Zevalin®)#	Relapsed low-grade, follicular B-cell non-Hodgkin's lymphoma
Elotuzumab (Empliciti®)	Multiple myeloma
Durvalumab (Imfinzi®)	Urothelial carcinoma
Daratumumab (Darzalex®)	Multiple myeloma
Brentuximab (Adcetris®)	Hodgkin lymphoma and anaplastic large-cell lymphoma
Blinatumomab (Blincyto®)	Precursor B-cell acute lymphoblastic leukemia
Avelumab (Bavencio®)	Metastatic Merkel cell carcinoma
Atezolizumab (Tecentriq®)	Urothelial carcinoma and metastatic non-small cell lung cancer
Alemtuzumab (Campath®)#	B-cell chronic lymphocytic leukemia

VII) Tyrosine Kinase Inhibitor

- Tyrosine kinases are a ***family*** of **enzymes** that are *involved* in ***several*** **important processes** within a cell, including **signal transduction** and **cell division**.

Imatinib (Gleevec®) (Glivec®)#

Imatinib is **used** *orally* to treat **chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs)** and a number of other malignancies.
Severe side effects; **fluid retention** and *risk of* **severe CHF**.

Nilotinib (Tasigna®)#

- **Nilotinib** is **used** *orally* to treat **Imatinib-*resistant* chronic myelogenous leukemia**.
- ***Severe side effects***; **fluid retention** and *risk of* **QT prolongation**.

Dasatinib (Sprycel®)#

- **Dasatinib** is **used** *orally* to treat **chronic myelogenous leukemia (CML)** and **Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL)**.
- ***Severe side effects***; **pulmonary arterial hypertension**.

Erlotinib (Tarceva®)#

- **Erlotinib** is **used** *orally* to treat **non-small cell lung cancer, pancreatic cancer** and ***several*** **other types** of **cancer**.
- ***Common side effects***; **diarrhea, nausea** and **acne-like skin rashes**.

Sorafenib (Nexavar®)#	Sunitinib (Sutent®)#

Sorafenib is used *orally* to treat ***advanced*** **renal cell carcinoma**, ***advanced*** **primary liver cancer**, and ***radioactive iodine resistant advanced*** **thyroid carcinoma**.
Sunitinib is used *orally* to treat **renal cell carcinoma**, Imatinib-resistant **gastrointestinal stromal tumor (GIST)** and **pancreatic neuroendocrine tumors**.
Most common side effects; **diarrhea, fatigue, hand & foot syndrome & hypertension**
- *Other agents* are used in **renal cell carcinoma**; Pazopanib (Votrient®), Temsirolimus (Torisel®), Interleukin-2 (Proleukin®), Everolimus (Afinitor®), Bevacizumab (Avastin®) and Aldesleukin.

Lapatinib (Tykerb®)#

- Lapatinib is used to treat ***metastatic*** **HER2-positive breast cancer**.
- *Common side effects*; **diarrhea, fatigue, nausea** and **rashes**.

VIII) Topoisomerase Inhibitors

- ***Inhibition*** of topoisomerase II ***enzyme*** (which aids in **DNA** ***unwinding***), ***prevents*** **re-ligation** of the **DNA strands**, and by doing so causes **DNA strands** to ***break*** (Cancer cells rely on this enzyme more than healthy cells, since they divide more rapidly).

Podophyllotoxin Derivatives

Etoposide (Toposar®)#	Teniposide (Vumon®)#

- Etoposide and Teniposide is a ***semisynthetic derivative*** of Podophyllotoxin from the ***rhizome*** of the wild mandrake (*Podophyllum peltatum*).
- Etoposide is used for; **testicular, bladder, prostate, lung, stomach** and **uterine, cancers. Hodgkin's** and **non-Hodgkin's lymphoma, mycosis fungoides, Kaposi's sarcoma, Wilm's tumor, rhabdomyosarcoma, Ewing's sarcoma, neuroblastoma, brain tumors**.
- Teniposide is used for **acute lymphocytic leukemia** (*particularly* in **children**).

Camptothecins

Topotecan (Hycamtin®)#	Irinotecan (Campto®)#

- Camptothecins are ***plant alkaloids*** originally isolated from the Chinese tree (Camptotheca; Happy tree)
- Irinotecan and Topotecan are ***semisynthetic derivatives*** of Camptothecin.
- Topotecan is used in **metastatic ovarian cancer** and **small cell lung cancer**.
- Irinotecan is used with 5-FU & leucovorin for ***treatment*** of **colorectal carcinoma**.

IX) Others

Interferon Alfa-2a (Roferon®-A)	Interferon Alfa-2b (Intron® A)

- Interferon-α-2a is *approved for*; **hairy cell leukemia, chronic myelogenous leukemia** and **AIDS-related Kaposi sarcoma**.
- Interferon-α-2b is *approved for*; **hairy cell leukemia, melanoma, AIDS-related Kaposi sarcoma**, and **follicular lymphoma**.
- ***Exact mechanism*** by which the Interferons are ***cytotoxic*** is **unknown**.
- *Common side effects*; **Flu-like symptoms** and **GI upset**.

L-Asparaginase (Kidrolase®)

- *Some* **neoplastic cells** *require* an **external source** of **Asparagine** because of ***limited capacity*** to **synthesize** ***sufficient*** **amounts** to ***support*** **growth** and **function**.
- **Asparaginase** works by ***breaking down*** **Asparagine**.
- **Pegaspargase** is a **PEGylated** ***formulation*** of **Asparaginase**.
- **Asparaginase** is **used** to treat ***childhood*** **acute lymphocytic leukemia**.

Procarbazine (Matulane®) (Natulan®)

- **Procarbazine** is **used** to treat **Hodgkin's disease** and **brain cancers**.
- **Procarbazine** ***rapidly*** **equilibrates** *between* **plasma** & **CSF** *after* **oral** administration.
- **Procarbazine** ***inhibits*** **MAO** ***enzyme***, *patients* should be **warned** ***against*** **ingesting foods** that ***contain*** *high levels* of **Tyramine**.
- It may ***cause*** a **Disulfiram-*like* reaction**.

Abiraterone Acetate (Zytiga®)

- **Abiraterone acetate** is a **steroidal CYP17A1** ***inhibitor*** (**Androgen synthesis inhibitor**) which is **used** in ***combination*** with **Prednisone** in **metastatic castration-resistant prostate cancer** (hormone-resistant or hormone-refractory prostate cancer).
- ***Side effects***; **Hypertension**, **hypokalemia**, **fluid retention**, **urinary tract infection** and **hepatotoxicity** *may occur*.

Enzalutamide (Xtandi®)

- **Enzalutamide** is an **oral** ***synthetic*** **non-steroidal antiandrogen**.
- **Enzalutamide** is **used** in **metastatic castration-resistant prostate cancer**.
- ***Side effects***; **asthenia**, **back pain**, **fluid retention** and **risk of seizure**.

Immunosuppressants

- **Immunosuppressantsts**; are **drugs** that ***inhibit*** or ***prevent*** **activity** of the **immune system**.
- **Immunosuppressantsts** are **used** in:
  - ***Prevent*** the **rejection** of **transplanted organs** and **tissues**.
  - ***Treat*** **autoimmune diseases** (e.g., **rheumatoid arthritis**, **multiple sclerosis**, **myasthenia gravis**, **psoriasis**, **vitiligo**, **systemic lupus erythematosus**, **sarcoidosis**, **focal segmental glomerulosclerosis**, **Behcet's Disease**, **pemphigus**, **Crohn's disease** and **ulcerative colitis**).
  - ***Other*** **non-autoimmune inflammatory diseases**; *such as* **ankylosing spondylitis**.

- ***Classification***;

I) **Glucocorticoids**; *see hormones*
II) **Calcineurin Inhibitors**.
III) **Mechanistic Target Of Rapamycin (mTOR) Inhibitors**.
IV) **Mycophenolates**.
V) **Immunomodulatory Derivatives of Thalidomide (IMiDs)**.
VI) **Cytotoxic Agents**; see cancer chemotherapy
VII) **Antibodies**.

Calcineurin (CaN) Inhibitors

- Calcineurin (CaN) is a Calcium and Calmodulin *dependent* Serine/Threonine protein Phosphatase, It *activates* the T cells of the immune system.

Cyclosporine (Sandimmun Neoral®)#

Cyclosporine is a *calcineurin inhibitor*, is a *lipophilic* cyclic polypeptide *extracted from* the soil fungus *Beauveria nivea*.
Cyclosporine is used (orally or IV) for prevent organ rejection in organ transplantation (Kidney, Liver and Heart), rheumatoid arthritis, psoriasis, Crohn's disease and nephrotic syndrome.
Cyclosporine eye drops (Restasis®) *used for* KeratoConjunctivitis Sicca (*severe dry eye syndrome*).
- *Metabolism*; primarily by CYP3A4.
Toxicity; NEPHROTOXICITY, hypertension, hyperglycemia, liver dysfunction, hyperkalemia, altered mental status, seizures and hirsutism.

Tacrolimus (Prograf®)#

Tacrolimus is a macrolide *calcineurin inhibitor* that is *isolated from* the soil fungus *Streptomyces tsukubaensis*.
Tacrolimus is *preferred over* Cyclosporine *because*; *increased* potency (10–100 times), *decreased* episodes of rejection.
Tacrolimus is used (orally or IV) for prevent organ rejection in organ transplantation (Kidney, Liver and Heart).
Tacrolimus *ointment* (Protopic®); used for atopic dermatitis, psoriasis and vitiligo.
- *Metabolism*; primarily by CYP3A4.
Toxicity; NEPHROTOXICITY, NEUROTOXICITY, hyperglycemia, hypertension and hyperkalemia.

Pimecrolimus (Elidel®)#

Pimecrolimus like Tacrolimus. It is available as a topical cream; used for atopic dermatitis, psoriasis and vitiligo.

Mechanistic Target Of Rapamycin (mTOR) Inhibitors

- Mechanistic Target Of Rapamycin (mTOR), which is a Serine/Threonine-*specific* protein kinase. mTOR *regulates* cellular metabolism, growth and proliferation.
- mTOR *inhibitors* include; Sirolimus (Rapamycin) as well as its *analogs* (called "rapalogs") such as Everolimus and Temsirolimus.

Sirolimus or Rapamycin (Rapamune®)

- Sirolimus is a macrolide produced by *Streptomyces hygroscopicus* and is *structurally similar* to Tacrolimus.
- It is used in renal transplantation and for LymphAngioleioMyomatosis (LAM).
- *Metabolism*; primarily by CYP3A4.
Sirolimus is used in coronary stent coating; *Antiproliferative action*; *inhibit* restenosis of the blood vessels by *reducing* proliferation.
Side effects; HYPERLIPIDEMIA, headache, nausea and diarrhea, leukopenia and thrombocytopenia.
Temsirolimus (Torisel®); an IV *prodrug* of Sirolimus; used in renal cell carcinoma.

Everolimus (Zortress®) (Certican®) (Evertor®) (Afinitor®) (Votubia®)

- It is used in; - Renal transplantation. - Advanced kidney cancer and breast cancer. - Neuroendocrine tumors (NET) of GI, lung or pancreas.
- Zortress®, Certican® and Evertor® *brands* are used transplantation medicine.
- Afinitor® and Votubia® *brands* are used in oncology.
- *Side effects*; like Sirolimus.

Mycophenolates

- Mycophenolic acid (Mycophenolate) *inhibits* an enzyme needed for the *growth of* T cells and B cells.
- Mycophenolic acid was *isolated from* the mold *Penicillium glaucus*.

Mycophenolate Mofetil (CellCept®)# | Mycophenolate Sodium (Myfortic®)#

Mycophenolate Mofetil and Mycophenolate Sodium are *hydrolyzed to* Mycophenolic Acid (*active moiety*).
Mycophenolic Acid is used in solid organ transplant (Kidney, Liver & Heart) in *combination with* Corticosteroids and Cyclosporine or Tacrolimus.
Toxicity; GI DISTURBANCES (nausea and vomiting, diarrhea, abdominal pain) headache, hypertension and *reversible* myelosuppression (*primarily* neutropenia).
Pregnancy; Mycophenolic acid is *associated with* miscarriage and congenital malformations.
Mycophenolate Sodium (Myfortic®); *delayed-release* enteric-coated tablets; to *minimize* the GI side effects *associated with* Mycophenolate Mofetil.

Immunomodulatory Derivatives of Thalidomide (IMiDs)

Thalidomide was first marketed in 1957 as a sedative drug but it was withdrawn from the market in the 1960s because of its disastrous teratogenic effects (Category X) when used during pregnancy (malformation of the limbs; about 10,000 cases were reported of infants and only 40% of these children survived).
Thalidomide (Immunoprin®) is an *immunomodulatory drug* and the prototype of the Thalidomide class.
- Thalidomide is *currently used* in the treatment of multiple myeloma and of a *complication of* leprosy.

Lenalidomide (Revlimid®)

- Lenalidomide is a *derivative of* Thalidomide used in multiple myeloma and myelodysplastic syndromes.
Pregnancy; Like Thalidomide; Category X.

Antibodies

Monoclonal Antibodies (mAbs)

- *See cancer chemotherapy.*

Belatacept (Nulojix®)#

- Belatacept is used for *prophylaxis* of acute rejection in renal transplantation.

Polyclonal Antibodies (pAbs)

Antilymphocyte Globulin (ALG) & Antithymocyte Globulin (ATG) (ATGAM®)

- ALG and ATG are an *infusion* of animal-antibodies *against* human T cells which is used in the *treatment of* acute rejection in organ transplantation.

Immune Globulin Intravenous (IGIV) (Flebogamma®)# (Liv-Gamma®)#

- IGIV is *prepared from* pools of thousands of healthy donors.
- IGIV *therapy* is used in a variety of conditions, *ranging from* immunoglobulin deficiencies *to* autoimmune disorders *to* HIV disease *to* bone marrow transplantation.

Hematopoietic Drugs

A) Drugs for Anemia

Erythropoietin

Folic Acid

Iron Supplements

Vitamin B_{12}

Drugs for Sickle Cell Disease

Erythropoiesis-Stimulating Agents (ESAs)

Epoetin alfa (Epiao®)# (Eprex®)# | **Epoetin beta** (NeoRecormon®)#

Darbepoetin alfa (Aranesp®)#

Methoxy polyethylene glycol-epoetin beta (Mircera®)#

Erythropoietin (EPO); is a ***glycoprotein hormone*** that ***controls*** **erythropoiesis** (*RBCs production*).

- **Peri-tubular cells** in the **kidneys** ***work as*** sensors that ***respond*** to **hypoxia** and ***mediate*** **synthesis** and **release** of **EPO**.

Recombinant **human erythropoietin**; **rhEPO** (**Epoetin alfa**, **Epoetin beta** and **Darbepoetin alfa**), *produced by* **recombinant DNA technology**.

- **Darbepoetin** is a ***modified form*** of **Erythropoietin** that is ***more heavily*** **glycosylated** with ***long-acting*** and ***delayed*** **onset of action** (half-life about three times that of epoetin alfa, it have no value in acute treatment of anemia).
- **Methoxy polyethylene glycol-epoetin beta**; is an ***isoform*** of **Erythropoietin** covalently attached to a long polyethylene glycol polymer with ***longer*** **half-life**.
- ***Administration*** (IV and SC).
  - **Epoetin alfa**; three times a week.
  - **Darbepoetin**; weekly.
  - **Methoxy polyethylene glycol-epoetin beta**; 2-week or monthly intervals.

Uses; **Anemia *associated with***; **end-stage renal disease** (not cleared by dialysis), **HIV**, **bone marrow disorders**, **prematurity** and **cancer**.

- ***Supplementation*** with **iron** may be *required to* ***ensure*** an **adequate response**.
- ***Dosages*** are ***adjusted*** to ***maintain*** a **target hemoglobin** up to, ***but not exceeding***, 10–12 g/dL (usually observed in about 10 days and an increase in hematocrit and hemoglobin levels in 2–6 weeks).
- ***Most common side effects***; **hypertension** and **thrombotic complications**.

FDA warning; in March 2007, the FDA issued a warning that **patients *with* chronic renal failure** or **cancer** whose ***serum*** **hemoglobin** is *raised to* ***more than*** **12 g/dL** ***with an*** **rhEPO** have ***greater*** **risk** of a **thrombotic event** or, in ***patients*** with ***advanced*** **head** and **neck cancers**, ***faster*** **tumor growth**.

Iron Supplements

- Iron is *stored mostly* in the liver as ferritin (iron-protein complex) *until needed by* the body, iron is *delivered* to the marrow for hemoglobin production by a *transport* protein, *namely* transferrin.
- Iron deficiency anemia (IDA) *results from* acute or chronic blood loss, from *insufficient* intake *during* periods of *accelerated growth* in children, and in *heavily* menstruating or pregnant women.
- Iron can be *supplemented by* the oral route or parenteral route;

Oral Iron Formulations

Ferrous Sulfate	Ferrous Gluconate	Ferrous Fumarate
Polysaccharide-iron Complex	Carbonyl Iron	

- A *wide variety* of oral iron preparations is *available*.
- Because Ferrous Iron is *most efficiently* absorbed, ferrous salts *should be used*.
- Ferrous Sulfate, Ferrous Gluconate and Ferrous Fumarate are *all effective* and *inexpensive* and are *recommended for* most patients.
- *Pharmacokinetics*:
  - Absorption; acidic conditions in the stomach *keep* iron in the reduced Ferrous form, which is the *more soluble* (if iron stores are adequate, less will be absorbed).
  - *About* 50-100 mg of iron can be *incorporated* into hemoglobin daily, *but* only *about* 25% of oral ferrous iron salt can be absorbed.
- Centers for disease control and prevention (CDC) *recommendations*;
  - *For* infants; 2-4 mg/kg/day of iron drops.
  - *For* school-age children and adolescent boys; 60 mg/day of iron.
  - *For* adults, adolescent girls and pregnancy; 60-120 mg/day of iron.
  - *For primary prevention* during pregnancy; 30 mg/day of iron.
- Repeat the anemia screening in *after* 4 weeks of iron supplements → *increase* in Hb concentration of *greater than* or *equal* to 1 g/dL → iron-deficiency anemia is *confirmed*, *continue* iron treatment for 2 more months, then *recheck* Hb concentration or Hct (*usually* 3–6 months).

Common side effects; (*dose-related*); GI disturbances *caused by local irritation* (nausea, abdominal cramps, constipation {if astringent} or diarrhea {*if irritant*}) and dark stools (Some patients have less severe GI side effects with one iron salt than another).

Drug Interactions;
- Iron *reduce* absorption of Levothyroxine.
- Iron *reduce amount of* Levodopa & Methyldopa *available to the body*.
- Proton pump inhibitors *reduce* iron absorption (*reduce the acidity*).

Lactoferrin (Pravotin®)#

- Lactoferrin (LF) is *one of* the transferrin proteins that *transfer* Iron to the cells and *control* the *level* of *free* Iron in the blood.
- Lactoferrin is *widely represented* in various *secretory fluids* (such as milk) and in neutrophils.
- It has antimicrobial activity (*decrease free iron for microbial growth*) and shows some antiviral activity. It has anti-inflammatory, antioxidant *activity and may inhibits* growth of some cancers.
- Lactoferrin can be *purified* from milk or *produced* recombinantly.

Administration of 30% Lactoferrin *saturated with* Iron (*called* Bovine Lactoferrin) (Pravotin®) can *used to* correct iron deficiency anemia with *less* GI side effects (70% of product *contain* free Lactoferrin can *correct excess* free Iron and *decrease* free Iron GI side effects) than *other traditional* Iron salts.

Parenteral Iron Formulations

Iron Dextran (CosmoFer®)#	**Iron Sucrose** (Venofer®)#
Sodium Ferric Gluconate Complex (Ferrlecit®)#	**Ferumoxytol** (Feraheme®)#
Iron Carboxymaltose (Ferinject®)#	**Iron Isomaltoside -1000** (Monofer®)#

- Parenteral iron *should be reserved for* patients with iron deficiency *who are*;
  - * *Unable to* tolerate oral iron.
  - * *Unable to* absorb oral iron.
  - * *Extensive* chronic anemia (such as chronic kidney disease).
- Parenteral administration *treats* IDA *rapidly*, *but produces* serious dose dependent toxicity.

Iron Dextran (low-and-high-molecular weight) can be given by **deep IM or IV infusion** (IV is most commonly due to local pain and tissue staining that occur with the IM), *due to* ***risk*** *of* a **hypersensitivity** reaction *with* **Iron Dextran**, **allergy test** ***should be*** **confirmed** ***before*** **administration**.

Sodium Ferric Gluconate Complex and **Iron Sucrose** are ***given only*** by the **IV route**. They appear to be ***less likely*** to cause **hypersensitivity reactions** (due to high-molecular-weight).

- ***Dose calculation***; Volume of product required (mL) = [weight (kg) x (14 - Actual Hb) x (2.145)]/C
  - Where C= concentration of elemental iron (mg/ml) in the product being used:
  - Iron dextran: 50 mg/mL. Iron sucrose: 20 mg/mL. Ferric gluconate: 12.5 mg/mL
- ***Chronic use*** of **parenteral iron**, it is important to ***monitor*** **iron storage** ***levels*** to ***avoid*** the **serious toxicity** ***associated with*** **iron overload**.
- ***Side effects*** of ***IV*** **Iron Dextran** ***therapy***; **headache**, **fever**, **arthralgias**, **nausea** and **vomiting**, **back pain**, **flushing**, **urticaria**, **bronchospasm**, and **rarely anaphylaxis** and **death**.

- ***Newer iron complexes***; can be *administered at* ***much*** **higher doses** ***than*** the **older complexes** with *very low levels* of **free iron** (low incidence to iron overload or toxicity) and *do not require* **test doses**.

Ferumoxytol;
- It was specifically *designed to* **reduce** **immunological reactivity** (***no allergy test***).
- It can be ***rapidly*** *administered* (IV rate of **30–60 seconds**) as a 510 mg dose with the **second IV injection** administered 2 to 8 days later.

Ferric Carboxymaltose;
- It is a ***newer formulation*** of **parenteral iron** which is ***consists of*** a **ferric hydroxide core** ***stabilized by*** a **carbohydrate shell**, allows for ***controlled delivery*** of **iron** to **target tissues**.
- **Dose**; **15 mg/kg IV** ***up to*** **1000 mg** may *repeat* **weakly**.
- ***Minimum*** **administration time**; </=15 minutes.
- ***Repeated weekly***; **not result** in ***accumulation*** in patients.
- ***No*** **allergy test**.

Iron Isomaltoside;
- It is a ***newer formulation*** of **parenteral iron** that has a **matrix structure** that *results in* ***very low levels*** of **free iron** and **labile iron**.
- **Dose**; ***higher doses***, **20 mg/kg** in a ***single visit*** (can cause iron correction in a single visit), ***may*** ***repeat*** **once** after **weak** (based on clinical judgement).
- ***Minimum*** **administration time**;
- **IV infusion**; ≤ 1000mg > 15 minutes - > 1000mg ≥ 30 minutes
- **IV injection**; 500 mg over 2 minutes.

Acute Iron Toxicity

- *Acute ingestion* of **10 tablets** of any commonly **oral iron preparations** can be *lethal* in **young children**;
  - **Necrotizing gastroenteritis**, with **vomiting**, **abdominal pain** and **bloody diarrhea** *followed by* **shock**, **lethargy** and **dyspnea**.
- *Urgent treatment* is **necessary**; **Whole bowel irrigation** and *administration* of **iron-chelating agent** such as **Deferoxamine** (***N.B.***; Activated charcoal does not bind iron and thus is ineffective).

Chronic Iron Toxicity (Iron Overload)

- It is also known as **hemochromatosis**; results when ***excess iron*** is ***deposited*** in the **heart**, **liver**, **pancreas** and **other organs**. It can lead to **organ failure** and **death**.
- It ***most commonly*** occurs in **thalassemia**.
- *Clinical manifestations*;
  - Liver disease (hepatomegaly, 13%, cirrhosis 13%).
  - Skin bronzing or hyperpigmentation (70%).
  - Amenorrhea, impotence, hypogonadism.
  - Arthropathy, osteopenia and osteoporosis.
  - Diabetes mellitus (48%).
  - Cardiomyopathy.
  - Hair loss.
  - Koilonychia (spoon nails).
- *Treatments*; the goal of therapy is to remove the iron before it can produce irreversible parenchymal damage;
  1) **Phlebotomy**; Once diagnosed blood is removed (phlebotomy), weekly phlebotomy; 7 mL/kg/phlebotomy (not to exceed 550 mL).
  2) **Chelation therapy**; In patients with hemochromatosis and heart disease, anemia, or poor venous access.
  3) **Surgical procedures**; In end-stage liver disease & severe arthropathy.

Iron Chelation Therapy

- *Chelation therapy*; is a **medical procedure** that involves the ***administration*** of ***chelating agents*** to ***remove*** **heavy metals** ***from the*** **body**.
- ***Most common forms*** of **heavy metal** intoxication; **iron**, **lead**, **arsenic**, **copper** or **mercury**.

Deferoxamine (Desferal®)#

- **Deferoxamine** is a ***parenteral iron chelator***.
- It acts by ***binding*** **free iron** in **bloodstream** and ***enhancing*** its ***elimination*** in the **urine**.
- ***Administration***; Parenteral (IV, IM or SC).
- ***Affinity***; *theoretically*, **100 parts** by weight of **Deferoxamine** is capable of ***binding approximately*** **8.5 parts** by weight of **ferric iron**.
- ***Contraindication***; **severe renal disease** or **anuria** (excreted primarily by kidney).

Deferiprone (Ferriprox®)#

- **Deferiprone** is an ***oral iron chelator***.
- ***Administration***; Oral (3 times a day).
- ***Affinity***; **3 molecules** of **Deferiprone** are ***capable of*** **binding** to **1 atom** of **Iron**.
- ***Warning***; **Deferiprone** ***may cause*** **fatal agranulocytosis**.

Deferasirox (Exjade®)#

- **Deferasirox** is an ***oral iron chelator***.
- ***Administration***; Oral (once daily).
- ***Affinity***; ***2 molecules*** of **Deferasirox** are ***capable of*** **binding** to **1 atom** of **Iron** which are subsequently ***eliminated by*** **faecal excretion**.
- ***Warning***; ***may cause*** **severe** and *sometimes* **fatal kidney problems** or **liver problems**.

Vitamin B_{12} Supplements

- **Vitamin B_{12}** ***serves as*** a **cofactor** for ***several essential*** **biochemical reactions**.
- **Intrinsic factor**, a protein *secreted by* the **stomach** that is *required for* **gastrointestinal uptake** of dietary **vitamin B_{12}**.
- ***Deficiency of*** **Vitamin B_{12}** ***leads to*** **megaloblastic anemia, gastrointestinal symptoms** and **neurologic abnormalities** (tingling "pins and needles" in the hands & feet).
- ***Initial therapy*** **100–1000 mcg** of **vitamin B_{12} IM every other day** for **1–2 weeks** to ***replenish*** **body stores**. ***Maintenance therapy***; of **100–1000 mcg** of **vitamin B_{12}** IM ***once*** a **month for life**.
- ***Various*** **organic groups** may be ***covalently*** **bound** to the **cobalt atom**, *forming different* **cobalamins**; *such as* **Cyanocobalamin**, **Hydroxocobalamin** and **Methylcobalamin**.

Cyanocobalamin (Betolvex®)#

- **Cyanocobalamin** is a **Vitamin B_{12} prodrug**.

It is ***available***; **oral tablets**, **sublingual**, **parenteral** (IM and SC, not given IV due to it results in more rapid excretion) and **nasal spray** (Naso-cyanocobalamin®).

It is the ***cheapest price of all*** and it is the ***most widely used*** *form of* **Vitamin B_{12}**.

Due to it is ***rapidly excreted*** into the **urine**, it is also available in the ***protein-bound formulation*** such as **Cyanocobalamin Zinc Tannate** (Betolvex®) to ***improve*** **Cyanocobalamin kinetics**.

Cyanocobalamin is ***converted to*** the **active form**, "**Methylcobalamin**" by **glutathione** and **other enzymes** and **co-factors**, ***much higher dose*** of **Cyanocobalamin** may cause **cyanide toxicity** (*due to depletion of glutathione*) ***especially*** in **renal failure patients**.

In cases of **cyanide poisoning** the **patient** is ***given*** **Hydroxocobalamin**, which is a ***precursor to*** **Cyanocobalamin**.

- A ***very serious allergic reaction*** to **Cyanocobalamin** is ***rare***.

Hydroxocobalamin (Depovit-B_{12}®)#

- **Hydroxocobalamin** is ***another*** **Vitamin B_{12} prodrug**.

It is ***available***; ***only*** **parenterally** (IM), IV ***only used*** *for* **cyanide poisoning**, *dose 5 g infusion in 15 min.*

It is ***preferred*** than **Cyanocobalamin** ***because*** it is ***rapid response*** and ***more highly*** **protein-bound** and therefore has ***longer half-life***.

Hydroxocobalamin has also been used in the ***treatment*** of **cyanide poisoning**. **Cyanide** ***displaces*** the **hydroxo** ligand forming a ***stable*** **Cyanocobalamin**.

Methylcobalamin or Mecobalamin (Methycobal®)#

Methylcobalamin is the ***active form*** of **Vitamin B_{12}**.

Methylcobalamin is ***produced from*** **Cyanocobalamin**.

It is ***available***; **oral tablets**, **sublingual**, **parenteral** (IM or IV) and **nasal spray**.

It has ***higher*** **bioavailability** (***better absorbed***).

It has a ***longer retention*** in **tissues** (*only one third of its dose is excreted*).

Methylcobalamin is the ***only form*** of **Vitamin B_{12}** that ***can cross*** the **blood-brain barrier** ***without*** **assistance** or **conversion**;
  - Its **methyl group** ***stimulates*** **Serotonin** ***production*** in **CNS** (**mood support**).
  - ***High doses*** of **Methylcobalamin** have also been used to ***effective*** in **multiple sclerosis**.

Folic Acid (Folate) Supplements

- Humans *cannot make* folates; *therefore*, Folic acid (Vitamin B_9) has to be *supplied* through the diet. The human body *needs* folate to *make* DNA, *repair* DNA and *methylate* DNA as well as to act as a cofactor in *certain* biological reactions.

Folate deficiency (*megaloblastic anemia*) may be *caused by*;

1) Increased demand (*pregnancy and lactation*).
2) Poor absorption (*disorder in small intestine*).
3) Alcoholism.
4) Drugs that are dihydrofolate reductase inhibitors (Methotrexate, Pyrimethamine and Trimethoprim).

- Folic acid is an *oxidized form*, it must be *converted to* active form Tetrahydrofolate (Tetrahydrofolic acid) in the *body* by dihydrofolate reductase (DHFR) *enzyme*.
- *Notes*;
  - # Folic acid intake *during* pregnancy has been *linked to* a *decrease* risk of neural tube defects (spina bifida) and some *other specific* kinds of birth defects.
  - # Folate is *necessary for* fertility in *both* men and women.
  - # Folic acid appears to *reduce* the risk of stroke due to *decrease* homocysteine concentration.
  - # Folic acid supplementation *may slightly increase* the risk of some cancers.

Folic Acid

- 1mg of folic acid *orally daily* is typically sufficient to *reverse* megaloblastic anemia (it may administrated parenterally; IM, SC and IV).
- *Usual adult dose for* folic acid deficiency; 400-800 mcg.

WARNING; Folic acid *should not* be given *alone* in *patients with* pernicious anemia *without* knowing whether they also have a Vitamin B_{12} deficiency.

N.B.;

- # *Patients with* iron overload usually *become* vitamin C deficient, *because* iron *oxidizes* vitamin C, vitamin C in doses > 200 mg for adults may be given in *divided doses*, starting *after* an initial month of *regular treatment* with *iron chelator*.
- # Iron Binding Dendrimers; is a *novel* iron(Fe^{3+})-selective chelator capable of *removing* dietary iron *from the* GIT and *preventing* the *development of* iron overload typical of haemochromatosis and thalassaemia.
- # Cobalamins has been *assigned to* pregnancy category C by the FDA, *do not* administer Cobalamins, *preserved* with Benzyl Alcohol to pregnant women (Benzyl Alcohol has been *associated with* serious adverse events and death).
- # *Large amounts* of Folic acid (>1,000 µg/daily) can *mask* the damaging effects of vitamin B_{12} *deficiency* by *correcting* the megaloblastic anemia *caused by* vitamin B_{12} *deficiency without* correcting the neurological damage that *also occurs*.

Drugs for Sickle Cell Disease

Hydroxyurea (Hydrea®)#

It is an *antineoplastic drug* *used in* **polycythemia vera** & **essential thrombocythemia**
It is also *used to reduce the rate* of **painful attacks** in **sickle-cell disease**.
It is also *used in* **AIDS** (*due to antiretroviral properties*).
- ***In sickle cell disease***; **Hydroxyurea** *increases* **fetal hemoglobin levels**, thus *diluting* the **abnormal hemoglobin S (HbS)** (*this process takes several months*).
- ***Common serious side effects***; **bone marrow suppression** and **cutaneous vasculitis**.

Pentoxifylline (Trental®)#

Pentoxifylline is a *methyl-xanthine derivative* that *inhibits* **phosphodiesterase enzyme** and *affects* **blood rheology**. It has been called a "*rheologic modifier*"
It *improves* **blood flow** by *increasing* **erythrocyte** and **leukocyte** *flexibility*. It also *inhibits* **platelet aggregation**.
It is *used* in the treatment of **peripheral vascular diseases** and in the **management of cerebrovascular insufficiency**.
It is *used* in patients with **intermittent claudication**.
It is *also effective* in **venous ulcer** with compression therapy.
- ***Dose***; 400 mg orally 3 times a day.

B) Myeloid Growth Factors

Granulocyte Colony–Stimulating Factors (G-CSF)

- **Granulocyte Colony–Stimulating Factors** (**G-CSF**); is a *glycoprotein* that *stimulates* the **bone marrow** to *produce* **granulocytes** and **stem cells** and *release them into* the **bloodstream**.

Filgrastim (Neupogen®) (Zarxio®) | Tbo-filgrastim (Granix®)

Peg-filgrastim (Neulasta®)

- **Filgrastim** is a *granulocyte colony-stimulating factor* (*G-CSF*) *analog*.
- It is *produced by* ***recombinant*** **DNA technology**, **G-CSF** *regulates* the **production** of **neutrophils** *within the* **bone marrow**.
- **Tbo-filgrastim** have ***slight*** **structural differences** than **Filgrastim**, the pharmacokinetic, safety and efficacy ***don't significantly differ***.
- **Peg-filgrastim** (*linked to* polyethylene glycol) has a human ***half-life*** of **15-80 hours**, ***much longer than*** **Filgrastim** (**3-4 hours**).
- ***Indications***;
  - **Neutropenia** *associated with* **congenital neutropenia**, **cyclic neutropenia**, **myelodysplasia** and **aplastic anemia**.
  - ***Secondary prevention of*** **neutropenia** ***in patients undergoing*** **chemotherapy**.
  - **Mobilization of peripheral blood cells in** ***preparation for*** **stem cell transplantation**.
- ***Administration***; **Filgrastim**; IV or SC. **Tbo-filgrastim** and **Peg-filgrastim**; SC only.
- ***Serious side effects***; **serious allergic reactions**, **bone pain** & ***rarely*** **splenic rupture**.

Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF)

Sargramostim (Leukine®)

- **Sargramostim** is a *recombinant granulocyte macrophage colony-stimulating factor*.
- ***Indications***; ***similar to*** those of **G-CSF**, ***administration***; IV or SC.
- ***Most common side effects***; **Fever**, **arthralgia** and **myalgia**.

C) Megakaryocyte Growth Factors

- **Megakaryocyte Growth** *and* **Development Factor** (**MGDF**), also *known as* ***Thrombopoietin*** (***THPO***); is a **glycoprotein hormone** *produced by* the **liver** and **kidney** which ***regulates*** the ***production*** of **platelets** by *stimulating* **megakaryocytes**.

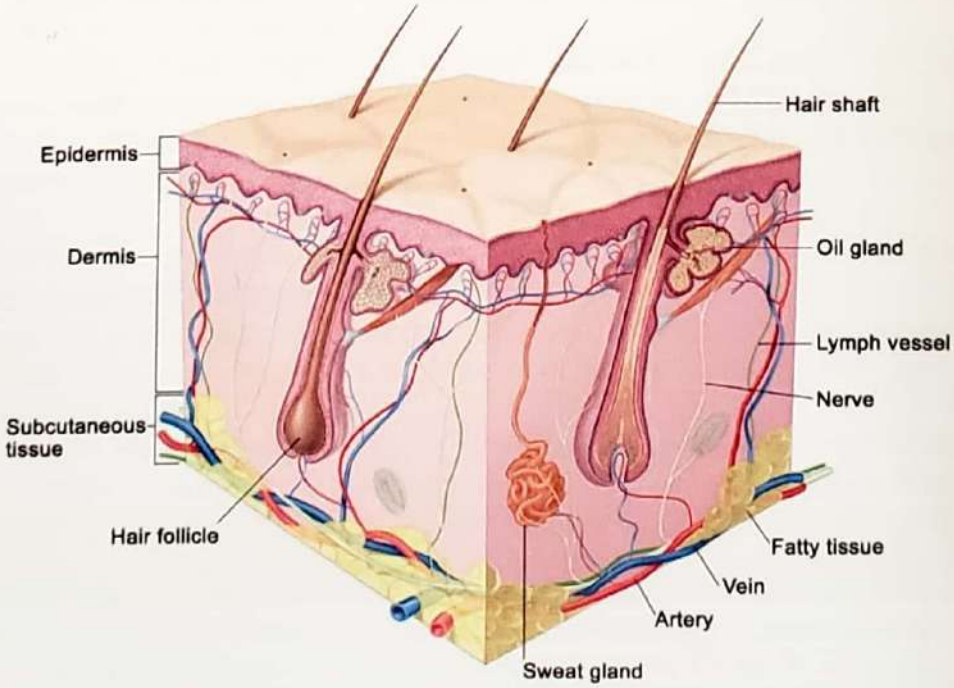
Oprelvekin (Neumega®)

- **Oprelvekin** is ***recombinant*** **interleukin eleven** (**IL-11**), is a **thrombopoietic growth factor** that ***increase*** **platelet production**.
- **IL-11** is a member of a family of **human growth factors** and is being ***produced*** in the **bone marrow**.
- ***Indications***; ***Prevention*** of **severe thrombocytopenia** & ***secondary prevention*** of **thrombocytopenia** ***in patients undergoing*** **chemotherapy**. ***Administration***; SC.
- ***Most common side effects***; **Fatigue**, **headache**, **dizziness**, **anemia**, **lung edema** and **arrhythmias**.

Romiplostim (Nplate®) | Eltrombopag (Promacta®)

- **Romiplostim** is an ***analog*** of **thrombopoietin**, ***approved for*** treatment **chronic idiopathic** (*immune*) **thrombocytopenic purpura** (**ITP**), ***administered*** **weekly** intervals via **SC injection**.
- **Eltrombopag** is an ***orally active small-molecule thrombopoietin-receptor agonist***, ***approved for*** treatment **chronic idiopathic** (*immune*) **thrombocytopenic purpura** (**ITP**).

Dermatology



Acne

- Composition of the skin layers;

Epidermis

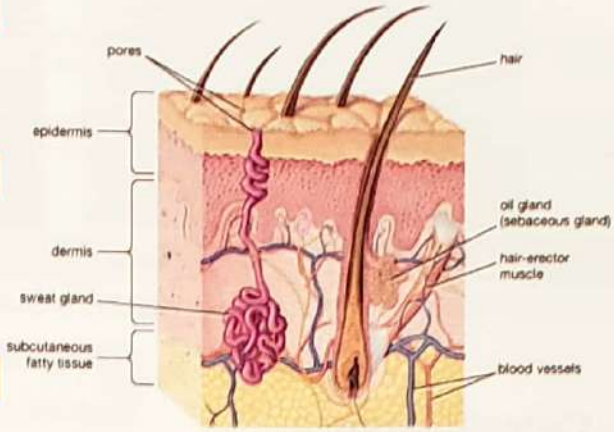
- *Produce* keratin (protect *against* harmful substances and control water released from the body).
- Also *produce* melanin which gives the skin color.

Dermis

- Contain **sebaceous** and **sweat *glands***.
- The dermis is also composed of matrix components such as **collagen** (which provides strength) and **elastin** (which provides elasticity).

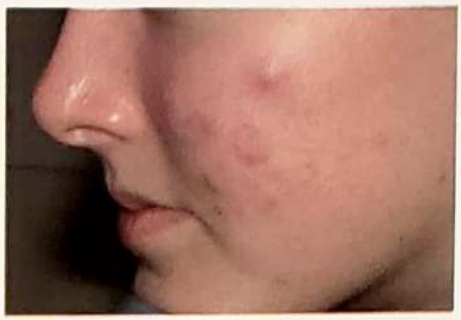
Subcutaneous Tissues

- Made up of **fat** (fat storage).

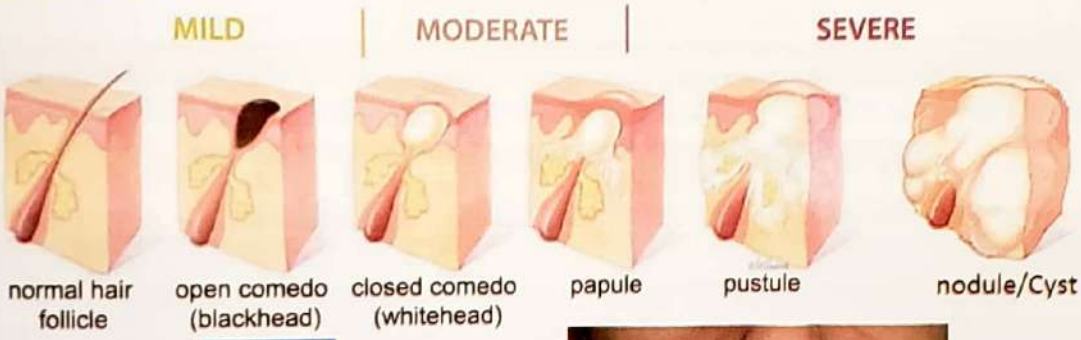


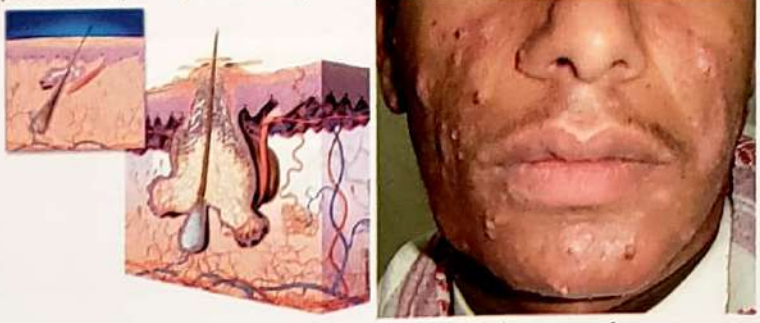
- Definition:-

- Is a ***common*** human **skin disease**; common in **adolescence**.
- ***Characterized by*** areas of skin with;
  Comedo (blackheads and whiteheads),
  Papules (pinheads),
  Pustule (papule filled with pus),
  Nodules (large papules),
  and possibly scarring, mainly on the **face**, **chest**, **shoulders** and **back** due to *disorder of* ***pilosebaceouse units***.



- Acne forms:-



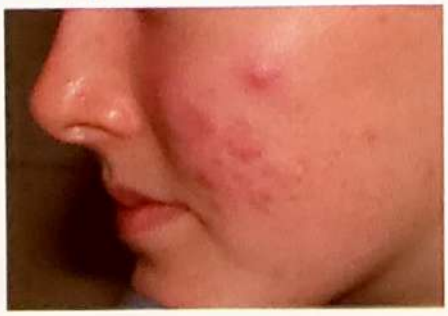


Cystic acne; when nodules filled with pus and it is most dangerous type of acne.

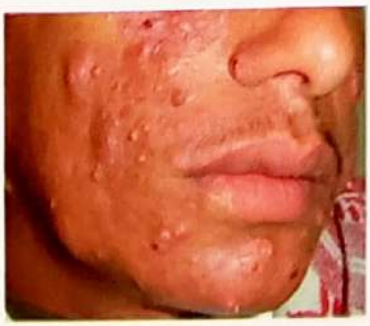
- Etiology and pathophysiology of acne;

- **Increase sebum secretion**; regulated by androgens in both male and female.
- **Abnormal clumping of epithelial horny cells within pilosebaceouse unit**.
- ***Propionibacterium acnes (P. acnes)***; convert sebum into free fatty acids, which irritates the follicle linings.
- ***Deficiency in* Linoleic acid**; Essential fatty acid, if not found sebaceous glands produce sebum with oleic acid (drier and firmer sebum) → irritation of the skin.

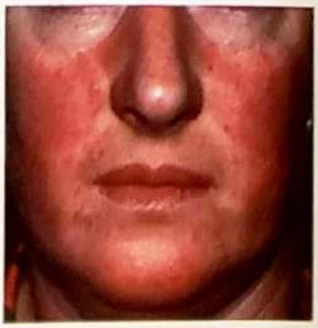
- Main types of acne;



Acne Vulgaris
Infections on the surface of the skin

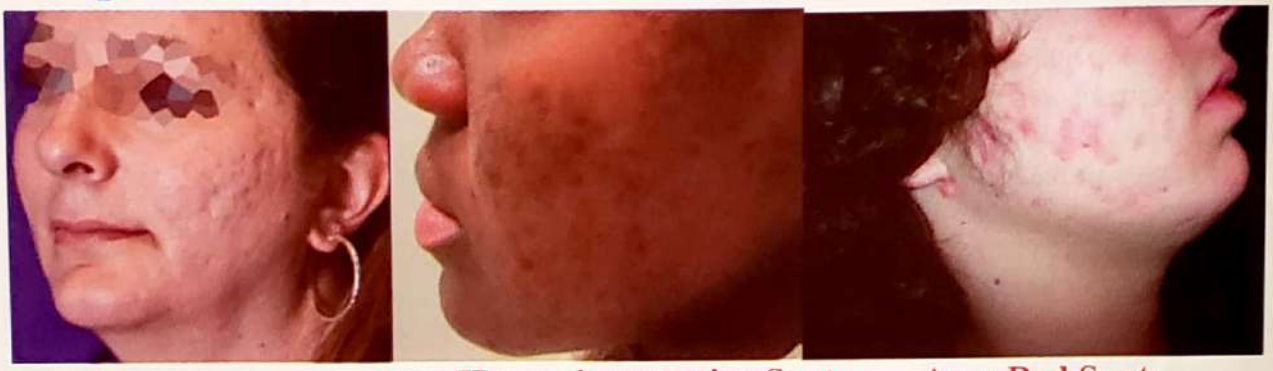


Cystic Acne
Deep infections that are nodule or cyst-like



Acne Rosacea
redness of the skin caused by histamine or other inflammatory mediators

- Complications;



Acne scars **Acne Hyperpigmentation Spots** **Acne Red Spots**

- Risk factors;

Stress	Acids	Menses
Coffee	Milk	Hormones changes
Diet	Zinc deficiency	Oral Contraceptives
Wheat	Antibiotic	Cosmetics
Deficiency of Essential Fatty	Heredity	Environmental factor & Physical trauma
Sun Exposure		

Pharmacological Treatment

A) Topical

Benzoyl peroxide (PanOxyl®)# - (Akneroxid®)#

- *Side effects*: Premature skin aging, slow healing and *increased* skin cancer risks.

Salicylic acid (0.5-3%)

- As **exfoliating agent**.

Sulfur (3-8%)

- **Keratolytic** and has an ***anti-bacterial effect***, with a bad odour.

Resorcinol (2-3%)

- **Keratolytic** and ***very effective*** when *combined with* **sulfur**.

Tretinoin (Retinoids) (Acne-Free®)# - (Acnetin®)#

- *Side effects*: ***excess irritation*** (cream less irritant than gel than lotion), **erythema**, ***increase*** risk of **sun burn** and **teratogenic**.

Adapalene [Retinoid-like compound] (AcneScave®)#

- *More effective* and *less irritant* (8-12 week).

Tazarotene (Retinoid-pro drug) (Acnitaz®)#

- Also *used for* **psoriasis**.

Topical Antibiotics (Erythromycin & Clindamycin) (Acni-Care®)# - (Acne-mycin®)

It *inhibits* ***P. acnes*** ⇨ ↓ **inflammatory response**.

Azelaic acid (Azaderm®)#

- The *least irritant* than benzoyl peroxide and retinoic acid.
- *Antibacterial*, ↓ *Keratinization* and ↓ *Pigmentation*.

Terrasil®

- It's a topical treatment for all types of acne (mild, severe, cystic and rosacea).

B) Systemic

Oral Antibiotics (Doxycycline) (Vibramycin®)# (Tabocine®)#

- *Initial dose*; **200 mg** (*2 capsules*) *orally* on the **first day**.
- *Maintenance dose*; **100 mg** *orally* **once** for **1 month**, Or **twice** in **severe cases** for **1 month**.

Isotretinoin (Roaccutane®)# (Netlook®)# (Isotretinoin®)#

Retinoid; ***inhibits*** **sebaceous gland** ***function*** and **keratinization**.
Used in ***sever nodyolocystic acne***; *dose* of 0.5-1 mg/Kg/day in 2 divided doses for 15-20 weeks.
Side effects: Cheilitis (90%), Conjunctivitis (40%), Irritation (40), Hypertriglyceridemia (25%), Bone or joint pain.
FDA Warning; **category: X**; Teratogenic; *Must not* be *used by* **women** and **adolescents** who are **pregnant** or who ***may become*** **pregnant**; EXTREMELY HIGH ***risk*** that SEVERE **birth defects**; *At least* **2 effective contraception** ***required*** *during* **therapy** and for *At least* **1 month** *after* the **last dose**.

Anti-androgens and hormones

- Estrogen (↓ **sebum** ***production***), Spironolactone & Corticosteroids (in ***sever inflammatory***)

C) Additional Treatments

Zinc

- Zinc Inhibits, 5-α reductase, Interleukin-6 and Tumor necrosis factor-α (TNF-α).

Glycolic acid

- Used as exfoliating agent (accelerate the exfoliation process of the skin).

Calcium

- Disruption of the skin's calcium gradient occurs in the infection sites of acne as well as in the crusting that follows a rosacea flare-up.

Essential Fatty Acids

- Linoleic acid is the most important one.

Soap

- **How do you know which soap is right for you?** To do so, look at face in a mirror in natural daylight (i.e., outside or near a window) and observe the various areas of face ⇨

1) **Oily skin**; ***salicylic acid soap***.
2) **Dry skin**; ***Pure Glycerin soap***.
3) **Normal skin**; ***plant-based soaps***.
4) **Combination skin**; ***oily and dry patch***.
5) **Sensitive skin**; ***hypoallergenic soaps***.

Others

- Vitamin A
- Vitamin E
- Selenium
- Magnesium

Skin Aging

- Skin aging is influenced by many factors including ultraviolet radiation, excess alcohol consumption, tobacco abuse and environmental pollution.
- Within the skin, aging is associated with a loss of fibrous tissue, slower rate of cellular re-newal, and a reduced vascular and glandular network.
- The subcutaneous tissue flattens, particularly in the face, hands and feet.
- Premature skin aging is the result of several factors such as intense physical and psychological stress, alcohol intake, poor nutrition, overeating, environmental pollution, and UV exposure.

- Combating Skin Aging:-

- ***Dietary Strategies*** to ***Promote Youthful Skin Appearance***;
  1) **Glycemic control**; High glycemic diet may contribute to inflammatory skin conditions such as acne, rosacea, psoriasis and eczema.
  2) **Fatty acids intake**; Fish oil rich in the omega-3 oils EPA and DHA inhibit the production of inflammatory metabolites.
  3) **Antioxidants**; Catechins from green tea, anthocyanins from dark berries and red cabbage, bioflavonoids from citrus, carotenoids such as lycopene and lutein from tomatoes, reservratrol from red wine and genistein from soy offer potent secondary antioxidant protection in the skin.
- ***Topical management:***
  1) **Sunscreen** (with ***dual protection*** against **UVA** and **UVB**)
  2) **Light daily moisturizer**; should include a combination of moisturizing agents, antioxidants, and bioactive peptides.
  3) **Intensive nighttime moisturizer**; containing hydrating moisturizers as well as the natural hormones dehydroepiandrosterone (DHEA) and melatonin will support structural regeneration within facial skin while sleep.
- ***Supplemental Nutrients*** to ***Support Skin Health:***

Curcumin	400 – 800 mg daily
Trans-Resveratrol	250 – 500 mg daily
Coenzyme Q10 (CoQ10)	100 – 200 mg daily
Selenium	200 – 400 mcg daily
Vitamin E	350 mg daily
Vitamin A	5000 IU daily
Fish oil	1400 mg EPA and 1000 mg DHA daily
Lycopene	15 mg daily
Vitamin D	5000 – 8000 IU daily
Green tea, standardized extract	725 – 1450 mg daily
Grape extract	150 mg daily
Blend of dark berry extracts	700 – 1400 mg daily
Fern extract	240 – 480 mg daily
Soy isoflavone blend	135 – 270 mg daily

Wrinkles

- Wrinkles are a natural part of aging, but they're most prominent on sun-exposed skin, such as the face, neck, hands and forearms.
- Although genetics are the most important determinant of skin structure and texture, sun exposure is the major contributor to wrinkles.
- **Causes**; Age, exposure to ultraviolet (UV) light, smoking, repeated facial expressions, gender (Women tend to develop more wrinkles around their mouths than men) and poor nutrition.
- **Sleep wrinkles**; are created and reinforced when the face is compressed against a pillow or bed surface in side or stomach sleeping positions during sleep.
- **Water-immersion wrinkling**; This is a temporary skin condition where the skin on the palms of the hand or feet becomes wrinkly.

- Medical treatments:-

- ***Topical treatment***; **Retinol, Vitamin C, Hydroxy acids, Coenzyme Q10, Copper peptides, Kinetin** and **Tea extracts**.

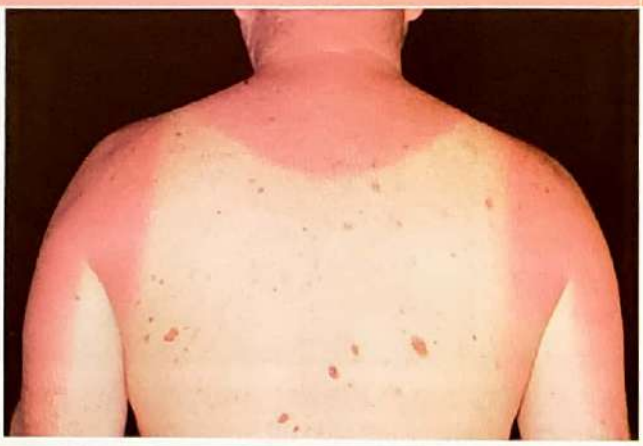
Striadril® - StriVectin® Wrinkle Cream

- **StriVectin®** includes a proprietary complex of skin firming agents, plasticizers, and skin hydrators which reduce stretch mark reduction.

- ***Cosmetic procedures*** and ***other techniques***;
  - **Botulinum Toxin Type A (Botox®)**; Wrinkle muscles relaxant, repeat injections are needed.
  - **Dermabrasion (Skin Peeling)**; Sanding down with a rapidly rotating brush
  - **Microdermabrasion**; vacuum suction over face, while aluminum oxide crystals essentially sandblast skin.
  - **Laser, light source** and **radiofrequency treatments**; destroys the outer layer of skin.
  - **Soft tissue fillers**: (**Restylane®**, **Juvederm®**); fat, collagen and hyaluronic acid are injected into deeper in wrinkles on the face.
  - **Face-lift Surgery**; removing excess skin and fat in the lower face and neck.

Sun Damage

Sunburn



- Sunburn is an acute, delayed, and transient inflammatory response of normal skin after exposure to UVR from sunlight or artificial sources.
- Sunburn is characterized by erythema and, if severe, by vesicles and bullae, edema, tenderness, and pain.

Suntan

- Sun tanning or simply tanning is the process whereby skin color is darkened or tanned.
- The process is most often a result of exposure to ultraviolet (UV) radiation from the sun or from artificial sources, such as a tanning bed.
- Artificial suntan made by using dihydroxyacetone (DHA) which react naturally with the proteins in skin to create tan that makes so many people feel and look better.

- Melanin is produced by cells called melanocytes in a process called melanogenesis.
- Melanocytes produce two types of melanin: pheomelanin (red) and eumelanin (very dark brown).
- Melanin protects the body by absorbing solar radiation.
- Excessive solar radiation causes direct and indirect DNA damage to the skin and the body naturally combats and seeks to repair the damage and protect the skin by creating and releasing further melanin into the skin's cells. With the production of the melanin, the skin color darkens.

- Sunscreen Agents;

- **Sun protection factor** (**SPF**) of a sunscreen is a laboratory measure of the effectiveness of sunscreen the higher the SPF, the more protection a sunscreen offers against UV-B (the ultraviolet radiation that causes sunburn).

$$\text{SPF} = \frac{\text{The amount of light that induces redness in sunscreen-protected skin}}{\text{The amount of light that induces redness in unprotected skin}}$$

- **SPF scale**; is not linear:
  - **SPF 15** ⇨ blocks 93% of UVB rays.
  - **SPF 30** ⇨ blocks 97% of UVB rays.
  - **SPF 50** ⇨ blocks 98% of UVB rays.
- So, one way of looking at this is that SPF 30 sunscreen ***only gives you 4% more protection*** than SPF 15 sunscreen.
- Sunscreens with really high SPFs, such as SPF 75 or SPF 100, do not offer significantly greater protection than SPF 30 and mislead people into thinking they have more protection than they actually do.
- **Sunscreen agents**; Sunscreen Applied 20-30 minutes before going outdoors and every two hours.
- **Sunblock agents**; Sunblock agents typically refers to opaque sunscreen that is effective at blocking both UVA and UVB rays and uses a heavy carrier oil to resist being washed off.
- **Substantivity**; Ability of the sunscreen to adhere to the skin while swimming or perspiring.
- **Water resistance**; Formula retain SPF after 40 min of activity in water, sweating and perspiring.
- **Very water resistance**; Formula retain SPF after 80 min of activity in water, sweating and perspiring.

Cold Sores (Fever Blisters)

- Also called fever blisters, are tiny, fluid-filled lesions that occur on and around the lips caused by certain strains of the ***Herpes simplex virus*** (**HSV**) **infection**; HSV-1.
- These blisters are often grouped together in patches.
- Cold sores usually heal within two weeks.
- Cold sores spread from person to person by close personal contact, such as kissing.

- ***Treatments***;

Acyclovir (Zovirax®)#

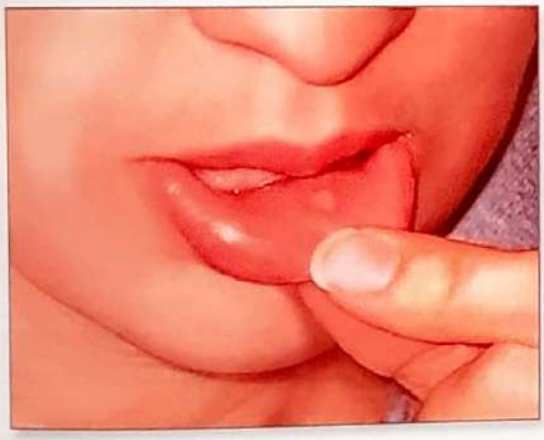
- One of the ***most commonly*** **used** **antiviral drugs**, it is primarily used for the ***treatment of herpes simplex virus*** infections, as well as in the treatment of **varicella zoster** (**chickenpox**) and **herpes zoster** (**shingles**)
- ***Dose***; ☞ **topically 4-6 times daily**; *reducing* the **duration** of **cold sores**

Docosanol (Abreva®)#

- **Docosanol**, also known as **behenyl alcohol**, it is ***saturated*** **fatty alcohol** used traditionally as an **emollient**, **emulsifier**, and **thickener** in *cosmetics*, **nutritional supplement**.
- **Abreva®**; *approved for* ***reducing*** the **duration** of **cold sores**.
- **Abreva®** ***shortens*** the **healing time** and the **length** ***of*** **time symptoms** *are* **present**.

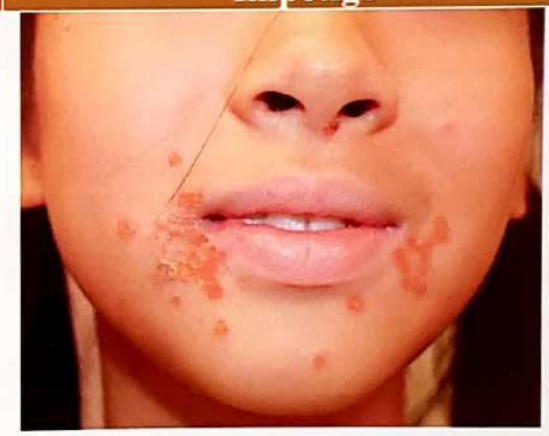
- ***Differential Diagnosis***;

Canker Sore (Aphthous Ulcers)



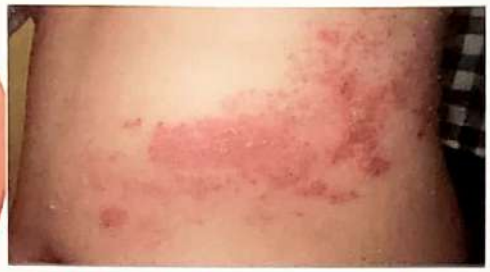
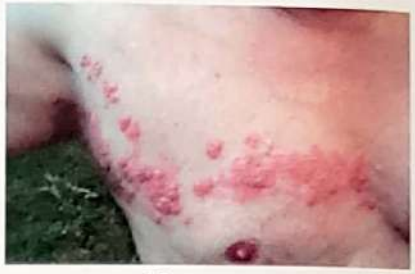
- Canker sores or aphthous ulcers, are small, shallow lesions that develop on the soft tissues in the mouth or at the base of the gums.
- Don't occur on the surface of the lips and aren't contagious.
- They can be painful, however, and can make eating and talking difficult.
- Most canker sores go away on their own in a week or two.
- Can used local anetheitc oral gel to decrease pain sensation; avoid benzocaine in childerin.

Impetigo

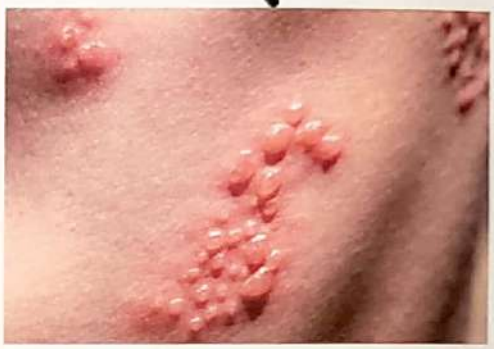


- Impetigo is a highly contagious skin bacterial infection that mainly affects infants and children.
- Impetigo usually appears as red sores on the face, especially around a child's nose and mouth.
- The sores burst and develop honey-colored crusts.
- Impetigo may clear on its own in two to three weeks, but antibiotics can shorten the course of the disease and help prevent the spread to others.

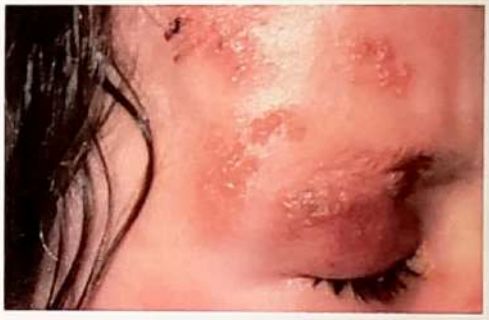
Shingles (Herpes zoster)

- Shingles is caused by the *varicella-zoster virus*, the same virus that causes chickenpox.
- Once chickenpox has resolved, the virus may remain inactive in nerve cells, years later, the virus may reactivate as shingles
- Shingles characterized by a painful skin rash with blisters in a limited area on one side of the body (left or right), often in a stripe.
- *Signs and Symptoms*;
  - **Pain**, **burning**, **numbness** or **tingling**.
  - **Red rash** that begins a ***few days*** *after* the **pain**.
  - **Fluid-filled blisters** that ***break open*** and **crust over**.
  - **Itching**.



- *Complications*;
  - Post-Herpetic neuralgia (PHN): occurs when damaged nerve fibers.
  - Vision loss: Shingles in or around the eye (**Ophthalmic shingles**) can cause painful eye infections that may result in vision loss.
  - Neurological problems: depending on which nerves are affected, shingles can cause an inflammation of the brain (encephalitis), facial paralysis, or hearing or balance problems.



- *Treatments*;

Antiviral Drugs

Acyclovir (Zovirax®)#

- *Dose*; **800 mg** ***orally*** **1*5** ***for*** **7-10 days**.

Famciclovir (Famvir®)#

- *Dose*; **500 mg** ***orally*** **1*3** ***for*** **7days**.

Valacyclovir (Valtrex®)#

- *Dose*; **1 g** ***orally*** **1*3** ***for*** **7days**.

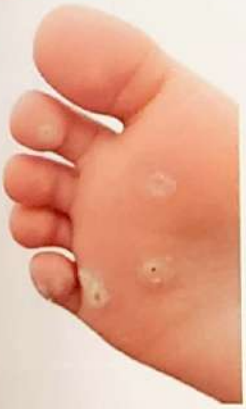
Analgesics

- NSAIDs; **Ibuprofen** and **Naproxen** for ***mild*** to ***moderate*** **pain**.
- Opioids; **Morphine** for ***severe*** **pain**.
- Local anesthetics; (Lidoderm®); **Lidocaine** patch as ***numbing agents***.
- TCAs, SSRIs and **Gabapentin** (Neurontin®), **Pregabalin** (Lyrica®) or **Duloxetine** (Cymbalta®) for ***post-herpetic neuralgia***.

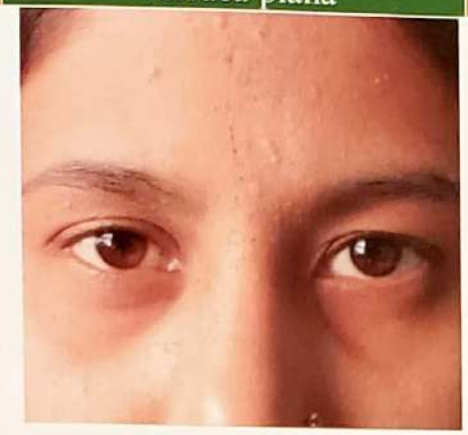
Warts (Verrucae)

- **Warts** are ***non-cancerous*** **skin growths** *caused by* a **virus** called ***Human papillomavirus*** (***HPV***).
- This virus causes a ***rapid*** **growth** of **cells** on the **outer layer** of the skin.
- It ***typically occurs*** on humans' **hands** or **feet** but often in ***other*** **locations**.

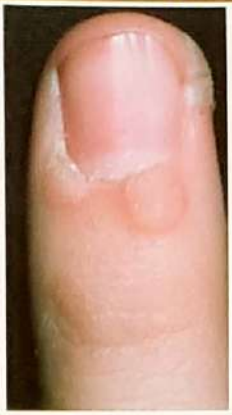
Plantar Wart
Verruca plantaris

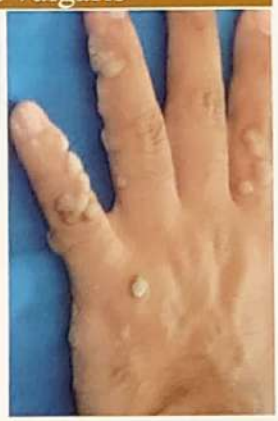


Plana or Flat Wart
Verruca plana

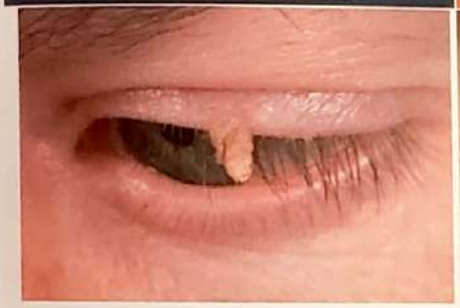


Common Wart
Verruca vulgaris

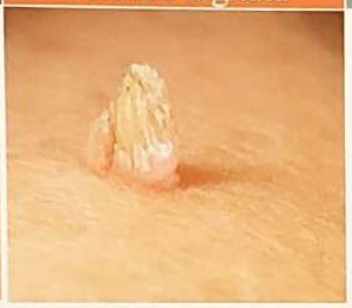




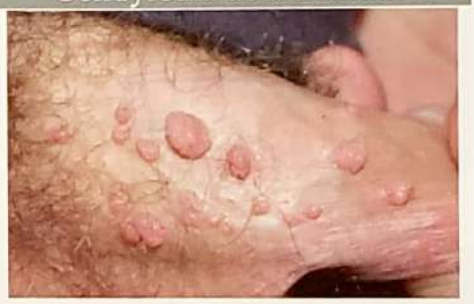
Filiform Wart
Verruca filiformis



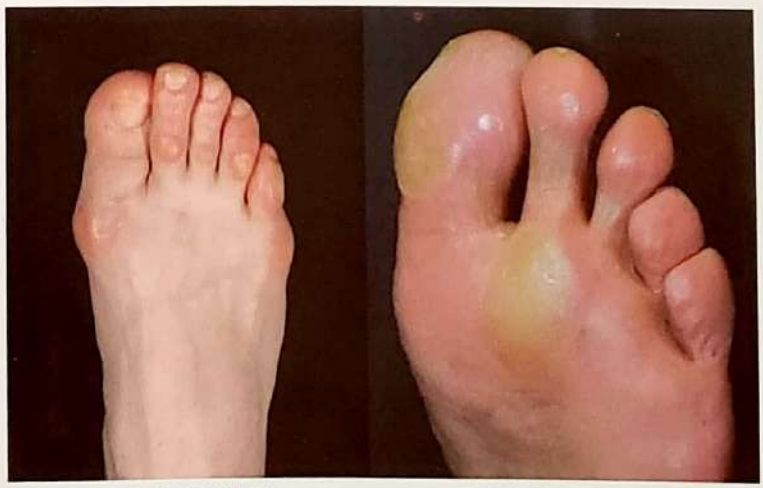
Digitate Wart
Verruca digitata



Genital Wart
Condyloma acuminatum



- ***Treatments***;
  - ***Medications***; **Salicylic acid** (keratolytic), **Cantharidin**, **Imiquimod** (**Aldara®**) [immune response modifier] and **Bleomycin** (**Blenoxane®**)
    - **Collomack® Salicylic acid** 20%, **Lactic acid** 5% and **Polidocanol** 2%
  - ***Procedures***; **Minor surgery**, **Laser surgery**, **Freezing** (cryotherapy or liquid nitrogen).
- ***Differential Diagnosis***;
  - **Calluses** & **corns** (***hyperkeratosis***); are areas of **thick**, **hardened**, **dead skin**.
  - ***Not*** **infection**.
  - They ***form*** to ***protect*** the **skin** and **structures** *under the* **skin** *from* **pressure**, **friction** and **injury**.
  - Treatment; ***keratolytic***; **Collomack®**

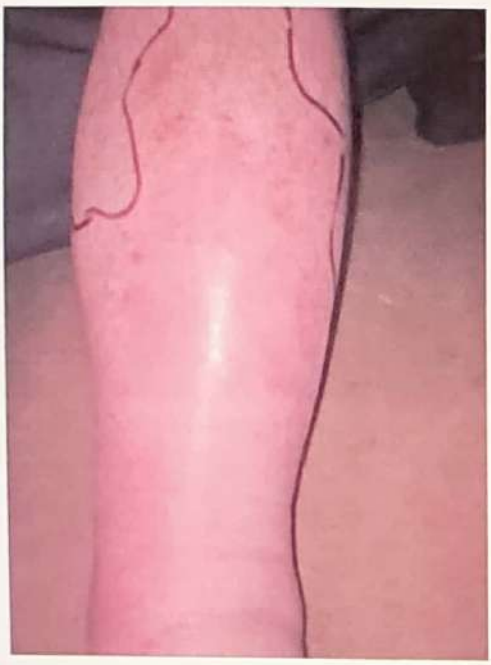


CORNS **CALLUSES**

Cellulitis & Erysipelas

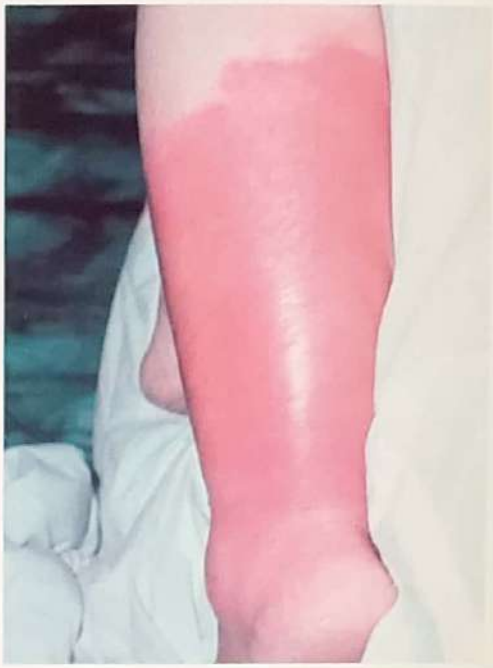
- They are **acute**, **painful** and ***potentially serious*** **infection** of the **skin** and **subcutaneous tissues**.
- The ***most common*** **causative organisms** are *Streptococcus* or *Staphylococcus spp.*
- *Treatments*; ***oral*** or ***pareteral*** **antibiotics**; **Penicillin**, **Clindamycin** or **Erythromycin**.

Cellulitis



- Symptoms; redness, swelling, tenderness, pain, warmth and fever.
- Infection of the deep layer of skin (dermis) and the layer of fat and tissues just under the skin (the subcutaneous tissues).
- More commonly seen in the lower limbs and usually affects one limb.

Erysipelas



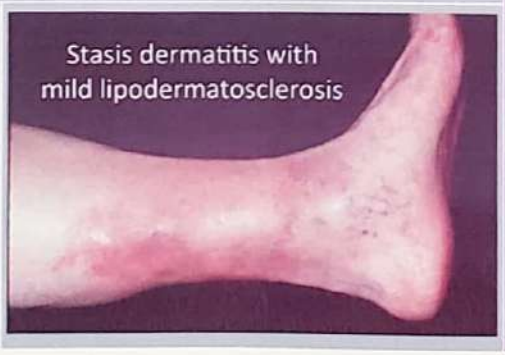
- Symptoms; local oedema, tenderness and warmth, Malaise, chills, and high fever (flu-like symptoms).
- Infection of the skin which is nearer to the skin surface (more superficial) than cellulitis.
- More well-defined edge.
- The face or a leg are commonly affected.
- The arm or upper thigh are the next most common areas to be affected.

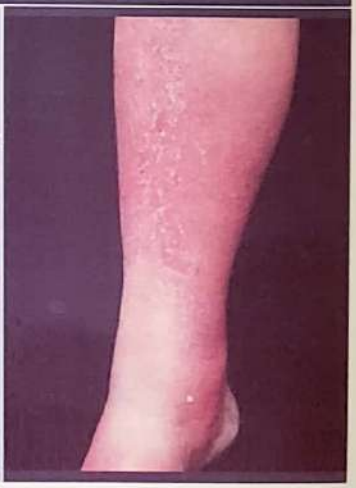
- *Differential Diagnosis*;

Stasis Dermatitis (Varicose Eczema)

- One of the most common signs of Varicose Veins and mostly misdiagnosed by clinics.
- Treatments;

1) Topical corticosteroids & topical (or oral) antihistamines.
2) Emollients.
3) Elevating the legs & compression therapy.
4) Venoactive drugs.
5) Procedure therapy (permanent relief).

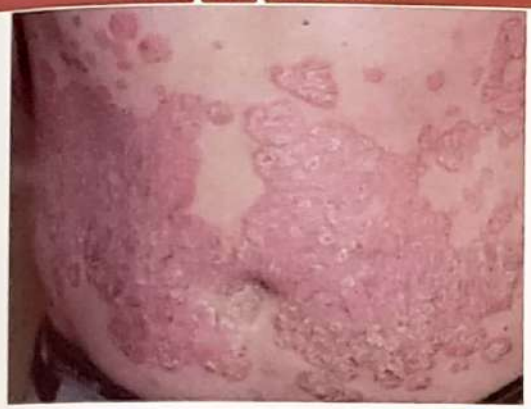




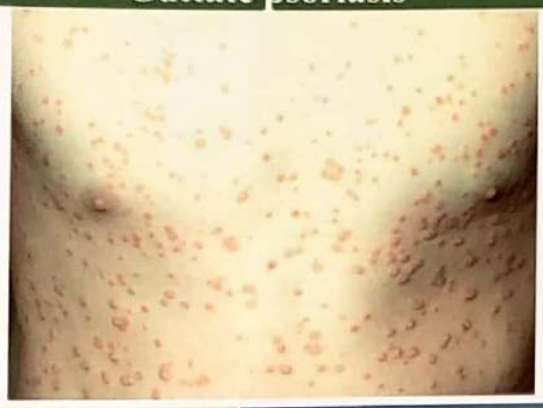
Psoriasis

- Psoriasis is an *immune-mediated* disease that affects the life cycle of skin cells.
- Psoriasis is a *chronic inflammatory skin disease*.
- Psoriasis causes cells to *build up rapidly* on the surface *of the* skin, *forming thick silvery* scales and itchy, dry, red patches that are *sometimes* painful.

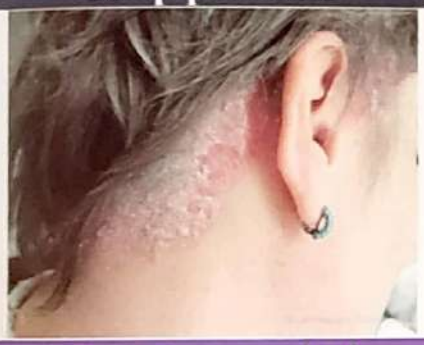
Plaque psoriasis



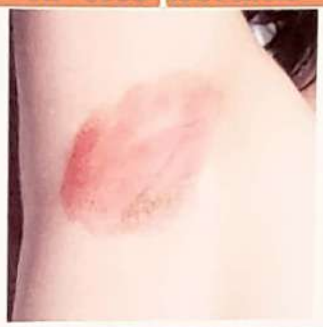
Guttate psoriasis



Scalp psoriasis

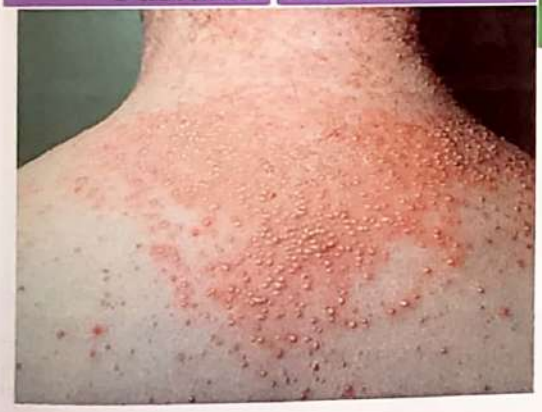


Inverse psoriasis

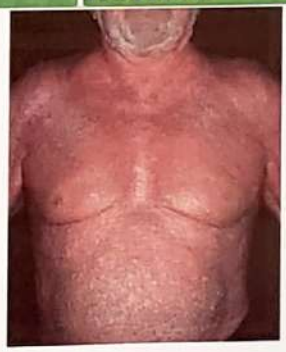


Nail psoriasis

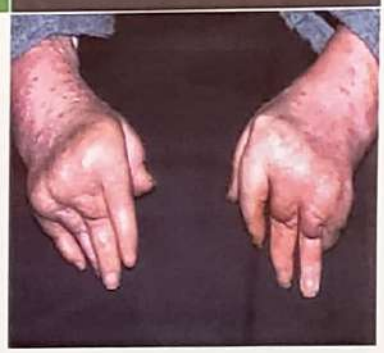
Pustular psoriasis



Erythrodermic psoriasis



Psoriatic arthritis



- *Treatments*;

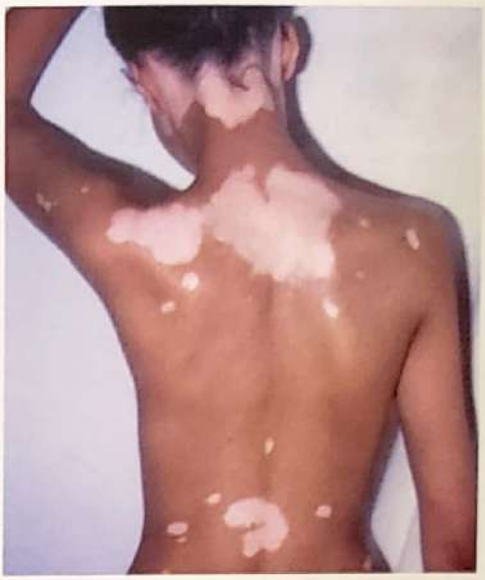
A) Topical Treatments;

1) Topical Corticosteroids.
2) Vitamin D Analogues; Calcipotriene (Dovonex®) and Calcitriol (Rocaltrol®).
3) Anthralin or Dithranol; Anthralin (Psoriatec®) - (Dritho-Scalp®)
4) Topical Retinoids; Tazarotene (Zarotex®)
5) Calcineurin Inhibitors; Tacrolimus (Prograf®) and Pimecrolimus (Elidel®)
6) Salicylic Acid 7) Coal Tar (Polytar®) 8) Moisturizers

B) Light therapy (phototherapy).

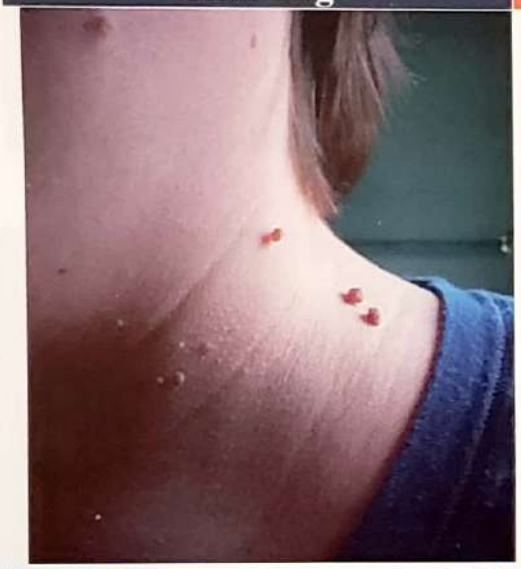
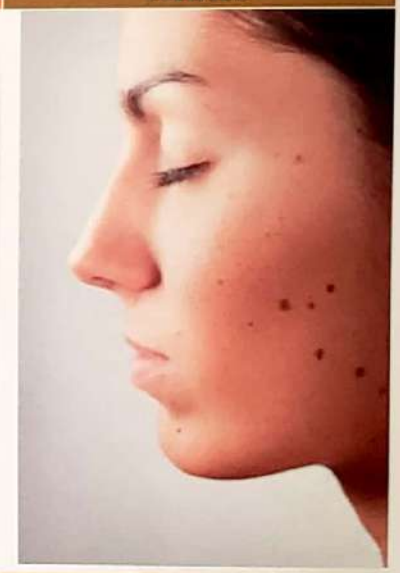
C) Systemic Treatments; 1) Retinoids; Acitretin (Soriatane®)
2) *Immunosuppressive*; Methotrexate, Cyclosporine (Sandimmune®) & Hydroxyurea (Hydrea®)
3) *Immunomodulator Drugs*; such as Infliximab (Remicade®).

Vitiligo



- Vitiligo is a *condition* in which the **skin** *loses* **melanin**; the **pigment** that *determines* the **color** of the **skin**, **hair** and **eyes**.
- Vitiligo usually *starts as* **small areas** of **pigment** *loss* that **spread** *with* **time**.
- There is *no cure* for **vitiligo**.
- The *goal of treatment* is to *stop* or *slow* the **progression** of *pigment* **loss**.
- The *exact cause* of vitiligo **isn't known**; It may be due to an **immune system disorder**.
- *Medical Therapies*;
  - *Topical* Corticosteroid.
  - *Topical* Psoralen.
  - *Oral* Psoralen.
  - *Depigmentation*.

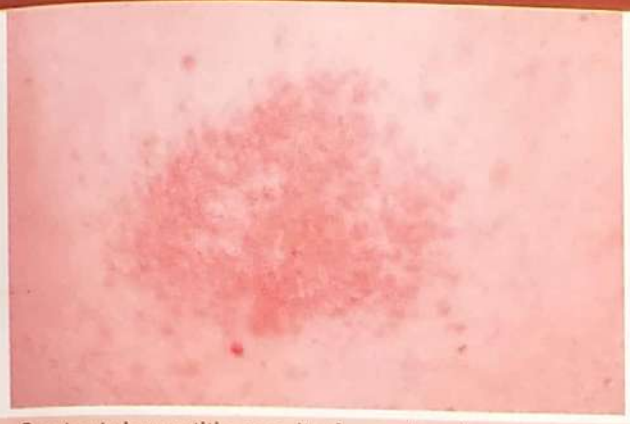
Skin Tag, Freckle and Moles

Skin Tag	Freckle	Moles
		
- Small piece of skin that looks like it's hanging off the skin. - Not painful and not dangerous. - More common in middle-aged, obese adults. - Usually found on the chest, beck, under the breasts, neck and armpits. - Treatments include freezing, tying off with a thread or suture, or cutting off.	- Small brown spot that is usually found on the face and arm. - Usually genetic or can be caused by exposure to the sun. - Not present at birth and not dangerous. - More common in people with red or light-colored hair and people with lighter skin. - Treatments: Sunscreens (to prevention), bleaching or fading creams, topical Retinoids, freeze with liquid nitrogen or laser treatment.	- Small tan or brown spots on the skin. - May be flat or raised. - Usually genetic, not present at birth and not dangerous. - Sun exposure in childhood causes an increase in the number of moles. - Most moles appear by age 20 or 30. - Irregular moles may develop into skin cancer called melanoma.

Dermatitis and Eczema

- **Dermatitis** is a general term that describes an ***inflammation*** of the **skin**.
- In ***some languages***, **dermatitis** and **eczema** are ***synonymous***.
- ***Other languages*** **dermatitis** implies an ***acute condition*** & **eczema** a ***chronic condition***.
- **Eczema** often referred to as **atopic dermatitis** (chronic inflammation of the skin).

Contact Dermatitis

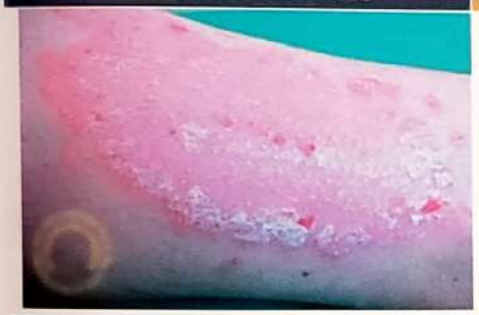


Contact dermatitis results from direct contact with certain substances called allergens
Common allergens include rubber, costume jewelry, perfume, cosmetics, hair dyes and poison ivy.

Atopic Dermatitis (Eczema)

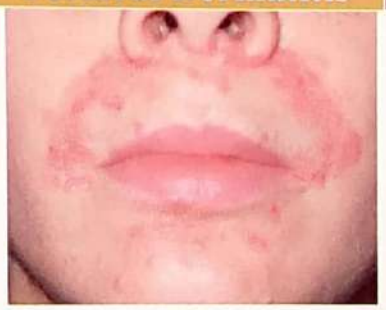
Occurs in the folds of the elbows, backs of the knees or the front of the neck.
It tends to flare periodically and then subside for a time, even up to several years.

Neurodermatitis



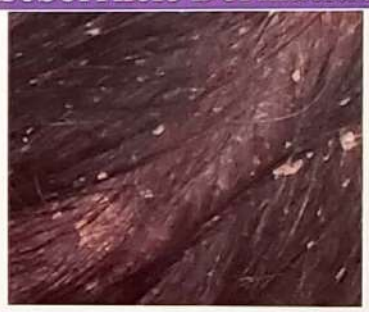
Neurodermatitis occurs because of repeated scratching.
Typicallyoccurs on the scalp, neck, wrist, upper forearm & ankle.

Perioral Dermatitis



usually affects the area around the mouth, but can also affect the areas around the nose, cheeks and eyes

Seborrheic Dermatitis

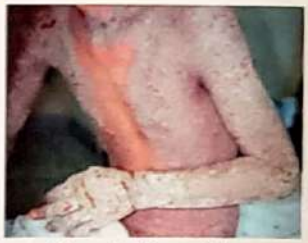


often found on oily areas of the body, such as the face, upper chest, back and scalp.

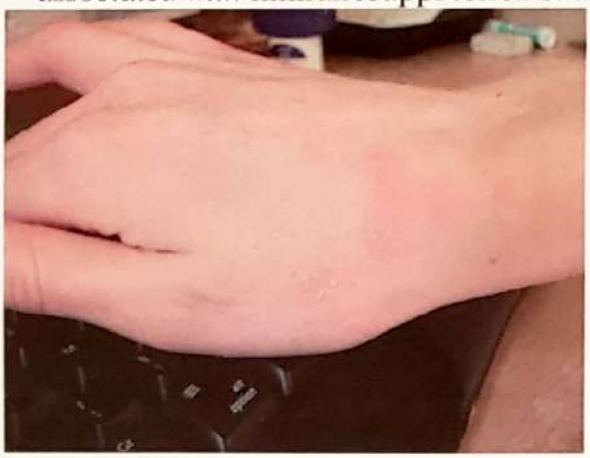
- ***Treatments***; ***all*** **types** of **dermatitis**, *occasional use* **antihistamines** can ***reduce*** **itching**.
  - *For* **Atopic Dermatitis**;
    - **Hydrocortisone**-*containing* **lotions**.
    - ***Immunomodulators***, such as **Tacrolimus** (**Protopic**®) and **Pimecrolimus** (**Elidel**®), affects the immune system and may help maintain normal skin texture and reduce flares of atopic dermatitis (***only used*** when **other treatments** have ***failed***).
  - *For* **Neurodermatitis**;
    - **Hydrocortisone** ***lotions*** and ***creams*** may *help* **soothe** the **skin**.
    - **Sedatives** and **tranquilizers** also may help to ***stop*** **scratching**.
  - *For* **Seborrehic Dermatitis**;
    - ***Shampoos*** contain **tar**, **zinc pyrithione**, **salicylic acid** or **ketoconazole**.
    - **Hydrocortisone** ***creams*** and ***lotions*** may **soothe** the **skin** and ***relieve*** **itching** (also may need ***treatment for*** a **secondary infection**).
  - *For* **Perioral Dermatitis**;
    - ***Self-limited*** which will ***resolve*** *within* a ***few months*** *without* **therapy**.
    - **Topical** ***less*** **potent** **corticosteroids** used in ***order*** to ***reduce*** **symptoms**.

Scabies and Lice

- **Scabies** is an *itchy*, *highly contagious* **skin condition** caused by an *infestation* by the **itch mite** *Sarcoptes scabiei*.
- *Direct* **skin-to-skin** *contact* is the *mode of transmission*.
- *Treatment* includes *oral* or *topical* **scabicidal drugs**.
- **Crusted scabies** is a *more severe* form of the **infection** often *associated with* **immunosuppression** such as **HIV** and **cancer**.



Crusted scabies



- *Treatments* of **Scabies**;

Permethrin (Ectomethrin®)# (Elimite®)

- **Permethrin** works by *paralyzing* and *killing* the **mites** used in **lice** and **scabies**
- *Formulations*; **cream 5%, liquid 1%** and **lotion 1%**.
- **Scabies**; *Cream*: *apply from* **head** *to* **toe**, *leave on* for **8-14 hours**, rinse; *may* **reapply** in **7 days** if **live mites** *reappear*.
- **Lice**; *apply to* **washed hair**, *leave on* **10 min**; may *repeat in* **7 days** if **lice** still present
- *Mild infections*; One application is normally sufficient for mild infections.
- *Moderate* to *severe infections*; applied **7-14 days** *later*.

Ivermectin (Iverzine®)#

- *Oral* **Ivermectin**; effective in eradicating scabies, often in a *single dose*.
- *Dose* ***in*** **Scabies**: 0.2 mg (200 mcg)/kg orally once, and repeated in 2 weeks.
- ***Not used*** for **pregnant** and **children** under **six years** of age (*less than* 15 kg).
- *Topical* **Ivermectin** have been found to be *effective for* **scabies**.

Crotamiton (Eurax®)#

- ***Applied*** **once** a **day** *for* **2-5 days**.

Benzyl Benzoate (Benzanil®)#

- **Benzyl benzoate** is used to treat **lice** and **scabies** infestations.
- ***Use*** **just one time** (in **severe**, *repeated* after **24 hours** *one time* anytime *within* **5 days**).

- **Lice** are **parasitic** *insects* that can be *found on* **people's heads**, and **bodies**, including **pubic area**.

- *Treatments* of **Lice**;

Malathion (Quick®)#

- *Topical* **Malathion** **0.5%** *applied* to **dry hair** and *washed off after* **8-12 hours**.
- It can be *re-applied* if *live* **lice** are *detected after* **7-10 days**.

Pyrethrins + Piperonyl butoxide (Licide®)#

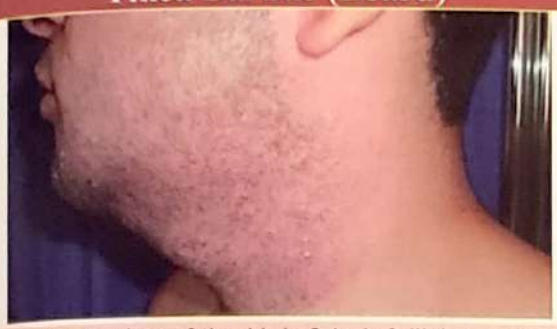
- The product is applied like a *shampoo* to **dry hair** for **10 minutes** and then *rinsed off* with **cool water**; *avoid* **hot water** causes VD, may *increase* **absorption** of **Pyrethrin**.
- Treatment may be repeated if necessary once in a 24-hour period.

Permethrin (Ectomethrin®)#	Benzyl alcohol lotion 5% (Ulesfia®)	Benzyl Benzoate (Benzanil®)

Tinea Infections

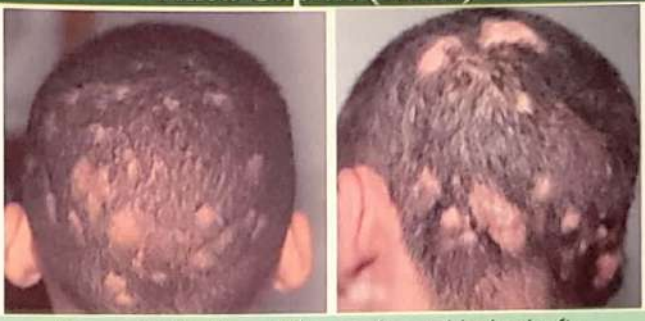
- **Dermatophyte infection** (**Ringworm** or **Tinea**) of the body is a ***fungal infection*** that develops on the **top layer** of the **skin**.

Tinea Barbae (Beard)



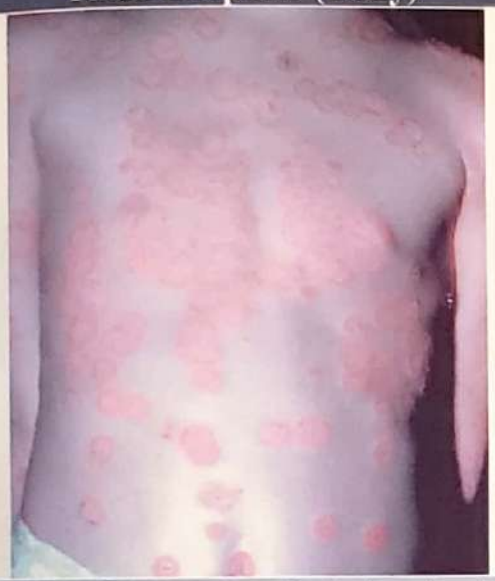
Fungal infection of the Hair & hair follicles of beard

Tinea Capitis (Head)



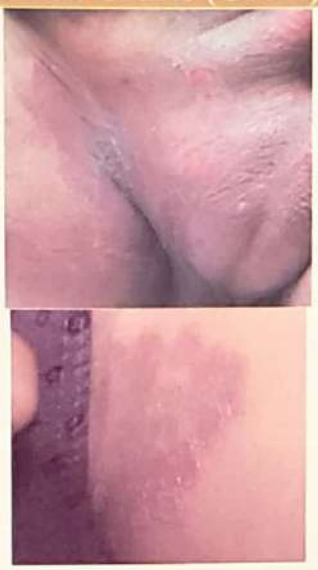
Fungal infection of the scalp and hair shafts

Tinea Corporis (Body)



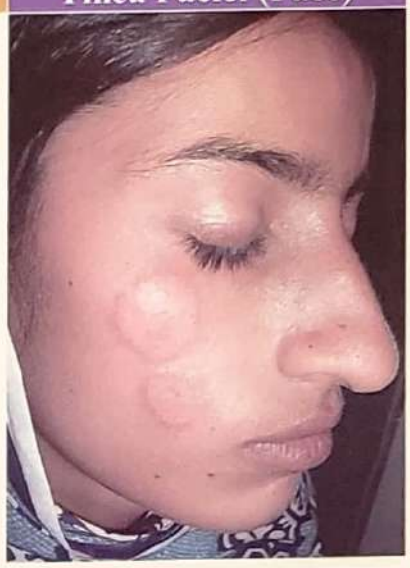
Circle of rash on the skin that's red and inflamed around the edge and healthy looking in the middle.

Tinea Cruris (Groin)



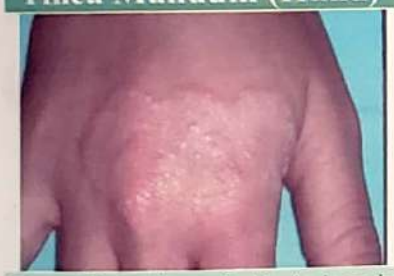
Fungal infection that affects the skin of the genitals, inner thighs and buttocks.

Tinea Faciei (Face)



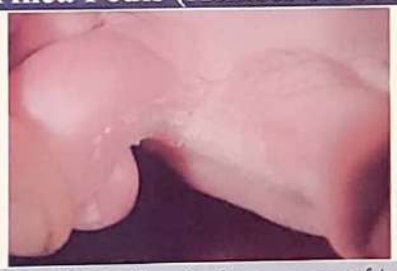
Fungal infection of the surface (superficial) skin of the face.

Tinea Manuum (Hand)



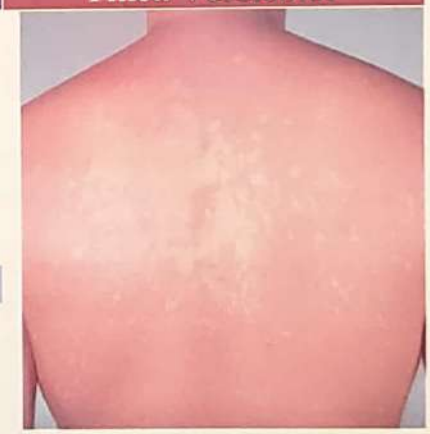
Fungal infection of skin in hands

Tinea Pedis (Athlete's Foot)



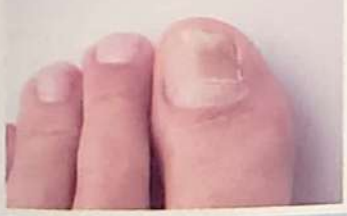
Fungal infection in the spaces of toes

Tinea Versicolor



The fungus interferes with the normal pigmentation of the skin, resulting in small, discolored patches.

Tinea Unguium (Nail)

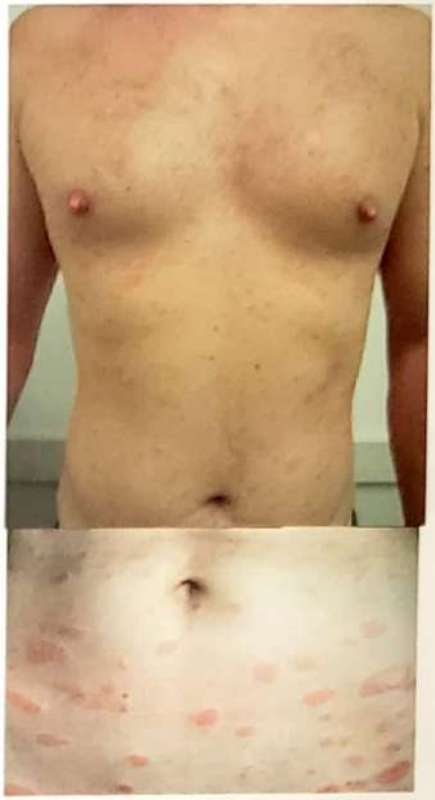


Fungal infection in nails

Treatments; see; **Antifungal** in ***Antimicrobial chapter***

Pityriasis Rosea

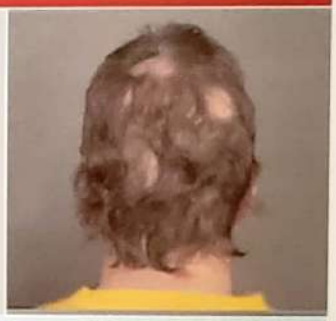
- Pityriasis rosea is a ***skin rash*** that *usually* *begins as* ***one*** **large circular** or **oval spot** on the **chest, abdomen** or **back**.
- Pityriasis rosea can ***affect*** *any age* **group**, but it ***most commonly*** occurs *between* the ages of **10** and **35 years**.
- It ***usually goes away*** on its own ***within*** **6 weeks**.
- Pityriasis rosea can *cause* itching, and ***treatment*** usually *focuses on* ***relieving*** **symptoms**.
- The ***exact cause*** of pityriasis rosea is ***unclear***, but its clinical presentation and ***immunologic reactions*** suggest a **viral infection** as a cause, Pityriasis rosea, however, ***isn't*** believed to be **contagious**.
- In ***most cases***, **pityriasis rosea** *goes away* on its own in 4-6 **weeks**.
- If the rash ***doesn't*** **disappear** by then or if the itching is bothersome, a variety of treatments can help: Corticosteroids and Antihistamines: Also can ***reduce*** **itching**.
- Antiviral drugs: such as Acyclovir (Zovirax®) may ***reduce*** the *duration of* **pityriasis rosea** by 1-2 weeks



Hair loss (Alopecia)

1) Alopecia Areata (AA)

- Alopecia areata is a condition that causes ***round patches*** of **hair loss**.
- Alopecia areata is thought to be an ***autoimmune condition***; this occurs when the **immune system** (***T-Lymphocytes***) ***mistakenly*** **attacks** and **destroys healthy body tissue**.
- Alopecia areata is seen in **men**, **women**, and **children**.
- ***Forms of*** Alopecia areata include:
  - **Alopecia Areata** → ***Patches*** of **hair** ***loss***.
  - **Alopecia Totalis** → ***Complete loss*** of **scalp hair**.
  - **Alopecia Universalis** → ***Total loss*** of all **body hair**.



- ***Treatments***;
  - If the alopecia areata is *localized* or *less than* 50% → **Topical treatments**.
  - If the alopecia areata is *localized* or ***higher than*** 50% → **Systemic treatments**.

A) *Topical treatments*;

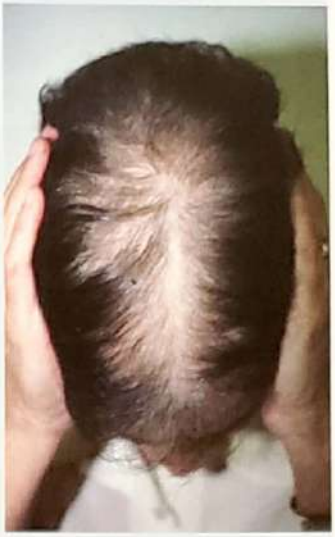
1) *Topical* Corticosteroids.
   - ***Intralesional injections***; Triamcinolone Acetonide (Kenalog®); ***every*** **4-6 weeks**.
   - ***Topical application***; Betamethasone Dipropionate (Diprosone®); ***twice*** *per* **day**.

2) *Topical* Immunotherapy.
   - Anthralin or Dithranol; (Psoriatec®) - (Dritho-Scalp®)
   - Minoxidil (Rogaine®); *applied* ***twice*** **per day**.

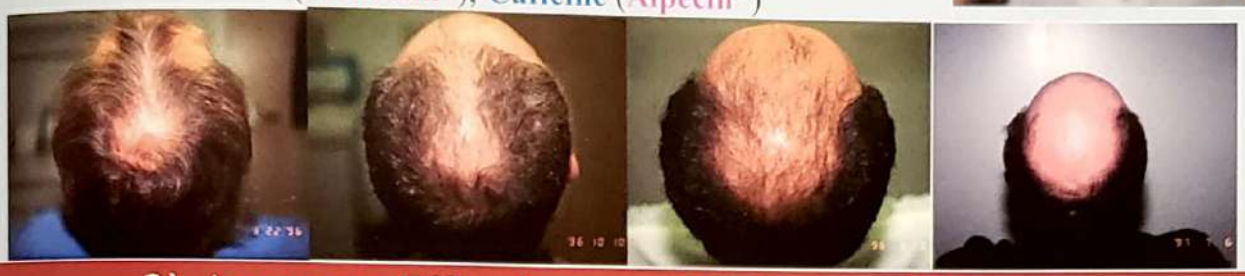
B) *Systemic treatments*;
- *Systemic Corticosteroids*; Prednisone (Hostacortin®)
- *Immunosuppressive Drugs*; Methotrexate and Cyclosporine (Sandimmune®)
- *Immunomodulator Drugs* (Biologics); Infliximab (Remicade®).

2) Androgenetic Alopecia (AGA)

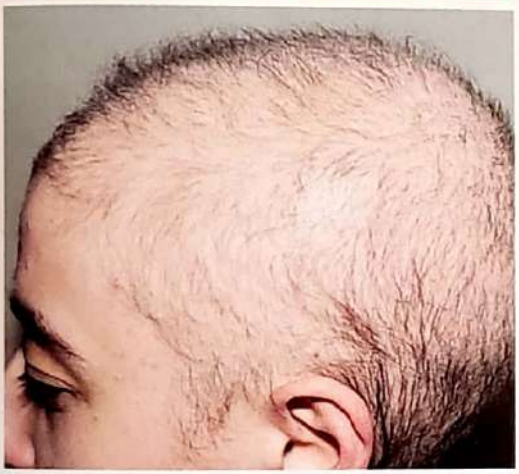
- Hair loss is *gradual*, with *miniaturization* of *genetically* programmed hair follicles.
  - *In* female: hair loss *occurs* in the **frontal hairline**.
  - *In* men: hair loss occurs in the ***fronto-temporal*** **regions** and on the **vertex** of the **scalp**, *depending on* **severity**.

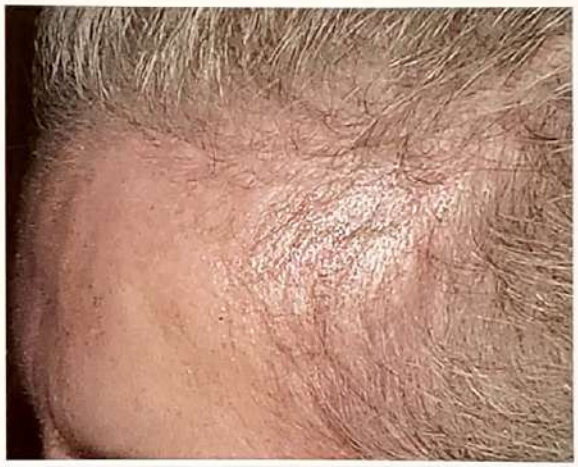


- *Treatments*;
  - **Minoxidil** (Rogaine®);
    - **Topical solution** 2% (*for women*) 5% (*for men*)
    - **Topical foam** 5% (*for sensitive patient*).
    - *Dose*; Apply 1 ml twice daily.
    - *Duration*; Hair growth may require **4 months** of therapy; DON'T ***stop*** **Minoxidil** by yourself.
  - **Finasteride** (ProHair®); **1 mg** orally for ***at least*** **3 months**.
  - *Other agents*; **Cyproterone + Ethinyl estradiol** (Diane-35®), **Spironolactone** (Aldactone®), **Alfatradiol** (Pantostin®), **Caffeine** (Alpecin®)



3) Anagen Effluvium and Telogen Effluvium





- *Anagen effluvium*; ***loss*** of **anagen** or ***growth*-phase hairs**; ~**90%** of the **hair**.
- It is ***caused by*** **radiation therapy** to the head and ***systemic*** **chemotherapy**, especially with **alkylating agents**.

- *Telogen Effluvium*; ***loss*** of **telogen** or ***growth*-phase hairs**; ~**10%** of the **hair**.
- It is ***caused by***; Emotional or physiological stress eating disorders, fever, childbirth, chronic illness, major surgery, anemia, severe emotional disorders, hypothyroidism and drugs.

4) Self-Induced Hair Loss

- Some damage to the hair is self-inflicted sometimes consciously or unconsciously the two main types of self-induced hair loss are Trichotillomania and Traction Alopecia.

Check Yourself

Answers Table; Page No.; 311

Day 1

1) Which of the following listed penicillins is an orally penicillin?

A) Penicillin G
B) Penicillin V
C) Procaine Penicillin
D) Benzyl-penicillin

2) Which of the following brands of Augmentin® is likely to be most effective in the treatment of recurrent or persistent acute otitis media in children; weight is 15 kg?

A) Augmentin® 228
B) Augmentin® 457
C) Augmentin® 375
D) Augmentin® ES-600

3) Which of the following listed 2nd generation cephalosporins available is acceptable taste and is available in strawberry taste in oral formulations?

A) Zinnat®
B) Ceclor®
C) Cefzil®
D) B and C

4) Which of the following 3rd generation cephalosporins is not used in premature neonates?

A) Cefotaxime
B) Ceftriaxone
C) Cefixime
D) Cefoperazone

5) Which of the following is likely to be most correct dose of Suprax® 100 mg/5 mL susp. in children; weight is 17.5 kg?

A) 5 mL orally twice
B) 7 mL orally once
C) 10 mL orally twice
D) 12 mL orally twice

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 2

1) Which of the following drugs is most effective in pseudomembranous colitis?

A) Vancomycin
B) Nystatin
C) Methicillin
D) Ceftriaxone

2) Which of the following β-lactams not cause cross-sensitivity with other β-lactams?

A) Carbenicillin
B) Aztreonam
C) Ticarcillin
D) Cefditoren

3) Which of the following antibiotics is effective in one single dose in UTI?

A) Fosfomycin
B) Cycloserine
C) Vancomycin
D) Daptomycin

4) Which of the following antibiotics is orally effective against MRSA, cSSSI & uSSSI?

A) Tigecycline
B) Linezolid
C) Vancomycin
D) Daptomycin

5) Which of the following antibiotics is likely to be most effective in the treatment of Toxoplasmosis during Pregnancy?

A) Rovamycin®
B) Klacid®
C) Zithromax®
D) Josaxin®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 3

1) Which of the following antibiotics may cause articular erosion in children?

A) Levofloxacin
B) Telithromycin
C) Azithromycin
D) All of the above

2) Which of the following antibiotics may cause Stevens Johnson syndrome (SJS)?

A) Nalidixic acid
B) Chloramphenicol
C) Co-Trimoxazole
D) Telithromycin

3) Which of the following antibiotics can cause prolong QT interval?

A) Nalidixic acid
B) Chloramphenicol
C) Co-Trimoxazole
D) Levofloxacin

4) Which of the following antibiotics in Zymar® eye drops?

A) Gatifloxacin
B) Moxifloxacin
C) Ciprofloxacin
D) Levofloxacin

5) Which of the following anti-tubercular drug is not used as first line therapy?

A) Rifampicin
B) Isoniazid
C) Ethambutol
D) Pyrazinamide
E) Cycloserine

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 4

1) Which of the following antifungal is a drug of choice for the treatment of several life-threatening mycoses?

A) Amphotericin B
B) Itraconazole
C) Griseofulvin
D) Terbinafine

2) Which of the following antifungal is a drug of choice for the treatment of Dermatophytosis?

A) Amphotericin B
B) Itraconazole
C) Nystatin
D) Terbinafine

3) Loceryl® and Exoderil® are common antifungal brands used for;

A) Ringworm
B) Onychomycosis
C) Athlete's foot
D) Tinea cruris

4) Which of the following antiviral brands can be used for influenza A infections?

A) PK-Merz®
B) Valtrex®
C) Zeffix®
D) Sovaldi®

5) Ribavirin is category X and should be avoided before 6 months of planning to pregnancy in;

A) Men
B) Women
C) Both men and women

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 5

1) Augmentin® XR tablets is effective in the treatment of community acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis in dose?

A) 2 tablets every 24 hours
B) 2 tablets every 12 hours
C) 1 tablets every 24 hours
D) 1 tablets every 12 hours

2) Which of the following brands of Azithromycin least affected by food?

A) Zithromax®
B) Xithrone®
C) Zisrocin®
D) Zithrokan®

3) Which of the following antibiotics is likely to be most effective as a single dose in the treatment of Chlamydia Infection?

A) Levofloxacin
B) Ofloxacin
C) Azithromycin
D) Doxycycline

4) Which of the following antibiotics may prolong QT interval?

A) Levofloxacin
B) Telithromycin
C) Azithromycin
D) All of the above

5) Lariam® is an antimalarial agent commonly used in prophylaxis in dose;

A) 250 mg once weekly
B) 250 mg twice weekly
C) 500 mg once weekly
D) 500 mg twice weekly

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 6

1) Which of the following antacid brands contain physical barrier to acid?

A) Maalox®
B) Epicogel®
C) Mucogel®
D) Gaviscon®

2) H_2RAs has marked effect on;

A) Nocturnal acid secretion
B) Meal-stimulated secretion
C) Both

3) Which of the following supplements Patients may needed during long term use of PPIs?

A) Vitamin B_{12}
B) Iron
C) Calcium and Magnesium
D) All of the above

4) *H. Pylori* treatment include all the following Except;

A) Metronidazole
B) Clarithromycin
C) Amoxicillin
D) Tetracycline
E) Vancomycin

5) Motilium® 30 mg supp is avoided in children < 10 years due to;

A) Fatal QT prolongation
B) Extrapyramidal symptoms
C) Tardive dyskinesia
D) Increase Prolactin

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 7

1) Which of the following is correct about concentration of Zofran® 4 mg ampoules?

A) Same as Zofran® 8 mg B) Double of Zofran® 8 mg C) Half of Zofran® 8 mg

2) Which of the following antiemetic brands can cause acute systemic toxicity, if used in pediatrics in full ampoule dose?

A) Zofran® 2mL
B) Emetrex®
C) Cortigen-B6®
D) Depo-Medrol®

3) Role of Atropine in Lomotil® is;

A) Decrease GI motility
B) Synergistic effect
C) Discourage abuse
D) Increase GI motility

4) Antimotility agents is contraindicated in

A) High fever
B) Bloody stool
C) Black stool
D) All of the above

5) Which of the following laxatives act after 12-72 hours?

A) Meta-mucil®
B) Picolax®
C) Dulcolax®
D) Senokot®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 8

1) Which of the following digestive and/or antispasmodic brands contraindicated in lactating women?

A) Buscopan®
B) Visceralgine®
C) Do-Spa®
D) Spasmo-digestin®

2) Which of the following brands of Mebeverine contain one of two components of Librax®?

A) Duspatalin®
B) Coloverin® SR
C) Coloverin®-D
D) Coloverin®-A

3) Which of the following brands contain Mesalamine and used for Inflammatory Bowel Disease (IBD)?

A) Pentasa®
B) Canasa®
C) Rowasa®
D) All of the above

4) Which of the following TNF-α inhibitors brands contain Infliximab?

A) Remicade®
B) Humira®
C) Cimzia®
D) Simponi®

5) Which of the following brands contain Ursodiol and used in Cholelithiasis?

A) Rowachol® B) Rowatinex® C) Ursofalk®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 9

1) Which of the following H_2RAs most potent?

A) Cimetidine
B) Ranitidine
C) Nizatidine
D) Famotidine

2) Sodium Bicarbonate in Zegerid® was added to;

A) Protect Omeprazole from acid degradation
B) Increase Omeprazole solubility
D) Act as antacid
C) Decrease Omeprazole drug interactions

3) Which of the following antiemetic brands are used as first line in NVP?

A) Diclegis®
B) Epidron®
C) Zofran®
D) Primperan®

4) Which of the following antimicrobials is good choice in traveler's diarrhea for pregnant women and children?

A) Zithromax®
B) Tavanic®
C) Vibramycin®
D) Septrin®

5) Which of the following antidiarrheal agents act as antisecretory?

A) Kaolin-Pectin
B) Methylcellulose
C) Racecadotril
D) Cholestyramine

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 10

1) Which of the following brands of second generation antihistamines is partially sedating?

A) Claritin®
B) Zyrtec®
C) Telfast®
D) Semprex®

2) Which of the following brands of antihistamines used off-label as an appetite stimulant?

A) Avil®
B) Donormyl®
C) Triactin®
D) Betaserc®

3) Which of the following brands of antihistamines is most likely used in insomnia?

A) Avil®
B) Donormyl®
C) Triactin®
D) Betaserc®

4) Which of the following brands of antihistamines is most likely used in Ménière's disease?

A) Avil®
B) Donormyl®
C) Triactin®
D) Betaserc®

5) Which of the following brands of antihistamines is most likely used in dry chough?

A) Anallerge®
B) Claritin®
C) Telfast®
D) Aerius®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 11

1) Which of the following brands is SABA?

A) Ventolin®
B) Serevent®
C) Foradil®
D) Onbrez®

2) Which of the following brands is Ultra-LABA?

A) Ventolin®
B) Serevent®
C) Foradil®
D) Onbrez®

3) Which of the following statements is correct about Foradil®?

A) Used for acute asthma
B) Used without ICS in chronic asthma
C) May used as monotherapy for COPD
D) None of the above

4) Which of the following bronchodilators has low therapeutic index?

A) Quibron®
B) Serevent®
C) Spiriva®
D) Atrovent®

5) Which of the following leukotriene modifiers not cause hepatotoxicity?

A) Zafirlukast
B) Montelukast
C) Zileuton

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 12

1) Which of the following brands of antihistamines is most likely used in Allergic rhinitis?

A) Anallerge®
B) Donormyl®
C) Aerius®
D) Avil®

2) Intranasal Corticosteroids are the first line therapy in

A) Mild allergic rhinitis
B) Moderate allergic rhinitis
C) Severe allergic rhinitis
D) B and C

3) Which of the following agents can cause rhinitis medicamentosa in long term use?

A) Oxymetazoline
B) Cromolyn
C) Azelastine
D) Ipratropium

4) Which of the following antitussives is act as peripheral cough reflex inhibitors?

A) Dextromethorphan
B) Benzonatate
C) Noscapine
D) Butamirate

5) Which of the following NSAIDs is recommended in the guidelines for treatment of cough associated with common cold?

A) Naproxen
B) Ibuprofen
C) Paracetamol
D) Diclofenac

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 13

1) Which of the following brands of antihistamines act as mast cell stabilizing effects in addition to their H1-blocking effects.

A) Anallerge®
B) Aerius®
C) Zaditen®
D) Claritin®

2) Which of the following ICS brands is prodrug and may cause fewer local side effects?

A) Alvesco®
B) Miflonide®
C) Azmacort®
D) Flixotide®

3) Local side effects of ICS such as oral candidiasis and hoarseness can be minimized by;

A) Deeply once inhalation in each dose
B) Inhalation just after meal
C) Gargle water and spit after each inhaled
D) Inhalation just before meal

4) Which of the following brands act as anti-IgE and used in allergic asthma?

A) Zyflo®
B) Xolair®
C) Intal®
D) Accolate®

5) Usual dose of Champix® in day no. 10 in quit smoking course in adult is;

A) 0.5 mg orally once a day.
B) 0.5 mg orally twice a day.
C) 1 mg orally once a day
D) 1 mg orally twice a day

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 14

1) Which of the following Hormones synthesized form DHEA?

A) Oxytocin
B) Dopamine
C) Serotonin
D) Testosterone

2) Which of the following brands used for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in pre-menopausal women.

A) Viagra®
B) Addyi®
C) Caverject®
D) Yohimbex®

3) Which of the following PDE-5 inhibitors has shorter duration of action?

A) Viagra®
B) Levitra®
C) Stendra®
D) Cialis®

4) Which of the following brands is more effective for premature ejaculation

A) Anafranil®
B) Joybox®
C) Cipralex®
D) Seroxat®

5) Which of the following agents is most effective to treat Trichomoniasis?

A) Doxycycline
B) Metronidazole
C) Clindamycin
D) Fluconazole

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 15

1) Citrate Therapy is used in calcium oxalate stones due to Citrate act as;

A) Alkalinizing agent
B) Acidifying agent
C) Form soluble complex
D) A and C

2) Struvite stones in urine are indicate to;

A) Infections
B) Acidic urine
C) Alkaline urine

3) Which of the following NSAIDs brands used as drug of choice in renal colic pain?

A) Voltaren®
B) Brufen®
C) Panadol®
D) Celebrex®

4) Which of the following brands may cause floppy iris syndrome during cataract surgery?

A) Cardura®
B) Flomax®
C) Rapaflo®
D) Xatral®

5) Which of the following agents act in adrenergic receptors to relax the detrusor muscles of the bladder to treat urinary incontinence?

A) Solifenacin
B) Mirabegron
C) Desmopressin
D) Finasteride

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 16

1) Which of the following agents if used with Flibanserin may increases the risk of severe hypotension and syncope?

A) Tyramine food
B) Nitrates
C) Alcohol
D) Nicotine

2) Which of the following PDE-5 inhibitors available in an orally disintegrating tablet?

A) Avanafil
B) Vardenafil
C) Tadalafil
D) Sildenafil

3) Which of the following brands may off-label used in retarded ejaculation?

A) Triactin®
B) Contramal®
C) Avodart®
D) Dexazone®

4) 5-α-Reductase inhibitors are most beneficial if the prostates larger than;

A) 10 g
B) 20 g
C) 30 g
D) 40 g

5) Duodart® brand contain combination of;

A) Finasteride + Tamsulosin
B) Dutasteride + Tamsulosin
C) Finasteride + Silodosin
D) Dutasteride + Silodosin

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 17

1) Which of the following NSAIDs is not contraindicated in patients with high risk for cardiovascular events?

A) Ibuprofen
B) Naproxen
C) Diclofenac
D) None of the above

2) Which of the following brands can overcome NSAID-associated bronchospasm?

A) Singulair®
B) Miflonide®
C) Ventolin®
D) None of the above®

3) NSAIDs should be used at the;

A) Lowest effective dose
B) Highest effective dose
C) Shortest possible duration of therapy
D) A and C

4) Which of the following brands may be beneficial in pregnancies to decrease the risk of pre-eclampsia?

A) Jusprin®
B) C-Retard®
C) Omega-3®
D) B and C

5) Which of the following statements is correct about Acetaminophen?

A) American name of Paracetamol
B) Active metabolite of Paracetamol
C) Prodrug of Paracetamol
D) None of the above

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 18

1) Which of the following brands is one of the most widely synthetic opioids used and available in different types of formulations?

A) Duragesic®
B) Dilaudid®
C) Dolophine®
D) Demerol®

2) Naloxone in Talwin® and Suboxone® is added to;

A) Discourage abuse
B) Synergistic effect
C) Decrease withdrawal symptoms
D) B and C

3) Lofexidine (Detoxydine®) is added in opioid detoxification regimens due to it act as;

A) Opioid Antagonist
B) Opioid Agonist
C) α_2 Agonist
D) Serotonin Agonist

4) Which of the following antispasticity agents act as $GABA_B$ receptors?

A) Diazepam
B) Baclofen
C) Tizanidine
D) None of the above

5) Which of the following brands may cause serious hepatocellular toxicity especially in liver impairment?

A) Norflex®
B) Sirdalud®
C) Myofen®
D) Myolgin®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 19

1) Which of the following NSAIDs has been historically favored as NSAID of choice for acute gout?

A) Ibuprofen
B) Naproxen
C) Sulindac
D) Indomethacin

2) Colchicine was historically used in acute gout in;

A) Lower dose
B) Higher doses until GI symptoms

3); Which of the following xanthine oxidase inhibitors act as direct non-competitively blocking effect?

A) Allopurinol
B) Febuxostat

4) Which of the following DMARDs is an abortifacient agent?

A) Methotrexate
B) Etanercept
C) Sulfasalazine
D) Adalimumab

5) Brand of Infliximab is;

A) Remicade®
B) Humira®
C) Simponi®
D) Cimzia®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 20

1) Glucosamine may increase risk of;

A) Bleeding
B) Hypertension
C) Blood glucose levels
D) All of the above

2) Which of the following brands of Vitamin D used as a single dose once a year?

A) Sterogyl®
B) Devarol-S®
C) One-Alpha®
D) Vi-De 3®

3) Bisphosphonates esophagitis can be reduced by;

A) Taken with 240 mL of mineral water
B) Taken 30 minutes before food
C) Patient should be remain upright
D) B and C
E) All of the above

4) Premarin® is a;

A) Conjugated Estrogens
B) Conjugated Progestins
C) Conjugated Testosterone

5) Forteo® dose is;

A) 20 mcg SC once a day
B) 60 mcg SC once a day
C) 100 mcg SC once a day
D) 150 mcg SC once a day

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 21

1) Which of the following brands of NSAIDs is a good choice in primary dysmenorrhoea?

A) Mobic®
B) Celebrex®
C) Ketolac®
D) Ponstan®

2) Maximum single dose of Paracetamol in healthy adults is:

A) 500 mg
B) 1 gm
C) 2 gm
D) 4 gm

3) Which of the following eye drops can be abused by mixing it with Heroin?

A) Toprex®
B) Mydriacyl®
C) Lumigan®
D) Patanol®

4) Which of the following application of Botox® is correct?

A) Prevent development of wrinkles
B) Muscle spasticity
C) Chronic migraine
D) All of the above

5) Which of the following is the most common serious side effects of Plaquenil®?

A) Hepatotoxicity
B) Ocular toxicity
C) Ototoxicity
D) Nephrotoxicity

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 22

1) Hypokalemia and metabolic alkalosis is the most common side effects of;

A) Amiloride
B) Hydrochlorothiazide
C) Mannitol
D) Spironolactone

2) Which of the following should be avoided in a patient with a history of severe anaphylactic reaction to sulfa medications?

A) Amiloride
B) Hydrochlorothiazide
C) Mannitol
D) Spironolactone

3) β-blockers must be tapered off gradually to avoid;

A) angina or hypertension
B) Hypotension and syncope
C) Arrhythmia
D) Withdrawal symptoms

4) Which of the following ACEIs is contraindicated in patient with sulfa allergy?

A) Capoten®
B) Zestril®
C) Coversyl®
D) Tritace®

5) Dry persistent cough associated with ACEIs can be resolved by;

A) Ferrous sulfate
B) Aspirin
C) Vitamin C
D) A and B

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 23

1) All of the following antihypotensive drugs are sympathomimetic; Except;

A) Effortil®
B) Gutron®
C) Corasore®
D) Astonin-H®

2) Which medication should be prescribed to all anginal patients to treat an acute attack?

A) Isosorbide dinitrate
B) Nitroglycerin patch
C) Nitroglycerin sublingual tablet or spray
D) Ranolazine

3) Which of the following is a first cytoprotective anti-ischemic agent?

A) Ranexa®
B) Vastarel® MR
C) Procoralan®
D) Randil®

4) Which is important to monitor in patients taking digoxin?

A) Chloride
B) Potassium
C) Sodium
D) Zinc

5) Which of the following is the most common side effect associated with fixed-dose hydralazine/isosorbide (BiDil®) dinitrate?

A) Diarrhea
B) Drug-induced lupus
C) Headache
D) Heartburn

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 24

1) Which of the following antiarrhythmic drug is mostly like to cause dry mouth, blurred vision and urinary hesitancy?

A) Metoprolol
B) Disopyramide
C) Dronedarone
D) Sotalol

2) All of the following are adverse effects of amiodarone except;

A) Cinchonism
B) Hypothyroidism
C) Hyperthyroidism
D) Pulmonary fibrosis

3) Which arrhythmia can be treated with lidocaine?

A) Atrial fibrillation
B) Atrial fibrillation
C) Supraventricular tachycardia
D) Ventricular tachycardia

4) Which of the following is a non-iodinated benzofuran derivative?

A) Dronedarone
B) Amiodarone
C) Sotalol
D) Dofetilide

5) Lidocaine is an antiarrhythmic and it is classified as

A) Class IA
B) Class IB
C) Class IC

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 25

1) Which must heparin bind to in order to exert its anticoagulant effect?

A) GP IIb/IIIa receptor
B) Thrombin
C) Antithrombin III
D) von Willebrand factor

2) Protamine sulfate is a Heparin antidote, While Idarucizumab (Praxbind®) is an antidote for;

A) Pradaxa®
B) Argatroban®
C) Angiomax®
D) Xarelto®

3) Which of the following drugs accelerates the conversion of plasminogen to plasmin?

A) Heparin
B) Warfarin
C) Argatroban
D) Reteplase

4) Bioavailability of Dabigatran Etexilate is increased up to 75%, if capsules;

A) Taken in empty stomach
B) Opened and pellets taken alone
C) Taken with food stomach
D) Taken with grapefruit juice

5) Which of the following fibrinolytics is a human plasminogen and bacterial streptokinase?

A) Urokinase
B) Anistreplase
C) Alteplase
D) Reteplase

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 26

1) Which one of the following drugs decreases cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase?

A) Fenofibrate
B) Niacin
C) Cholestyramine
D) Lovastatin

2) Pregnant hyperlipidemia patients, which of the following drugs should be avoided because of a risk of harming the fetus?

A) Cholestyramine
B) Ezetimibe
C) Fenofibrate
D) Pravastatin

3) Which of the following is a major toxicity associated with gemfibrozil therapy?

A) Bloating and constipation
B) Cholelithiasis
C) Hyperuricemia
D) Liver damage

4) Which of the following options can help patient to manage this adverse effect of niacin therapy?

A) Used aspirin 30 min. before niacin
B) Used aspirin 30 min. after niacin
C) Increase dose of niacin SR to 1000 mg
D) Continue the current dose of niacin

5) Coenzyme Q10 can be used in patient taking statins to decrease;

A) Cholelithiasis
B) Rhabdomyolysis
C) Hepatotoxicity
D) Hemolysis

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 27

1) Which of the following diuretics has a unique mechanism of action?

A) Natrilix® SR
B) Zaroxolyn®
C) Esidrix®
D) Burinex®

2) Which of the following is an antianginal drug that has the dual properties of a nitrate and potassium channel activators?

A) Procoralan®
B) Randil®
C) Vastarel® MR
D) Ranexa®

3) Chromatopsia is a common side effects of;

A) Inocor®
B) Lanoxin®
C) BiDil®
D) Digibind®

4) In 2009, the FDA issued a public-health warning about the possible interaction between Clopidogrel and Omeprazole. Which of the following CYP450 isoenzymes is most included in this interactions?

A) CYP3A4
B) CYP2C19
C) CYP2C18
D) CYP1A2

5) Which of the following brands act as phosphodiesterase inhibitor and affects blood rheology?

A) Doxium®
B) Reparil®
C) Trental®
D) Daflon®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 28

1) Which one of the following is a short-acting hypnotic?

A) Phenobarbital
B) Diazepam
C) Chlordiazepoxide
D) Triazolam

2) Which of the following sedative–hypnotic agents utilizes melatonin receptor agonist as the mechanism of action to induce sleep?

A) Zolpidem
B) Eszopiclone
C) Ramelteon
D) Suvorexant

3) Which of the following sedative–hypnotic agent act as orexin antagonists as the mechanism of action to induce sleep?

A) Zolpidem
B) Eszopiclone
C) Ramelteon
D) Suvorexant

4) This drug used in the management of insomnia facilitates the inhibitory actions of GABA, but it lacks anticonvulsant or muscle-relaxing properties and has minimal effect on sleep architecture.

A) Buspirone
B) Eszopiclone
C) Ramelteon
D) Phenobarbital

5) Which of the following is an antidote for benzodiazepines

A) Anexate®
B) Buspar®
C) Rozerem®
D) Belsomra®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 29

1) Which of the following antidepressants should be avoided in this patient with angle-closure glaucoma?

A) Amitriptyline
B) Sertraline
C) Bupropion
D) Mirtazapine

2) Which antidepressant is the most sedating?

A) Cymbalta®
B) Wellbutrin®
C) Trittico®
D) Cipralex®

3) SSRIs are much less effective than tricyclic antidepressants in the management of

A) Bulimia
B) Chronic pain of neuropathic origin
C) Generalized anxiety disorder
D) Obsessive-compulsive disorder

4) Which of the following SSRIs has much longer half-life?

A) Fluoxetine
B) Sertraline
C) Citalopram
D) Escitalopram

5) Which agent is best known to have the side effect of decreasing the thyroid function of the patient being chronically treated with this agent?

A) Carbamazepine
B) Lithium
C) Valproic acid
D) Chlorpromazine

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 30

1) Which of the following agents is wakefulness-promoting?

A) Modafinil
B) Atomoxetine
C) Clonidine
D) Guanfacine

2) Which of the following antipsychotic agents may have the best chance to improve his apathy and blunted affect?

A) Neurazine®
B) Haldol®
C) Clopixol®
D) Risperdal®

3) Which of the following is the most common side effects of Clozapine?

A) Hair loss
B) Anemia
C) Thrombocytopenia
D) Agranulocytosis

4) Which antipsychotic agent has been most associated with significant QT interval prolongation?

A) Thioridazine
B) Risperidone
C) Aripiprazole
D) Lurasidone

5) Which of the following antipsychotic agents is available in a LAI (long-acting injectable) formulation?

A) Asenapine
B) Clozapine
C) Quetiapine
D) Risperidone

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 31

1) Which one of the following combinations of antiparkinsonian drugs is an appropriate treatment plan?

A) Amantadine, Carbidopa & Entacapone
B) Levodopa, Carbidopa & Entacapone
C) Pramipexole, Carbidopa & Entacapone
D) Ropinirole, Selegiline & Entacapone

2) Which of the following antiparkinsonian drugs may cause vasospasm?

A) Amantadine
B) Bromocriptine
C) Carbidopa
D) Entacapone

3) Modest improvement in the memory of patients with Alzheimer's disease may occur with drugs that increase transmission at which of the following receptors?

A) Serotonergic
B) Dopaminergic
C) Cholinergic
D) Adrenergic

4) Which of the following agents is available as a patch for once-daily use and is likely to provide steady drug levels to treat Alzheimer's disease?

A) Rivastigmine
B) Donepezil
C) Memantine
D) Galantamine

5) Which of the following tests is needed during Gilenya® therapy to monitoring it is side effects?

A) CRP
B) EEG
C) CBC
D) ECG

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 32

1) Which of the following antiepileptics would be effective in children without the disadvantages of excessive sedation or tolerance development?

A) Diazepam
B) Ethosuximide
C) Gabapentin
D) Phenobarbital

2) Which of the following drugs is most useful for the treatment of absence seizures?

A) Topiramate
B) Tiagabine
C) Levetiracetam
D) Lamotrigine

3) With chronic use in seizure states, the adverse effects of this drug include coarsening of facial features, hirsutism and gingival hyperplasia.

A) Carbamazepine
B) Ethosuximide
C) Phenytoin
D) Tiagabine

4) Neural tube defects may occur with which of the following antiseizure drugs?

A) Ethosuximide
B) Vigabatrin
C) Phenobarbital
D) Valproic acid

5) The preferred treatment of status epilepticus is intravenous administration of;

A) Chlorpromazine
B) Diazepam
C) Succinylcholine
D) Tranylcypromine

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 33

1) All of the following brands that can used in acute attacks of migraine contraindicated in patients with coronary artery disease, Except;

A) Tylenol® No.3
B) Imitrex®
C) Zomig®
D) Ergomar®

2) Cefaly® device is a transcutaneous electrical nerve stimulation device that is used in;

A) Migraine Acute Attacks
B) Migraine Prophylaxis
C) Status Migrainosus
D) Tension-type Headache

3) Which of the following is a potent analgesic but a weak anesthetic?

A) Etomidate
B) Halothane
C) Midazolam
D) Nitrous oxide

4) Which one of the following is a potent intravenous anesthetic but a weak analgesic?

A) Propofol
B) Ketamine
C) Fentanyl
D) Isoflurane

5) A vasoconstrictor added to a solution of lidocaine for a peripheral nerve block will

A) Reduce bleeding
B) Increase the duration of local anesthetic
C) Both A and B
D) Neither A nor B

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 34

1) Which one of the following is a short-acting hypnotic and better for sleep induction compared to sleep maintenance?

A) Lorazepam
B) Diazepam
C) Zaleplon
D) Eszopiclone

2) Which of the following brands of SSRIs is indicated only for obsessive-compulsive disorder (OCD)?

A) Prozac®
B) Lustral®
C) Seroxat®
D) Faverin®

3) The risk of Wellbutrin® seizures can be minimized by the following;

A) Dosage titration every 2 days.
B) Not less than 150 mg/dose or 450 mg/day.
C) Both A and B
D) Neither A nor B

4) Which of the following brands may cause livedo reticularis?

A) PK-Merz®
B) Parkinol®
C) Stalevo®
D) Apokyn®

5) Which of the following anticonvulsant are now widely abused?

A) Lamictal®
B) Depakene®
C) Trileptal®
D) Lyrica®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 35

1) All of the following hormones brands misused as performance enhancement in athletes, Except;

A) Norditropin®
B) Cidoteston®
C) Deca-Durabolin®
D) Sandostatin®

2) Which of the following agents used off-labeled in esophageal variceal bleeding?

A) Octreotide
B) Somatropin
C) Menotropin
D) Carbetocin

3) Dose of Dostinex® in reduce prolactin levels is;

A) 1 mg on the first day after delivery.
B) 0.25 mg every 12 hours for two days.
C) 0.5 mg/week spread out over a week

4) All of the following hormones brands used in preparation for In Vitro Fertilization (IVF), Except;

A) Pregnyl®
B) Merional®
C) Decapeptyl®
D) Depo-Provera®

5) Which of the following is brands used in the treatment of hyperthyroidism?

A) Neo-Mercazole®
B) Eltroxin®
C) Thyrolar®
D) Cytomel®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 36

1) To decrease risk of suppress endogenous corticosteroids secretions; Which of the following is the BEST TIME to take daily dose of systemic corticosteroids?

A) 6-8 AM
B) 6-8 PM
C) 1-4 AM
D) 1-4 PM

2) Systemic corticosteroids are used in 3rd trimester of pregnancy to promoting maturation of fetal lung due to;

A) Production of β_2-receptors
B) Production of surfactant
C) Decrease lung secretion
D) Decrease lung spasm

3) Which of the following statements is correct regarding Lantus®?

A) It is a "peakless" insulin
B) Control postprandial hyperglycemia.
C) Prolonged duration due to long-chain fatty acids.
D) It may be administered IV

4) Which of the following brands for diabetes would be least likely to cause weight gain?

A) Amaryl®
B) Victoza®
C) NovoNorm®
D) Actos®

5) Metformin dose in type 2 DM is;

A) Minimum tolerated dose
B) Maximum tolerated dose
C) 1000 mg/day
D) 850 mg/day

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 37

1) All of the following are side effects of Estrogens, Except;

A) Na^+ and water retention
B) Breasts tenderness
C) Weight gain
D) Acne and hirsutism

2) Which of the following brands contain Progestin has potent mineralocorticoid antagonist?

A) Yasmin®
B) Cilest®
C) Microlut®
D) Minulet®

3) All of the following agent are abortifacient agent, Except;

A) Mifepristone
B) Methotrexate
C) Misoprostol
D) Levonorgestrel

4) Which of the following brands is Emergency Contraceptive?

A) Microlut®
B) Contraplan II®
C) Depo-Provera®
D) None of the above

5) Ortho Evra® is

A) Contraceptive Patch
B) Contraceptive Vaginal ring
C) Contraceptive Implants
D) None of the above

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 38

1) Which of the following is the route of administration of Syntocinon® in induction of labor?

A) IM
B) SC
C) IV infusion
D) IV bolus

2) Which of the following brands of corticosteroids is faster in onset of action?

A) Solu-Cortef®
B) Hostacortin®
C) Solu-Medrol®
D) Diprofos®

3) SGLT2 Inhibitors are contraindicated in patients with

A) eGFR <60 mL/min/1.73 m^2
B) eGFR <30 mL/min/1.73 m^2
C) eGFR >60 mL/min/1.73 m^2
D) eGFR >30 mL/min/1.73 m^2

4) Dose of Clomid® is

A) 1 tab. (50 mg) daily for 5 days, starting from the 5th day of woman's cycle.
B) 1 tab. (50 mg) daily for 5 days, starting from the 1st day of woman's cycle.

5) Depo-Provera® injection are repeated every;

A) 1 months
B) 3 months
C) 6 months
D) 8 months

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 39

1) Which drug in the ABVD regimen is the most likely cause of his pulmonary toxicity?

A) Doxorubicin (Adriamycin)
B) Bleomycin
C) Vinblastine
D) Dacarbazine

2) Which of the following brands is associated with hemorrhagic cystitis?

A) Endoxan®
B) Leukeran®
C) Purinethol®
D) Adrucil®

3) Which of the following agents is associated with interstitial pulmonary fibrosis?

A) Cisplatin
B) Doxorubicin
C) Busulfan
D) Paclitaxel

4) Abraxane® (Paclitaxel) is not associated with hypersensitivity reactions and neurotoxicity than Taxol® (Paclitaxel) due to;

A) Sustained release formulation
B) Albumin-bound formulation
C) Micronized formulation
D) A and C

5) Nexavar® and Sutent® are used in;

A) Renal cell carcinoma
B) Colorectal cancer
C) Chronic myelogenous leukemia
D) None of the above

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 40

1) Which of the following drugs used to prevent allograft rejection can cause hyperlipidemia?

A) Tacrolimus
B) Belatacept
C) Mycophenolate Mofetil
D) Sirolimus

2) Which of the following drugs specifically inhibits calcineurin in the activated T lymphocytes?

A) Tacrolimus
B) Belatacept
C) Mycophenolate Mofetil
D) Sirolimus

3) Which of the following side effects is correct about Sandimmun Neoral®?

A) Nephrotoxicity
B) Neurotoxicity
C) Hyperlipidemia
D) GI Disturbances

4) Myfortic® is better than CellCept® due to;

A) Minimize GI side effects
B) Delayed-release enteric-coated
C) Less Neurotoxicity
D) A and B

5) All of the following brands are available in oral and IV formulations, Except;

A) Prograf®
B) Sandimmun Neoral®
C) Myfortic®
D) A and B

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 41

1) Which of the following is most likely to be in patients with chronic renal insufficiency?

A) Cyanocobalamin
B) Deferoxamine
C) Folic Acid
D) Erythropoietin

2) Which of the following iron formulation can be taken in a single visit?

A) Ferumoxytol
B) Ferric Carboxymaltose
C) Iron Isomaltoside

3) Which of the following cobalamin can penetrate blood-brain barrier without assistance or conversion?

A) Cyanocobalamin
B) Hydroxocobalamin
C) Methylcobalamin

4) Which of the following is a parenteral iron chelator?

A) Deferoxamine
B) Deferiprone
C) Deferasirox

5) Which of the following might be beneficial to reduce the frequency of painful crises in a patient with sickle cell disease?

A) Epoetin alfa
B) Filgrastim
C) Hydroxyurea
D) Sargramostim

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 42

1) All of the following are cytotoxic drugs, Except;

A) Monoclonal Antibodies
B) Antimetabolites
C) Alkylating Agents
D) Microtubule Inhibitors

2) Which of the following anticancer is oral prodrug?

A) Cytoxan®
B) Xeloda®
C) Leukeran®
D) None of the above

3) Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) are associated with;

A) Anthracyclines
B) Platinum Salts
C) Taxanes
D) Vinca Alkaloids

4) Pravotin® is a

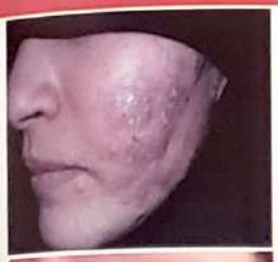
A) Oral Ferrous Sulfate
B) Parenteral Iron
C) Transferrin proteins
D) Bovine Lactoferrin

5) Oprelvekin (Neumega®) is a

A) Recombinant interleukin-1
B) Recombinant interleukin-6
C) Recombinant interleukin-11
D) None of the above

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 43

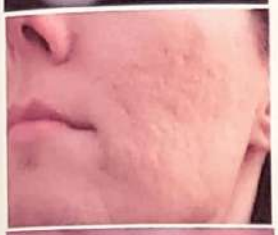


1) Which of the following is correct diagnosis regarding to photo?

A) Acne vulgaris

B) Cystic acne

C) Acne Rosacea

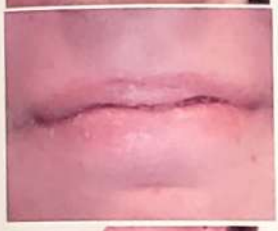


2) Which of the following is correct diagnosis regarding to photo?

A) Acne scars

B) Acne Hyperpigmentation Spots

C) Acne Red Spots

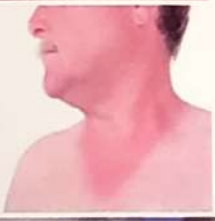


3) Which of the following is correct diagnosis regarding to photo?

A) Skin Aging

B) Isotretinoin Therapy

C) Fatty acid deficiency



4) Which of the following is correct diagnosis regarding to photo?

A) Sunburn

B) Erysipelas

C) Stasis dermatitis

5) Which of the following is correct diagnosis regarding to photo?

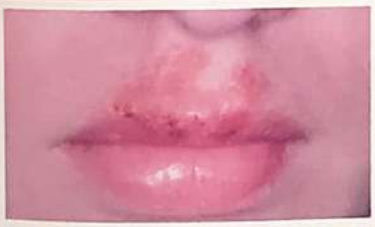
A) Before and after Botox

B) Before and after Phototherapy

C) Before and after Laser therapy

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 44

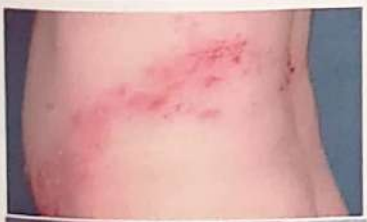


1) Which of the following is correct diagnosis regarding to photo?

A) Impetigo

B) Canker Sore

C) Cold Sore

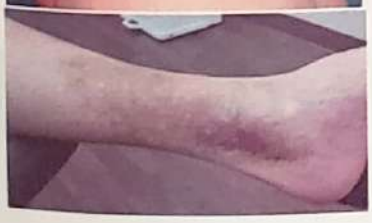


2) Which of the following is correct diagnosis regarding to photo?

A) Dermatitis

B) Shingles

C) Erysipelas

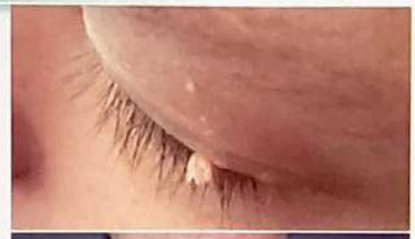


3) Which of the following is correct diagnosis regarding to photo?

A) Lipodermatosclerosis

B) Erysipelas

C) Cellulitis



4) Which of the following is correct diagnosis regarding to photo?

A) Filiform wart
B) Common wart
C) Plantar Wart

5) Which of the following is correct diagnosis regarding to photo?

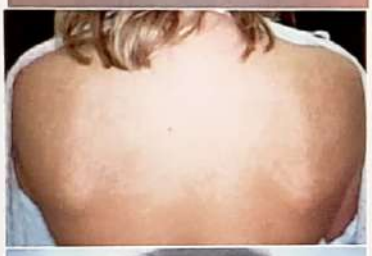
A) Dermatitis
B) Skin Rash
C) Guttate psoriasis

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 45

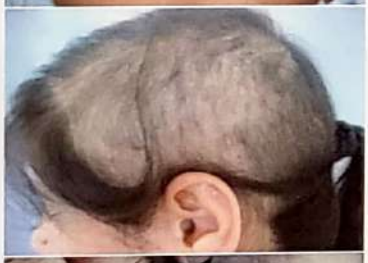
1) Which of the following is correct diagnosis regarding to photo?

A) Tinea Corporis
B) Pityriasis Rosea
C) Tinea Versicolor



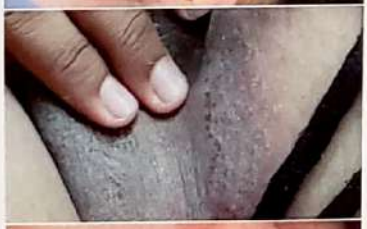
2) Which of the following is correct diagnosis regarding to photo?

A) Tinea Corporis
B) Vitiligo
C) Tinea Versicolor



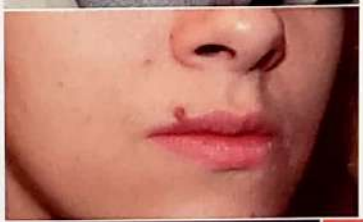
3) Which of the following is correct diagnosis regarding to photo?

A) Alopecia Areata
B) Telogen effluvium
C) Anagen effluvium



4) Which of the following is correct diagnosis regarding to photo?

A) Tinea Barbae
B) Tinea Cruris
C) Tinea Capitis



5) Which of the following is correct diagnosis regarding to photo?

A) Moles
B) Freckle
C) Skin Tag

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Answers Table

	1	2	3	4	5
Day 1	B	D	D	B	B
Day 2	A	B	A	B	A
Day 3	A	C	D	A	E
Day 4	A	D	B	A	C
Day 5	B	B	C	D	A
Day 6	D	A	D	E	A
Day 7	A	B	C	D	A
Day 8	D	D	D	A	C
Day 9	D	A	A	A	C
Day 10	B	C	B	D	A
Day 11	A	D	C	A	B
Day 12	C	D	A	B	A
Day 13	C	A	C	B	D
Day 14	D	B	C	A	B
Day 15	D	A	A	B	B
Day 16	C	B	A	D	B
Day 17	D	A	D	A	A
Day 18	A	A	C	B	D
Day 19	D	B	B	A	A
Day 20	D	A	E	A	A
Day 21	D	B	B	D	B
Day 22	B	B	A	A	D
Day 23	D	C	B	B	C
Day 24	B	A	D	A	B
Day 25	C	A	D	B	B
Day 26	D	D	B	A	B
Day 27	A	B	B	B	C
Day 28	D	C	D	B	A
Day 29	A	C	B	A	B
Day 30	A	D	D	A	D
Day 31	B	B	C	A	D
Day 32	B	D	C	D	B
Day 33	A	B	D	A	C
Day 34	C	D	D	A	D
Day 35	D	A	C	D	A
Day 36	A	B	A	B	B
Day 37	D	A	D	B	A
Day 38	C	A	B	A	B
Day 39	B	A	C	B	A
Day 40	D	A	A	D	C
Day 41	D	C	C	A	C
Day 42	A	B	D	D	C
Day 43	B	A	B	A	A
Day 44	A	B	A	A	C
Day 45	B	C	C	B	A

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Drug Index

(Generic Name & Drug Class)

A

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Q

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T

List of Medical Abbreviations Used in Index

ACEI; Angiotensin-Converting Enzyme Inhibitor
ACTH; Adrenocorticotropic Hormone
ARB; Angiotensin II Receptor Blocker
ARNI; Angiotensin-Receptor Neprilysin Inhibitor
CAI; Carbonic Anhydrase Inhibitor
CCB; Calcium Channel Blocker
COMT; Catechol-O-Methyltransferase
GnRH; Gonadotropin-releasing Hormone
G-CSF; Granulocyte Colony–Stimulating Factors
mAb; Monoclonal Antibody
MAOI; Monoamine Oxidase Inhibitor
NMDA; N-Methyl-D-Aspartate
NRI; Norepinephrine Reuptake Inhibitor
SERM; Selective Estrogen Receptor Modulator
SNRI; Serotonin/Norepinephrine Reuptake Inhibitor
SPRM; Selective Progesterone Receptor Modulator
SSRI: Selective Serotonin Reuptake Inhibitor
GM-CSF; Granulocyte Macrophage Colony-Stimulating Factor

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* Check Yourself
* Drug Index

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