TABLE 7–2 Cholinoceptor types and their postreceptor mechanisms.

Receptor Type	G Protein	Postreceptor Mechanisms
M_1	G_q	↑ IP_3, DAG cascade
M_2	G_i	↓ cAMP synthesis
M_3	G_q	↑ IP_3, DAG cascade
M_4	G_i	↓ cAMP synthesis
M_5	G_q	↑ IP_3, DAG cascade
N_M	None	Na^+/K^+ depolarizing current
N_N	None	Na^+/K^+ depolarizing current

TD

CHOLINERGICS

DIRECT

NON SELECTIVE

ACETYLCHOLINE

-primary NT in all autonomic gangla at the synpases between parasympathetic postganglion

-primary NT at the somatic (voluntary) skeletal muscle NMJ

MOA: Act on both M & N receptors. Activates M1 - M3 receptiors in all peripheral tissues

USES:

Miotic during ocular surgery

SE: DUMB BELSS

Notes:

-Short lived DOA: 5-30sec

-Rapidly hydrolyzed by AchE

-Results to increased secretion, smooth muscle contraction (except in vascular smooth muscle where it causes relaxation) and changes in heart rate

MUSCARINIC

BETANECHOL *CARBACHOL*

MOA: Activates M1-M3 receptors

Uses: Bladder and Bowel Atony (post surgery or spinal cord injury)

SE: Cyclospasm, Diarrhea, Urinary Urgency, Vasodilation, Reflex tachycardia, Sweating

Notes:

-Results to increased secretion, smooth muscle contraction (except in vascular smooth muscle where it causes relaxation)

-Resistant to AchE, orally active, act on M receptors only

CARBACHOL - for glaucoma, used as miotic

PILOCARPINE *CIVEMELINE*

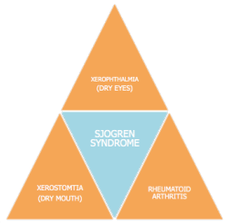
MOA: Activates M3 receptors on ciliary muscle (increasing aqueous humor outflow) & salivary glands (increasing salivation)

Uses: Glaucoma, Sjogren syndrome, Sicca Syndrome

SE: DUMB BELSS

Notes:

-Good lipid solubility compared to choline esters



NICOTINIC

NICOTINE *VARENICLINE*

MOA: Activates nicotinic Ach receptors (Nn & Nm)

Uses: Smoking cessation

SE: Generalized ganglionic stimulation (hypertension, tachycardia, nausea, vomiting, diarrhea)

Notes:

-OVERDOSE leads to convulsions, paralysis & coma

-Activates autonomic post ganglionic neurons (both sympa & parasymp) & skeletal muscle neuromuscular end plates

-DOA: 1-6 hr only

VARENICLINE - Selective partial agonist at nicotinic receptors; DOA 12-24h

INDIRECT

NEOSTIGMINE *PYRIDOSTIGMINE PYSOSTIGMINE AMBENONIUM* DEMECARIUM (Carbamates) *ECHOTHOPHATE (Organophosphate)*

MOA: Inhibits AchE

Uses:

-Myasthenia gravis (treatment)

-Reversal of nondepolarizing NM blockade

-Glaucoma (physostigmine, echothiophate, demecarium)

SE: DUMB BELSS

Notes:

-Muscarinic effects are blocked by ATROPINE

-NEOSTIGMINE: poor lipid solubility, oral, DOA 30min-2hr

-PYRIDOSTIGMINE: poor lipid solubility, oral, DOA 4-8hr

-PHYSOSTIGMINE: good lipid solubility, able to enter CNS, DOA 4-8hr

-ECHOTHIPATE: moderate lipid solubility, DOA 2-7days

-Other organophosphates:

MALATHION (Scabicide), and **PARATHION** (Insectidide): high lipid solubility, DOA 7-30 days

SARIN, TABUN, SOMAN: Nerve Gases

EDROPHONIUM

MOA: Inhibitis AchE

Uses:

-Myasthenia gravis (diagnosis - Tensilon Test)

-Differentiation of cholinergic crisis & myasthenic crisis

SE: DUMB BELSS

Notes:

IV, short lived, DOA 5-15mins

RIVASTIGMINE *GALANTAMINE DONEPEZIL TACRINE*

MOA: Inhibits AchE

Uses: **Alzheimer's Disease**

SE: DUMB BELSS

Notes:

RIVASTIGMINE is available at transdermal patch

DONEPEXIL is combined with Memantine (NMDA antagonist) for Alzhemer's Dementia)

ORGANOPHOSPHATE POISONONING

D iarrhea
U rination
M iosis
B rochospasm
B radycardia
E xcitation (skeletal muscle & CNS)
L acrimation
S weating
S alivation

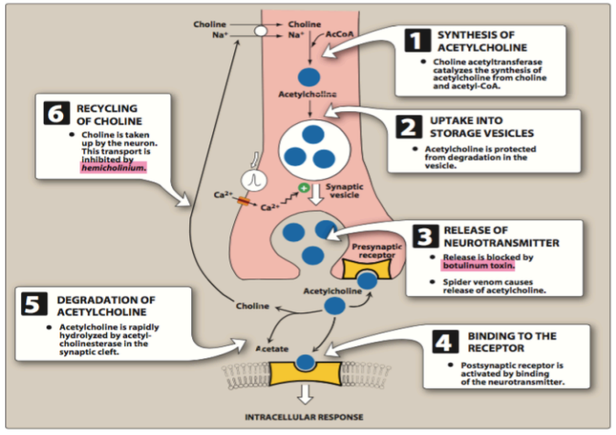
ORGANOPHOSPHATE POISOING TREATMENT

ATROPINE

MOA: Competitvely blockas ALL muscarinic receptors
Uses: Mydriatic, Cycloplegic, FIRST CHOICE ANTIDOTE FOR ORGANOPHOSPHATE
Notes: No effect on nicotinic signs of toxicity. Notorious for causing hyperthemia

PRALIDOXIME

MOA: Binds phosphorus of organophosphates. Breaks organophosphate bond with cholinesterase (regenerate active AchE)
Uses: Antidote for EARLY stage cholinesterase inhibitor poisoning; Can relieve skeletal muscla & endplate block
SE: Muscle weakness
Notes: Must be administered before 6-8 hours of organophosphate bond with cholinesterase; has oxime group which has high affinity for phosphorus



TD

ANTI CHOLINERGICS

ANTI MUSCARINIC

SELECTIVE

IPRATROPIUM *Tiotropium Umeclidinium Glycovrronium*

MOA: Blocks M3 (bronchial smooth muscle). Prevents vagal stimulated brochoconstriction

USES: **Acute Asthma, COPD**

SE: Alice in Wonderland

DICYCLOMINE *Hyoscyamine Glycopyrrolate*

MOA: Completitvely blocks M3 receptors

Uses: IBS, minor diarrhea, decreased acid secretion in GIT

SE: Alice in Wonderland

Available in PO & IV forms, relatively short half life (6hrs). Other name: Dicycloverine

OXYBUTYNIN *Darifenacin, Solifenacin, Tolteradine, Trospium, Imidafenacin*

MOA: Slightly blocks M3 receptors. Reduces detrusor muscle tone.

Uses: Urge incontinence, Post operative spasms

SE: Alice in Wonderland

Available as patch (may cause pruritus)

NON SELECTIVE

ATROPINE *Homatropine, Cyclopentolate, Tropicamide*

PROTOTYPE NONSELECTIVE MUSCULAR BLOCKER

MOA: Competitvely blocks all muscarinic receptors

Uses: Mydriatic, Cycloplegic, **1st choice for Organophosphate poisoning**, Bradycardia, Hypersalivation

SE: Atropine Toxicity (Alice in Wonderland)

BENZTROPINE *Biperiden Trihexyphenidyl*

MOA: Competitvely blocks all muscarinic receptors. Restores NT balance in basal ganglia.

Uses: **Parkinsons Dse**

SE: Alice in Wonderland

Notes: Reduces tremors more than bradykinesia or ridgidity

SCOPOLAMINE

MOA: Competitively blocks all muscarinc receptors. Antagonize histamine & serotonin

Uses: **Motion sickness;** decreased acid secretion in GIT; N/V

SE: Alice in Wonderland

Notes: Applied as transdermal patch

ANTI NICOTINIC

NEUROMUSCULAR BLOCKER

DEPOLARIZING

SUCCINYLCHOLINE

NON DEPOLARIZING

1) TUBOCURARINE
2) PANCURONIUM
3) ATRACURONIUM
4) VEROCURONIUM
5) ROCURONIUM

GANGLION BLOCKER

HEXAMEHTHONIUM

MOA: Competively blocks Nn nicotinic receptors

Uses: Hypertension (obsolete), Hypertensive emergencies

SE: Postural hypotension, Sexual Dysfunction, Constipation, Dry mouth, Blurred vission

CHOLINESTERASE REGENERATOR

PRALIDOXIME

MOA: Binds phosphorus of organophosphate. BReask organophosphate bond with cholinesterase. Regenerate active AchE.

Uses: Antidote for early stage cholinesterase inhibitor poisoning (organophosphate & nerve gas poisoning); can relieve skeletal muscle & endplate block

SE: muscle weakness

Notes: must be administered before 6-8 hours of organophosphate bond with cholinesterase occurs; has oxime group which has high affiniity for phosphate

TABLE 8–1 Effects of muscarinic blocking drugs.

Organ	Effect	Mechanism
CNS	Sedation, anti-motion sickness action, antiparkinson action, amnesia, delirium	Block of muscarinic receptors, several subtypes
Eye	Cycloplegia, mydriasis	Block of M_3 receptors
Bronchi	Bronchodilation, especially if constricted	Block of M_3 receptors
Gastrointestinal tract	Relaxation, slowed peristalsis, reduced salivation	Block of M_1, M_3 receptors
Genitourinary tract	Relaxation of bladder wall, urinary retention	Block of M_3 and possibly M_1 receptors
Heart	Initial bradycardia, especially at low doses, then tachycardia	Tachycardia from block of M_2 receptors in the sinoatrial node
Blood vessels	Block of muscarinic vasodilation; not manifest unless a muscarinic agonist is present	Block of M_3 receptors on endothelium of vessels
Glands	Marked reduction of salivation; moderate reduction of lacrimation, sweating; less reduction of gastric secretion	Block of M_1, M_3 receptors
Skeletal muscle	None	

TABLE 8–2 Effects of ganglion-blocking drugs.

Organ	Effects
CNS	Antinicotinic action may include reduction of nicotine craving and amelioration of Tourette's syndrome (mecamylamine only)
Eye	Moderate mydriasis and cycloplegia
Bronchi	Little effect; asthmatic patients may note some bronchodilation
Gastrointestinal tract	Marked reduction of motility, constipation may be severe
Genitourinary tract	Reduced contractility of the bladder; impairment of erection (parasympathetic block) and ejaculation (sympathetic block)
Heart	Moderate tachycardia and reduction in force and cardiac output at rest; block of exercise-induced changes
Vessels	Reduction in arteriolar and venous tone, dose-dependent reduction in blood pressure; orthostatic hypotension usually marked
Glands	Reductions in salivation, lacrimation, sweating, and gastric secretion
Skeletal muscle	No significant effect

ATROPINE TOXICITY

Hot as a hare	Atropine fever
Dry as a bone	Atropine flush
Blind as a bat	Decreased secretions
Red as a beet	Tachycardia
Mad as a hatter	Arrhythmias
	Constipation
	Blurred vision
	CNS Toxicity

Contraindications to Muscarinic Blockers

Caution in infants
Acute angle closure glaucoma
Benign Prostatic Hyperplasia

TD

Type	Tissue	Actions
$Alpha_1$	Most vascular smooth muscle Pupillary dilator muscle Pilomotor smooth muscle Bladder trigone, prostatic smooth muscle Liver (in some species, eg, rat)	Contracts (↑ vascular resistance) Contracts (mydriasis) Contracts (erects hair) Contraction Stimulates glycogenolysis
$Alpha_2$	Adrenergic and cholinergic nerve terminals Platelets Some vascular smooth muscle Fat cells Pancreatic β (B) cells	Inhibits transmitter release Stimulates aggregation Contracts Inhibits lipolysis Inhibits insulin release
$Beta_1$	Heart Juxtaglomerular cells of kidney	Stimulates rate and force Stimulates renin release
$Beta_2$	Airways, uterine, and vascular smooth muscle Liver (human) Pancreatic β (B) cells Somatic motor neuron terminals (voluntary muscle) Heart	Relaxes Stimulates glycogenolysis Stimulates insulin release Causes tremor Stimulates rate and force
$Beta_3$	Fat cells	Stimulates lipolysis
Dopamine, (D_1)	Renal and other splanchnic blood vessels	Dilates (↓ resistance)
Dopamine, (D_2)	Nerve terminals	Inhibits adenylyl cyclase

ADRENERGICS/ SYMPATHOMIMETICS

DIRECT

NON SELECTIVE

EPINEPHRINE

MOA:

A1: vasocontricstion, increase BP

B1: increase HR, conduction & contractility

B2: bronchodilation

Uses: Cardiac arrest, Anaphylaxis (DOC), Asthma, COPD, Hemostasis

SE: Hypertension, Tachycardia, Ischemia, Hyperglycemia

Notes: Inactive PO; do not enter CNS significantly; short DOA; can cross placenta (may cause fetal anoxia)

NOREPINEPHRINE

MOA:

A1: vasocontricstion, increase BP

B1: increase HR, conduction & contractility

B2: bronchodilation

(not so much B2 activity)

Uses: Neurogenic shock, Cardiogenic shock (last resort)

SE: Extreme vasospasm, Tissue necrosis, Excessive BP increase, Arrythmias, infarction, Reflex Bradycardia

Notes: Compensatory vagal reflexes tend to overcoe the direct positive chronotropic effects; Alpha>Beta; Inactive PO; do not enter CNS significantly; short DOA

DOPAMINE

MOA:

Alpha 1: vasoconstriction, increase BP

B1: increase HR, conducion & contractility

D1: vasodilation in splanchnic & renal blood vessels

Uses: Cardiogenic shock, heart failure

SE: CVS disturbance, arrhytmias

Notes: Inactive PO; do not enter CNS significantly; short DOA; very effective in renal failure associated with shock

DOPAMINE
LOW DOSE (1-5mcg/kg/min) Vasodilation in splanchnic & renal vascular beds via D1 receptors Increased renal blood flow & urine output
MEDIUM DOSE (5-15mcg/kg/min) Increased renal blood flow, HR, cardiac contractility & CO via B1 receptors
HIGH DOSE (>15mcg/kg/min) Vasoconstriction & increased BP via A receptors

ISOPROTERENOL

MOA: non selective beta adrenegric receptors activator;

B1: increased HT, conduction & contractility

B2: bronchodilation

Uses: Asthma

SE: CVS disturbance, arrhythmias

Notes: synthetic catecholamine, not readily taken up into nerve endings

ALPHA

ALPHA 1

PHENYLEPHRINE

Pseudoephedrine, Oxymetazoline, Tetrahydrozoline, Midodrine, Naphazoline, Xylometazoline

MOA:

A1: vasoconstriction, increase BP

Uses: Nasal congestin, mydriatic, drug-induced hypotension, orthostatic hypotension, spinal shock

SE: Rebound nasal congestion (Rhinitis medicamentosa);supine HPN, stroke, MI, piloerection, urinary retention

Avoid PSEUDOEPHEDRINE in 1st term, may cause Gastroschisis

ALPHA 2

CLONIDINE

MOA:

A2: decrease central sympathetic outflow

Uses: HPN, Cancer pain, Opioid withdrawal

SE: Sedation, rebound HPN, dry mouth

Taper use prior to d/c to avoid rebound HPN;

Treat rebound HPN with PHENTOLAMINE;

When taken PO, there is initial increase in BP then will go down once the drug enters the CNS

METHYLDOPA

Guanfacine, Guanabenz, Dexmedetomidine, Tizanidine

MOA:

A2: decrease central sympathetic outflow

Uses: Preecmplasia, GHPN, sedative (Dexmedetomidine), muscle relaxant (Tizanidine)

SE: Sedation, Hemolytic Anemia (+) Coomb's test

APRACLONIDINE

Brimonidine

MOA: decreases secretion of aqueous humor

Uses: Glaucoma

SE: Blurring of vision, dry mouth, hyperemia, pruritus, eye discomfort

BETA

BETA 1

DOBUTAMINE

MOA: B1: increase HR & contractility

Uses: Acute heart failure, Cardiogenic shock

SE: Tachycardia, arrhythmias, tachyphylaxis, HPN, eosinophilic myocarditis, premature ventricular beats, angina, dysnea, fever, HA, nausea

BETA 2

SALBUTAMOL ALBUTEROL TERBUTALINE ISOXUPRINE RITODRINE

MOA:

B2: bronchodilation

USES:

SALBUTAMOL: Acute Asthma attach DOC

TERBUTALINE, RITODRINE, ISOXUPRINE: Tocolysis for preterm labor

SE: tachycardia, tremors, nervousness, restllessness, arrhythmias when used excessively, loss of responsiveness (tolerance)

May precipiate arrhythmias in COPD and heart disease

ISOXUPRINE: used as vasodilator in Reynaud's phenomenon; may cause maternal pulmonary edema

INDIRECT

REUPTAKE INHIBITOR

RELEASERS

PHENYLPROPANOLAMINE

MOA: Act mainly by causing release of NE, but also has direct agonist activity at some adrenegic receptors; activates A & B adrenegic receptors in respi mucosa

Uses: nasal vasoconstrictor, appetite supressant

May preciptate Hemorrhagic stroke esp in women

TD

ADRENERGIC ANTAGONISTS

ALPHA

NON SELECTIVE

IRREVERSIBLE

PHENOXYBENZAMINE

MOA: blocks A1>A2 irreversibly

Uses: Pheochromocytoma (presurgical)

SE: Orthostatic hypotension, Reflex tachycardia, GI irritation, MI

Forms covalent bond w alpha receptors (effects last for several days)

REVERSIBLE

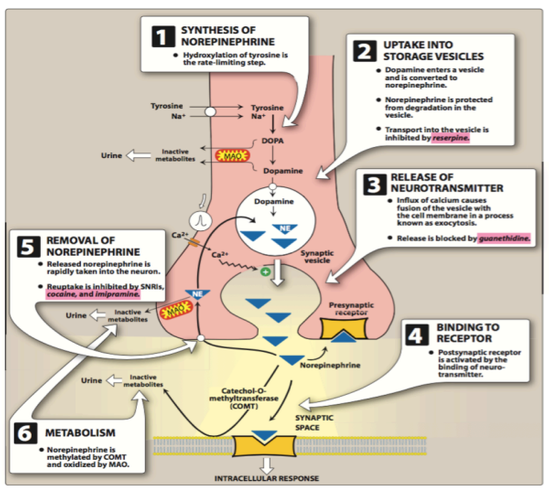
PHENTOLAMINE

Tolazoline

MOA:MOA: blocks A1>A2 rerversibly

Uses: Pheochromocytoma (presurgical), Antidote to A1 agonist overdose, Rebound HPN

SE: Orthostatic hypotension, Reflex tachycardia, GI irritation



ALPHA 1

PRAZOSIN

Doxazosin, Terazosin, Tamsulosin, Silodosin, Alfuzosin

MOA: Blocks A1 adrenergic receptors

Uses: BPH, HPN

SE: First dose orthostatic hypotension, Reflex tachycardia (less chance), dizziness, drowsiness, headache, weakness, asthenia, nausea, edema

TAMSULOSIN - most selective for prostatic smooth muscle

DOXAZOSIN, TAMSULOSIN, SILODOSIN & ALDUZOSIN - not indicated in females for tx of HPN

INTRINSIC SYMPATHOMIMETIC ACTIVITY:

-partial agonist activity
-lowers BP with modest reduction in HR
-advantage in treating patients with asthma bec these drugs are less likely to cause bronchospasm
-Acebutolol, Pindolol, Carteolol, Bopindolol, Oxprenolol, Celiprolol, Penbutolo

BETA BLOCKERS IN DM:

-masking of premonitory symptoms of hypoglycemia from insulin overdosage (tachycardia, tremor, anxiety)
-impaired hepatic mobilization of glucose

BETA

NON SELECTIVE

PROPANOLOL

Pindolol, Timolol, Labetalol, Carvedilol, Nadolol, Levobunolol, Metipranolol, Carteolol

MOA:blocks B1 & B2 receptors. Blocks sympathetic effects on heart & BP. Reduces renin release

Uses: Angina prophylaxis, HPN, Arrythmias, migraine, performance anxiety, hyperthyroidism, glaucoma

SE: bronchospasm, AV block, heart failure, CNS sedation, erectile dysfunction

Notes:

May mask symptoms of hypOglycemia in DM

CARVEDILOL & LABETALOL - combined A & B blockade (may used in pheochromocytoma

PROPANOLOL - IUGR, small placenta & congenital abnormalities have been reported with use, but no adequate & well-contracted studies conducted

METIPRANOLOL - used as ophthalmic drops for Glaucoma

BETA 1

ATENOLOL

Betaxolol, Esmolol, Acebutolol, Metoprolol, Alprenolol, Nebivolol, Bisoprolol

MOA: selectively blocks B1 receptors. Blocks sympathetic effects on heart & BP

Uses: Angina, HPN, heart failure, SVT (Esmolol only)

SE: Bronchospasm (less chance), AV block, heart failure, CNS sedation, erectile dysfunction

Notes:

Masks symptoms of hypOglycemia in DM

ESMOLOL - shortest half life (Esmall-LOL)

BETAXOLOL - may aslso be used as ophthalmic solution for glaucoma

ATENOLOL - use of this cardioselective BB during pregnancy has been shown to lower birthweights & impair fetal growth

DRUGS FOR GLAUCOMA

TD

Decrease secretion of aqueous humor from ciliary epithelium

- Alpha 2 Agonist → Apraclonidine
- Beta blocker → Timolol
- Carbonic Anhydrase Inhibitor → Acetazolamide, Dorzolamide
- Osmotic agents → Mannitol

FLOW OF AQUEOUS HUMOR
Ciliary body → Posterior chamber → Anterior chamber angle → Pupil → Anterior chamber → Trabecular meshwork → Canal of Schlemm → Uveosacral veins

Reciprocal control of Pupil:
SANS – pupillary dilator muscle
PANS – pupillary constrictor

Ciliary Muscle
(controls accommodation)
PANS (primary control of muscarinic receptors)
Insignificant contributions from SANS

Ciliary Epithelium
Important receptors with permissive effect on aqueous humor secretion

Increasae outflow of aqueous humor

- Canal of Schlemm → Prostaglandins → Latanoprost
- Uveosacrall veins → Alpha agonist → Epinphrine
- Trabecular meshwork → Cholinergic → Pilocarpine, Physostigmine

TD

ANTI HPN

SYMPATHOPLEGICS

CNS Sympathetic Outflow Blockers

CLONIDINE

MOA: activates A2 adrenergic recetors

Uses: HPN, cancer pain, opioid withdrawal

SE: sedation, rebound HPN, dry mouth

Taper use prior to d/c to avoid rebound HPN

Antidote: **PHENTOLAMINE**

METHYL-DOPA

MOA: activates A2 adrenergic recetors

Use: **Preeclampsia**

SE: sedation, **hemolytic anemia, (+) coombs test**

Adrenergic Blockers

Alpha 1 Selective

PRAZOSIN *Doxazosin, Terazosin, Tamsulosin, Silodosin, Alfuzosin*

MOA: Blocks A1 adrenergic receptors

Uses: BPH, HPN

SE: First dose orthostatic hypotension, Reflex tachycardia (less chance), dizziness, drowsiness, headache, weakness, asthenia, nausea, edema

TAMSULOSIN - most selective for prostatic smooth muscle

DOXAZOSIN, TAMSULOSIN, SILODOSIN & ALDUZOSIN - not indicated in females for tx of HPN

Beta Non Selective

PROPANOLOL *Pindolol, Timolol, Labetalol, Carvedilol, Nadolol, Levobunolol, Metipranolol, Betaxolol, Bisoprolol, Nebivolol*

MOA:blocks B1 & B2 receptors. Blocks sympathetic effects on heart & BP. Reduces renin release

Uses: Angina prophylaxis, HPN, Arrythmias, migraine, performance anxiety, hyperthyroidism, glaucoma

SE: bronchospasm, AV block, heart failure, CNS sedation, erectile dysfunction

Notes:

May mask symptoms of hypOglycemia in DM

CARVEDILOL & LABETALOL - combined A & B blockade (may used in pheochromocytoma

PROPANOLOL - IUGR, small placenta & congenital abnormalities have been reported with use, but no adequate & well-contracted studies conducted

METIPRANOLOL - used as ophthalmic drops for Glaucoma

Nerve Terminal Blockers

RESERPINE

MOA: irreversibly blocks the VMAT

Uses: HPN (obsolete)

SE: sedation, severe psychiatric depression, suicidal ideation

Avoid in px with hx of derpression

GUANETHIDINE *Guanadrel*

MOA: inhibit vesicular release of NE from the post synaptic neuron

Uses: HPN (obsolete)

SE: sedation, severe psychiatric depression, suicidal ideation

Avoid in px with hx of depression

Ganglion Blockers

HEXAMETHONIUM *Timethaphan Mecamylamine*

MOA: competitively blocks Nn Ach receptors

Uses: HPN (obsolete), HPN emergencies

SE: postural hypotension, dry mouth, blurred vision, constipation, sexual dysfunction

ANGIOTENSIN ANTAGONISTS

ACE Inhibitors

CAPTORPRIL Enalapril, Benazepril, Fosinopril, Lisinopril, Quinapril, Ramipril, Trandolapril, Moexipril, Perindopril, Imidapril

MOA: inhibits ACE & formation of angiotensin II. Decrease aldosterone secretion

Uses: HPN, HF, post-MI, DM nepropathy

SE: cough, taste disturbance, angioedema, hypotension, teratogen, hyperK

-slows ventricular remodelling & increases survival in HF

-delays progression of DM nephropathy

-use of drugs that act on RAAS during 2nd & 3rd trim reduces renal function & increases fetal & neonatal morbidity & death. D/c as soon as pregnancy is detected (fetal hypotension, neonatal skull hypoplasia, anuria, renal failure, renal dysplasia)

-may further decrease GFR in px w renal artery stenosis bec of dilation of the efferent arterioles

CAPTOPRIL - short t 1/2. necessitating 2-4x a day administration

ARBs

LOSARTAN *Candesartan, Valsartan, Irbesartan, Eprosartan, Telmisartan, Azilsartan, Valsartan*

MOA: blocls AT1 receptors in vascular smooth muscle & renal cortex. Decreases aldosterone secretion.

Uses: HPN, HF, DM nephropathy

SE: hypotension, teratogen, hyperK, hypoglycemia, anemia, diarrhea

-ARBs are as effective as ACEi but has less cough

-Slows ventricular remodelling & increases survival in HF

-delays progression of DM nephropathy

use of drugs that act on RAAS during 2nd & 3rd trim reduces renal function & increases fetal & neonatal morbidity & death. D/c as soon as pregnancy is detected (fetal hypotension, neonatal skull hypoplasia, anuria, renal failure, renal dysplasia)

-may further decrease GFR in px w renal artery stenosis bec of dilation of the efferent arterioles

DIURETICS

Thiazides

HYDROCHLORTHIAZIDE *Chlorthalidone, Indapamide, Metalazone*

MOA: inhibits Na-Cl trasnporter in DCT; cause moderate diuresis & reduced excretion of Ca

Uses: HPN (1st line), HF, hypercalciuria, renal Ca stones, nephrogenic DI

SE: hypoK met alka, dilutional hypoNa, K wasting, hyperGLUC, sulfa allergy

METOLAZONE - appears in cord blood & crosses plaenta & may cause hypoK, hypoNa, hypoglycemia, jaundice & thrombocytopenia

Loop Diuretics

FUROSEMIDE *Bumetanide, Torsemide, Ethacrynic acid*

MOA: inhibit Na-K-2Cl transporter in TAL of Henle. Cause powerful diuresis & increased Ca excretion

SE: hypoK met alka, K wasting, dehydration, ototoxicity, sulfa allergy, hyperuricemia, hypomagnesemia, nephritis, hypoCa

ETHACRYNIC ACID - a loop diuretic that is not a sulfur derivative & can be given in px with sulfur allergy

RENIN INHIBITOR

Aliskerin

MOA: inhibits renin. Prevents conversion of angiotensinogen to angiotensin I

Usesu: HPN

SE: HA, diarrhea, cough, rash, hyperK, increase in serum Crea, renal impairment, angioedema

-Fetal harm may cocur when given during pregnancy

of drugs that act on RAAS during the 2nd & 3rd term reduces renal function & increases fetal & neonatal morbidity & death

VASODILATOR

CCB

Dihydropyridine

NIFEDIPINE *Amlodipine, Felodipine, Nicardipine, Nisoldipine, Clevidipine, Isradipine, Levamlopidine, Lacidipine, Lercanidipine*

MOA: blocks voltage gatedL-type Ca channels (vascular > cardiac)

Uses: Angina, HPN

SE: constipation, pretibial edema, nausea, flushing, dizziness

-greater vasodilator effect than cardiodepressant effect

Non Dihydropyridine

VERAPAMIL *Diltiazem*

MOA: blocks voltage gated L-type Ca channels (cardiac > vascular)

Uses: angina, HPN, SVT migraine

SE: costipation, pretibial edema, nausea, flushing, dizzinesss, gingival hyperplasia, HF, AV block, sinus depression

-excessive cardiac depression may occur

Older Oral

HYDRALAZINE

MOA: alters intracellular Ca metabolism. relaxes arteriolar smooth muscle; decreases afterload

Uses: HPN, HF (in combination with ISDN)

SE: edema, reflex tachycardia, MI, drug-induced lupus

-Combination tx w ISDN for HF is more effective than ACEi in blacks

MINOXIDIL *Diazoxide*

MOA: opens K channels in vascular smooth muscle cuaisng hyperpolarization, muscle relaxtaion & vasodilation

Uses: HPN, alopecia

SE: edema, reflex tachycardia, angina, pericarditis, pulmo HPN, hypertrichosis, hirsutism, salt & water retention

-requires concomitant use of diuretics & BBs to block compensatory responses

Parenteral

NITROPRUSSIDE

MOA: relaxes venouse & arteriolar smooth muscle by increasing NO --> increases cGMP causing smooth muscle relaxation

Uses: HPN emergency, acute HF, cardiogenic shock, controlled hypotension

SE: hypotension, HA, cyanide toxicity

-not commonly used bec it is very light sensitive, has short duration of action; given as continuous infusion

FENOLDOPAM

MOA: D1 agonist; causes arteriolar vasodilation of the afferent& efferant arterioles; increases renal blood flow

Uses: HPN emergency

SE: hypotension, hypoK -

short duration of action: 10 mins

TD

DRUGS FOR ANGINA PECTORIS

VASODILATORS

NITRATES

ULTRA SHORT

AMYL NITRITE

MOA: release NO, increases cGMP & relaxes smooth muscle esp vascular

Uses: Cyanide Poisoning

SE: reflex tachycardia, orthostatic hypotension, headache, methemoglobinemia

ROA: inhalational

SHORT

NITROGLYCERINE *ISDN, ISMN*

MOA: release NO, increases cGMP & relaxes smooth muscle esp vascular

Uses: Angina, acute coronary syndrome

SE: reflex tachycardia, orthostatic hypotension, headache, tolerance (transdermal)

Dangerous hypotension with PDE inhibitors such as Sildenafil

First pass effect is ~90% (NTG)

NTG also decrease plt aggregation

Nitrate-induced headache: due to meningeal blood vessel vasodilation

LONG

TRANS-DERMAL

CCBS

DIHYDRO-PYRIDINE

NIFEDIPINE

Amlodipin
Felodipin
Nicardipin
Nisoldipin
Clevidipin
Isradipine

MOA: blocks voltage gatedL-type Ca channels (vascular > cardiac)

Uses: Angina, HPN

SE: constipation, pretibial edema, nausea, flushing, dizziness

Greater vasodilator effect than cardiodepressant effect

NON DIHYDROPYRIDINE

VERAPAMIL

MOA: blocks voltage gated L-type Ca channels (cardiac > vascular)

Uses: angina, HPN, SVT migraine

SE: constipation, pretibial edema, nausea, flushing, dizzinesss, gingival hyperplasia, HF, AV block, sinus depression

Excessive cardiac depression may occur

DILTIAZEM

MOA: blocks voltage gated L-type Ca channels (cardiac > vascular)

Uses: angina, HPN, SVT migraine

SE: costipation, pretibial edema, nausea, flushing, dizzinesss, gingival hyperplasia, HF, AV block, sinus depression

Excessive cardiac depression may occur

CARDIAC DEPRESSANT

CCBs

BETA BLOCKERS

PROPANOLOL

Pindolol, Timolol, Labetalol, Carvedilol, Nadolol, Levobunolol, Metipranolol

MOA:blocks B1 & B2 receptors. Blocks sympathetic effects on heart & BP. Reduces renin release

Uses: Angina prophylaxis, HPN, Arrythmias, migraine, performance anxiety, hyperthyroidism, glaucoma

SE: bronchospasm, AV block, heart failure, CNS sedation, erectile dysfunction

May mask symptoms of hypOglycemia in DM

OTHERS

METABOLISM MODIFIERS

TRIMETAZIDINE

MOA: inhibit beta oxidation of FA by inhibiting 3-ketoacyl-coA thiolase which enhances glucose oxidation. Prevents decrease in ATP in ischemic/hypoxic state

Uses: angina pectoris, tinnitus, dizziness

SE: EPS, gait instability, restless leg syndrome I

Interacts with MAO inhibitors

RANOLAZINE

MOA: reduces a late, prolonged Na current in myocardial cells --> increase Ca expulsion via Na-Ca exchanger --> decrease intracellular Ca --> decrease cardiac force & work load. May also modify FA oxidation

Uses: prophylaxis of angina

SE: QT prolongation, nausea, constipation, dizziness

CYP3A4 inhibitors increase Ranolazine concentration & DOA

IVABRADINE

MOA: increase funny Na current in SA node, decreases hyperpolarization, induces inward pacemaker current --> decrease HR & cardiac work

Uses: prophylaxis of angina, HF

SE: bradycardia, HPN, atrial fibrillation

Complex IV (cytochrome oxidase) of the ETS is affected by cyanide.

Antidote for cyanide poisoning: Lilly Cyanide Kit: inhaled amyl nitrite + IV sodium nitrite + IV sodium thiosfulate

MONDAY DISEASE: due to occupational exposure to nitrates; alternating development of tolerance (during work week) & loss of tolerance (over the weekend) every Monday

THERAPEUTIC STRATEGIES IN ANGINA:

-defect that causes angina pain is inadequate coronary oxygen delivery relative to the myocardial oxygen requirement

-can be corrected in 2 ways:

- increasing oxygen delivery
- reducing oxygen requirement

DRUGS THAT CAN CAUSE GINGIVAL HYPERPLASIA:

NapaCa-Pangit ng gingiVa mo!

Nifedipine
Cyclosporine
Phenytoin
Verapamil

	Nitrates Alone	Beta Blockers or Calcium Channel Blockers Alone	Combined Nitrates and β Blockers or Calcium Channel Blockers
Heart rate	*Reflex increase*	**Decrease**	**Decrease**
Arterial pressure	**Decrease**	**Decrease**	**Decrease**
End-diastolic pressure	**Decrease**	*Increase*	**Decrease**
Contractility	*Reflex increase*	**Decrease**	No change or decrease
Ejection time	**Reflex decrease**	*Increase*	No change
Net myocardial oxygen requirement	**Decrease**	**Decrease**	**Decrease**

TD

DRUGS USED IN HEART FAILURE

POSITIVE INOTROPES

CARDIAC GLYCOSIDE

DIGOXIN *Digitoxin*

MOA: **inhibits Na/K ATPase**; Increase intracellular Ca increasing cardiac contractility

Uses: HF, nodal arrhythmias

SE: narrow therapeutic index, arrythmias, vomiting, diarrhea, visual changes

Reduced clerance with Quinidine, Amiodarone, Cyclosporine, Diltiazem & Verapamil.

Arrythmogenesis increased by hypoK, hypoMg & hyperCa

BETA AGONIST

DOBUTAMINE (B1 seletive); DOPAMINE

Not appropriate for chronic failure because of tolerance, lack of orak efficacy & significant arrhythmogenic effects

PDE INHIBITORS

INAMIRINONE MILRINONE

Increase cAMP by inhibiting its breakdown by phosphodiesterase; increase intracellular Ca; vasodilation

Should not be used in chronic failure because they increase morbidity & mortality

VASODILATORS

Dramatically effective in CHF due to increased afterload (eg: continuing HPN in an individual who has just had an infarct)

NITROPRUSSIDE NITROGLYCERIN

For **acute severe failure with congestion**

HYDRALAZINE ISDN

Have been shown to reduce mortality in African Americans

MISCELLANEOUS

BNP ANALOG

NESIRITIDE - increase cGMP; may be used for acute decompensated failure but has not been shown to reduce mortality

DIURETICS

FIRST LINE therapy for both systolic & diastolic failure

FUROSEMIDE - immediate reduction of pulmonary congestion & severe edema associated with acute HF

SPIRINOLACTONE & EPLERENONE - have significant long-term benefits & can reduce mortality in chronic failure

ACE INHIBITORS & ARBS

FIRST LINE DRUGS for Chronic Heart Failure

Reduced aldosterone secretion, salt & water retention and vascular resistance

Decrease morbidity & mortality in chronic heart failure

BETA BLOCKERS

CARVEDILOL
LABETALOL
BISOPROLOL
NEBIVOLOL
METOPROLOL

Reduced progression of chronic heart failure B blockers are not of value in acute failure & may be detrimental if systolic dysfunction is marked

SACUBITRIL

Used in combination with Valsartan for HF

It is a prodrug that is activated to **Sacubitrilat**, which inhibiits the enzyme: Neprilysin (responsible for the degradation of ANP & BNP - two BP lowerong peptides that work mainly by reducting blood volume. This enzyme also degrades Bradykinin - an inflammatory mediator exerting potent vasodilatory action

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DIGITALIS TOXICITY

-Increase by hypoK, hypoMg & hyperCa
- Loop diuretics & thiazides may significantly reduce serum K & precipitate Digitalis Toxicity
- Digitalis-induced vomiting may deplete serum Mg & similarly facilitate toxicity

CORRECTION OF DIGITALIS TOXICITY

-Correction of K/Mg deficiency
-Antiarrhythmic drugs
  -drug of choice: **LIDOCAINE**
  -electronic pacemaker may be required in severe cases
-Digoxin Antibodies
  -Fab fragments; Digibind
  -may save patients who would otherwise die

NARROW THERAPEUTIC INDEX

WALA C PaPa V DiTo

Warfarin
Aminoglycosides
Lithium
Amphotericin B
Carbamazepine
Phenobarbital
Phenytoin
Vancomycin
Digoxin
Theophylline

What drugs have been shown to improve SURVIVAL in cases of HF?

ABA, buhay kappa!

ACE inhibitors
Beta blockers
Aldosterone antagonist

TD

ANTI ARRHYTHMICS

1 CLASS 1 SODIUM CHANNEL BLOCKERS acts on phase 0

A — A prolong AP

MOA: Use- & state- dependect block of Na channels influx; some block K channels influx. Slowed conduction velocity & pacemaker activity; prolonged AP duration & refractory period

*Mnemonic: **D**ouble **Q**uarter **P**ounder*

PROCAINAMIDE

Uses: Atrial & ventricular arrhythmias, esp after MI

SE: arrythmias, hypotension, lupus-like syndrome

HyperK exacerbates cardiac toxicity

Crosses into breast milk

DISOPYRAMIDE

Uses: Atrial & ventricular arrhythmias

SE: arrythmias, hypotension, marked antimuscarinic effects, HF

HyperK exacerbates cardiac toxicity

Crosses into breast milk

QUINIDINE

Uses: Atrial & ventricular arrhythmias, **Malaria**

SE: arrythmias (torsades), hypotension, Cinchonism (headache, vertigo, tinnitus), cardiac depression, GI upset, autoimmune reactions (ITP), hemolytic anemia

HyperK exacerbates cardiac toxicity

Crosses into breast milk. Use with extreme caution in pregnant patients

Reduces clearance of Digoxin

Treatment of Class 1A Overdose:
-Sodium Lactate to reverse drug-induced arrhythmias
-Pressor sympathomimetics to reverse drug-induced hypotension if indicated

B — B shortens AP

LIDOCAINE / Mexilentine / Tocainide / Phenytoin

*Mnemonic: **T**omato **L**ettuce **M**ayo **P**lease*

Grp 1B - slows recovery of Na channels from inactivation leading to prolonged ERP

Selectively affects ischemic or depolarized Purkinje & ventricular tissue (little effect on ECG)

MOA: Highly seletive use & state- dependent Na influx block; minimal effect in normal tissue; no effect on K influx

Uses: DOC for ventricular arrhythmias post MI, Digoxin-induced arrythmias

SE: CNS stimulation, cardiovascular depression, arrythmias, allergy, agranulocytosis (Tocainide)

Only affect ischemic tissue

HyperK exacerbates cardiac toxicity

LIDOCAINE is the least cardiotoxic among conventional anti arrhythmics; never given PO due to significant first pass effect

PHENYTOIN - increased incidence of major malformations (orofacial clefts, cardiac defects, fetal hydantoin syndrome effect) & cognitive defects has been reported for pregnant who use it for epilepsy; also secreted in human milk

C — C no effect on AP duration

FLECAINIDE / Propafenone / Encainide / Moricizine

*Mnemonic: **M**ore **E**xtra **F**ries **P**lease*

Grp 1C - powerful depressant of Na current

Can markedly slow conduction velocity in atrial & ventricular cells

ECG effects: no effect on ventricular AP duration or QT interval; increase QRS duration

MOA: Selective use & state- dependent block of Na influx; slowed conduction velocity & pacemaker activity

Uses: refractory arrhythmias

SE: increased arrhythmias (proarrhythmic effects), CNS excitation

HyperK exacerbates cardiac toxicity

Contraindicated for post MI arrhythmias

Enters breast milk

2 CLASS 2 BETA BLOCKERS acts on phase 4

primarily cardiac beta-adrenoceptor blockade & reduction in cAMP: reduction in both Na & Ca currents, suppression of abnormal pacemakers

AV node is particularly sensitive to blockers, PR interval usually prolonged

PROPANOLOL / Metoptolol / Timolol

MOA: Blocks Beta receptors; slowed pacemaker activity

Uses: Post MI prophylaxis against sudden death, Thyrotoxicosis

SE: bronchospasm, cardiac depression, AV block, hypotension

In CHF, reduces progression and decreases incidence of potentially fatal arrhythmias

SOTALOL is a beta blocker anti arrhythmic that has Class 3 properties. Sotalol & Amiodarone aslo have group 2 effects

METOPROLOL & TIMOLOL is concentrated in breast milk

ESMOLOL

MOA: Selectively blocks beta 1 receptors; slowed pacemaker activity

Uses: Acute perioperative & thyrotoxic arrhythmias, SVT

SE: bronchospasms, cardiac depression, AV block, hypotension

3 CLASS 3 K CHANNEL BLOCKERS acts on phase 3

Hallmark: prolongation of AP duration
-caused by blockade of K influx that are responsible for repolarization of AP
-results in increase ERP & reduces the ability of the heart to respond to rapid tachycardia

ECG: increase QT interval

*Mnemonic: **K**, SAD ☹*

S — SOTALOL

MOA: K influx block & beta adrenoceptor block

Uses: Ventricular arrhythmias, AFib, SVT

SE: dose-related torsades de pointes, excessive beta blockade (sinus bradycardia, asthma)

Drug present in breast milk

A — AMIODARONE / Dronedarone / Vernakalant

MOA: Strong K influx block produces marked prolongation of AP & refractory period. Grp 1 activity slows condution velocity; grp2 & 4 activity confers additional antiarrythmic activity

Uses: refractory arrhythmias, used off-label in many arrhythmias

SE: microcrystalline deposits in cornea & skin, thyroid dysfunction (hyper or hypo), paresthesia, tremor, pulmonary fibrosis

MOST EFFICACIOUS of all anti arrhythmics

Has the longest t1/2

Can cause fetal harm (cardiac, thyroid, neurodev, neurological & growth defects in neonates)

Amiodarone Toxicity:
Pulmonary fibrosis
Paresthesias
Tremors
Thyroid dysfxn
Corneal deposits
Skin deposits

D — DOFETILIDE / Ibutilide

MOA: Selectively K influx block; prolonged AP & QT interval

Uses: Treatment & prophylaxis of AFib

SE: torsades de pointes

Drugs that cause Agranulocytosis:
CCCAPPIT Me!
Clozapine
CoTrimoxazole
Colchicine
Aminopyrine
Phenylbutazone
PTU
Indomethacin
Tocainide
Methimazole

4 CLASS 4 CALCIUM CHANNEL BLOCKERS

AV conduction velocity is decreased & ERP increased

ECG: PR interval is consistently increased

Effective in arrhythmias that must traverse Ca-dependent cardiac tissues (AV node)

Cause a state- & use- dependent selective depression of Ca currents

NON DHYDROPYRIDINE

DILTIAZEM

MOA: blocks voltage gated L-type Ca channels (cardiac > vascular)

Uses: angina, HPN, SVT migraine

SE: costipation, pretibial edema, nausea, flushing, dizzinesss, gingival hyperplasia, HF, AV block, sinus depression

Excessive cardiac depression may occur

Should be avoided in ventricular tachycardia

VERAPAMIL

MOA: blocks voltage gated L-type Ca channels (cardiac > vascular)

Uses: angina, HPN, SVT migraine

SE: costipation, pretibial edema, nausea, flushing, dizzinesss, gingival hyperplasia, HF, AV block, sinus depression

Excessive cardiac depression may occur

Should be avoided in ventricular tachycardia

DIURETICS

TD

SALT EXCRETION

PCT

-carries out isoosmotic reabsorption of amino acids, glucose & numerous cations
-major site for NaCl & NaHCO3 reasbsorption (60-70%)
-site of uric acid transport

CARBONIC ANHYDRASE INHIBITORS

ACETALOZAMIDE
Dorzolamide
Brinzolamide
Dichlorphenamide
Methazolamide

MOA: inhibits carbonic anhydrase; in glaucoma, secretion of aqueous humor is reduced; in mountain sickness, metabolic acidosis increases respiration

Uses: glaucoma, mountain sickness, edema with alkalosis

SE: drowsiness, paresthesias, sulfa allergy, renal Ca stones, K wasting, hyperCl NAGMA, hepatic enceph in cirrhotic px

Enters the breast milk
Diuresis is self limiting after 2-3 days

TAL

-responsible for a significant % of NaCL reabsorption via Na-K-2CL transporter
-site of Ca & Mg reabsorption
-Prostaglandins are important in maintainung glomerular filtration

LOOP DIURETICS

FUROSEMIDE
Bumetanide
Torsemide
Ethacrynic acid

MOA: inhibit Na-K-2Cl transporter; cause powerful diuresis & increase Ca excretion

Uses: HF, pulmonary edema, HPN, hyperCa, acute renal failure, anion overdose

SE: hypoK metab alkalosis, K wasting, dehydration , ototoxicity, sulfa allergy, hyperuricemia, hypoCa, hypoMg, nephritis

Synergistic ototoxicity with Aminoglycosides
Efficacy decreased by NSAIDS

LOOP DIURETICS TOXICITY
OH DANG!
Ototoxicity
Hypokalemia
Dehydration
Allergy to Sulfa
Nephritis
Gout

DCT

-actively pumps Na & Cl out of the lumen of the nephron via Na-Cl transporter
-responsible for ~5-8% of Na reabsorption
-Ca is also reabsorbed in this segment under the contol of PTH

THIAZIDE

HYDROCHLORTHIAZIDE
Chlorthalidone
Indapamide
Metolazone
Bendroflumethiazide
Hydroflumethiazide
Methyclothiazide
Polythiazide
Quinethazone
Trichlormethiazide

MOA: inhibit Na-Cl transporter; cause moderate diuresis & reduced Ca excretion

Uses: HPN, HF, hypercalciuria, renal Ca stones, nephrogenic DI

SE: hypoK metab alka, dilutional hypoNa, K wasting, sulfa allergy, hyperGLUC

Synergistic effect with Loop diuretics
Efficacy decreased by NSAIDS

CCD

-last tubular site of Na reabsorption
-responsible for reabsorbing 2-5% of total filtered Na
-under te influence of aldosterone, reasbsoption of Na occurs via channels, accompanied by an equivalent loss of K or H+
-primary site of acidification of urine
-last site of K excretion

K SPARING

ALDOSTERONE ANTAGONISTS

SPIRINOLACTONE
Eplerenone

MOA: steroid inhibitors of cytoplasmic aldosterone receptor; reduce K exretion

Uses: hyperaldosteronism, HPN, HF, hypoK

SE: hyperK, gynecomastia (spiriniolactone), impotence, BPH, hypoC metab acidosis

EPLERENONE - reduces progression of DM nephropathy & reduces mortality in post MI

GYNECOMASTIA
Spirinolactone
Digoxin
Cimetidine
Alcohol
Ketoconazole

ENACS INHIBITORS

AMILORIDE
Triamterene

MOA: inhibits ENaC epithelial sodium channels; reduces Na reabsorption & K excretion

Uses: hypoK

SE: hyperK, acute renal failure (with indomethacin), kidney stones, metabolic acidosis

Should never be given with K supplements

WATER EXCRETION

OSMOTIC

MANNITOL
Glycerin
Isosorbide
Urea

MOA: osmotically retains water in tubule by reducing reabsorption in PCT, descending loop of Henle & CD; in the periphery, mannitol extracts water from cells

Uses: rhabdomyolysis, hemolysis, increased ICP, acute glaucoma

SE: transient volume expansion (hypoNa, pulmonary edema, followed by HyperNa), headache, N/V, dehydration

Used to maintain high urine flow

ADH

AGONIST

VASOPRESSIN
Desmopressin
Terlipressin

MOA: agonists at V1 & V2 ADH receptors; activate insertion of aquporin in water channles in collecting tubule; vasoconstricton

Uses: central DI, nocturnal enuresis, hemophilia, von Willerbrand's dse

SE: hypoNa, HPN

Increses the Factor VIII activity in mild hemophilia A or von Willerbrand dse

TERLIPRESSIN:not recommended during pregnancy as it can cause uterine contrxn & may decrease uterine blood flow; may have harmful effects on pregnany & fetus

ANTAGONIST

CONIVAPTAN Tolvaptan
Lixivaptan
Demeclocycline Lithium

MOA: antagonist at V1 & V2 receptors

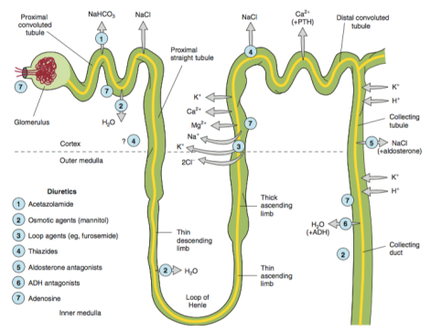
Uses: SIADH, hypoNa

SE: infusion site rxns, hyperKa, nephrogenic DI, renal filaure (lithium, demeclocycline), bone & teeth abnormalities (demeclocycline)

Central Pontine Myelinolysis may occur with rapid correction of hypoNa

LIXIVAPTAN is considered an Orphan Drug

Group	Amount in Urine NaCl	$NaHCO_3$	K^+	Body pH
Carbonic anhydrase inhibitors	↑[a]	↑↑↑[a]	↑[a]	Acidosis[b]
Loop diuretics	↑↑↑↑	—	↑	Alkalosis
Thiazides	↑↑	↑,—	↑	Alkalosis
K^+-sparing diuretics	↑	—	↓	Acidosis



TD

DYSLIPIDEMIA DRUGS

STATINS
DOC FOR HIGH CHOLESTEROL

SIMVASTATIN
Atorvastatin, Rosuvastatin, Fluvastatin, Pravastatin, Lovastatin, Pitavastatin

MOA: inhibits rate-limiting enzyme in cholesterol biosynthesis. Increased hepatic cholesterol uptake. Increased high-affinity LDL receptors. Decreased LDL levels. Causes modest reduction in triglycerides.

Uses: Hypercholesterolemia (high LDL), ACS/ atherosclerotic vascular dse (primary & secondary prevention), Ischemic stroke

SE: hepatotoxicity, myopathy, rhabdomyolysis, GI distress

Increased risk of mupotahy & rhabdomyolysis when used with fibrates.

Given before bedtime bec cholesterol synthesis predominantly occurs at night.

Contraindicated for use in pregnant bec safety is not established and no appraent benefit.

SIMVASTATIN & LOVASTATIN - prodrugs; all the rest are active form

ROSUVASTATIN, ATORVASTATIN & SIMVASTATIN - greater maximal effect that other statins

If given with resins, give at least 1hour before or 4 hours after resin administration (resins decreases the absorption of statins).

Has CYP450 dependent metabolism.

BILE ACID RESINS

CHOLESTYRAMINE
Colesevelam
Colestipol

MOA: binds bile acids, preventing their reabsorption & increasing cholesterol utilization for replacement --> upregulates LDL receptors ---> modestly lowers LDL levels

Uses: Hypercholesterolemia (high LDL), pruritus in cholestasis, digitalis toxicity

SE: constipation, bloating, gritty tase, steatorrhea, gallstones (rare), malabsorption (vit K)

Increases TGs & VLDL in patients with high TGs.

Treat constipation with fiber supplements/ psyllium.

Avoid in patients with diverticulitis.

Interferes with absorption of some drugs & vitamins.

Shoudl be taken with meals.

Non-absorbable polymers that bind bile acids & similar steroids in the intestines preventing their absorption

CHOLESTEROL ABSORPTION BLOCKERS

EZETIMIDE

MOA: selective inhibitor of NPC1L1 transporter, decreasing interstinal absorption of cholesterol & other phytosterols --> decreases choleterol hepatic pool, increases hepatic LDL receptors --> decreases LDL & phytosterols

Uses: hypercholesterolemia (high LDL), phytosterolemia

SE: hepatotoxicty (increased with statin use), myositis

Synergistic LDL-lowering effect with statins.

Considered a prodrug.

SITOSTEROL

MOA: Cholesterol analog, takes the place of dietary & biliary cholesterol, decreasing intestinal absorption of cholesterol & other phytosterols

Uses: hypercholesterolemia (high LDL), phytosterolemia

SE: GI upset, bloating, impotence (rare), coronary events

NIACIN
DOC FOR LOW HDL

MOA: decreases catabolism of apoA1; decreases VLDL syntheis & secretion from the liver; decreases LDL cholesterol concentrations; increases HDL cholesterol

Uses: hypercholesterolemia (low HDL, high LDL/VLDL)

SE: flushing, pruritus, rashes, acathosis nigricans, GI irritation, hepatotoxicity (mild), hyperuricemia, IGT, arrythmias, amblyopia

Avoid in patients with PUD.

Potentiates effects of anti hypertensives (vasodilators, ganglion blockers).

Decreases fibrinogen and increase t-PA

FIBRATES
DOC FOR HIGH TGs

GEMFIBROZIL
Fenofibrate
Bezafibrate

MOA: activates PPAR-alpha & increases expression of lipoprotein lipase & apolipoproteins (apo-AI, apo-AII); lowers TGs; decreases secretion of VLDL; increases HDL

Uses: DOC for hyperTGs; hypercholesterolemia (low HDL, high LDL), fat redistribution syndrome

SE: nausea, rashes, leukopenia, hemoconcentration, incrreased risk of cholesterol gallstones

Increased risk of myopathy & rhabdomyolysis when used with statins.

Avoided in px with hepatic or renal dysfunction.

May increase LDL in px with familial combined hyperlipoproteinemia.

Higher risk of gallstine formation if given w/ resins

DISADVANTAGEOUS ANTI DYSLIPIDEMIC COMBINATIOS:

FIBRATE + RESIN = increased risk of cholelithiasis

STATIN + RESIN = impaired statin absorption

STATIN + FIBRATE = increased risk of myopathy & rhabdomyolysis

DRUGS THAT CAUSE CUTANEOUS FLUSHING:

V Vancomycin
A Adenosine
N Niacin
C CCBs

ASPIRIN pretreatment reduces flushing.

Other Anti-Dyslipidemic:
PROBUCOL
Antioxidant that inhibit the oxidation of LDL & lowers cholesterol in the blood by increasing rate of LCL catabolism in cholesterol elimination from the body. It may inhibit early states of cholesterol biosynthesis & slightly inhibit dietary cholesterol absorption. May also inhibit the oxidation & tissue deposition of LDL, thereby inhibiting atherogenesis; Used to lower LDL & HDL cholesterol, yet has little feect on serum TG or VLDL.

TD

HISTAMINERGIC AGENTS

H1 BLOCKERS

1st generation

DIPHENHYDRAMINE

Brompheniramine, Chlorpheniramine, Cyclizine, Meclizine, Buclizine, Hydroxyzine, Promethazine, Cyproheptadine, Clemastine, Tripelennamine

MOA: competitive pharmacologic block of peripheral & CNS H1 receptor plus alpha & muscarinic receptor block. Anti motion sickness effect.

Uses: hay fever, angioedema, motion sickness, insomnia, dystonia, anti-emetic (Promethazine), for serotonin syndrome (Cyproheptadine)

SE: drowsiness, ALICE in wonderland, anorexia, orthostatic hypotension

More likley to block autonomic receptors, also has alpha1 blocking & local anesthetic effect.

CYCLIZINE - more anti motion sickness action, less sedative & autonomic effects.

PROMETHAZINE - less antimotion sickness, more sedative & autonomic effects.

Usual half life: 4-12hours

2nd generation

CETIRIZINE

Loratadine, Fexofenadine, Desloratadine, Levocetirizine, Terfenadine, Astemizole, Ebastine, Azelastine, Bilastine, Rupatadine

MOA: competitive pharmacologic block of peripheral H1 receptors; No autonomic or anti motion sickness

Uses: hay fever, angioedema, urticaria

SE: None

Fatal arrhythmias from interaction between azoles/erythromycin & terfenadine/astemizole.

Usual half life: 12-24hours

H2 BLOCKERS

CIMETIDINE

Ranitidine, Famotidine, Nizatidine

MOA: competitive pharmacologic block of H2 receptors

Uses: PUD, Zollinger-Ellison syndrome, GERD; For nocturnal acid secretions

SE: CPY450 inhibitor & antiadrogen effects like gynecomastia (Cimetidine only); decreases hepatic blood flow

Used in ICU setting to prevent gastric erosion & hemorrhage.

Reduction of nocturnal acid secretion in gastric & duodenal ulcer, accelerate heaing & prevent recurrences.

Usual half life: 1-3 hours

Receptor Subtype	Distribution	Postreceptor Mechanisms	Prototypic Antagonist
H_1	Smooth muscle	G_q; ↑ IP_3, DAG	Diphenhydramine
H_2	Stomach, heart, mast cells	G_s; ↑ cAMP	Cimetidine
H_3	Nerve endings, CNS	G_i; ↓ cAMP	Clobenpropit[b]
H_4	Leukocytes	G_i; ↓ cAMP	—
5-$HT_{1D/1B}$	Brain	G_i; ↓ cAMP	—
5-HT_2	Smooth muscle, platelets	G_q; ↑ IP_3, DAG	Ketanserin
5-HT_3	Area postrema (CNS), sensory and enteric nerves	Ligand-gated cation channel	Ondansetron
5-HT_4	Presynaptic nerve terminals in the enteric nervous system	G_s; ↑ cAMP	Tegaserod (partial agonist)

TD

SEROTONIN: 5HT

5HT1D

Gi; decrease cAMP

Brain

Effect: Synaptic inhibition

SUMATRIPTAN

Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Zolmitriptan

MOA: 5HT1D receptor agonist; cause vasoconstriction; modulates neurotransmitter release

Uses: DOC for acute migraine, cluster headache

SE: paresthesia, dizziness, chest pain, coronary vasospasm, injection site rxn

All are per orem except for Sumatriptan which can also be given intranasally, trandersmal, & IV.

All has 2-27 hrs DOA excet for Sumatriptan DOA: 2-4h

5HT2

Gq; increase IP3, DAG

Smooth muscle, platelets

Effects: CNS excitation, smooth muscle contraction/relaxation, vasodilation, diarrhea, brochoconstriction

VASOSELECTIVE

ERGOTAMINE

Dihydroergotamine Methylsergide

MOA; partial agonist at alpha and 5HT2 receeptors, some have potent agonist effect at Dopamine receptors

Uses: migraine, cluster headache

SE: GI upset, vasospasm, gangrene, uterine spasm, retroperitoneal fibrosis (Methysergide only)

Antidote: NITROPRUSSIDE

Can cause epinephrine reversal due to partial agonist effect on alpha receptors.

UTEROSELECTIVE

ERGONOVINE

Methylergonovine

MOA: partial agonist at alpha & 5-HT receptors, some have potent agonist effect at dopamine receptors

Uses: postpartum bleeding, migraine

SE: GI upset (nausea, vomiting, diarrhea), uterine spasm, abortion

The uterus becomes more sensitive to ergots during pregnancy, produce very powerful & long-lasting contraction, leading to decreased bleeding.

Nevery give before delivery of placenta.

Methylergometrine/ Methylerobasin (other name of Methylergonovine) is a homolg of ergonovine.

5HT3

Ligand gated ion channel

Area postrema (CNS), sensory & enteric nerves

Effect: vomiting

ONDANSETRON

Granisetron, Dolasetron, Palonosetron, Alosetron

MOA: 5HT3 receptor antagonist; blocks chemoreceptor trigger zone & enteric nervous system 5HT3 receptors

Uses: chemotherapy & postoperative vomiting; irritable bowel disease (Alosetron only)

SE: diarrhea, headache, malaise, QRS & QT prolongation (Dolasetron only), constipation (Alosetron only)

5HT4

Gs, increase cAMP

Presynaptic nerve terminals in enteric nervous system

Effect: intestinal motility

VERTIGO DRUGS

BETAHISTINE

MOA: strong antagonist of H3 receptor (leads to increased levels of NT: histamine, Ach, NE, serotonin & GABA), and weak agonist of H1 receptor (causes local vasodilation & increased permeability in the inner ear)

Uses: balance disorders or to alleviate vertigo symptoms associated with Meniere's disease

CINNARIZINE

MOA: an anti histamine & CCB; promotes cerebral blood flow

Uses: cerebral apoplexy, post trauma cerebral symptoms & cerebral atherosclerosis; more commonly prescribed for nausea & vomiting due to motion sickness, chemotherapy, vertigo or Meniere's disease

DIMENHYDRINATE

First generation anti histamine used for nausea, vomiting, and dizziness caused by motion sickness.

DRUGS USED FOR MIGRAINE

FLUNARIZINE

Selective calcium entry blocker with calmodulin binding properties and H1 antagonistic activity.
Effective in the prophylaxis of migraine, occlusive peripheral vascular disease, vertigo and as adjuvant therapy for epilepsy

TD

PROSTAGLANDINS

PGE1

Gs, Gq

Vascular smooth muscle relaxataion, protective effects on gastric mucosa, maintains PDA

MISOPROSTOL
Gemeprost

MOA: Activates EP receptors. Causes increased HCO3 & mucus secretion in stomach. Uterine contraction.

Uses: PUD, prevention of NSAID-induced gastric mucosal injury, abortifacient

SE: abdominal pain, diarrhea, uterine cramping, miscarriage, teratogenic effect (Moebius syndrome)

May also be used together with Mifepristone or Methotrexate as safe abortifacient.

ALPROSTADIL

MOA: Activates EP receptors, causes vascular smooth muscle relaxation & vasodilation.

Uses: Maintenance of PDA, erectile dysfunction

SE: apnea, hypotension, arrhythmia, priapism, lightheadedness

Given as injection into the cavernosa for erectile dysfunctiion

PGE2

Gs, Gq

Vascular smooth muscle relaxation, maintains PDA, increase uterine tone

DINOPROSTONE
Sulprostone

MOA: Low concentrations: contract; Higher concentration: relax uterine & cervical smooth muscle; soften cervix at term before induction with oxytocin

Uses: induction of labor (cervical ripening), abortifacient

SE: cramping, fetal trauma

Approved abortifacient in the 2nd trimester. Although effective in inducing labor, it produces more SE than other oxytocins

PGF2ALPHA

Gq

Increases uterine tone, decreases IOP

CARBOPROST
Bimatoprost, Travoprost, Unoprostone

MOA: activates F2alpha receptors

Uses: control of postpartum hemorrhage, for refractory postpartum bleeding, abortifacient

SE: vomiting, diarrhea, transient bronchoconstriction

LATANOPROST
Bimatoprost, Travoprost, Unoprostone

MOA: activates FP receptors; increase outflow of aqueous humor, reduces intraocular pressure

Uses: glaucoma

SE: alters color of the iris causing permanent eye color change

May cause vomiting, diarrhea, transient bronchoconstriction if given systematically

PGI2

Gs,

Vascular smooth muscle relaxation (peripheral, pulmonary, coronary)

EPOPROSTENOL
Beraprost, Iloprost, Treprostinil

MOA: activates IP receptors. Causes vasodilation. Reduces platelet aggregation.

Uses: pulmo HPN, reduces platelt aggregation in dialysis machines

SE: hypotension, flushing, headache

TD

ASTHMA DRUGS

BRONCHODILATORS

BETA AGONIST

SABA

SALBUTAMOL
ALBUTEROL
Levalbuterol, Terbutaline, Metaproterenol, Pirbuterol, Procaterol, Fenoterol, Bitolterol

MOA: activates beta2 receptors in bronchial smooth uscle, causes bronchodilation

Uses: acute asthma attacks (DOC)

SE: tachycardia, tremors, nervousness, restlessness, arrhythmias when used excessively, loss of responsiveness (tolerance, tachyphylaxis)

May precipitate arrhytmias in patients with concurrent COPd and heart disease.

Usual DOA: 204 hrs

All are given inhalational. Salbutamol & Terbutaline is also available PO.

Terbutaline can also be given IV.

LABA

FORMOTEROL
Arformoterol, **B**ambuterol, **C**eneterol, **V**ilanterol, **I**ndacaterol, **O**lodaterol, **S**almeterol
mnemonic: FAB C VIOS

MOA: activates beta2 receptors in bronchial smooth muscle, causes bronchodilation. Potentiation of corticosteroid action.

Uses: asthma prophylaxis (not for acute relief)

SE: tachycardia, tremors, nervousness, restlessness, arrhythmias when used excessively, loss of responsiveness (tolerance, tachyphylaxis)

Increase asthma mortality when used alone.

May precipitate arrhythmias.

Usual DOA: 12hrs

MUSCARINIC ANTAGONIST

IPRATROPIUM
Tiotropium, Umeclinidium, Glycoyrronium

MOA: blocks muscarinic receptors in bronchial smooth muscle; prevents vagal-stimulared bronchoconsstriction

Uses: acute asthma, COPD

SE: dry mouth, blurred vision, anti cholinergic effects

Less toxic than beta agonists in aptients with COPD.

Tiotropium & Umeclidinium have longer DOA than Ipratropium.

Ipratropium given as aerosol has little systemic effects.

Has no effect on the chronic inflammation aspect of bronchial asthma.

Glycopyrronium does not cross the BBB, and consequently has no to few central effects. It may be used as a monotherapy as maintenance for COPD. It may also be used as an anti-spasmodic & reduce salivation with some anesthetics.

METHYLXANTHINE

THEOPHYLLINE
Aminophylline, Pentoxifylline, Doxofylline

MOA: phosphodiesterase inhibition; adenosine receptor antagonist; causes bronchodilation

Uses: asthma (prophylaxis against nocturnal attacks); intermittent claudication (Pentoxifylline only)

SE: CNS stimulation (insomnia, seizure, anorexia), cardiac stimulation (arrhythmias), tremors, increased BP, diuresis, increase GI motility

Antidote in overdosage: BETA BLOCKERS

Higher clearance in adolescents & smokers.

Narrow therapeutic window.

Usual DOA: 12hrs

Causes bronchodilation & increased strength of contraction of diaphragm

ANTI INFLAMMATORY

MAST CELL STABILIZER

CROMOLYN
Nedocromil, Lodoxamide

MOA: prevents calcium influx and stabilize mast cells --> preventing degranulation and release of histamine, leukotrienes and other mediators

Uses: asthma prophylaxis, allergies (ophthalmic, nasopharyngeal, gastrointestinal)

SE: cough, airway irritation

No bronchodilator action but can prevent bronchoconstriction caused by atntigens (both in the early and late BA responses).

Unusually insoluble chemicals so rarely used.

May be given as ophthalmic solution for allergic conjunctivitis.

May also be given (Off-label) for Food allergy and IBD.

CORTICOSTEROIDS

FLUTICASONE
Beclomethasone, Budesonide, Ciclesonide, Flunisolide, Mometasone, Triamcinolone

MOA: inhibitor of phospholipase A2; reduces expression of cyclooxygenase

Uses: asthma prophylaxis (DOC), COPD, allergic rhinitis, first line treatment for moderate to severe BA, anti inflammatory for auto immune diseases & cancer, for immune suppresion

SE: oropharyngeal candidiasis, minimal systemic steroid toxicity (ex. adrenal suppression), mild growth retardation

Inhibit synthesis of arachidonic acid by inhibiting phospholipase A2. REduces expression of COX and LT.

Increase responsiveess of beta receptos in the airway.

Bind to intracellular receptors and activate glucocorticoid response elements in the nucleus leading to sythesis if substances that prevent full expression of inflammation & allergy.

For status asthmaticus: use IV Prednisolone or Hydrocortisone.

Prednisolone is the active metabolite of Prednisone.

Ciclesonide has lowest systemic steroid toxicity.

LEUKOTRIENE ANTAGONIST

LEUKOTRIENE SYNTHESIS INHIBITOR

ZILEUTON

MOA: inhibitor of 5-lipooxygenase; reduces synthesis of leukotrienes; preevnts airway inflammation & bronchoconstriction

Uses: asthma prophylaxis; exercise-, antigen- & aspirin-induced bronchospam

SE: flulike synrome, headache, drowsiness, dyspepsia, hepatitis, elevation of liver enzymes, hepatotoxic

No bronchodilayor action.

Not recommended for acute BA attack

LEUKOTRIENT RECEPTOR ANTAGONIST

MONTELUKAST
Zafirlukast, Pranlukast

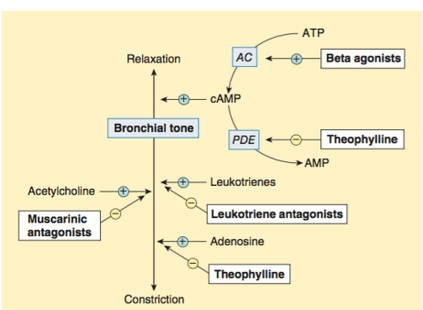
MOA: blocks cysteinyl leukotriene-1 receptor for leukotrienes C4, D4 & E4; prevents airway inflammation & bronchoconstriction

Uses: asthma prophylaxis, exercise-, antigen-, and aspirin-induced bronchospasm

SE: GI upset, insomnia, neuropyschiatric effects, Churg-Strauss syndrome (rare)

No bronchodilator action.

Not recommended for acute BA attack.



ANTI IGE ANTIBODY

OMALIZUMAB

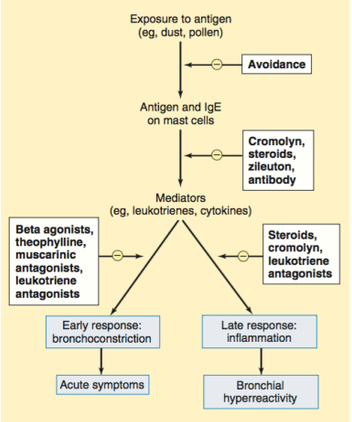
MOA: binds IgE antibodies on mast cells; reduces reaction to inhaled antigen

Uses: prophylaxis of severe, refractory asthma not responsive to all other drugs

SE: fever, angioedema, anaphylactin reactions, idiopathic severe thrombocytopenia, nasopharyngitis, upper abdominal pain

Binds IgE antibodies on sensitized mast cells & prevents activation by BA triggers & subsequent release of inflammatory mediators.

Humanized murine monoclonal antibody, very expensive & only administered IV.



DRUGS FOR COUGH

TD

MUCOLYTIC

N-ACETYLCYSTEINE

Carbocisteine, Ambroxol, Bromhexine, Erdosteine

MOA: decrease sputum activity; usually derivatives of cysteine; reduce disulfide bridges that bind glycoproteins to other proteins such as albumin; act as antioxidant & may reduce airway inflammation

Uses: cough (available as IV, PO, IM & inhalational forms)

SE: chest tightness, disagreeable odor, drowsiness, fever, hemoptysis, increased volume of bronchial secretions, irritation of tracheal or bronchial tract, nausea, rhinorrhea, stomatitis, vomiting

Orally avaialble drugs are well-tolerated, but of little benefit in acute respiratory condition

EXPECTORANT

GUIAFENESIN

MOA: may act as irritant to gastric vagal receptors, & recruit efferent parasympathetic reflexes that cause glandular exocytosis of a less viscous mucus mixture

Uses: cough

SE: drowsiness, incomplete or infrequent bowel movements, inducing of a relaxed easy state, stomach cramps, headache, rash, nausea, vomiting, stomach upset

Are often emetics (Ipecac, Guiafenesin)

ANTITUSSIVES

CENTRALLY ACTING

OPIOID

DEXTROMETHORPHAN

Codeine

MOA: decreased sensitivity of the medullary/ CNS cough centers to peripheral stimuli & decreased mucosal secretion

Uses: cough

SE: decrease secretions in the bronchioles, thickens sputum & inhibit ciliary activity, reducing clearance of thickened sputum; constipation

MORPHINE may be effective but indicated only in intractable cough from bronchial carcinoma,

DEXTROMETHROPHAN has no addictive potential, no analgesic effect, produces less constipation and inhibition of mucociliary clearance.

NON OPIOID

BUTAMIRATE CITRATE

MOA: act through receptors in the brainsteam to inhibit cough

Uses: cough

SE: somnolence, nausea, vomiting, diarrhea, dizziness, hypotension

Centrally acting antitussive but is neither chemically or pharmacologically related to opioids

PERIPHERALLY ACTING

LEVODROPOPIZINE

MOA: non opioid drug with a peripheral action by inhibiting the afferent pathways that generate the cough reflex (modulates C-fiber activity)

Uses: cough

SE: nausea, vomiting, heartburn, diarrhea, fatigue, weakness, drowsiness, dizzines, headache, palpitations

Doses not cause side effects such as constipation or respiratory depression which can be produced by opioid antitussive.

OTHERS

VITEX NEGUNDO (LAGUNDI)

Inhibits PDE III & inhibits Ca2+ entry (acts as CCB), which partly explain its bronchodilatory effects.

Considered a potent anti inflammatory agent & acts via inhibition of COX2 without much interfering COX1 pathways.

Traditionally used in hyperactive respiratory disorder, has medicinal importance in asthma.

TD

HEMATOPOIETIC DRUGS

RBC

IRON

FERROUS SULFATE

oral: Ferrous gluconate, Ferrous fumarate, Ferrous carbonate
parenteral: Iron dextran, Sodium ferric gluconate complex, Iron sucrose

MOA: required for the biosynthesis of heme & heme-containing proteins, including hemoglobin & myoglobin

Uses: iron deficiency anemia, iron supplementation

SE: black stools (may obscure acute GI loss)

ACUTE OVERDOSE: necrotixing gastroenteritis, abdominal pain, bloody diarrhea, shock, lethargy, dyspnea

CHRONIC IRON OVERDOSE: hemochromatosis, organ failure (heart, liver, pancreas, etc), death

IRON CONTENT
Fe carbonate / Carbonyl Iron – 100%
Fe fumarate – 33 %
Fe sulfate, dried – 30%
Fe sulfate, hydrated – 20%
Ferric ammonium sulfate – 18%
Fe gluconate – 12%

VITAMIN

CYANOCOBALAMIN
Hydroxocobalamin
Methylcobalamin

MOA: cofactor required for essential enzymatic rxns to methionine, & metabolize methylmalonyl-CoA

Uses: Vit B12 deficiency, megaloblastic anemia (pernicious anemia, gastric resection)

SE: no significant toxicity

Parenteral form is required for pernicious anemia & other malabsorption syndrome.

Hydroxocobalamin has a longer t1/2 than cyanocobalamin.

Has a storage of up to 5yrs in the liver.

Mecobalamin is the shorter term for Methylcobalamin.

FOLIC ACID
Folacin (Pteroglutamic acid), Folinic acid/ Leucovorin, L-methylfolate

MOA: precursor of an essential donor of methyl groups used for synthesis of amino acids, purines, & deoxynucleotide

Uses: megaloblastic anemia, prevention of neural tube defects (spina bifida), prevention of coronary artery disease

SE: no significant toxicity

Folic acid is not toxic in overdose but large amounts can partially compensate for Vit B12 deficiency & put people with unrecognized Vit B12 deficiency (which are not compensated by folic acid).

Only modest amounts are stored in the body.

EPO

EPOETIN ALFA
Darbepoetin alfa, Methoxypolyethylene glycol-epoetin alfa

MOA: agonist of erythropoietin receptors expressed by red cell progenitors

Uses: anemia esp associated with chronic renal failure, HIV infection, cancer, prematurity, for prevention of the need for transfusion in px undergoing certain types of elective surgery

SE: HPN, thrombosis, pure red cell aplasia

Hemoglobin levels hould be maintained <12g/dL.

Performance-enhancing drug in athlete (prohibited use)

Darbepoietin is once a week administration, while Methoxy Polyethylene Glycol -Epoetin Beta is 1-2x per month administration.

DEFEROXAMINE (Deferasirox, Deferiprone)
Class: Heavy Metal Chelator
MOA: Chelates excess iron
Uses: Acute iron poisoning, hemochromatosis not adequately treated by phlebotomy
SE: hypotension, ARDS, neurotoxicity, increased susceptibility to infections
DEFEROXAMINE is used for acute intoxication (IV dorm) while DEFERASIROX & DEFERIPRONE are for chronic (oral)

PLATELET

OPRELVEKIN (IL-11)
Thrombopoietin, Eltrombopag, Romiplastim

MOA: recombinant form of an endogenous cytokine; activates IL-11 receptors

Uses: secondary prevention of thrombocytopenia in px undergoing cytotoxic chemotherpay for non myeloid cancers

SE: fatigue, headache, dizziness, anemia, fluid accumulation in the lungs, transient atrial arrhythmias

Given SC OD.

ELTROMBOPAG
Small- molecule thormbopoietin (TPO)-receptor agonist that interacts with human TPO receptor transmembrane domain of human TPO-receptor & initiates signaling cascades that induce proliferation & differentiation of megakaryocytes from bone marrow progenitor cells; used for treatment of thrombocytopenia in adults & pediatric px >5yr with chronic ITP with insufficient response to corticosteroids, Ig or splenectomy.

ROMIPLASTIN
Fusion antibody-peptide that is a thrombopoietin receptor agonist; stimulates proliferation, differentiation, & activity of monocytes, neutrophils eosinophils, & macrophages; Used for thrombocytopenia

GRANULOCYE

MYELOID GROWTH FACTOR

FILGRAMSTIM
Sargramostim, Pegfilgramstim, Plerixafor, Lenogramstim

MOA: binds receptors on myeloid progenitor & stimulates cell maturation & proliferation; accelerates neutrophil recovery & reduces incidenceof infection

Uses: neutropenia assoc with chemotherapy, myelodysplasia, aplastic anemia; mobilization of peripheral blood ells in preparation for hematopoietic stem cell transplantation

SE: bone pain (arthralgia), fever, edema, splenic rupture

Pegfilgrastim has a longer t1/2.

PERIPHERALLY ACTING

PLERIXAFOR

A hematopoetic stem cell mobilizer; blocks binding of stromal cell-derived factor-1-alpha, found on bone marrow stromal cells, to the CXC chemokine receptor 4 (CXCR4).

The inhibition results in the mobilization of progenitor & hematopoietic stem cells from the bone marrow into peripheral blood.

Used for mobilization of hematopoietic stem cells to peripheral blood for collection and subsequent autologous transplantation in patients with NHL & Multiple Myeloma.

TD

DRUGS USED IN COAGULATION DISORDERS

ANTIPLATELET

ASPIRIN
Acetylsalicylic acid/ ASA

MOA: nonselective, irreversible COX 1&2 inhibitor; reduces platelet production of thromboxane A2, a potent stimulator of plt aggregation

Uses: prevention of arterial thrombosis (MI, TIA, CVD), inflammatory disorders (rhematic fever, Kawasaki dse, Juvenile RA)

SE: GI toxicity, tinnitus, hypersensitivity, hyperventilation, HAGMA, increased bleeding time, nephrotoxicity (AKI, interstitial nephritis)

Associated with Reye Syndome in children.
Do not use as NSAID for gout.
TRIFLUSAL ia a salicyclic acid derivative.

GPIIb/IIIa INHIBITORS

ABCIXIMAB
Eptifibatide
Tirofiban

MOA: inhibits plt aggregation by interfering with GPIIb/ IIIa binding to fribrinogen & other ligands

Uses: used during PCI to prevent thrombosis; adjunct to thrombolysis, acute coronary syndrome (unstable angina, NSTEMI)

SE: bleedung, thrombocytopenia

Prevents vessel restenosis, reinfarction and death.

ADP INHIBITORS

CLOPIDOGREL
Ticlopidine, Prasugrel, Ticagrelor

MOA: irreversibly inhibits binding of ADP to plt receptors, reducing plt aggregation

Uses: prevention & treatment of arterial thrombosis (stroke, TIA, unstable angina), prevention of restenosis after PCI, ACS)

SE: bleeding, nausea, dyspepsia, hematologic (neutropenia, leukopenia, thrombotic thrombocytopenia purpura - Ticlopidine)

GI & hematologic SE are more common with Ticlopidine.
Additive effects with Aspirin.
TICAGRELOR specifically inhibits ADP subtype P2Y; in contrast to other antiplt drugs, it has a binding site different from ADP, making it an allosteric antagonist

PDE INHIBITORS

DIPYRIDAMOLE
Cilostazol

MOA: inhibits phosphodiesterase III & increases cAMP in plt & blood vessels; inhibits plt aggregation & causes vasodilation; inhibit uptake of adenosine by endothelial cells & RBC, thus increasing adenosine levels leadings to inhibition of plt aggregation

Uses: prevention of thromboembolic complications of cardiac valve replacement, secondary prevention of ischemic stroke (with aspirin), intermittent claudication (Cilostazol only)

SE: headache (bec it is a vasodilator), palpitations

DYIRIDAMOLE, by itself, has little or no benefit.

CILOSTAZOL is contraindicated in heart failure

ANTICOAGULANT

INDIRECT

HEPARIN

MOA: activates antithrombin III (inactivates thrombin of FIIa, FIXa, FXa by forming a stable complex with them)

Uses: DVT, PE, MI, unstable angina, adjuvant to PCI & thrombolytics, Afib, DOC for anticoagulation during pregnancy, given with thrombolytics for revascularization procedures, given with GPIIb-IIIa inhibitors for angioplasty & stent placement

SE: bleeding, heparin-induced thrombocytopenia, osteoporosis with chronic use

Monitor with aPTT

Antidote: PROTAMINE SULFATE

Administered IV or SC.

SULODEXIDE: a heparinoid consisting of 80% heparin & 20% dermatan sulfate

WARFARIN
Dicumarol, Anisindione

MOA: inhibits Vit K epoxide reductase (responsible for γ-carboxylation of the Vit -dependent clotting factors II, VII, IX, X, Protein C & Protein S

Uses: chronic anticoagulation (DVT, Afib, valve replacement) EXCEPT IN PREGNANCY

SE:bleeding, warfarin-induced necrosis (for px with protein C & S deficiency), teratogen (bone defects, hemorrhage)

Monitor effects with PT.

Antidote: VITAMIN K (slow) or FFP (fast)

Narrow therapeutic window.

Active ingredient in most rat poisons

Highly protein-bound

LMW HEPARIN

ENOXAPARIN
Dalteparin, Tinzaparin, Danaparoid, Fondaparinux, Nadroparin

MOA: binds & potentiates effects of antithrombin III on factor Xa (more selective). Less effect on thrombin.

Uses: DVT, PE, MI, unstable angina, adjuvant to PCI & thrombolytics, Afib

SE: bleeding, less risk of thrombocytopenia

Does not require aPTT monitoring.

Protamine sulfate is only partially effective in reversing effects.

Advantage over regular heparin is higher bioavailability and t1/2

FONDAPARINUX is given SC OD

DIRECT

LEPIRUDIN
Desirudin, Bivalrudin, Argatroban, Dabigatran

MOA: binds to thrombin's active site and inhibits its enzymatic action

USES: anticoagulation in px with heparin-induced-thrombocytopenia, percutaneous coronary angioplasty (with aspirin)

SE: bleeing, effect-prolonging antibodies, anaphylaction rxnx

Monitor effect with aPTT

No reversal agents exist

Used with caution for px with renal insufficiency

DABIGATRAN is P, while all the rest are parenteral

BIVALIRUDIN also inhibits platelet activation

THROMBOLYTIC

T-PA DERIVATIVES

ATEPLASE
Anistreplase, Reteplase, Streptokinase, Tenecteplase, Urokinase

MOA: tissue plasminogen activator analog; converts plasminogen to plasmin, which degrades the fibrin & fibrinogen causing thrombolysis

Uses: acute MI, ischemic stroke, PE

SE: bleeding, cerebral hemorrhage, reperfusion arrhthmias

Loss of effectiveness (on 2nd use) and allergic rxn may be observed with Streptokinase

Antidote: AMINOCAPROIC ACID

Tx shoudl be done within 6hrs, better if within 3hrs

STREPTOKINASE forms a complex with endogenous plasminogen, thus catalyzing the conversion of plasminogen to plasmin

tPA is selective for fibrin-bound plasminogen

PRO CLOTTING

ANTIPLASMIN / AMINOCAPROIC ACID

TRANEXAMIC ACID

MOA: competitively inhibits plasminogen activation by inhibiting tPA

Uses: prevention & treatment of acute bleeding episodes in px with high risk of bleeding (hemophilia, intracranial aneurysms, menstrual, obstetrics, thrombolytics, postoperative)

SE: thrombosis, hypotension, myopathy, diarrhea

Contraindicated in DIC

VITAMIN K

Vit K1 (Phytonadione), Vit K2 (Menadione), Vit K3 (Phytomenadione)

MOA: increases supply of reduced Vit K, which is required for synthesis of functional Vit K-dependent clotting & anticlotting factors

Uses: Vit K deficiency, antidote to warfarin, prevention of hemorrhagic diatheses in newborns

SE: severe infusion rxn when administered too fast (dyspnea, chest & back pain)

Vit K3 (menadione) should NEVER be used in therapeutics (ineffective)

ADH AGONIST

DESMOPRESSIN
Vasopressin, Telipressin

MOA: vasopressin V2 receptor agonist

Uses: hemophilia A, von Willerbrand dse, central DI

SE: headache, flushing, nausea, hyponatremia, seizures

Increases the factor VIII activity of px with mild hemophilia A or vWdse

SERINE PROTEASE INHIBITOR

APROTININ

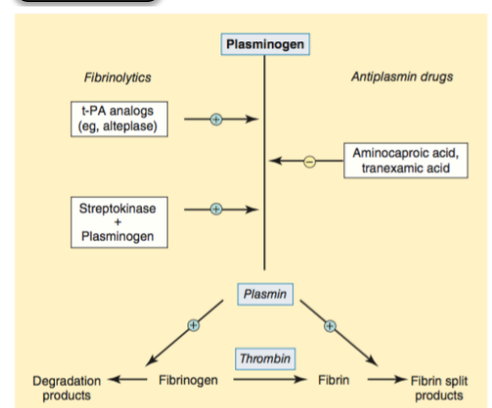
MOA: inhibits plasmin & plasmin-streptokinase complex in px who have received Streptokinase

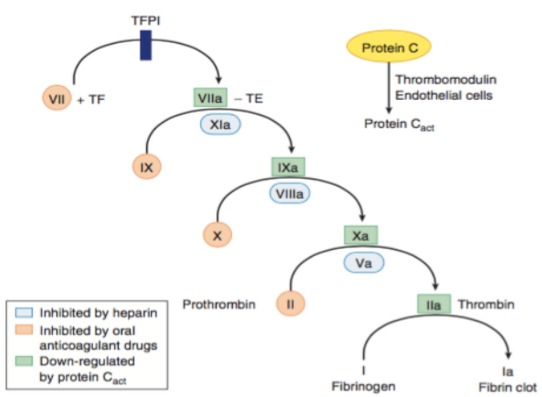
Uses: post-op or intra-op bleeding

SE: increased risk of renal failure, heart attack & stroke

May reduce bleeding by as much as 50% (in many types of surgeries)

Removed from the market in 2007 due to mortality





Property	Heparins	Warfarin
Structure	Large acidic polysaccharide polymers	Small lipid-soluble molecule
Route of administration	Parenteral	Oral
Site of action	Blood	Liver
Onset of action	Rapid (minutes)	Slow (days); limited by half-lives of preexisting normal factors
Mechanism of action	Activate antithrombin III, which inactivates coagulation factors including thrombin and factor Xa	Impairs post-translational modification of factors II, VII, IX and X
Monitoring	aPTT for unfractionated heparin but not LMW heparins	Prothrombin time
Antidote	Protamine for unfractionated heparin; protamine reversal of LMW heparins is incomplete	Vitamin K_1, plasma, prothrombin complex concentrates
Use	Mostly acute, over days	Chronic, over weeks to months
Use in pregnancy	Yes	No

OTHER DRUGS USED FOR COAGULATION DISORDERS:

- Anti Hemophilic factor
- Anti-inhibitor coagulant complex
- Anti-thrombin III
- Factor VIIa, VIII, IX complex
- Somatostatin: Tx of intestinal & pancreatic fistulae, excessive secretion from endocrine tumors of the GIT, acutre severe GI hemorrhage, ERCP

CONTRAINDICATIONS TO THROMBOLYSIS:

- History of CVD hemorrhage at any time
- Non hemorrhagic stroke or other cerebrovascular event within the past year
- Marked hypertension (>180/110 mmHg) at any time during the acute presentation
- Suspicion of aortic dissection
- Active internal bleeding (excluding menses)

TD

NSAIDS

SALICYLATES

ASPIRIN

Salsalate, Sodium Salicylate, Choline Salicylate, Magnesium Salicylate

MOA: nonselective, irreversible COX 1 & 2 inhibitor; reduce platelet production of thromboxaneA2, a potent stimulator of platelet aggregation

Uses: prevention of arterial thrombosis (MI, TIA, CVD), inflammatory disorders (rheumatic fever, Kawasaki dse, juvenile rheumatoid arthritis)

SE: GI toxicity, nephrotoxicity, tinnitus, hypersensitivity, hyperventilation, HAGMA

Uncoupler of oxidative phosphorylation.

Associated with REYE SYNDROME in children.

Prevents uric acid excretion (don't use in gout).

Low doses undergo first order kinetics, while high doses undergo zero order reaction.

Long term use reduces the risk of colon cancer (unknown/ not well understood mechanism)

NON SELECTIVE NSAIDS

IBUPROFEN

Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Ketoprofen, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmentin, Mefenamic acid, Bromfenac, Meclofenamate, Suprofen, Aceclofenac

MOA: nonselective reversible COX1 & COX2 inhibitor; inhibits prostaglandin synthesis

Uses: analgesia (musculoskeletal, headache, dysmenorrhea), antipyretic, anti-inflammatory

SE: GI bleeding (less than aspirin), nephrotoxicity (AKI & interstitial nephritis), hypersensitivity rxn

Long term use reduces the risk of colon cancer.

MISOPROSTOL prevents NSAID-induced gastritis.

NSAIDS (in general) may cause premature closure of ductus arteriosus.

IBUPROFEN & INDOMETHACIN can be used to close PDA.

IBUPROFEN & NAPROXEN have moderate effectiveness.

IBUPROFEN is relatively safe but with short half-life of 2 hrs.

NAPROXEN & PIROXICAM have longer half-lives NSAIDs may interfere with ASA's antithrombotic action.

KETOROLAC

Dexketoprofen

INTRAVENOS NSAID

MOA: nonselective reversible COX1 & COX2 inhibitor; inhibit prostaglandin synthesis

Uses: post-surgical analgesic control (moderate to to severe, short term), mainly used for analgesia, not for anti inflammatory effect

SE: high risk for GI toxicity & nephrotoxicity, allergic rxns

Use generaly restricted to 72hrs only (due to GI & renal damage)

INDOMETHACIN

MOA: nonselective reversible COX1 & COX2 inhibitor; inhibit prostaglandin synthesis

Uses: anti inflammatory (gout, arthritis, ankylosing spondylitis), closure of PDA

SE: GI toxicity, pancreatitis, nephrotoxicity, serious hematologic rxns (aplastic anemia, thrombocytopenia), BM suppression

Inhibits COX1>COX2

Indomethacin has greater anti inflammatory effect compared to other NSAIDs

COX2 SELECTIVE

CELECOXIB

Etoricoxib, Parecoxib, Rofecoxib, Valdecoxib

MOA: selective COX2 inhibitor; inhibits prostaglandin synthesis

Uses: analgesiam antipyretic, anti inflammatory

SE: GI bleeding (reduced risk), nephrotoxicity, MI & stroke (rofecoxib & valdecoxib only), rash

Coxibs are 10-20x COX2> COX1

50% less GI SE compared to nonselective NSAIDs

ROFECOXIB & VALDECOXIB - withdrawn due to increased incidence of thrombosis

MELOXICAM is a preferentially COX2 selective inhibitor

PARACETAMOL

Phenacetin

MOA: selectively inhibits COX3; weak COX1 & COX2 inhibitor; inhibits prostaglandin synthesis

Uses: analgesica (mild), antipyretic

SE: hepatotoxicity, renal papillary necrosis & interstitial nephritis (phenacetin only), methemoglobinemia, hemolytic anemia

Increased hepatotoxicity with alcohol use.

Preferred antipyretic in children (does NOT cuse Reye's syndrome)

Antidote: N-ACETYLCYSTEINE

Half life: 2-3hrs

PARACETAMOL OVERDOSE:

- DOSAGE
  - Toxic Dose: 150mg/kg (21 Paracetamol 500mg tab)
  - Lethal Dose: 15g (30 Paracetamol 500mg tab)
- TREATMENT
  - Antidote is N-acetylcysteine
  - Supportive management
  - Gastric decontamination with activated charcoal

TD

ANTI GOUT

MICROTUBULE ASSEMBLY INHIBITOR

COLCHICINE

MOA: inhibits microtubule assembly and LTB4 production leading to decreased macrophage migration and phagocytosis

Uses: gout, familial mediterranean fever

SE: diarrhea, nauses, vomiting, abdominal pain, hepatic necrosis, acute renal failure, DIC, seizure, hair loss, bone marrow depression (aplastic anemia), peripheral neuritis, myopathy

Diarrhea is the adverse effect which signals toxicity from colchicine

GOAL OF TREATMENT:
Prompt alleviation of pain & disability
- Bed Rest
- Mainstay treatment during Acute Attack:
  NSAIDs (first line), Colchicine, Glucocorticoids

URICOSURIC

PROBENECID
Sulfinpyrazone

MOA: compete with uric acid for reabsorption in the proximal tubules; increase uric acid excretion

Uses: gout

SE: GI irritation, rashes, nephrotic syndrome (probenecid only), aplastic anemia, sulfa allergy

May precipitate acute gout during early phase of drug action (prevent by coadministering with colchicine or indomethacin).

Inhibit secretion of other weak acids (penicillin, methotrexate).

May be given together with antimicrobial agents (particularly penicillins) to prolong therapeutics effects by inhibiting renal tubular secretion of antibiotics

XANTHINE OXIDASE INHIBITOR

ALLOPURINOL

MOA: active metabolite (alloxanthine) irreversibly inhibits xanthine oxidase and lowers production of uric acid

Uses: 1st line for chronic gout, tumor lysis syndrome

SE: GI upset, rash, peripheral neuritis, vasculitis, bone marrow dysfunction, aplastic anemia, cataracts

Inhibits metabolism of mercaptopurine and azathioprine.

Witheld for 1-2 wk after an acute episode of gouty arthritis (coadministered with colchicine or indomethacin to avoid an acute attack)

FEBUXOSTAT

MOA: non purine reversible inhibitot of xanthine oxidase (more selective than allopurinol); lowers production of uric acid

Uses: chronic gout, tumor lysis syndrome, allopurinol tolerance

SE: liver function abnormalities, headache, GI upset, rash, liver dysfuncion (febuxostat)

Witheld for 1-2 wk after an acute episode of gouty arthritis (coadministered with colchicine or indomethacin to avoid an acute attack)

Febuxostat is a newer non-purine inhibitor of xanthine oxidase; more effective than allopurinol

OTHERS

PEGLOTICASE

A novel urate-lowering recombinant mammalian urate oxidase enzyme (an enzyme absent in humans which converts uric acid to allantoin)

ANAKIMURA, CANAKINUMAB, RILONACEPT

IL-1 pathway inhibitor

Used for acute gout in px with contraindication to, or who are refractory to traditional therapies like NSAIDs and/or Colchicine

NSAIDs in Gout: INDOMETHACIN
- Indomethacin & other NSAIDs also inhibits urate crystal phagocytosis
- Indomethacin is commonly used in the initial treatment of gout as the replacement for colchicine
- Aspirin is not used due to its renal retention of uric acid at low doses

Consider HYPOURICEMIC DRUG THERAPY:
- After 2 episodes of acute attack
- Serum uric acid >9mg/dl
- (+) Uric acid stones
- (+) Tophi or chronic gout

ANTI BACTERIAL

TD

BACTERIAL CELL WALL SYNTHESIS INHIBITORS

- PENICILLINS
- CEPHALOSPORINS
- CARBAPENEMS
- MONOBACTAMS
- BETA LACTAM INHIBITORS
- GLYCOPEPTIDE
- PEPTIDE ANTIBIOTICS
- CYCLOSERINE
- DAPTOMYCIN
- FOSFOMYCIN

BACTERIAL PROTEIN SYNTHESIS INHIBITORS

- AMINOGLYCOSIDES
- TETRACYCLINES
- CHLORAMPHENICOL
- MACROLIDE
- LINCOSAMIDE
- OXAZOLIDINONE
- STREPTOGRAMIN

NUCLEIC ACID SYNTHESIS INHIBITORS

- SULFONAMIDES
- TRIMETHOPRIM
- FLUOROQUINOLONES

MISCELLANEOUS

- NITROIMIDAZOLE
- NITROFURANTOIN
- PSEUDOMONIC ACID
- POLYMYXINS
- MACROCYCLIC

TD

PENICLLINS

NATURAL PENICILLINS

PENICILLIN G, V

- MOA: binds to penicillin-binding proteins; inhibits transpeptidation in bacterial cell walls
- Uses: DOC for syphilis, for streptococcal, pneumococcal, meningococcal, G(+) bacilli, spirochete infection
- SE: hypersensitivity, complete cross-allergenicity with other penicillins, GI disturbances, seizures
- Renal tubular reabsorption inhibited by Probenecid.
- Inactivated by beta-lactamase (penicillinase)
- Benzathine Penicillin & Procaine Penicillin: long acting IM preparations.
- Given IM but Pen V can be given PO.
- Increased activity against enterococci when given together with aminoglycosides.
- Narrow spectrum.

ISOXAZOLYL PENICILLINS

METHICILLIN

Nafcillin, Oxacillin, Cloxacillin, Dicloxacillin

- MOA: binds to penicillin-binding proteins; inhibits transpeptidation in bacterial cell walls
- Uses: staphylococcal infections
- SE: hypersensitivity, complete cross-allergenicity with other penicillins, GI disturbances, interstitial nephritis (methicillin), neutropenia (nafcillin)
- Resistant to inactivation by beta lactamase (penicillinase).
- Biliary clearance.
- Very narrow spectrum.

AMINO PENICILLINS

AMPICILLIN AMOXICILLIN

- MOA: binds to penicillin-binding proteinsl inhibits transpeptidation in bacterial cell walls
- Uses: infections due to enterococci, Listeria monocytogenes, E.coli, Proteus mirabilis, H.influenzae, Moraxella catarrhalis (HELPSE)
- SE: hypersensitivity, cross-allergenicity, GI upset, pseudomembranous colitis & rash (Ampicillin)
- Inactivated by beta-lactamse (penicillinase).
- Enhanced effect when used with beta-lactamase inhibitors (Clavulanic acid, Sulbactam)
- Synergistic effect with Aminoglycosides.
- Ampicillin undergoes enterohepatic recirculation.

ANTI PSEUDOMONAL PENICILLINS

PIPERACILLIN

Ticarcillin, Carbenicllin

- MOA: binds to penicillin-binding proteins; inhibits transpeptidation in bacterial cell walls
- Uses: greater activity against G(-) infections; infections due to Pseudomonas, Enterobacter & Klebsiella
- SE: hypersensitivity, complete cross-allergenicity with other penicillins, GI disturbances
- Inactivated by beta lactamse (penicillinase).
- Enhanced effect when used with beta lactamase inhibitors (Clavulanic acid, Tazobactam).
- Synergistic with Aminoglycosides against Pseudomonas

CEPHALOSPORINS

TD

1ST GEN

CEFAZOLIN, CEFADROXIL, CEPHALEXIN, CEPHALOTHIN, CEPHAPRIN, CEPHRADINE

MOA: binds to penicillin-binding proteins; inhibits transpeptidation in bacterial cell walls

Uses: surgical prophylaxis, bone infections, infections due to gram (+) cocci (staphylococci & common streptococci(, E.coli & Klebsiella pneumoniae, skin & soft tissue infections, UTI

SE: hypersensitivity, cross-allergenicity (partial with penicillins, complete with cephalosporins), injection site reactions, phlebitis, GI upset

Increases nephrotoxcity of Aminoglycosides.

Do not cross the BBB.

Minimal activity against gram (-) cocci, enterococci, MRSA & most gram (-)

CEPHALOSPORINS CAUSING DISULFIRAM REACTION:
Cefamandole
Cefmetazole
Cefotetan
Cefoperazone

CEFTRIAXONE
Best CNS penetrance!

1ST GEN CEPHALOSPORINS:
FADer, help me FAZ my PHarmacology boards!
ceFADroxil
ceFAZolin
cePHalothin
cePHapirin
cePHradine
cePHalexin

2ND GEN

CEFACLOR, CEFAMANDOLE, CEFMETAZOLE, CEFONICID, CEFUROXIME, CEFPROZIL, CEFORANIDE, CEFOXITIN, CEFOTETAN, LORACARBEF

MOA: binds to penicillin-binding proteins; inhibits transpeptidation in bacterial cell walls

Uses: added coverage for infections due to Haemophilus, Enterobacter & Neisseria

SE: hypersensitivity, cross-allergenicity (partial with penicilins, complete with cephalosporins), injection site reactions, phlebitis, GI upset, disulfiram reaction (Cefamandole, Cefotetan)

Increases nephrotoxicity of Aminoglycosides.

Do not cross the BBB.

Slight less activity against gram (+) but extended gram (-) activity.

CEFUROXIME has improved action against pneumococcus & H.influenza

CEFOTETAN & CEFOXITIN have good activity against B.fragilis & thus are used for abdominal & pelvic infections.

All are pregnancy category B.

2ND GEN CEPHALOSPORINS:
In a FAMily gathering you see your FOXy cousin wearing a FUR coat & drinking TEa
ceFAMandole
ceFOXitin
ceFURoxime
cefoTEtan
FAC! LORA the PROfessional AZhOLE is still on the FONe.
ceFAClor
LORAcarbef
cefPROzil
cefmetAZOLE
ceFONicid

3RD GEN

CEFOPERAZONE, CEFOTAXIME, CEFTAZIDIME, CEFTIZOXIME, CEFTRIAXONE, CEFIXIME, CEFPODOXIME, PROXETIL, CEFDINIR, CEFDITOREN PIVOXIL, CEFTIBUTEN, MOXALACTAM

MOA: binds to penicillin-binding proteinsl inhibits transpeptidation in bacterial cell walls

Uses: decreased gram (+) coverage; increased gram (-) activity (Pseudomonas, Bacteroides, against Providencia, Serratia, Neisseria, Haemophilus; DOC for gonorrhea (Ceftriaxone & Cefixime)

SE: SE: hypersensitivity, cross-allergenicity (partial with penicilins, complete with cephalosporins), GI upset, disulfiram reaction (Cefoperazone)

Synergistic effect with Aminoglycosides.

All hvae renal excretion except CEFOPERAZONE & CEFTRIAXONE.

All can penetrate the BBB except CEFOPERAZONE & CEFIXIME.

CEFTRIAXONE & CEFOTAXIME are the most active Cephs against Penicillin-resistant Streptococcus pneumoniae.

CEFTIZOXIME is commonly used against Bacteroides.

Should be reserved against serious infection except Ceftriaxone & Cefixime.

CEFTRIAXONE has a very good CNS penetration.

CEFTAZIDIME has a very good action on Pseudomonas.

All are pregnancy category B.

3RD GEN CEPHALOSPORINS:
FEnge PO ng PERA to FIX my TTTTTv!
ceFEtamet
cefPOdoxin
cefoPERAzone
ceFIXime
cefTazidime
cefoTaxime
cefoTizoxime
cefTibuten
cefTriaxone

4TH GEN

CEFEPIME, CEFTAROLINE, CEFPIROME

MOA: binds to penicillin-binding proteins; inhibits transpeptidation in bacterial cell walls

Uses: wide coverage against gram (+) & gram (-) bacteria, MRSA (Ceftaroline)

SE: hypersensitivity, cross-allergenicity (partial with penicilins, complete with cephalosporins), GI upset

Resistant to beta-lactamase.

Broad gram (-) activity.

In some sources, Ceftaroline belongs to the 5th gen Cephalosporins.

More resistant to beta-lactamase produced by Enterobacter, Hemophilus, Neisseria, & Pneumococcal.

Has improved stability to chromosomal lactamse.

Ceftaroline used for MRSA.

CEFTOLOZANE
- A novel cephalosporin, usually combined with Tazobactam, used for the treatment of complicated urinary tract & intraabdominal infections;
- Very good activity against gram (-) organisms including Pseudomonas aeruginosa, most extended-spectrum-beta-lactamase-producing organisms & some anaerobes.

TD

BACTERIAL CELL WALL SYNTHESIS INHIBITORS

CARBAPENEMS

IMIPENEM CILASTIN

Ertapenem, Meropenem, Doripenem

MOA: binds to penicillin-binding proteins; inhibits trasnspeptidation in bacterial cell walls

Uses: wide coverage against gram (+) & gram (-) bacteria; for serious infections such as pneumonia & sepsis

SE: hypersensitivity, cross-allergenicity (partial with penicillins), GI upset, CNS toxicity (confusion, encelopathy, seizures)

Reserved for serious life-threatening infections.

CILASTIN inhibits renal metabolism (hydrolysis) of imipenem by DIHYDROPEPTIDASE.

Given IV.

MONOBACTAMS

ASTREONAM

MOA: binds to penicillin-binding proteins; inhibits transpeptidation in bacterial cell walls

Uses: infections resistant to beta lactamses produced by gram (-) rods including Klebsiella, Pseudomonas & Serratia

SE: GI upsaet, superinfection, vertigo, headache, hepatoxicity, skin rash

Resistant to beta-lactamase.

No cross-allergenicity with penicillins.

No activity against gram (+) bacteria or anaerobes.

Given IV. Renal excretion.

Synergistic with AG.

BETA LACTAM INHIBITORS

CLAVULANIC ACID

Sulbactam, Tazobactam

MOA: inhibits inactivation of penicillins by bacterial beta-lactamase (penicillinase)

Uses: infections against beta-lactamase produding gonococci, streptococci, E.coli & H.influenzae

SE: hypersensitivity, cholestatic jaundice

Usual combinations: Amoxicillin-Clavulanate, Ampicillin-Sulbactam, Piperacillin-Tazobactam.

Most active against plasmid encoded beta lactamases (gonococci, streptococci, E.coli & H.influenzae).

Not good inhibitor of inducible chromosomal beta lactamases (Enterobacter, Pseudomonas, Serratia)

GLYCOPEPTIDE

VANCOMYCIN

Teicoplanin, Dalbavancin, Telavancin

MOA: inhibits cell wall synthesis by binding to D-Ala-D-Ala terminus of nascent peptidoglycan --> inhibit transglycosylation --> prevents elongation & crosslinking of peptidoglycan chain

Uses: serious infections caused by drug-resistant organisms (MRSA), sepsis, endocarditis & meningitis, pseudomembranous colitis

SE: red man syndrome, nephrotoxicity, ototoxicity, chills, fever, phlebitis

Reserved for serious life-threatening infections.

Treat red man syndrome by slowing the rate of infusion.

Narrow spectrum.

VRSA & VRE are due to D-Ala-D-Lactate formation.

Teicoplanin & Telavancin are not absorbed in the GIT thus used for bacterial enterocolitis; they are also eliminated unchanged in the urine.

Decrease dose for renally impaired patients.

Dalbavancin has very long t1/2 (6-11 days) which permits once-weekly dosing & is more active han Vancomycin.

PEPTIDE ANTIBIOTIC

BACITRACIN

MOA: interferes with the late stage in gram (+) organisms

Uses: infections due to gram (+) bacteria

SE: nephrotoxicity

Reserved for topical use only due to marked nephrotoxicity.

CYCLOSERINE

MOA: blocks incorporation of D-Ala into the pentapeptide side chain of peptidoglycan

Uses: drug-resistant tuberculosis (2nd line drug)

SE: neurotoxicity (tremors, seizures, psychosis)

Only used as a second-line agent in TB.

DAPTOMYCIN

MOA: binds to cell membrane causing depolarization & rapid cell death

Uses: infections caused by G(+) bacteria including sepsis & endocarditis

SE: myopathy

More rapidly bactericidal than Vancomycin.

Inactivated by pulmonary surfactant so cannot be used against pneumonia.

Monitor creatine phosphokinase weekly to check for severity of myopathy.

NOT bactericidal (only destabilizes bacterial cell membrane).

FOSFOMYCIN

MOA: inactivates the enxyme UDP-N-acetylglucosamine-3-enolpyruvyltransferase which is important in peptidoglycan synthesis (very early stage of bacterial cell wall sythesis) --> prevents formation of N-acetylmuramic acid.

Uses: uncomplicated UTI

Safe for pregnant px.

Renal excretion.

Resistance emerges rapidly.

Synergistic with Beta Lactam & Quinolones

DRUGS OF LAST RESORT

I AM Your Last Shot at Victory

Imipenem
Amikacin
Meropenem
Linezolid
Streptogramins
Vancomycin

TD

BACTERIAL PROTEIN SYNTHESIS INHIBITORS

AMINOGLYCOSIDES

GENTAMICIN Tobramycin

MOA: inhibit protein synthesis by binding to 30S subunit; bactericidal

Uses: infections caused by aerobic gram (-) bacteria (E.coli, Enterobacter, Klebsiella, Proteus, Providencia, Pseudomonas, Serratia), Endocartitis (caused by staphylococci, streptococci, enterococci), ocular infections

SE: nephrotoxicity (reversible), ototoxicity (irreversible), neuromuscular blockade

Synergistic effect with cell wall synthesis (beta lactam & vancomycin) inhibitors due to enhancement of transport to the inside of the bacterial cell.

Given IM or IV only.

Have concetraion dependent killing.

Are not capable of penetrating the BBB.

Low tissue penetration.

Mechanism of Resistance: plasmid-meadiated formation of inactivating enzymes "group transferase" --> catalyze the acetylation of amine functions & the transfer of phosphoryl or adenylyl grps to the oxygen atoms of the hydroxyl grps of AG.

Gentamicin & Tobramycin are the most vestibulotoxic & nephrotoxic.

AMIKACIN

MOA: inhibit proetin synthesis by binding to 30s subunit. Cidal.

Uses: infections caused by aerobic gram (-) bacteria (E.colim Enterobacter, Klebsiella, Proteus, Providencia, Pseudomonas, Serratia), TB 2nd line drug

SE: nephrotoxicity (reversible), ototoxicity (irreversible), neuromuscular blockade

Synergistic effect with beta lactam antibiotics.

Least resistance but narrowest therapeutic window.

STREP-TOMYCIN

MOA: inhibit protein synthesis by binding to 30s subunit. Cidal.

Uses: TB, Tularemia, Bubonic plague, Brucellosis, Enterococcal endocarditis

SE: hypersensitivity, nephrotoxicity (reversible), ototoxicity (vestibulotoxic irreversible), neuromuscular blockade, teratigen (congenital deafness), injection site rxns

Syngergistic effect with beta lactam antibiotics.

Given IM.

Has widespread resistance.

For Streptomycin, resistance is due to changes in the ribosomal binding site.

If given together with Pens, can be used for enterococcal endocarditis, TB plague & Tularemia

NEOMYCIN Kanamycin, Paromomycin

MOA: inhibit protein synthesis by binding to 30s subunit. Cidal.

Uses: skin infections, bowel preparations for elective surgery (to decrease aerobic flora), hepatic encephalopathy, visceral leishmaniasis (Paromomycin)

SE: hypersensitivity, nephrotoxicity (reversible), ototoxicity (irreversible), neuromuscular blockade

Limited to topical & oral use (Neomycin).

Reverse neuromuscular blockade with calcium gluconate & neostigmine.

Kanamycin is the most ototoxic.

SPECTI-NOMYCIN

MOA: inhibit protein synthesis by binding to 30s subunit. Cidal.

Uses: drug-resistant gonorrhea, gonorrhea in penicillin-allergic px

SE: nephrotoxicity (reversible), ototoxicity (irreversible), neuromuscular blockade, anemia

No cross-resistance with other drugs used in gonorrhea.

Given IM.

TETRACYCLINES

DOXYCYCLINE Minocycline, Tigecycline, Demeclocycline, Lymecycline

MOA: binds 30s ribosomal subunit. Static.

Uses: infections caused by M.pneumoniae, chlamydiae, rickettsiae & Vibrio; PUD, lyme disease, Malaria prophylaxis, Amoebiasis, SIADH (demeclocycline), acne, CAP, bronchitis (doxycycline)

SE: GI disturbance, teratogen (tooth enamel) dysplasia/ discoloration), hepatotoxicity, nephrotoxicity, photosensitivity, reversible vestibulotoxicity (esp minocycline)

Divalent cations impair oral absorption (minimal for Doxycycline).

Tigecycline has the broadest spectrum & has the longest t1/2 (30-36hrs).

Do not drink with milk (decreased absorption with divalent cations like Calcium).

High Vd, cross the placenta, enterohepatic recycling.

All are excreted renally EXCEPT Doxycycline (bile).

Resistance is due to development of efflux pumps for active extrusion of Tetracyclines & the formation of ribosomal protection proteins that interfere with Tetracycline binding (but not present with Tigecycline except in Proteus & Pseudomonas).

Tigecycline is given IV only & is unaffected by common Tetracycline resistance mechanisms.

Group Pregnancy Category D

CHLORAMPHENICOL

MOA: inhibits transpeptidation (catalyzed by peptidul influenzae) at 50S subunit. Static.

Uses: meningitis (S.pneumoniae, H.influenzae, N.meningitidis), backup for Salmonella, Rickettsia & Bacteroides

SE: GI disturbances, aplastic anemia (idiosyncratic), gray baby syndrome, dose-related anemia

Inhibits hepatic drug-metabolizing enzymes causing many drug interactions.

Given PO and IV.

Able to cross the placenta & BBB.

Resistance is due to the formation of acetyltransferase that inactivates drug.

Usually caused as topical agent: Chloramphenicol Palmitate & Chloramphenicol Na Succinate

MACROLIDES

ERYTHROMYCIN Azithromycin, Clarithromycin, Telithromycin, Roxithromycin

MOA: binds to 50s ribosomal subunit. Static.

Uses: CAP, Pertussis, Diphtheria, Chlamydial infections, MAC

SE: GI upset, cholestatic hepatitis, hepatotoxicity, QT prolongation, drug interactions, rare fulminant hepatic failure (Telithromycin)

All macrolides inhibit CYP450 EXCEPT Azithromycin.

Azithromycin has the highest Vd & slowest elimination.

Telithromycin is used for macrolide-resistance.

Good oral bioavailability but Azithromycin absorption is impeded by food.

Half-lives: Erythromycin (2hrs), Clarithromycin (6hrs), Azithromycin (24-48hrs).

Resistanace is due to development of efflux pumps & production of methylase enzyme.

Cross-resistance among macrolides: complete ore partial resistance with drugs acting on the 50s.

LINCOSAMIDE

CLINDAMYCIN Lincomycin

MOA: binds to 50s subunit. Static.

Uses: skin & soft tissue infection, anaerobic infections, backup drug against gram (+) cocci, endocarditis prophylaxis (penicillin-allergy), PCP pneumonia, toxoplasmosis

SE: GI disturbances, skin rash, neutropenia, hepatic dysfunction, pseudomembranous colitis (C.defficile overgrowth)

Cross-resistance bertween clindamycin & macrolide is common.

Resistance is due to methylation of binding sites & enzymatic inactivation.

G(-) aerobes are resistant because of poor penetration through the outer membrane.

OXAZOLIDINONE

LINEZOLID Tedizolid

MOA: binds to 23s ribosomal RNA of 50s subunit. Static.

Uses: infections caused by drug-resistant gram(+) cocci such as Staphylococci & Enterococcus (MRSA, VRSA, VRE), Listeria, Corynebacteria

SE: bone marrow suppresion, thrombocytopenia, neutropenia, serotonin syndrome (when given together with serotonergic drugs such as SSRIs), neuropathy, optic neuritis

Resistance is due to decreased affinity of drug to binding site.

STREPTOGRAMIN

Quinupristin -Dalfopristin

MOA: binds 50s subunit. Cidal.

Uses: infections caused by drug-resistant gram(+) cocci such as Staphylococci & E.faecium (MRSA, VRSA, VRE)

SE: injection site reactions, severe arthalgia-myalgia syndrome

Inhibits CYP450 enzymes, causing multiple drug interactions.

FUSIDANE

Fusidic Acid, Na Fusidate

MOA: inhibits transloction process during protein synthesis

Uses: topical antimicrobial against most common skin pathogens including S.aureus

An antibiotic isolated from the fermentation broth of Fusidum coccineum

AMINOGLYCOSIDES
TETRACYCLINE
30S

CHLORAMPHENICOL
ERYTHROMYCIN
LINCOSAMIDES
LINEZOLID
STREPTOGRAMINS
50S

TD

NUCLEIC ACID SYNTHESIS INHIBITORS

SULFONAMIDES

SILVER SULFADIAZINE
Mafenide Acetate

MOA: inhibits dihyropteorate synthase. Static.

Uses: burn infections

SE: GI upset, acute hemolysis in G6PD deficiency, nephrotoxicity, hypersensitivity (assume cross-hypersensitivity, SJS/TEN), hematotoxicity, drug interactions, kernicterus

Displaces protein binding of other drugs/bilirubin

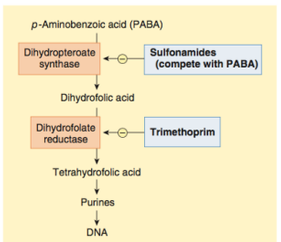


FIGURE 46–1 Inhibitory effects of sulfonamides and trimethoprim on folic acid synthesis. Inhibition of 2 successive steps in the formation of tetrahydrofolic acid constitutes sequential blockade and results in antibacterial synergy.

TRIMETHOPRIM

CO-TRIMOXAZOLE

MOA: sequential blockade of dihydropteroate synthase (SULFAMETHOXAZOLE) and dihydrolate reductase (TRIMETHOPRIM). Cidal.

Uses: urinary tract, respiratory, ear & sinus infections (Haemophilus, Moraxella, Aeromonas), P.jiroveci pneumonia, Toxoplasmosis, Nocardiosis, Cholera (backup), Typhoid fever, Shigellosis

SE: GI upset, acute henolysis in G6PD deficiency, nephrotoxicity, hypersensitivity (assume cross-hypersensitivity, SJS/TEN), hematotoxicity, drug interactions, kernicterus

Dipslaces protein binidng of other drugs/bilirubin.

Low solubility in acidic urine causeing formation of stones.

Resistance is duet to plasmin-mediated (decreased intracellular accumulation of the drug, increased production of PABA by bacteria, decreased sensitivity of dihydropteroate synthetase to sulfas and production of dihydrofolate reductase that has decreased affinity for the drug).

Sulfonamides are formulated in a 5:1 ratio with Trimethoprim.

FLUOROQUINOLONES

1st generation

Nalidixic acid, Cinoxacin, Rosoxacin, Oxolinic acid

2nd generation

CIPROFLOXACIN, Ofloxacin, Norfloxacin, Lomefloxacin, Enoxacin

MOA: inhibits DNA replication by binding to DNA gyrase & topoisomerase IV. Cidal.

Uses: UTI & GIT infections, gram (-) rods (such as Shigella, Salmonella, ETEC & Campylobacter), gonococc, gram (+) cocci, atypical pneumonia, tuberculosis (2nd line drug), infections of soft tissue, bones & joints; intraabdominal MDR organisms (such as Pseudomonas, Enterobacter)

SE: GI distress, CNS effects (dizziness, headache), insomnia, skin rash, abnormal LFTs, tendonitis & tendon rupture

Avoid use in young children & pregnant women.

Enhance toxiicty of methylxanthine (Theophylline).

Ciprofloxacin is the most active agent against gram(-) organisms esp Pseudomonas.

General properties of quinolones: good oral bioavailability, high Vd, t1/2 3-8hrs, absorption is impeded by antacids, elimination is via kidneys by tubular secretion (may compete probenecid for excretion) except Moxifloxain.

Norfloxacin does not achieve adequate plasma levels for use in systemic infections.

3rd generation

LEVOFLOXACIN
Gemifloxacin, Moxifloxacin, Sparfloxacin, Grepafloxacin, Gatifloxacin, Pazufloxacin, Tosufloxacin, Balofloxacin

MOA: inhibits DNA replication by binding to DNA gyrase & topoisomerase IV. Cidal.

Uses: lung infections caused by gram (+) cocci, atypical pnuemonia (Chlamydia, Mycoplasma), TB (2nd line drug)

SE: GI distress, CNS effects (dizziness, headache), tendinitis, QTc prolongation

Avoid use in young children & pregannat women.

Enhance toxicity of methylxanthines (Theophylline).

Grepafloxaxin withdrawn due to severe cardiotoxicity (arrhythmias); Gatifloxacin has also been withdrawn due to DM.

Moxifloxacin has hepatic clearance --> lower urinary levels. so use in UTI is not recommended.

High resistnance esp for C.jejuni, gonococci, G(+) cocci like MRSA, pseudomonas & serratia.

Are used as alternative to Ceftriaxone & Cefixime in gonorrhea.

Ofloxacin can be used against C.trachomatis. Respiratory quinolones.

Moxifloxacin & Gemifloxacin are the newest members of this family & are considred to have the broadest sprectrum of activity with increased activity against anaerobes & atypical agents.

Elimination is via the kidneys by tubular secretion (may compete with probenecid for excretion) except Moxifloxacin.

Never use Moxifloxacin in UTI.

Levofloxacin is used in CAP cause by Chlamydia, Mycoplasma, & Legionella.

Gemifloxacin, Levofloxacin, & Moxifloxacin can prolong Q

Levofloxacin has superior activity against gram(+) bacteria inclusing S.pnuemoniae

All have relaibely long t1/2 permitting once daily dosing.

Oral absorption is impared by cations.

Gatifloxacin can cause hyperglycemia in DM px, & hypoglycemia in px receiving OHA.

4th generation

TROVAFLOXACIN
Alatrofloxacin, Prulifloxacin, Clinafloxacin

MOA: inhibits DNA replication by binding to DNA gyrase & topoisomerase IV. Cidal.

Uses: broad spectrum activity gram (-) & (+), enhanced activity against anaerobes

SE: GI distress, CNS effects (dizziness, headache), tendinitis, QTc prolongtaion, hepatotoxicity (Trovafloxacin)

Avoid use in young children & pregnant women.

Enhance toxicity of methylxanthine (theophylline).

Widest spectrum of activity among FQ.

TD

MISCELLANOUS ANTIBIOTICS

NITROIMIDAZOLE

METRONIDAZOLE
Tinidazole, Secnidazole

MOA: reactive reduction by ferredoxin forming free radicals that disrupt free electron transport chain. Cidal.

Uses: anaerobic or mixed intra-abdominal infections, vaginitis (Trichomonas, Gardnerella), pseudomembranous colitis, brain abscess, protozoal infections

SE: GI irritation, metallic taste, headache, dark urine, leukopenia, dizziness, ataxia, neuropathy, seizures, disulfiram rxn

DOC for Amoebiasis, Giardiasis & Pseudomembranous colitis

NITROFURAN

NITROFURATOIN

MOA: forms multiple reactive intermediates when acted upon by bacterial nitrofuran reductase --> disrupt protein, RNA & DNA synthesis. Cidal.

Uses: uncomplicated UTI (exceot Proteus & Pseudomonas)

SE: anorexia, nausea, vomiting, skin rashes, pulmonary infiltrates, phototoxicity, neuropathies, hemolysis in patients with G6PD deficiency

Proteus & Pseudomonas are resistant.

Contraindicated in renal insufficiency.

PSEUDOMONIC ACID

MUPIROCIN

MOA: inhibits staphylococcal isoleucyl tRNA synthetase. Cidal.

Uses: gram(+) cocci including methicillin-susceptible & MRSA, for minor skin infections such as Impetigo

SE: epistaxis, stinging or burning sensation on the skin, mild skin rash, headache

Only used topically (available as intranasal ointment).

Do not used over large infected areas such as decubitus ulcers or open surgical wound (may lead to resistance).

Single OD dose can prevent recurrent UTI.

Acidification of urine enhances activity.

Adjust dose in renal patients.

POLYMYXINS

POLYMYXIN B
Polymyxin E

MOA: attach to and disrupt bacterial cell membrane, bind & inactivate endotoxin. Cidal.

Uses: gram (-) bacteria; for salvage therapy of Acinetobacterm Enterobacteriaceae & Pseudomonas aeroginosa

SE: eosiophilia, fever, nephrotoxicity, neurotoxicity, rash, urticaria

Proteus & Neisseria are resistant.

For topical use only (to limit toxicity).

MACROCYCLIC

FIDAXOMICIN

MOA: inhibits bacterial protein synthesis by binding to the sigma subunit of RNA polymerase. Static.

Uses: gram (+) bacteria only, C.defficili in adults

SE: nausea, vomiting, abdominal pain, GI bleeding, anemia, neutropenia

Granted Orphan Drug Status for C.difficile in children.

Narrow spectrum.

ANTI TB DRUGS

TD

H — **ISONIAZID**

- MOA: inhibits mycolic acid synthesis. Cidal.
- Uses: TB (active, latent, prophylaxis)
- SE: hepatitis, neurotoxicity (seizures, neuritis, insomia), acute hemolysis in G6PD deficienct, drug-induced lupus, drugs interactions
- Most important drug used in TB (first line agent).
- Prevent neurotoxicity by co-administering PYRIDOXINE (Vit B6).
- Liver metabolism by acetylation (Filipinos are fast acetylators.)
- Potent CYP450 inhibitor.
- Less active against other mycobacteria.
- Structural congener of pyridoxine.
- High level resistance due to deletion of KatG gene which codes for catalase-peroxidase enzyme involved in bioactivation of INH, low level resistatnce due to deletion of inhA gene which encodes the target enzyme which is an acyl protein reductase.
- Best taken 1 hr before or 2hrs after meals.

R — **RIFAMPICIN**

Rifabutin, Rifapentine, Rifaximin

- MOA: inhibits DNA-dependent RNA polymerase --> inhibits RNA production. Cidal.
- Uses: TB (active, latent), atypical mycobacterial infections, leprosy, prophylaxis for meningococcal & staphylococcal carriers states, drug-resistant infections (MRSA, PRSP)
- SE: red-orange body fluids, light chain proteinuria, skin rash, thrombocytopenia, nephritis, hepatotoxicity, flulike syndrome, anemia, cholestasis
- Also considered a first line agent for PTB.
- Potent CYP450 inducer.
- Rapid development of resistance if used alone.
- Delays the emergence of resistance to dapsone.
- RIFAXIMIN is a Rifampin derivative that is not absorbed in the GIT, and so is used for the prevention of hepatic encephalopathy, for treatment of traveler's diarrhea (off-label use: for IBS & pseudomembranous colitis).
- Resistance is due to changes of drug sensitivity of the polymerase enzyme.
- Undergoes enterohepatic recirculation.
- Orange-colored metabolites.
- Delay emergence of resistance to Dapsone.
- Rigabutin equally effective as anti-mycobacterial agent with less drug interaction and it is the preferred anti-TB for AIDS patients.
- Best taken 1 hr before or 2hrs after meal.

Z — **PYRAZINAMIDE**

- MOA: unknown; converted to active PYRAZINOIC ACID under acidic condition of macrophage lysosomes; Static but can be cidal on actively dividing mycobacteria
- Uses: TB (active)
- SE: hepatotoxicity, non gouty polyarthralgia, asymptomatic hyperuricemia, myalgia, GI irritation, rash, porphyria, photosensitivity
- Also known as "sterilizing agent" used during the first 2months of therapy.
- Most hepatotoxic anti TB drug.
- Require metabolic conversion via Pyrazinamide in MTb.
- Resistance is via mutation in pncA gene which codes for pyrazinamidase & increased efflux systems.
- Decreased dose in hepatic & renal patients.
- Take with meals.

E — **ETHAMBUTOL**

- MOA: inhibits arabinosyl transferases involved in the synthesis of arabinogalactan in mycobacterial cell wall. Static
- Uses: TB (active), atypical mycobacterial infections
- SE: visual disturbances (decreased visual acuity, red-green color blindness, retrobulbar neuritis, retinal damage), headache, confusion, hyperuricemia, peripheral neuritis
- Perform base ophthalmologic examination before starting antimycobacterila therapy.
- Resistance is due to mutation in emb gene.
- Dose adjustment is needed in renal px.
- Always used in combination with other drugs for TB.
- Taken with meals.

S — **STREPTOMYCIN**

- MOA: inhibit protein synthesis by binding to S12 ribosomal subunit. Cidal.
- Uses: TB (for drug-resistant strains), tularemia, bubonic plague, brucellosis
- SE: hypersensitivity, nephrotoxicity (reversible), ototoxicity (vestivulotoxic, irreversible). neuromuscular blockade, teratogen (congenital deafness), injection site rxns
- Synergistic effect with beta lactam antibiotics.
- Given IM.

MOST HEPATOTOXIC

ALTERNATIVE ANTI MYCOBACTERIAL DRUGS:

AMIKACIN: streptomycin-resistant or MDR mycobacterial strains
CIPROFLOXACIN, OFLOXACIN: active against strains of M.tuberculosis resistant to first line agents
ETHIONAMIDE: no cross resistance with INH; SE: severe GI irritation & neurotoxicity
P AMINODSALICYLIC ACID (PAS)**:** rarely used bec primary resistance is common; SE: GI irritation, PUD, hypersensitivity rxns, effects on kidney, liver, & thyroid function
CAPREOMYCIN: SE: ototoxicity, renal dysfunction
CYCLOSERINE: peripheral neuropathy, CNS dysfunction

DRUGS FOR LEPROSY

TUBERCULOID LEPROSY

DAPSONE AND RIFAMPICIN

DAPSONE

ACEDAPSONE

MOA: inhibititon of folic acid synthesis. Static.

Uses: leprosy, PCP pneumonia (backup)

SE: GI irritation, fever, skin rashes, methemoglobinemia, acute hemolysis in px with G6PD deficiency

Most active drug against M.leprae.

Usually used in combination with Rifampicin & Clofazimine.

Acedapsone is a a respiratory form of dapsone which has drug action that can last for several months.

LEPROMATOUS LEPROSY

DAPSONE, RIFAMPICIN, AND CLOFAZIMINE

CLOFAZIMINE

MOA: binds to guanine bases in bacterial DNA. Cidal.

Uses: leprosy (sulfone-resistance)

SE: GI irritation, skin discoloration (ranging from orange to red brown to nearly black)

TD

DRUGS FOR ATYPICAL MYCOBACTERIA

PROPHYLAXIS

CLARITHROMYCIN or AZITHROMYCIN with or without RIFABUTIN in patients with CD4 countt less than 50/L

TREATMENT

AZITHROMYCIN or CLARITHROMYCIN with ETHAMBUTOL and RIFABUTIN

TD

ANTI FUNGAL AGENTS

ALTER CELL MEMBRANE

POLYENES

AMPHOTERICIN B

MOA: binds to regosterol in fungal cell membranes, foming artificial pores. Cidal.

Uses: systemic fungal infections (Aspergillus, Blastomyces, Candida albicans, Cryptococcus, Histoplasma, Mucor)

SE: infusion rxns (chills, fever, muscle spasms, hypotension), nephrotoxicity (RTA with Mg & K wasting)

Control infusion rxns by slowing rate of infusion & premedication with antihistamines.

Additive nephrotoxicity with other nephrotoxic drugs (aminoglycosdies).

Lipid formulations: Ambisome, Amphotec, Abelcet.

Highly lipid soluble, poorly absorbed in the GIT.

High Vd except in the CNS with a t1/2 of 2weeks.

Resistance is due to decreased level of ergosterol or change in membrane structure.

Has the widest antifugal spectrum.

NYSTATIN

MOA: binds to ergosterol in fungal cell membranes, forming artificial pores. Cidal.

Uses: candidiasis (oropharyngeal, esophageal, vaginal)

SE: nephrotoxicity (severe)

Minimal mucocutaneous absorption.

Available as a siwh and swallow preparation.

AZOLES

KETOCONAZOLE

MOA: inhibit fungal P-450-dependent enzymes blocking ergosterol synthesis. Static.

Uses: chronic mucocutaneous candidiasis, dermatophytosis

SE: GI disturbances (vomiting, diarrhea), rash, hepatotoxicity, drug interactions

Narrow antifungal spectrum.

Potent CYP450 inhibitor (affect phase I metabolism).

Interferes with steroid hormone synthesis.

Resistance is due to changes in the sensitivity of target enzyme.

Rarely used due to drug interaction & narrow spectrum.

FLUCONAZOLE

Vorixconazole, Posaconazole

MOA: inhibits fungal P-450-dependent enzymes blocking ergosterol synthesis. Static.

Uses: candidiasis (esophageal, oropharyngeal, vulvovaginitis), coccidiodomycosis, cryptococcal meningitis (treatment & prophylaxis)

SE: GI disturbances (vomiting, diarrhea), rash, hepatotoxicity

Alternative to Ampho B in the tx of C.neoformans

As effective as Ampho B in candidemia.

Has a good CNS permeability.

POSACONAZOLE - broadest spectrum triazole (the only azole with activity against Rhizopus sp /mucormycosis).

Potent CYP450 inhibitor.

ITRACONAZOLE

MOA: inhibits fungal P450-dependent enzymes blocking ergosterl synthesis. Static.

Uses: blastomycosis, sporotrichosis, dermatophytosis, chromoblastomycosis, alternative for infections due to aspergillus, coccidiodes, cryptococcus & histoplasma, candida

SE: GI disturbances (vomiting, diarrhea), rash, hepatotoxicity

Much more selective for fungal cells than ketoconazole but with poor entry into CNS.

May also be used for subcutaneous chromoblastomycosis.

CLOTRIMAZOLE

MOA: inhibit fungal P450-dependent enzymes blocking ergosterol synthesis. Static.

Uses: mucocutaneous candidiasis, dermatophytosis, seborrheic dermatitis, pityriasis versicolor

SE: none significant when administered topically

Limited to topical use because of systemic toxicity.

ALLYLAMINE

TERBINAFINE

Butenafine, Naftifine

MOA: interfere with ergosterol synthesis by inhibiting fungal squalene oxidase. Cidal.

Uses: dermatophytosis, onychomycosis

SE: GI upset, rash, headache, taste disturbances, hepatotoxicity

Accumulated in keratin.

Given PO & topical.

More effective than griseofulvin in onchomycosis.

ECHINOCANDIN

CASFOFUNGIN

Anidulafungin, Micafungin

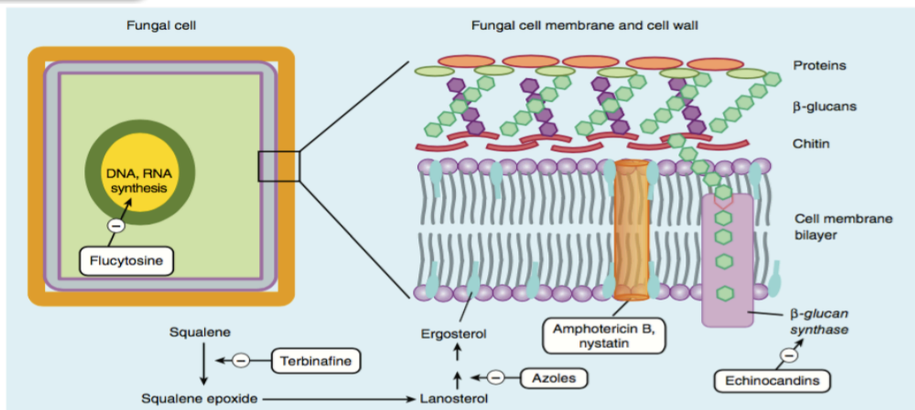
MOA: inhibits b-glucan synthase decreasing fungal cell wall synthesis. Static.

Uses: disseminated & mucocutaneous candidiasis, salvage therapy for invasive aspergillosis

SE: headache, GI distress, fever, rash, flushing (histamine release), elevated liver enzymes

All are given IV.

MICAFUNGIN can increase levels of cyclosporine & tacrolimus.



BLOCKS NUCLEIC ACID SYNTHESIS

FLUCYTOSINE

MOA: accumulated in fungal cells by the action of permease & converted by cytosine deaminase to 5-FU, which inhibits thimidylate synthase. Static.

Uses: cryptococcosis, systemic candidal infections, chromoblastomycosis

SE: myelosuppression, alopecia, hepatotoxicity

Selective toxicity occurs bec mammalian cells have low levels of permease & deaminase.

Syngergistic with Amphotericin.

Decrease dose in renal px.

Resistance is due to decreased activity of fungal permease & deaminase.

Has synergistic effect when given with Ampho B & Triazoles

DISRUPTS MICROTUBULE FUNCTIONS

GRISEOFULVIN

MOA: interferes with microtubule function; inhibits synthesis & polymerization of nucleci acids. Static.

Uses: dermatophytosis

SE: headachem mental confusion, GI irritation, photosensitivity, hepatotoxicity, disulfiram rxn, drug interactions

Accumulates in keratin.

Potent CYP450 inducer.

Contraindicated in porphyria.

Given PO.

Absorption is increased by intake of fatty meal.

Resiatnce is due to decreased transport of drug into the fungal cell wall.

ANTIVIRAL AGENTS

TD

FOR HERPES

ACYCLOVIR
Valacyclovir, Penciclovir, Famciclovir, Docosanol, Trifluridine

MOA: activated by viral thymidine kinase (TK) to form the inhibitor viral DNA polymerase

Uses: infections due to HSV1, HSV2, VZV

SE: nausea, diarrhea, headache, delirium, tremor, seizures, hypotension, nephrotoxicity (crystalluria)

No activity against strains of HSV with absent thymidine kinase activity.

DOCOSANOL inhibits the fusion between the HSV envelope & plasma membranes.

TRIFLURIDINE is a fluorinated pyrimidine nucleoside.

VALOMACICLOVIR is an investigational agent which acts as an inhibitor of viral DNA polymerase for shingles & EBV.

Given PO, topical & IV.

Dose adjustment in renal px.

Resistance is due to changes in viral DNA polymerase.

VALACYCLOVIR is a prodrug that is converted to Acyclovir and reached plasma levels 3-5x (longert t1/2) more than acyclovir.

PENICICLOVIR does not cause chain termination.

FAMCICLOVIR is a prodrug which is converted to Penciclovir in vivo.

GANCYCLOVIR
Valganciclovir

MOA: inhibits viral DNA polymerase causing chain termination

Uses: infections due to CMV, HSV1, HSV2, VZV

SE: leukopenia, thrombocytopenia, mucositis, hepatotoxicity, seizures, neutropenia

No activity against strains of HSC with absent TK activity.

Given as IV of intraocular implant (for CMV retinitis).

CMV resistance is due to mutation in viral DNA polymerase & in the gens that code for the activating viral phosphotransferase.

VALGANCICLOVIR is a prodrug of Gangciclovir with increased oral bioavailability.

CIDOFOVIR

MOA: inhibits viral DNA polymerase, causing chain termination

Uses: CMV retinitis, mucocutaneous HSV infections, acyclovir-resistance, ganciclovir-resistance, genital warts, molluscum contagiosum

SE: nephrotoxicity

Active against strains of HSV with absent TK activity.

Resistance is due to mutation in DNA polymerase.

Dose adjustment in renal px.

FORCARNET

MOA: inhibits viral RNA polymerase, DNA polymerase & HIV reverse transcriptase; binds to pyrophosphate binding site

Uses: CMV retinitis, acyclovir-resistance, HSV infections in px with AIDS

SE: nephrotoxicity, electrolyte abnormalities (hypocalcemia), genitourinary ulceration, CNS effects (headache, hallucinations, seizures)

Active against strains of HSV with absent TK activity.

Does not require phosphorylation for antiviral activity.

Resistance is due to mutation in DNA polymerase gene.

Dose adjustment in renal px.

FOR HIV

NRTI

ZIDOVUDINE
Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir, Zalcitabine

MOA: inhibit HIV reverse transcriptase after phosphorylation by cellular enzymes

Uses: HIV inefction, prevention of maternal-fetal HIV transmission

SE: lactic acidosis with hepatic steatosis
ZIDOVUDINE - bone marrow suppresion
ABACAVIR - hypersensitivity
DIDANOSINE - pancreatitis
STAVUDINE, ZALCITABINE - peripheral neuropathy

NNRTI

DELAVIRINE
Efevirenz, Etravirine, Nevirapine, Rilpivirine

MOA: inhibit HIV reverse transcriptase, no phosphorylation required

Uses: HIV infection

SE: DELAVIRDINE, NEVIRAPINE -rash, increased AST/ALT
EFAVIRENZ - teratogenicity, ETRAVIRINE - increased cholesterol, triglycerides

PROTEIN INHIBITORS

INDINAVIR
Amprenavir, Atazanavir, Darunavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir, Fosamprenavir, Boceprevir, Telaprivir

MOA: inhibit viral proetin processing

Uses: HIV infection

SE: hyperlipidemia, fat redistribution, hyperglycemia, insulin resistance, acanthosis nigricans,
ATAZANAVIR, FOSAMOPRENAVIR, LOPINAVIR, NELFINAVIR, SAQUINAVIR -GI distress & diarrhea
ATAZANAVIR - peripheral neuropathy
AMPRENAVIR - rash
INDINAVIR - hyperbilirubinemia & nephrolithiasis

ENTRY INHIBITORS

FUSION INHIBITOR
ENFUVIRTDE

MOA: binds to gp41 subunit of viral envelope glycoproetin, preventing fusion of viral & cellylar membranes

Uses: HIV infection

SE: injection site rxns, hypersensitivity, increased incidence of bacterial pneumonia

No cross-resiatnce with other anti HIV drugs

CCR5 RECEPTOR ANTAGONIST
MARAVIROC

MOA: blocks viral attachment via transmembrane chemokine receptor CCR5

Uses: HIV infection

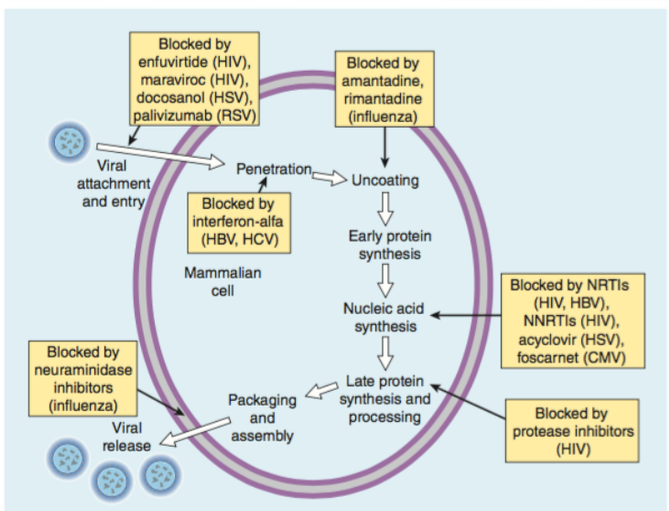
SE: cough, diarrhea, muscle & joint pain, increased hepatic transaminases

Minimal cross-resistance with other anti HIV drugs

RALTEGAVIR

Integrase inhibitor (an enzyme essential for replication of HIV) leading to inhibition of strand transfer

DI: avoid usuing Rifampicin concomitantly (lowered blood levels)



FOR INFLUENZA

AMANTADINE
Rimantadine

MOA: inhibit earl step replication & prevent uning by binding to M2 proton channels

Uses: influenza A only

SE: GI irritation, dizziness, cerebellar dyfunction(ataxia, dysarthria), livedo reticularis

Virtually obsolete in terms of usage.

Amantadine is also used in treating Parkinsonism.

OSELTAMIVIR
Zanamivir, Peramivir

MOA: inhibits neuraminidase; decreases release of progeny virus

Uses: influenza A & B, shortens duration of symptoms

SE: OSELTAMIVIR - GI effects
ZANAMIVIR - bronchospasm in asthmatics

OSELTAMIVIR - presently the drug of choice for influenza (including H1N1)

FOR HBV HCV

INTERFERON ALPHA

MOA: degrades viral RNA via activation of host ce RNAase (ribonuclease)

Uses: HBV infection, HCV infection, Kaposi sarcoma, genital warts

SE: alopecia, myalgia, depression, flu-like syndrome, thyroid dysfunction, hearling loss

Contraindications include autoimmune disease, history of cardiac arrhythmias & pregnancy

LAMIVUDINE
Adefovir dipivoxil, Entecavir, Telbivudine, Tenofovir, Clevudine

MOA: inhibits HBV DNA polymerase

Uses: Hep B infection, HIV infection (Lamivudine)

SE: ADEFOVIR - lactic acidosi, rena & hepatic toxicity
ENTECAVIR - headache, dizziness, fatigue, nausea

Coinfection between HBV & HIV may increase the risk of pancreatitis with Lamivudine use.

RIBAVIRIN

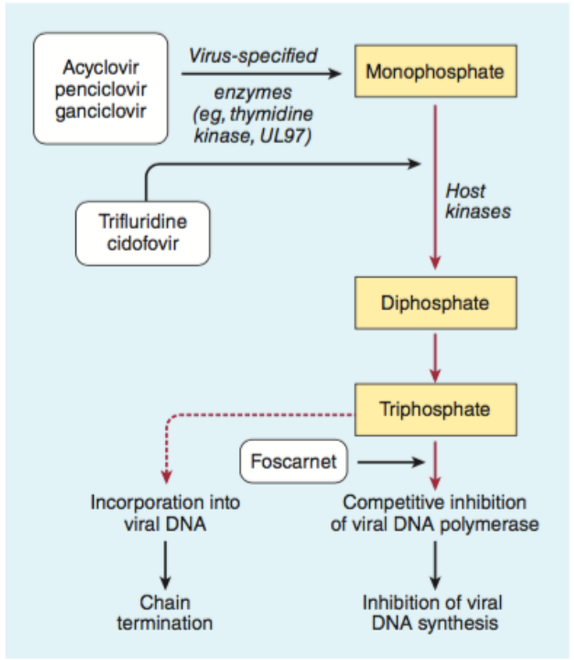
MOA: inhibits guanosine triphosphate formation; prevents capping of viral mRNA; blocks RNA-dependent RNA polymerases

Uses: HCV infection, RSV infection

SE: hemolytic anemia, conjunctival & bronchial irritation, teratogen

Early IV administration of Ribavirin decreases mortality in viral hemorrhagic fevers.

Other drugs for RSV: Pavilizumab (monoclonal antibody against RSV antigen)



MISCELLANEOUS ANTIVIRALS:

IMIQUINOD –an immune response modifier effective for external genital & perianal warts

INOSINE ACEDOBEN DIMEPRANOL –licensed for the tx of cell mediated immune deficiencies assoc with viral infections; used for genital warts, herpes virus infection, subacute sclerosing panecephalitis & other conditions

SOFOSBUVIR –a nucleotide prodrug that undergoes metabolism to the active uridine analog triphosphate, an inhibitor of Hep C virus RNA-dependent polymerase; used for Hep C

TD

ANTI MALARIA

BLOOD SCHIZONTIZIDE

CHLOROQUINE
Hydroxychloroquine, Amodiaquine, Piperaquine

MOA: prevents polymerization of heme into hemozoin

Uses: malaria (non-falciparum, chloroquine-sensitive), chemoprophylaxis (chloroquine-sensitive areas), RA, amebic liver abscess

SE: GI irritation, skin rash, headaches, peripheral neuropathies, myocardial depression, retinal damage, auditory impairment, psychosis

May precipitate porphyria.

QUININE
Quinidine gluconate

MOA: complexes with DNA to prevent strand separation; blocks DNA replication & transcription

Uses: malaria (chloroquine-resistance), severe falciparum malaria (quinidine)

SE: cinchonism (headache, tinnitus, vertigo), hemolysis in G6PD deficiency, blackwater fever

Quinine is commonly used with doxycyline or clindamycin to limit toxicities.

DOC for malaria in pregnant px

MEFLOQUINE

MOA: unknown

Uses: chemoprophylaxis (chloroquine-resistant areas), alternative to quinune in acute attacks of falciparum malaria

SE: GI distress, skin rash, headache, dizziness, cardiac conduction defects, psychiatric disorders (psychosis), neurologic symptoms, seizures

ATOVAQUONE-PROGUANIL

MOA: Atovaquone disrupts mitonchondrial electron transport (blood & tissue schizonticide); Proguanil inhibits folate synthesis (sporonticide)

Uses: tx and chemoprophylaxis (chloroquine-resistant P.falciparum)

SE: abdominal pain, nausea, vomiting, diarrhea, headaches, rash, increased liver enzymes

DOXYCYLINE

MOA: impairs progeny of malarial apociplast genes, resulting in abnormal cell division

Uses: chemoprophylaxis (MDR)

SE: GI disturbance, teratogen (tooth enamel dysplasia/ discoloration), hepatotoxicity, nephrotoxicity, photosensitivity, vestibulotoxicity

Do not drink with milk (decreased absorption).

HALOFANTRINE
Lumefantrine

MOA: unknown

Uses: malaria (chloroquine-resistance), severe falciparum malaria (quinidine)

SE: abdominal pain, diarrhea, vomiting, cough, rash, headache, pruritus, elevated liver enzymes, cardiotoxicity (prolongs PR & QT interval), teratogen

Lumefantrine used in combination with Artemether (Co-Artem)

ARTEMISIN
Artesunate, Artemether, Dihydroartemisinin

MOA: forms toxic free radicals in malarial food vacuole

Uses: malaria (uncomplicated falciparum, quinine-resistant)

SE: nausea, vomiting, diarrhea

ARTEMETHER-LUMEFANTRINE is the DOC for uncomplicated falciparum malaria in the Philippines.

Artemisinin-based combination therapy is currently the first line of malaria tx recommended by WHO for children, adult & preganct women in 2nd or 3rd trimester.

Due to potential embryotoxicity of Artemisinin identified in animal studies, it is not considered safe for use in 1st trimester.

SULFADOXINE-PYRIMETHAMINE

MOA: sequential blockade of folic acid synthesis, blood schizonticide; sporonticide (pyrimethamine)

Uses: malaria (chlorine-resistant P.falciparum)

SE: skin rashes, GI distress, hemolysis, kindey damage, drug interactions, folic acid deficiency (pyrimethamine)

Competition for plasma protein binidng sites with other drugs.

Pyrimethamine is a long-acting folate antagonist.

TISSUE SCHIZONTIZODE

PRIMAQUINE

MOA: forms electron-transferring redox compounds that acts as cellular oxidants

Uses: malaria (radical cure of P.vivax & ovale), terminal prophylaxis (vivax, ovale), PCP, pneumonia

SE: GI distress, pruritus, headaches, methemoglobinemia, hemolysisin G6PD deficiency

Should be used with a blood schizonticide.

Eradicates hypnozoites in the liver, preventing malarial relapse.

ATOVAQUONE-PROGUANIL

GAMETOCIDE

SPORONTICIDE

SULDADOXINE-PYRIMETHAMINE

PROGUANIL

OTHERS

MEPACRINE

QUINACRINE-ATABRINE

Used in the tx & prevention of malaria.

May also be used as an immunodulatory agaent.

TD

DRUGS FOR AMEBIASIS

TISSUE AMEBICIDE

CHLOROQUINE

EMETINE
Dehydroemetine

MOA: inhibit protein synthesis; blocks ribosomal movement along mRNA

Uses: backup drug for severe intestinal & extraintestinal amebiasis

SE: GI distress, muscle weakness, CVS dysfunction (arrhythmias & CHF)

Reserved only for situations when metronidazole cannot be used.

METRONIDAZOLE
Tinidazole, Secnidazole

MOA: reactive reduction by ferredoxin forming free radicals that disrupt ETC

Uses: severe intestinal & extraintestinal amebiasis (DOC), trichomoniasis, giardiasis, bacterial vaginosis, anaerobic infections (B.fragilis, C.difficile), PUD

SE: GI irritation, metallic taste, headache, dark urine, leukopenia, dizziness, ataxia, neuropathy, seizures, disulfiram rxn

NITAZOXANIDE

MOA: reactive reduction by ferredoxin forming free radicals that disrupt ETC

Uses: metronidazole-resistatnt amebiasis, giardiasis, cryptosporidiosis (DOC)

SE: GI distress

LUMINAL AMEBICIDE

DILOXANIDE FUROATE

MOA: unknown

Uses: asymptomatic cyst of E.histolytica (DOC)

SE: flatulence, nausea, abdominal cramps

IODOQUINOL

MOA: unknown

Uses: mild to severe intestinal amebiasis

SE: GI distress, thyroid enlargement, skin rxns due to iodine toxicity, neurotoxicity (peripheral neuropathy, visual dysfunction)

Usually used in combination with Metronidazole

PAROMOMYCIN

MOA: inhibits protein sysnthesis; binds to 16s ribosomal subunit

Uses: asymptomatic cyst carriers (backup), intestinal amebiasis, cryptosporidiosis

SE: headache, dizziness, rashes, arthralgia

Disease Form	Drug(s) of Choice	Alternative Drug(s)
Asymptomatic intestinal infection	Diloxanide furoate	Iodoquinol, paromomycin
Mild to moderate intestinal infection	Metronidazole *plus* luminal agent (see above)	Tinidazole *or* tetracycline *or* erythromycin *plus* luminal agent
Severe intestinal infection	Metronidazole *or* tinidazole *plus* luminal agent	Tetracycline *or* emetine *or* dehydroemetine *plus* luminal agent
Hepatic abscess and other extraintestinal disease	Metronidazole *or* tinidazole *plus* luminal agent	Emetine *or* dehydroemetine *plus* chloroquine (for liver abscess) *plus* luminal agent

DRUGS FOR PNEUMOCYTOSIS AMD TOXOPLASMOSIS

CO TRIMOXAZOLE

MOA: sequential blockade of dihydropteroate synthase (Suldamethoxazole) and dihydrofolate reductase (Trimethoprim)

Uses: prophylaxis & treatment of penumocytosis (DOC), prophylaxis (T.gondii, I.belli)

SE: GI upset, acute hemolysis in G6PD deficiency, nephrotoxicity, hypersensitivity (assume cross-hypersensitivity, SJS/TEN), hematatoxicity, drug interactions, kernicterus

Displaces protein binding of other drugs/bilirubin.

Recommended at CD4 count <200

PENTAMIDE

MOA: unknown; probably inhibits glycolysis or interferes with nucleic acid metabolism

Uses: prophylaxis & treatment of pneumocytosis (backup), trypanosomiasis

SE: respiratory stimulation followed by depression, hypotension, hypoglycemia, anemia, neutropenia, hepatitis, pancreatitis

Administered by nasal spray (aerosol).

SULFADIAZINE-PYRIMETHAMINE

Pyrimethamine +Clindamycin

MOA: sequential blockade of dihydropteroate synthase (Sulfadiazine) and dihydrofolate reductase (Pyrimethamine)

Uses: prophylaxis & treatment of Toxoplasmosis (DOC)

SE: gastric irritation, glossitis, neurologic symptoms (headache, insomnia, tremors, seizures), hematotoxicity (megaloblastic anemia, thrombocytopenia), pseudomembranous colitis (clindamycin)

TD

DRUGS FOR TRYPANOSOMIASIS

TRYPANOSOMA BRUCEI RHODIENSE, EAST AFRICAN

SURAMIN

MOA: unknown; probably inhibits glycolysis or interfres with nucleic acid metabolism

Uses: african sleeping sickness (hemolymphatic stage), onchocerciasis (backup)

SE: fatigue, nausea, vomiting, seizures, shock, fever, rash, headache, paresthesia, neuropathies, renal abnormalities (proteinuria), chronic diarrhea, hemolytic anemia, agranulocytosis

Does not cross the BBB.

Used in combination with Melarsoprol

MELARSOPROL

MOA: organic arsenical; inhibits ezyme sulfhydryl groups in trypanosomes

Uses: african sleeping sickness (DOC)

SE: GI irritation, reactive encephalopathy

Crosses the BBB.

Given IM.

Considerably administered with Suramin.

TRYPANOSOMA BRUCEI GAMBIENSE, WEST AFRICAN

PENTAMIDINE

MOA: unknown; probably inhibits glycolysis or interfere with nucleic acid metabolism

Uses: african sleeping sickness (hemolymphatic stages), prophylaxis for pneumocytosis, Kala-azar (visceral leishmaniasis

SE: respiratory stimulation followed by depression, hypotension, hypoglycemia, anemia, neutropenia, hepatitis, pancreatitis

Do not cross the BBB>

ELORNITHINE

MOA: suicide inhibitor of ornithine decarboxylase

Uses: advanced West African sleeping sickness (DOC)

SE: diarrhea, vomiting, anemia, thrombocytopenia, leukopenia, seizures

Crosses the BBB.

Considerably less toxic than Melarsoprol.

LEISHMANIA

SODIUM STIBOGLUCONATE

Meglumine antimonate, Amphotericin, Miltefosine

MOA: unknown; probably inhibits glycolysis or interferes with nucleic acid metabolism

Uses: Na Stibogluconate (DOC except in India)

SE; GI symptoms, fever, headache, myalgias, arthralgias, rash, sterile abscesses, cardiotoxicity (T-wave changes, QT prolongation)

Alternative drugs include:

VISCERAL (KALA-AZAR): Pentamidine, Miltefosine

CUTANEOUS: Fluconazole, Metronidazole

MUCOCUTANEOUS: Amphotericin B

TRYPANOSOMA CRUZI, AMERICAN

NIFURTIMOX

MOA: inhibits trypanothione reductase

Uses: Chaga's disease (DOC), African sleeping sickness (backup), mucocutaneous leishmaniasis

SE: nausea, vomiting, abdominal pain, fever, rash, restlessness, insomia, neuropathies, seizures

Does not cross the BBB.

SEDATIVE - HYPNOTIC DRUGS

LM

BENZODIAZEPINES
[Binds GABA-A receptor subunits to increase FREQUENCY of Cl⁻ channel opening; membrane hyperpolarization]

SHORT ACTING
[T½: 1.5 - 2.5h]

MIDAZOLAM *(Brotizolam, Triazolam, Oxazepam, Etizolam)*

Uses: Anesthesia induction
Preop sedation
Acute Anxiety
Panic attacks
Insomnia [Triazolam]

SE: Anterograde amnesia
Rebound insomnia/anxiety
Dec. psychomotor skills
Dependence liability
Unwanted daytime sedation

Notes: Decreased REM sleep
Avoid during 1st trimester
Floppy infant syndrome
Inceased oral cleft risk

INTERMEDIATE ACTING
[T½: 12h]

LORAZEPAM *(Alprazolam, Estazolam, Clonazepam, Lormetazepam, Nitrazepam, Temazepam)*

Uses: Status epilepticus
Skeletal muscle relaxant
Tranquilizers
Seizure d/o [Clonazepam]
Bipolar d/o [Clonazepam]
Anxiety d/o [Clonazepam]
Panic d/o [Clonazepam]
Insomnia [Estazolam]

SE: Anterograde amnesia
Dec. psychomotor skills
Dependence liability
Respiratory depression
Unwanted daytime sedation

Notes: Lorazepam preferred over Diazepam in Status epilepticus due to its long distribution T½

LONG ACTING
[T½: 100h]

DIAZEPAM *(Chlorazepate, Chlordiazepoxide, Flurazepam, Quazepam, Flunitrazepam)*

Uses: Status Epilepticus
Skeletal muscle relaxant
Anesthesia
Anxiety/Seizure d/o
Alcohol withdrawal
Insomnia [Flurazepam]

SE: Anterograde amnesia
Dec. psychomotor skills
Dependence liability
Respiratory depression
Unwanted daytime sedation

Notes: Flunitrazepam (Rohypnol) used as a Date-rape drug (odorless colorless, tasteless, anterograde amnesia effect)

BARBITURATES
[Binds GABA-A receptor sites; increases DURATION of Cl⁻ channel opening; blocks glutamic acid neurotransmission; at high doses blocks Na channels]

ULTRA SHORT
[T½: 4-9m]

THIOPENTAL *(Methohexital, Thiamylal)*

Uses: Anesthesia induction
Increased ICP

SE: Acute intermittent porphyria; Extension of CNS depressant actions; dependence liability greater than Benzos

Notes: Additive CNS depression if taken with ethanol; CYP450 inducer

SHORT-INTERMEDIATE
[T½: 15 - 50h]

PENTOBARBITAL *(Secobarbital, Amobarbital, Butalbital, Butabarbital, Talbutal, Aprobarbital)*

Uses: Insomnia
Preop sedation

SE: Acute intermittent porphyria; Extension of CNS depressant actions; dependence liability greater than Benzos

Notes: Additive CNS depression if taken with ethanol; CYP450 inducer

LONG ACTING
[T½: 118h]

PHENOBARBITAL *(Mephobarbital, Primidone)*

Uses: Status epilepticus
Seizure d/o
Insomnia
Hyperbilirubinemia (Gilbert Syndrome)

SE: Severe Cardio/respi depression; Extension of CNS depressant actions; dependence liability greater than Benzos

Notes: May be excreted unchanged in the urine; Additive CNS depression if taken with ethanol; CYP450 inducer

OTHERS

IMIDAZOPYRINE

ZOLPIDEM *(Zaleplon, Eszopiclone)*

MOA: Binds selectively to a subroup of GABA-A receptors to enhance membrane hyperpolarization

Uses: Insomnia
Delayed sleep onset

SE: Few amnestic effects
Dependence liability (less)

Notes: Lack anti-convulsant, anti-anxiety and muscle relaxant effects; very rapid onset of action; effects reversed by FLUMAZENIL

MELATONIN RECEPTOR AGONIST

RAMELTEON

MOA: Activates Melatonin receptors (MT1 and MT2) in the suprachiasmatic nuclei thus decreasing latency of sleep onset

Uses: Insomnia

SE: Dizziness
Fatigue
Decreased testosterone
Increased prolactin

Notes: Minimal rebound insomnia
Minimal abuse liability
Minimal withdrawal s/sx

ANXIOLYTIC

BUSPIRONE

MOA: Partial agonist at 5HT1A and possibly D2 receptors

Uses: Generalized anxiety d/o

SE: Non-specific chast pain
Tachycardia/palpitations
Dizziness/nervousness
Tinnitus/GI distress
Paresthesia
Pupillary constriction

Notes: No anticonvulsant effect
No muscle relaxant effect
Minimal CNS depression

***FLUMAZENIL* [T½: 30m]**

MOA: Antidote; antagonist at benzodiazepine sites on GABA-A receptor
Uses: Benzodiazepine overdose
SE: Agitation, Confusion, Precipitates benzodiazepine withdrawal syndrome for those with benzodiazepine dependence
Notes: Seizure and arrhythmias may occur for those who took TCAs and benzodiazepines

MNEMONICS:
BENZodiazepines = Mercedes Benz (Fast Frequency)
BARBiturates = Barbed wire (Duration)
TAYOpental = TAYO agad (shortest acting)
Chlordiazepoxide = longest spelling (longest T½: 36-200h)

Most catastrophic symptom of sedative-hypnotic withdrawal?
- REBOUND SUICIDE

ANTI-SEIZURE DRUGS

LM

TONIC-CLONIC & PARTIAL

VALPROIC ACID
(Sodium Valproate)
MOA: Blocks Na channels, enhances K channel permeability
Uses: Bipolar d/o Acute Mania (DOC); GTC seizure (DOC); Absence seizure (DOC); Partial seizure; Myoclonic seizure
SE: NTD, Spina bifida, Hepatotoxicity (esp. in infants), wt. gain, GI upset, drowsiness, nausea, tremor, alopecia
Notes: CYP450 inhibitor; same effect on Ca channels as Ethosuximide

LAMOTRIGINE
(Zonisamide)
MOA: Blocks Na and Ca channels, decreases Glutamate
Uses: Partial seizure (DOC); GTC seizure; Myoclonic & absence seizure; Bipolar d/o
SE: SJS/TEN [Lamotrigine], severe skin reaction [Zonisamide], Dizziness, ataxia, nausea, rash
Notes: Undergoes glucuronidation reaction

PHENYTOIN
(Fosyphenytoin, Mephenytoin, Ethotion)
MOA: Blocks voltage gated Na channels
Uses: Generalized tonic-clonic seizure (DOC); Partial seizure (DOC); Status Epilepticus; Arrhythmias (Grp 1B action)
SE: Nystagmus, diplopia, sedation, Gingival hyperplasia, Hirsutism, Fetal hydantoin syndrome
Notes: Phenytoin preferred in prolonged therapy for Status epilepticus because it is less sedating; Fostomycin is a water-soluble prodrug

CARBAMAZEPINE
(Oxcarbazepine, Eslicarbazepine)
MOA: Blocks voltage gated Na channels; dec. Glutamate release
Uses: Trigeminal neuralgia (DOC); GTC seizure (DOC); Partial seizure (DOC); Bipolar d/o
SE: SJS, Spina bifida, craniofacial anomalies, hyponatremia [Oxcar], Diplopia, cognitive dysfunction, drowsiness, bloody dyscrasias
Notes: CYP450 inducer; can cause auto-induction
Oxcarbazepine has less drug interactions

MYOCLONIC

VALPROIC ACID
(Sodium Valproate)
[SAME]

LAMOTRIGINE
(Zonisamide)
[SAME]

CLONAZEPAM
MOA: Binds GABA-A receptors to increase frequency of Cl channel opening; membrange hyperpolarization
Uses: Absence seizure; Myoclonic seizure; Infantile spasms
SE: Anterograde amnesia, decreased psychomotor skills. unwanted daytime sedation, respiratory depression, tolerance, dependence liability

ABSENCE

VALPROIC ACID
(Sodium Valproate)
[SAME]

CLONAZEPAM
[same]

ETHOSUXIMIDE
(Phensuximide, Methsuximide)
MOA: Decreases Ca currents (T-type) in thalamus
Uses: Absence seizures
SE: GI distress, lethargy, headache, behavioral changes
Notes: long half-life

FETAL HYDANTOIN SYNDROME
- Upturned nose
- Mild mid facial hypoplasia
- Long upper lip with thin vermillion border
- Lower distal digital hypoplasia

ADJUNCTS

PHENOBARBITAL
(Primidone)
MOA: Binds to GABA-A receptor sites and increases DURATION of Cl channel opening
Uses: GTC seizure; Partial seizure; Status epilepticus; Insomnia; Hyperbilirubinemia (Gilbert syndrome)
SE: Acute intermittent porphyria, extended CNS depressant actions, tolerance, dependence liability
Notes: Primary anticonvulsant in infants, children, and pregnant

DIAZEPAM
(Lorazepam, Clorazepate)
MOA: Binds to GABA-A receptor sites and increases FREQUENCY of Cl channel opening
Uses: Status epilepticus
SE: Anterograde amnesia, unwanted daytime sedation, respiratory depression, dec. psychomotor skills, tolerance, dependence liability

GABAPENTIN
(Pregabalin)
MOA: Binds Ca channels; Inc GABA release; inhibits neuronal discharge from seizure foci
Uses: Absence seizure; Neuropathic pain (post herpetic neuralgia); Migraine
SE: Dizziness, sedation, ataxia, nystagmus, tremor
Notes: Eliminated in the kidneys in the unchanged form

LEVETIRAZETAM
MOA: Binds synaptic vesicular protein 2 (SV2A) inhibiting hyper synchronisation of epileptiform burst firing; modifies synaptic release of Glutamate and GABA
Uses: Juvenile myoclonic epilepsy; GTC seizure; Partial seizure
SE: Hallucination, psychosis, irritability, dizziness, sedaation
Notes: Minimal drug interactions, eliminated in kidneys unchanged

TOPIRAMATE
(Felbamate)
MOA: Actions on phosphorylation (Na, Ca, GABA, Glutamate, Carbonic anhydrase)
Uses: Lennox-gestaut syndrome; West syndrome; Migraine; GTC seizure; Refractory seizures [Felbamate]
SE: Psychomotor slowing, Memory impairment, Acute myopia glaucoma, urolithiasis, Hepatic and hematoxicity [Felbamate]

GENERAL ANESTHESIA

LM

INHALED
[Facilitate GABA mediated inhibition; block brain NMDA and ACh-N receptors]

GAS

NITROUS OXIDE
- Uses: Anesthesia for minor OR and dental procedures
- SE: Euphoria, Megaloblastic anemia bronchodilation
- Notes: Lowest potency (highest MAC) least cardiotoxicity

VOLATILE LIQUIDS

DESFLURANE
- Uses: General anesthesia
- SE: Bronchospasm
  Peripheral vasodilation
- Notes: All other inhaled anesthetic causes bronchodilation

SEVOFLURANE
- Uses: General anesthesia
- SE: Renal insufficiency
  Peripheral vasodilation

ISOFLURANE
- Uses: General anesthesia
- SE: Catecholamine induced arrhythmias, peripheral vasodilation

ENFLURANE
- Uses: General anesthesia
- SE: Spike and wave activity in EEG, muscle twiitching, breath holding
- Notes: Has pungent odor limiting use

HALOTHANE
- Uses: General anesthesia
- SE: Malignant hyperthermia (if used with Succinylcholine), Post-operative hepatitis

METHOXYFLURANE
- Uses: General anesthesia
- SE: Renal insufficiency

INTRAVENOUS

BARBITURATES

THIOPENTAL
(Methohexital, Thiamylal)
- MOA: Increases DURATION of Cl channel opening
- Uses: Anesthesia induction
  Inceased ICP
- SE: Dependence liability
  Acute intermittent porphyria
  Tolerance
  Extension of CNS depression
- Notes: Additive CNS depression w/ ethanol
  CYP450 inducer
  Rapid entry into the brain (<1min)

BENZODIAZEPINES

MIDAZOLAM (Brotizolam, Triazolam, Oxazepam, Etizolam, Lorazepam)
- MOA: Inceases FREQUENCY of Cl channel opening
- Uses: Anesthesia induction
  Preop sedation
  Anxiety/panic attacks
- SE: Anterograde amnesia, unwanted daytime sedation, dependency liability, post-op Respi depression
- Notes: Antidote is FLUMAZENIL
  Adjucnt with inhalational anesthetics and IV opioids
  Slow onset but longder DOA

DISSOCIATIVE

KETAMINE
- MOA: Blocks glutamate and NMDA receptors
- Uses: Dissociative anesthesia (Analgesia, amnesia and catatonia but with retained consciousness)
- SE: Emergence delirium (Post-op effects: disorientation, hallucination, excitation), cardiovascular stimulation, HPN, inc. ICP
- Notes: Reduce Emergence delirium with pretreatment of Benzodiazepine

OPIOIDS

FENTANYL
(Morphine, Alfentanyl, Remifentanil)
- MOA: Interact with μ (mu) or δ (sigma), and κ (kappa) receptors for endogenous opioid peptide
- Uses: General anesthesia
- SE: Respiratory depression
  Chest wall deformity, constipation
- Notes: Antidote is NALOXONE
  Neuroleptanesthesia (analgesia + anesthesia) happens when given with Droperidol and NO
  Faster recovery [Remifentanyl]

MISCELLANEOUS

ETOMIDATE
- MOA: Modulates GABAa receptors (β3 subunit)
- Uses: General anesthesia (in patients with limited cardiorespiratory reserve)
- SE: Pain on injection, myoclonus
  Post-op N/V, Adrenocortical suppression
- Notes: Minimal effect on Cardiorespi function
  No analgesic property

PROPOFOL
(Fospropofol)
- MOA: Potentiates GABA-A receptors
  Blocks Na channels
- Uses: General anesthesia for prolonged sedation esp. in ICU/OPD patients
- SE: Bradycardia, hypotension, vasodilation, priapism
  paresthesia [Fospropofol]
- Notes: Milk of amnesia

DEXMETOMIDINE
- MOA: A2 receptor agonist, decrease sympathetic tone with attenuation of neuroendocrine and hemo-dynamic response to anesthesia and surgery and cause sedation and analgesia

LM

LOCAL ANESTHETICS

[Blockade of Na channels slow, then prevents axon potential propagation]

ESTERS

SHORT ACTING

PROCAINE
(Novocaine, Chloroprocaine)

Uses: Extravasation complications from venipuncture, inadvertent intraarterial inections

SE: Light headedness, sedation, Restlessness, nystsagmus, Cardiorespiratory depression
Antibody formation (allergy)

Notes: Shortest T½ among LAs

LONG ACTING

TETRACAINE

Uses: Local/spinal/epidural/ topical/ophthalmic anesth

SE: Most allergenic among LAs

Notes: Primarily for spinal (2-3h)

SURFACE ACTING

BENZOCAINE
(Butamben)

Uses: Local/topical anesthesia

SE: Light headedness, sedation, Restlessness, nystsagmus, Cardiorespiratory depression
Skin irritation
Antibody formation (allergy)

Notes: Topical use only

COCAINE

MOA: Intrinsic sympathometic activity; vasoconstriction

Uses: Local/topical anesthesia

SE: Severe HPN, cerebral hemorrhage, arryhthmias, MI, stroke, abuse liability

Notes: Only LA that vasoconstricts
Topical use only

MNEMONICS:
ESTERS have only 1 'i' in their names
AMIDES have 2 'i's in their names

PROCAINE = shortest T½
- a PRO finishes the race fastest

ROPIVACAINE = longest T½
- at the end of a long ROPE

AMIDE

MEDIUM ACTING

LIDOCAINE

Uses: Antiarrhythmic (1B) used post-MI, digitalis toxicity

SE: Light headedness, sedation, Restlessness, nystsagmus, Cardiorespiratory depression

Notes: Topical, infiltration, spinal, epidural, IV, peripheral
Give with EPI to decrease systemic absorption

PRILOCAINE (Mepivacaine)

Uses: Local/dental anesthesia

SE: Methemoglobinemia
Light headedness, sedation, Restlessness, nystsagmus, Cardiorespiratory depression

Notes: Administer methylene blue for methemoglobinemia

LONG ACTING

BUPIVACAINE
(Levobupivacaine)

Uses: Local/epidural/intrathecal

SE: Severe cardiotoxicity
Hypotension, arrhythmias

Notes: Treat cardiotoxicity with INTRALIPID/LIPOSOMAL forms (Fat emulsion in TPN)

ROPIVACAINE

Uses: Local/epidural anesthesia

SE: Cardiotoxicity (less than Bupivacaine)

Notes: Longest T½ among LAs
Treat cardiotoxicity with INTRALIPID/LIPOSOMAL forms (Fat emulsion in TPN)

Why NOT to inject LA into an abscess? Lidocaine won't work in an acidic environment (below pKa = charged form will predominate), thus will not be able to cross the cell membrane and excert its action

LM

SKELETAL MUSCLE RELAXANTS

NEUROMUSCULAR BLOCKERS

NON-DEPOLARIZING
[Competitive antagonists at skeletal muscle nicotinic acetylcholine receptors]

SHORT ACTING

MIVACURIUM
- Uses: Intubation; General anesthesia
- SE: Respiratory paralysis, apnea
  Histamine release (moderate)
- Notes: Metabolized by pseudocholinesterase
  Short DOA (10-20m)

INTERMEDIATE ACTING

ATRACURIUM (Cisatracurium)
- Uses: Intubation; General anesthesia; Mechanical ventillation facilitation
- SE: Bronchospasm; seizures; Respiratory paralysis; apnea
  Histamine release
- Notes: Undergoes **HOFFMAN elimination** (rapid spontaneous breakdown)

VECURONIUM
- Uses: Intubation; General anesthesia
- SE: Respiratory paralysis, apnea
  Minimal cardiovascular effects
- Notes: Undergoes elimination in **BILE**
  Muscle relaxation potentiated by inhaled anesth, aminogly, quinidines

ROCURONIUM
- Uses: Intubation; General anesthesia
- SE: Hypersensitivity, apnea
  Respiratory depression
- Notes: **SUGAMMADEX** is a novel reversal agent; slight antimuscarinic effect
  Used in patients w/ renal impairment
  Most rapid onset (60-120s)

LONG ACTING

TUBOCURARINE
- Uses: Prolonged relaxation during OR; Intubation; General anesthesia
- SE: **Ganglion block (hypotension),** Recurarization, Respi paralysis
  Prolonged apnea, histamine release
- Notes: C/i in myocardial ischemia

PANCURONIUM
- MOA: Moderate block on cardiac muscarinic receptors
- Uses: **Euthanasia; lethal injection; Strychnine poisoning**; intubation
  General anesthesia
- SE: Recurarization, tachycardia, apnea
  Respiratory paralysis, HPN
- Notes: May cause heart block

MALIGNANT HYPERTHERMIA
- Rare interaction between succinylcholine with inhaled anesthetics
- Life-threatening condition characterized by massive Ca release from sarcoplasmic reticulum to skeletal muscle
- Early sign: Trismus (contraction of jaw muscles)
- Tx: DANTROLENE

DEPOLARIZING

SUCCINYLCHOLINE
- MOA: Agonist at ACh-N causing initial twitch then persistent repolarization, followed by long flaccid paralysis
- Uses: Malignant hyperthermia, hyperK, Inc. IOP, regurgitation (aspiration)
  Arryhthmia, muscle pain
- Notes: **DANTROLENE** for malignant hyperthermia; metabolized by pseudocholinesterase (plasma)
  a.k.a **SUXAMETHONIUM**

OTHERS

CENTRALLY ACTING SPASMOLYTICS

BACLOFEN
- MOA: GABA-B agonist; facilitate spinal inhibition of motor neurons
- Uses: Cerebral palsy spasticity; stroke
  Multiple sclerosis
- SE: Sedation, weakness, dizziness
  Confusion, nausea, headache

ORPHENADRINE *(Chlorphenesin, Methocarbamol, Cyclobenzapirine)*
- MOA: Inhibits muscle stretch reflex
- Uses: Acute spasm from muscle injury; Inflammation
- SE: Strong antimuscarinic effects

DIAZEPAM
- MOA: Facilitates GABAergic transmission in the CNS
- Uses: Cerebral palsy spasm; stroke
  Spinal Cord injury; acute spasm
- SE: Anterograde amnesia, unwanted daytime sedation, respiratory depression, tolerance

TIZANIDINE
- MOA: α2 adrenoreceptor agonist in the SC
- Uses: Multiple sclerosis spasm; stroke; Amyotropic lateral sclerosis
- SE: Weakness, sedation, hypotension

DIRECT ACTING MUSCLE RELAXANTS

DANTROLENE
- MOA: Blocks RyR1 Ca-release channels in the skeletal muscles
- Uses: Malignant hyperthermia; spasm due to CP, MS, and SCI
- SE: Muscle weakness

OTHERS

EPERISONE
- Class: Antispasmodic
- MOA: Relaxes both skeletal and vascular smooth muscles
- Uses: Reduces myotonia, improves circulation, suppresses pain relfex

LM

ANTI-PARKINSONISM

DOPA-PRECURSOR

LEVODOPA-CARBIDOPA
- MOA: L is a dopa precursor, while C inhibits peripheral metabolism via dopa decarboxylase
- Uses: Parkinson Dse. (DOC)
- SE: GI upset, dyskinesia, behavioral changes, On-off phenomena Wearing-off phenomena, Postural HPN, arrhythmia
- Notes: C/i in px with hx of PSYCHOSIS Use with COMT to prolong DOA HPN crisis if used with MAOIs

DOPA-AGONIST

ERGOT

BROMOCRPITINE *(Pergolide, Cabergoline, Piribedil)*
- MOA: Partial agonist at D2 receptors, leading to inh of prolactin release
- Uses: Levodopa intolerance, Hyper-prolactinema, intermittent claudication, tremors
- SE: Pulmonary infiltrate/fibrosis, Eryhthromelalgia, anorexia, N/V, Dyskinesia, behavioral change
- Notes: PRIBEDIL can act as D3 agonist and as A2 adrenergic antagonist

NON-ERGOT

PRAMIPEXOLE *(Ropinirole)*
- MOA: Partial agonist at D2 and D3 receptors; smooths out fluctuations in Levodopa response
- Uses: Restless leg syndrome On-off phenomenon
- SE: Behavioral changes, confusion Compulsive gambling, overeating, hypersexuality, uncotrollable tendency to fall asleep
- Notes: C/i with active PUD, recent MI, or psychotic illness

APOMORPHINE
- MOA: Partial agonist at D3 receptors; Antagonist at 5HT3 and Alpha adrenoreceptors
- Uses: Off-periods, erectile dysfunction, Alcoholism, Opiate addiction, Alhzeimer's Disease
- SE: Severe nausea, dyskinesia, Hypotension, drowsiness, sweating
- Notes: Use TRIMETHOBENZAMIDE to prevent severe nausea

MAO INHIBITORS

SELEGILINE *(Rasagiline)*
- MOA: Selectively inh MAO-B decreasing degradation of dopamine; Inc response to Levo-Carbidopa
- Uses: Only as adjunct to Levodopa; Can be given alone [Rasagiline]
- SE: Insomnia, mood changes, Dyskinesia, GI distress, hypoTN
- Notes: May cause agitation, delirium, and death if used with Meperidine Serotonin syndrome if used with SSRIs, TCSs, and Meperidine

COMT INHIBITORS

ENTACAPONE *(Tolcapone)*
- MOA: Blocks L-dopa metabolism by inhibiting COMT in periphery and CNS; prolong L-dopa response
- Uses: Wearing-off phenomena Adjunct to Levodopa
- SE: Orange urine, NMS, sleep disturbance, rhabdomyolysis, Hepatotoxicity [Tolcapone]
- Notes: Entacapone (periphery) Tolcapone (periphery + CNS)

ANTICHOLINERGICS

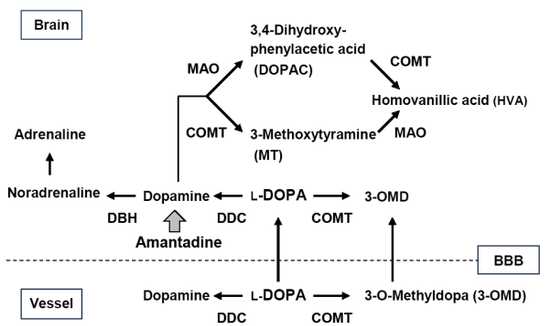
BENZTROPINE *(Biperiden, Trihexyphenidyl, Procyclidine)*
- MOA: Decreases excitatory actions of cholinergic neurons by blocking muscarinic receptors
- Uses: Adjunct for Parkinson's dse. and EPS caused by antipsychotics
- SE: Atropine-like effects, confusion Inattention, drowsiness, Delusions, hallucinations
- Notes: Improves tremor and rigidity Exacerbate tardive dyskinesia

OTHERS

AMANTADINE
- MOA: Potentiates dopaminergic function (synthesis, release, reuptake)
- Uses: Parkinson's dse; Influenza
- SE: Livedo reticularis, behavioral changes, GI disturbances, urinary retention, peripheral edema
- Notes: Improves bradykinesia, tremor, and rigidity; anti-muscarinic action

ROTIGOTINE
- MOA: Dopamine agonist
- Uses: Restless leg syndrome
- Notes: Used as OD transdermal patch providing slow and constant doses

Figure 1. L-DOPA metabolism and mechanisms of amantadine



Note: MAO: monoamine oxidases, COMT: catechol-O-methyltransferase, DDC: dopa decarboxylase, DBH: dopamine-β-hydroxylase

ON-OFF PHENOMENA
- Alternating periods of improved mobility and akinesia, occurring a few hours to days during treatment

WEARING-OFF PHENOMENA
- Deterioration of drug effect in between doses
- Due to progressive destruction of nigrostriatal neurons that occurs with disease progression

DRUGS for HUNTINGTON'S DISEASE

TETRABENZAMINE / RESERPINE
- MOA: Deplete amine transmitters esp Dopa from nerve endings by reversibly inhibiting VMAT2, resulting in decreased uptake of monoamines
- Uses: reduces chorea severity
- SE: hypoTN, sedation, depression, diarrhea

DRUGS for TOURETTE'S SYNDROME

HALOPERIDOL / PIMOZIDE
- MOA: Blocks central D2 receptor
- Uses: Reduces vocal and motor tic frequency and severity
- SE: Parkinsonism, dyskinesia, sedation, blurred vision, dry mouth, visual disturbance, arrhythmia [Pimozide]

MNEMONICS:

LIVEDO RETICULARIS
Drugs that cause LR: "A MAN reads fHM and GQ"
- **Aman**tadine
- **H**ydroxyurea
- **M**inocycline
- **G**emcitabine
- **Q**uinidine

ANTI-PSYCHOTICS

LM

TYPICALS / CLASSICAL

[Block of D2 receptors >> 5HT2 receptors]

CHLORPROMAZINE *(Thiothexene, Flupentixol, Promethazine, Levomepromazine)*

Uses: Shizophrenia, manic phase of BPD

SE: **CORENAL** and **LENS** deposits, failure of ejaculation, EPS, tardive dyskinesia, Hyperprolactinemia, marked seadtion, NMS

Notes: May also block α and histamine receptor, Protoype antipsychotic [Promethazine]

THIORIDAZINE *(Fluphenazine, Perphenazine, Prochlorperazine, Trifluoperazine)*

Uses: Schizophrenia, antiemesis and preop sedation [Prochlorperazine]

SE: **RETINAL deposits** [Thioridazine], failure of ejaculation, EPS, tardive dyskinesia, Hyperprolactinemia, Cardiotoxicity

Notes: Strongest autonomic effects [Thioridazine] Only antipsychotic w/ **FATAL OVERDOSE**

HALOPERIDOL *(Droperidol)*

Uses: Schizophrenia, manic phase of BPD, Huntington's dse, Tourette's syndrome

SE: Neuroleptic Malignant Syndrome, Extrapyramidal symptoms (major), Tardive dyskinesia, Hyperprolactinemia

Notes: Causes the **MOST EPS** of all typicals Weakest autonomic effects, least sedating among aypicals

ATYPICALS

[Block of 5HT2 receptors >> D2 receptors]

CLOZAPINE

Uses: Refractory and suicidal schizophrenia

SE: DM, weight gain, myocarditis, ileus, Agranulocytosis, hypersalivation, seizure

Notes: **REDUCES SUICIDE RISK** Prominent wt. gain, hyperglycemia, Agarnulocytosis, and seizures

QUETIAPINE

Uses: Schizophrenia, BPD manic phase

SE: Somnilence, fatigue, sleep, paralysis, Hypnagogic hallucinations, cataracts, Priapism, Prolonged QT (TDP)

Notes: Safe in pregnancy

ZIPRAZIDONE

Uses: Schizophrenia, BPD manic phase

SE: EPS, QT prolongation (TDP)

Notes: Inc mortality in elderly with dementia-related psychosis

OLANZAPINE

Uses: Schizophrenia, BPD, anorexia, depression

SE: Weight gain, hyperglycemia, Hyperlipidemia, agranulocytosis

Notes: Prominent wt. gain and hyperglycemia Safe in pregnancy

RISPERIDONE *(Paliperidone)*

Uses: Schizophrenia, BPD, depression, Intractable hiccups, Tourette's syndrome

SE: Hyperprolactinemia, photosensitivity, EPS, insomnia

Notes: Only antipsychotic used for the **YOUTH and ELDERLY**

ARPIPRAZOLE

Uses: MDD, cocainde dependence, autism, Schizophrenia, BPD manic phase

SE: **LEAST SEDATING atypical**

LITHIUM [Mood stabilizer]

MOA: Uncertain; Decreases cAMP

Uses: Recurrent depression, BPD, schizoaffective

SE: **EBSTEIN ANOMALY**, tremor, sedation, aphasia, thyroid enlargement, Neprogenic DI Bradycardia, renal dysfunction, dysrhythmia

Notes: C/i in sick sinus syndrome, treat overdose with **HEMODIALYSIS** narrow therapeutic index

ANTI-DEPRESSANTS

LM

TRICYCLIC-ANTIDEPRESSANTS

IMIPRAMINE (*Clomipramine, Desipramine, Amitryptiline, Nortriptyline, Doxepin, Protriptyline, Trimipramine*)

MOA: Block NE and 5-HT transporters
Like SNRis + significant ANS blockade

Uses: MDD , Bipolar disorders, Acute panic attacks, Phobias, Enuresis, ADHD, OCD [Clomipramine]

SE: Excessive sedation, fatigue, confusion, α-blocking effects, sympathomimetic effects, ortho hypo, cardiomyopathy, arrhythmia, tremors, weight gain

Notes: Additive depression of the CNS with other central antidepressants
3Cs of overdose: Coma, Convulsions, Cardiotoxicity
Imipramine metabolized to Despiramine
Amitriptyline metabolized to Nortriptylin

SSRI

FLUOXETINE (*Paroxetine, Citalopram, Escitalopram, Sertraline, Fluvoxamine, Vilazodone)*

MOA: Inhibits neuronal reuptake of serotonin by inhibiting Serotonin Transporter (SERT)

Uses: OCD (DOC), MDD (first line), Anxiety, Panic attacks, Anxiety, PTSD, Bulimia, Premenstrual dysphoria, Alcohol dependence, Premature ejaculation [Dapoxetine]

SE: N/V, headache, anxiety, agitation, Drowsiness, insomnia, Erectile dysfxn, EPS, QT prolongation [Citalopram], Withdrawal syndrome

Notes: CYP 450 inhibitors - Fluoxetine, Fluvoxamine, and Paroxetine
Serotonin syndrome when used w MAOIs
May decrease appetite = weight loss
Inc. risk for suicide in children and/or adolescents

SNRI

VENLAFAXINE (*Duloxetine, Desvenlafaxine, Milnacipran)*

MOA: Inhibits neuronal reuptake of serotonin and NE by binding to both transporters

Uses; MDD, Fibromyalgia, Perimenopausal symptoms, Diabetic neuropathy, Neuropathic pain, Chronic pain DOs

SE: Dizziness, insomnia, sedation, GI distress, HPN and CNS stimulation [Venlafaxine], Hepatotoxicity [Duloxetine], Withdrawal syndrome even in just 1 missed dose, Anticholinergic effects

Notes: Differ from TCA in lacking blockade of H1, M, and Alpha receptors
Inc risk for suicide in children and adoles
Venlafaxine has less affinity for NE transporters, Milnacipram more selective for NE reuptake

TETRACYCLIC/UNICYCLIC ANTIDEPRESSANTS

AMOXAPINE (*Maprotiline)*

MOA: Strong NE reuptake inhibitor, weak serotonin reuptake inhibitor, blocks Dopamine D2 receptors

Uses: Major depression

SE: Akathisia, Parkinsonism, seizures, Amenorrhea-galactorrhea syndrome, Cardiotoxicity

Notes: Lowers seizure threshold [Amoxapine]

MIRTAZAPINE

MOA: Inc amine release from nerve endings by antagonism of presynaptic α2 adreno-receptors

Uses: Major depression, Appetite stimulation, Sedation/sleeping aid

SE: Weight gain, marked sedation, diizziness, blurred vision, nightmares

Notes: Significant muscarinic receptor and α2 blocking effect

BUPROPION

MOA: Inhibits neuronal reuptake of dopamine and NE; Inc. Dopa and NE activity

Uses: Major depression, smoking cessation, Alcohol dependence, improves mood

SE: Weigh loss, agitation, dizziness, dry mouth, aggravation of psychosis, priapism

Notes: Lowers seizure threshold
Resembles amphetamine in chem struct.

SEROTONIN ANTAGONISTS

TRAZODONE (*Nefazodone, Vortioxetine)*

MOA: Blocks 5-HT2A receptors, weak inhibitor of NE and 5HT transporters
Blocks SERT [Nefazodone], blocks 5-HT2C receptors [Trazodone]

Uses: Major depression, Hypnosis/sleeping aid [Trazodone]

SE: Sedation, GI disturbance, Ortho hypo, Priapisim [Trazodone], Hepatotoxicity [Nefazodone], Hyperprolactinemia

Notes: May cause arrhythmias in Px with pre-existing cardiac diseases
Modest α1 and H1 receptor blockade
Short T½ to be given BID or TID

MAOI

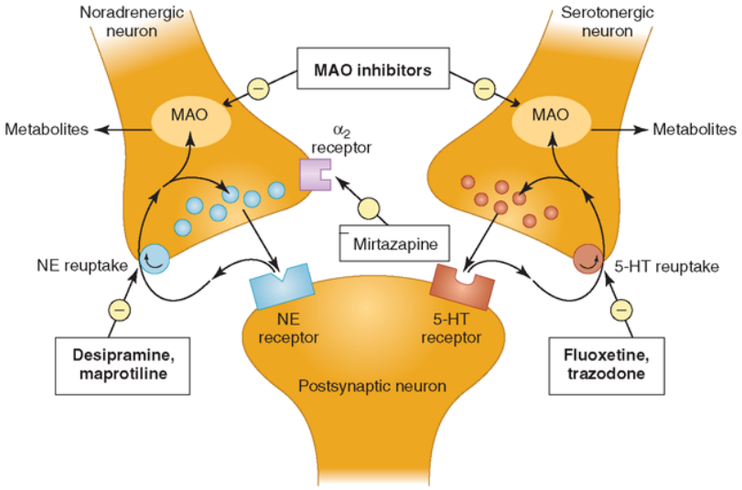
PHENELZINE (*Tranylcypromine, Isocarboxazid, Selegiline)*

MOA: Inhibits MAO A and B; Inc CNS levels of NE and Serotonin

Uses: Major depression unresponsive to other drugs, Anxiety, Phobic features, Hypochondriasis

SE: Dizziness, insomnia, orthohypo, blurred vision, arrhythmia, diarrhea, seizure, hyperthermia, CNS stimulation

Notes: HYPERTENSIVE CRISIS when taken with tyramine
SEROTONIN SYNDROME when taken with SSRIs
Nonselective MAOI [Tranylcypromine]
MAO-B Selective [Selegiline]



Source: Trevor AJ, Katzung BG, Kruidering-Hall M, Masters SB: *Katzung & Trevor's Pharmacology: Examination & Board Review*, 10th Edition: www.accesspharmacy.com

	Malignant hyperthermia	Serotonin Syndrome	Neuroleptic Malignant Syndrome
Onset	Within minutes	Within hours	1-3 days
Precipitating Drug	Volatile anesthetics (Halothane, Succinylcholine)	SSRIs, MAOIs, TCAs, Meperidine, MDMA, St. John's Wort	Antipsychotics
Mechanism	Massive Calcium release from SR	Excess Serotonin	Dopamine Antagonism
Clinical Features	**F**ever **(FART CH)** **A**cidosis **R**habdomyolysis **T**rismus **C**lonus **H**PN	**F**ever **(FAT CHilD)** **A**gitation **T**remor **C**lonus **H**yperreflexia **D**iaphoresis	**F**ever **(FEVER)** **E**ncephalopathy **V**itals unstable **E**levated CPK **R**igidity
1st – Line Treatment	Dantrolene	Sedation, Paralysis, intubation, ventilation	Diphenhydramine
Other Treatment	Cooling	Cooling Cyproheptadine Chlorpromazine	Cooling, Dantrolene, Bromocriptine, Amantadine, Diazepam

MNEMONICS:

DRUGS for causing ERECTILE DYSFUNCTION
"SOREE, Sore Penis can't Fuck Hard"

SSRI	**S**pironolactone
Opiates	**P**ropanolol
Risperidone	**F**inasteride
Ethanol	**H**ydrocholothiazide
Estrogen	

SEROTONIN SYNDROME:
- Severe muscle rigidity, myoclonus, hyperthermia, Cardiovascular instability, seizures
- Drugs implicated: MAOIs, TCAs, MDMA (ecstasy) Dextromethorphan, meperidine, St. Johns Wort

"FAT CHilD"

Fever	**C**lonus
Agitation	**H**yperreflexia
Tremor	**D**iaphoresis

MNEMONICS:

Drugs causing PRIAPISM
"Tigas PeniS Qu, AyaW Bumaba"

Trazodone	**A**lprostadil
Papaverine	**W**arfarin
Sildenafil	**B**upoprion
QUetiapine	

OPIOID ANALGESICS / ANTAGONISTS

LM

AGONIST

FULL

MORPHINE *(Hydromorphone, Oxymorphone)*

MOA: Strong agonist at μ receptors
Uses: Severe pain, pain associated with Acute MI, Inc. Pulmonary edema, adjunct in anesthesia
SE: Miosis, restlessness, respiratory depression, postural hypotension, inc. ICP, constipation, urinary retention, pruritus, addiction liability
Notes: Exerts hemodynamic effects on the pulmonary circulation
Significant 1st pass effect

FENTANYL *(Sufentanil, Alfentanil, Remifentanil, Ohmefentanyl)*

MOA: Strong agonist at μ receptors
Uses: Severe pain, adjunct in anesthesia, Breakthrough Cancer pain
SE: Same w [Morphine] except Miosis
Notes: May be given Transdermal / Lollipop [Ohmefentanyl] most potent (18000x)

MEPERIDINE

MOA: Strong agonist at κ and μ receptors
Uses: Moderate - severe pain, Labor analgesia, Spasmodic pain (biliary, renal), Preop sedation
SE: Seizures, less addiciton liability + [Morphine] SE except Miosis
Notes: HYPERTENSIVE CRISIS when taken with Tyramine

METHADONE *(Levomethadyl Acetate, Levorphanol)*

MOA: Strong agonist at μ receptors
Uses: Moderate - severe pain, Opioid dependence/withdrawal
SE: Same w [Morphine] except Miosis
Notes: Used in Methadone Maintenance Therapy (MMT) for opioid dependence

PARTIAL

HYDROCODONE *(Oxycodone)*

MOA: Strong agonist at κ and μ receptors
Uses: Mod - sev pain, Cancer pain, Neuropathic pain, Opioid dependence/wiithdrawal
SE: Hypogonadism, hearing loss, + other [Morphine] SEs
Notes: There is genetic variation in the metabolism of codeine and its derivative

DEXTROMETHORPHAN *(Codeine)*

MOA: Decreases sensitivity of cough receptors depressing the medullary cough center through sigma receptor stimulation
Uses: Cough suppression
SE: Hallucinations, confusion, excitation, inc or dec pupil size, nystagmus, seizure, coma, respiratory depression, addiction
Notes: Serotonin syndrome when used with SSRIs or MAOIs

WEAK

PROPOXYPHENE *(Levopropoxyphene, Dextropropoxyphene)*

MOA: Weak agonist at κ and μ receptors
Uses: Mild - mod pain, Opioid withdrawal, Restless leg syndrome
SE: Seizures, pulmonary edema, fatal arrhythmias + other [Morphine] SEs
Notes: Withdrawn due to fatal cardiotoxicity (group 1C antiarrhythmic activity) [Levopropoxyphene] as antitussive

MIXED

NALBUPHINE *(Buprenorphine, Butorphanol, Pentazocine, Levallorphan)*

MOA: Strong agonist at κ receptors
Weak antagonist at μ receptors
Uses: Mod - sev pain, opioid dependence/withdrawal, balanced anesthesia
SE: Sedation, dizziness, sweating, nausea, anxiety, hallucinations, nightmares, tolerance, dependence, respiratory depression,
Notes: Reduces craving in alcohol dependence, effect resistant to Naloxone reversal

ANTAGONIST

NALOXONE *(Naltrexone, Nelmefene, Alvimopan, Methylnaltrexone)*

MOA: Competitively blocks μ, δ, and κ receptors; Rapidly reverses effects of opioid agonists
Uses: Opioid overdose, opioid and alcohol dependence [Naltrexone]
SE: Pruritus, nausea, vomiting
Notes: Precipitates abstinence syndrome in patients with opioid dependence
Reduces craving in alcohol, nicotine, and opioid dependence [Naltrexone]

DUAL ACTING

TRAMADOL *(Tapentadol)*

MOA: Weak agonist at μ receptor
Uses: Moderate pain, chronic pain syndromes, fibromyalgia, neuropathic pain
SE: Seizures, nausea, dizziness, pruritus, constipation
Notes: Lowers seizure threshold
C/i in patients with Hx of epilepsy
Serotonin syndrome when used w SSRI

RECEPTOR	FUNCTIONS	AFFINITY
μ (Mu)	Supraspinal and spinal analgesia; Sedation; **Inhibition of respiration** Slowed GI transit Modulation of hormone and NT release	Endorphins > Enkephalins > Dynorphins
δ (delta)	Supraspinal and spinal analgesia; Modulation of hormone and NT release; **Development of tolerance**	Enkephalins > Endorphins And Dynorphins
κ (Kappa)	Supraspinal and spinal analgesia; Sedation; psychomimetic effects; **Slowed GI transit**	Dynorphins > Endorphins And Enkephalins

TD

HYPOTHALAMIC AND PITUITARY HORMONES

HYPOTHALAMUS

GNRH ANALOGUE

LEUPROLIDE
Gonadorelin, Goserelin, Histrelin, Nafarelin, Triptorelin

MOA: Inc. LH/FSH secretion with intermittent dose, but reduces LH/FSH secretion with prolonged administration

Uses: Ovarian suppression, Endometriosis, Myoma Uteri, Precocious puberty, Advanced Prostate cancer

SE: Hot flushes, sweats, headache,light headedness, nausea, osteoporosis, gynecomastia, reduced libido, dec. Hematocrit

Temporary exacerbation of precocious puberty/ prostateCA

Apoplexy/blindness during the 1st few wks of therapy (Tx: coadminister FLUTAMIDE)

ANRH ANTAGONIST

GANIRELIX
Cetrorelix, Abarelix, Degarelix

MOA: Blocks GnRH receptors, reducing LH/FSH production

Uses: Prevents premature LH surgeduring controlledovarian hyperstimulation, Prostate CA

SE:nausea, headache, Hot flushes, gynecomastia, Dec libido/Hct

Des NOT cause a tumor flare-up if used for Prostate CA

DEGARELIX for Prostate CA

GANIRELIX prevents LH surge

ANTERIOR PITUITARY

GROWTH HORMONE

AGONIST

SOMATROPIN

MOA: increases release if IGF-1 in the liver & cartilage; stimulates skeletal muscle growth, amino acid transport, protein synthesis & cell proliferation

Uses: growth hormone deficiency, genetic dses assoc with short stature (Turner, Noonan, Prader-Willi), failure to thrive due to chronic renal failure or SGA, AIDS wasting, improve GI function in px who underwent intestinal resection that led to malabsorption syndrome

SE: peripheral edema, myalgia, arthralgia, intracranial HPN, pseudotumor cerebri, slipped capital femoral epiphysis, progression of scoliosis, hyperglycemia

Performance-enhancing drug (increases muscle mass) that is banned by athletics committees.

Given SC

MECASERMIN

MOA: a recombinant IGF-1 agonist; stimulates skeletal muscle growth, amino acid transport, protein synthesis & cell proliferation

Uses: for children unresponsive to GH therapy

SE: hypoglycemia, increased LFT, intracranial HPN

Remedy to hypoglycemia: give px some snacks prior to dose

ANTAGONIST

PEGVISOMANT

MOA: a GH receptor antagonist (blocks GH receptor)

Uses: acromegaly

SE: diarrhea, nausea, flu-like symptoms, elevated LFTs, hypersensitivity rxn

Onset of action is expected within 2 wks of use

OCTREOTIDE
Lanreotide

MOA: somatostatin analog; suppresses the release of GH, glucagon, insulin, IGF-1, serotonin & GI peptides

Uses: acromegaly, pituitary adenoma (GH-secreting), carcinoid, gastrinoma, glucagonoma, variceal bleeding, gigantism

SE: GI disturbances, gallstones, arrhythmias/ cardinal conduction abnormality

Can alter requirements for antidiabetic agents

Regular release: given BID-QID SC

If slow release: every 4wks IM

Are long acting synthetic analogs of somatostatin

GONADOTROPINS

FSH

FOLLITROPIN ALFA
Menotropins, Urofollitropin, Follitropin Beta

MOA: activates FSH receptors; mimics effects of endogenous FSH

Uses: controlled ovarian hyperstimulation, infertility due ro hypogonadotropic hypogonadism in men

SE: headache, depression syndrome (ovarian enlargement, ascites, hypovolemia, shock), multiple pregnancies in women, gynecomastia in men

FOLLITROPIN ALFA & BETA are recombinant FSH forms while UROFOLLITROPIN is a purified preparation from urine of postmenopausal women

LH

CHORIOGONDO-TROPIN ALFA
HCG, Menotropins, Lutropin Alfa

MOA: gonadotrophin analog; actives LH receptors; mimics effects of endogenous LH

Uses: initiation of ovulation during controlled ovarian hyperstimulation (ovulation induction), ovarian follicle development in women with hypogonadotropic hypogonadism, male hypogonadotric hypogonadism

SE: headache, depression, edema, ovarian hyperstimulation syndrome, multiple pregnancies in women, gynecomastia in men, hypersensitivity

CHORIOGONADOTROPIN ALFA is arecombinat hCG while LUTROPIN os a recombinant LH

hCG given IM

MIXED

MENOTROPINS

Mixture of FSH & LH from postmenopausal women

PROLACTIN

BROMOCRIPTINE
Pergolide, Cabergoline, Quinagolide

MOA: dopamine agonist; inhibits prolactin release from the pituitary gland; also slightly inhibits GH release (in high doses); dopaminergic effects on CNS motor control & behavior

Uses: hyperprolactinemia, pituitary adenoma (prolactin-secreting), acromegaly, Parkinsons dse

SE: GI disturbance, nausea, headache, lightheadedness, orthostatic hypotension, fatigue, behavioral change, erythromelalgia, Raynauds phenomenon (vasospasm), pulmonary infiltrates (in high doses)

Given PO or vaginally (for hyperprolactinemia).

Contraindicated in px with history of psychotic illness

POSTERIOR PITUITARY

OXYTOCIN

OXYTOCIN
Desmoxytocin

MOA: activates oxytocin receptors; stimulates utreine contraction & labor; stimulates mammary glands, lactation & milk let-down

Uses: labor induction, labor augmentation, control of postpartum hemorrhage

SE: fetal distress, placental abruption, uterine ruptue, fluid retention (water intoxication), hyponatremia, heart failure,seizures, hypotension

Contraindications: fetal distress, prematurity, abnormal presentation, CPD & predispositions for uterine rupture

ATOSIBAN is an oxytocin receptor blocker; not yet FDA approved since there is concern about increased rates of infant death

CARBETOCIN is an agonist of peripheral Oxytocin receptors

VASOPRESSIN

AGONIST

DESMOPRESSIN

MOA: ADH agonist; relatively selective for V2 receptors; Vasopressin V2 receptor agonist which causes insertion of water channels in the collecting duct leading to more water reabsorption --> decrease the excretion of water; act on extra renal V2 receptors to increase FVIII and vWF

Uses: central DI, hemohilia A, vWdse, esophageal variceal bleeding, primary nocturnal enuresis (pediatric px), colon diverticula

SE: GI disturbance, headaches, flushing, nausea, hyponatrremia, seizures, allergic rxns

May be given intranasally, PO or IV

Also contracts vascular smooth muscle via V1 receptor leading to vasoconstriction (used as a tx for esophageal varices or colon diverticula)

ANTAGONIST

CONIVAPTAN
Tolvaptan, Lixivaptan

MOA: antagonist at V1a, V2 receptors; reduces renal excretion of water in conditions assoc with increased vasopressin

Uses: SIADH, hyponatremia in hospitalized px, offset fluid retention in acute heart failre & SIADH which causes hyponatremia (dilutional)

SE: infusion site rxns, hyperK

Central Pontine Myelinolysis may cocur with rapid correction of hypoNatremia

TOLVAPTAN is more selective for V2 receptors

THYROID DRUGS

TD

HYPOTHYROIDISM

T4

LEVOTHYROXINE

MOA: activation of nuclear receptors results in gene expression with RNA formation & protein synthesis

Uses: hypothyroidism, myxedema coma

SE: dry skin, sweating, tachycardia, nervousness, tremor, weight loss, weakness, heat intolerance

T4 dose must be lowered in px with CVS dse or longstanding hypothyroidism (increased cardiosensitivity).

Thyrotropin (a recombinant human TSH) is also available.

Maximum effect is seen after 6-8 wks of therapy.

T3

LIOTHYRONINE

Same MOA with Levothyroxine.

Liothyronine has a faster onset but shorter half life.

MIXED

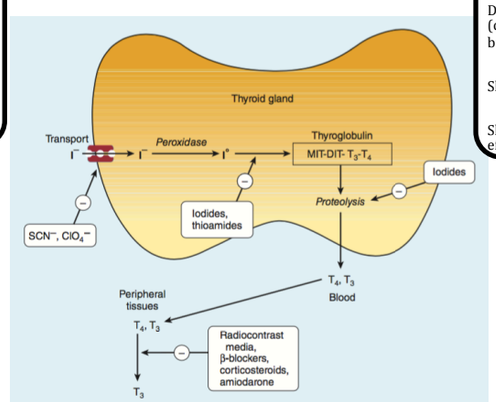
LIOTRIX

Same MOA.

Liotrix is a 4:1 ratio of T4:T3

MYXEDEMA COMA TREATMENT

- IV loading dose of Levothyroxine (300-400 mcg), followed by 50-100mcg daily
- IV Hydrocortisone is indicated if the px has associated adrenal or pituitary insufficiency



HYPERTHROIDISM

THIOAMIDE

PROPYLTHIOURACIL

MOA: inhibits thyroid peroxidase rxns; blocks iodine organification; inhibits peripheral conversion of T4 into T3

Uses: hyperthyroidism, thyroid storm

SE: maculopapular pruritic rash, GI distressm fulminant hepatitis, agranulocytosis, urticaria, vasculitis, lupus-like syndrome, lymphadenopathy, hypoprothrombinemia, exfoliative dermatitis, polyserositis, arthralgia, hypothyroidism

DOC for pregant hyperthyroid px (does not enter placenta & breastmilk).

Shorter DOA 6-8hrs

Slow onset of action (3-4 wks for full effect)

METHIMAZOLE

Carbimazole

MOA: inhibits thyroid peroxidase rxns; blocks iodine organification

Uses: hyperthyroidism, thyroid storm

SE: maculopapular pruritic rash, GI distress, cholestatic jaundice, agranulocytosis, urticaria, vasculitis, lupus-like syndrome, lymphadenopathy, hypoprothrombinemia, exfoliative dermatitis, polyserositis, arthralgia, hypothyroidism, altered sense of taste or smell

DOC for nonpregnant hyperthyroid px bec longer DOC (24h).

Cross the placenta (teratogen).

Prenatal exposure causes APLASTIA CUTIS CONGENITA.

Slow onset of action (3-4 wks for full effect).

Thiamazole is the other name of Methimazole.

IODINE

POTASSIUM IODIDE

Lugol's Solution/ Potassium Iodide Saturated Solution [KISS]

MOA: inhibit iodine organification & hormone release; reduce size & vascularity of thyroid gland

Uses: hyperthyroidism, thyroid storm, preparations for surgical thyroidectomy to reduce the size & vascularity of the thyroid gland, radiation prophylaxis

SE: iodism, acneiform rash, swollen salivary glands, mucus membrane ulcerations, conjunctivitis, rhinorrhea, drug fever, metallic taste, bleeding disorders, anaphylactoid rxns

Should not be used alone (escape 2-8wks).

Prevent radiation-induced thyroid damage.

Prenatal exposure causes fetal goiter.

Onset is faster compared to Thionamides (2-7days) but effect is transient (thyroid gland escapes iodine block after several weeks of treatment)

BETA BLOCKERS

PROPANOLOL

Esmolol, Metoprolol, Atenolol

MOA: blocks beta receptors (control HR & other cardiac abnormalities of severe thyrotoxicosis); slows pacemaker activity; inhibits peripheral conversion of T4 into T3 (Only Propanolol)

Uses: hyperthyroidism esp thyroid storm, adjunct to control tachycardia, HPN & AFib, post MI prophylaxis against sudden death

SE: bronchospasm, cardiac depression, AV block, hypotension, bradycardia

ESMOLOL may be uase to treat thyrotoxicosis-related arrhythmias.

Causes clinical improvement WITHOUTaltering thyroid hormone levels.

Onset is within hours but DOA is also short (4-6hrs)

IODIDE

RADIOACTIVE IODINE 131

MOA: emits beta rays causing destruction of thyroid parenchyma

Uses: hyperthyroidism

SE: hypothyroidism (permanent), sore throat, sialitis

Preferred treatment for most patients.

Permanent cure of thyrotoxicosis without surgery & no effect on other tissues.

Advantages include easy administration, effectiveness, low expenses & absence of pain.

Contraindicated in pregnant women or nursing mothers.

Patient should be euthyroid or on BB before RAI.

Onset of action is 6-12wks.

Maximym effect sen in 3-6months

ANTI THYROID DRUGS INHIBITING PERIPHERAL CONVERSTION OF T4 INTO T3

•HYDROCORTISONE•PTU•PROPANOLOL•

DRUG-INDUCED HYPERTHYROIDISM

CAM

•CLOFIBRATE•AMIODARONE•METHADONE•

THYROID STORM TREATMENT

1) PTU – blocks thyroid hormone synthesis
2) IODIDE (KISS) – retards release of thyroid hormone
3) PROPANOLOL – controls CVS manifestations
4) HYDROCORTISONE – protects against shock & blocks peripheral conversion of T4 to T3

WOLFF-CHAIKOFF EFFECT

•IODINE INGESTION CAUSE HYPOTHYROIDISM•

JOD-BASEDOW PHENOMENON

•IODINE INGESTION CAUSE HYPERTHYROIDISM•

TD

CORTICOSTEROIDS

AGONIST

GLUCOCORTICOIDS

SHORT ACTING

HYDROCORTISONE/ CORTISOL

MOA: activates glucocorticoid receptors leading to altered gene transcription; suppreses inflammtaion; replaces cortisol when deficient

Uses: adrenal insufficiency associated with life threatening shock, chronic adrenal insufficiency (Addisons Dse), congenital adrenal hyperplasia, insect bites, contact dermatitis, status asthmaticus, thyroid storm

SE: none common when used topically or at physiologic replacement doses

Low potency: Desonide

Medium potency: Fluticasone, Mometasone

High potency: Desoximetasone, Clobetasol

INTERMEDIATE RELEASE, DELAYED RELEASE

PREDNISONE

Prednisolone, Methylprednisolone, Meprednisone, Dexamethasone, Betamethasone, Triamcinolone

MOA: suppresses inflammation & immune response

Uses: wide variety of inflammatory, allergic, autoimmune (collagen & rheumatic dse etc), & neoplastic dses (hematopoeitic cancers), prevention of organ transplant rejection, asthma, lung maturation in preterm labor (Betamethasone & Dexamethasone), chemotherapy-induced vomiting, hypercalcemia, mountain sickness)

SE: adrenal suppression, growth inhibition, muscle wasting, osteoporosis, salt retention, glucose intolerance, behavioral changes (psychosis)

BETAMETHASONE hastens fetal lung maturation.

PREDNISOLONE is the active metabolite of Prednisone.

This group has a long t1/2, reduced salt-retaining effect & better penetration of lipid barriers

MINERALOCORTICOIDS

FLUDROCORTISONE

Dexoycortisone

MOA: strong agonist of mineralocorticoid receptors; increase Na reabsorption, K & H excretion

Uses: chronic adrenal insufficiency (Addisons Dse), congenital adrenal hyperplasia, adrenal replacement therapy post adrenalectomy

SE: salt & fluid retention, hypoK, CHF, muscle wasting, osteoporosis, glucose intolerance, behavioral changes

Additive hypoK with loop diuretics & thiazides.

DEOXYCORTICOSTERONE is the precursor of aldosterone.

FLUDROCORTISONE also has significant glucocorticoid activity.

Aldosterone is implicated in myocardial & vascular fibrosis & baroreceptor function.

ANTAGONIST

SYNTHESIS INHIBITORS

AMINOGLUTETHIMIDE

MOA: inhibits desmolase, blocking conversion of cholesterol to pregnenolone; reduces synthesis of all hormonally active steroids

Uses: breast cancer, Cushing sydnrome

SE: skin rash, hepatotoxicity, hypothyroidism

Abused by body builders to lower circulating levels of cortisol in the body & prevent muscle loss.

KETOCONAZOLE

MOA: inhibits cholesterol side-chain cleavage, cytochrome P450 enzymes & other enzymes necessary for synthesis of all steroids

Uses: adrenal carcinoma, hirsutism, breast cancer, prostate cancer, Cushing syndrome, fungal infections

SE: hepatotoxicity, many drug interactions, androgenuc effect

Potent inhibitory of CYP450 enzymes

METYRAPONE

MOA: selective inhibitor of steroid 11-hydroxylation, interfering with cortisol & corticosterone synthesis

Uses: diagnostic testing for adrenal function, Cushing syndrome

SE: dizziness, GI disturbances

DOC for pregnant px with Cushing syndrome.

RECEPTOR INHIBITORS

GLUCOCORTICOID

MIFEPRISTONE (RU486)

MOA: competitive inhibitor at the GC receptor as well as progesterone receptor

Uses: Cushing syndrome

SE: abdominal pain & cramping, uterine cramping, nausea, headache, vomiting, diarrhea, dizziness, vaginal bleeding

Also used as an approved abortifacient for medical abortion (usually together with Misoprostol).

MINERALOCORTICOID

SPIRONOLACTONE

MOA: blocks aldosterone receptors

Uses: for hypoK due to ther diuretics, for post MI, hyperaldosteronism

SE: hyperK, anti-androgenic effect (gynecomastia)

Also with weak antagnist effect at the androgen receptor

TD

GONADAL HORMONES AND INHIBITORS

PART1

ESTROGENS

AGONIST

ETHINYL ESTRADIOL
Mestranol, Estradiol Cypionate, Premarin, Estriol

MOA: activates estrogen receptors; leads to changes in rates of transcription of estrogen-regulated genes

Uses: primary hypogonadism, postmenopausal hormonal replacement therapy, osteoporosis, contraception, intractable dysmenorrhea

SE: breakthrough bleeding, nausea, breast tenderness, migraine, thromboembolism (DVTs), gallbladder dse, hypertriglyceridemia, HPN, premature closure of epiphysis in young females, increased risk of breast & endometrial cancer (remedy: add progesterone to the preparation)

ETHINYL ESTRADIOL has low bioavailability PO/ TD/ IM/ intravaginal

ESTRADIOL CYPIONATE is IM with longer t1/2.

PREMARIN is a mixture of conjugated estrogen used in HRT

Effects of estrogen: growth of genital stuctures & secondary sexual characteristics, modifies serum protein level & decrease bone resorption, enhances coagulability of blood, increases TG & HDL levels while decreasing LDL, if given as continuous infusion will inhibit FSH & LH

SYNTHETIC ESTROGEN (NONSTEROID)

DIETHYLSTILBESTROL

MOA: activates estrogen receptors; leads to changes in rates of trancription of estrogen-regulated genes

Uses: atrophic vaginitis, HRT, prevention of adverse pregnancy outcomes, metastatic prostate cancer

SE: breakthrough bleeding, nausea, breast tenderness, migraine, thromboembolism (DVTs), gallbladder dse, hypertriglyceridemia, HPN, premature closure of epiphysis in young females, increased risk of breast & endometrial cancer (remedy: add progesterone to the preparation)

Associated with infertility, ectopic pregnacy, clear cell vaginal adenocarcinoma in daughters of mothers who took DES.

ANTAGONIST

SERM

TAMOXIFENE Toremifene

MOA: estrogen antagonist actions in breast tissue & CNS; estrogen agonist effects in uterus, liver & bone

Uses: hormone-responsive breast cancer, prophylaxis of breast CA esp in high risk

SE: hot flushes, thromboembolism (DVTs), endometrial hyperplasia, endometrical cancer

Prevents osteoporosis in post menopausal women & decreases risk of atherosclerosis at the risk of causing Endometrial cancer.

FLUVESTRANT is full estrogen receptor antagonist (no agonist effect) used in hormone receptor positive metastatic breast cancer.

TORIMEFENE is structurally related to Tamoxifen

RALOXIFENE

MOA: estrogen antagonist actions in breast tissue, uterus & CNS; estrogen agonist effects in liver & bone; increase bone mineral density

Uses: osteoporosis, breast cancer prevention

SE: hot flushes, thromboembolism (DVTs)

Reduces incidence of breast cancer in women who are very high risk.

No estrogenic effects on endometrial tissue.

CLOMIPHENE

MOA: partial agonist of estrogen receptors in pituitary; reduces negative feedback by Estradiol; increases FSH & LH output

Uses: induction of ovulation for women who want to get pregnant

SE: hot flushes, eye symptoms (afterimages), headache, constipation, reversible hair loss, ovarian enlargement, multiple pregnancy (10%)

Increased risk of low-grade ovarian cancer with long term use.

FULVESTRANT

Pure estrogen receptor antagonist in all tissues usedin breast CA resistant to Tamoxifen

AROMATASE INHIBITOR

ANASTROZOLE
Letrozole, Exemestane

MOA: reduces estrogen synthesis by inhibiting aromatase

Uses: breast cancer, precocious puberty

SE: hot flushes, musculoskeletal disorders, osteoporosis, joint pains

Effective against breast cancers that have become resistant to Tamoxifen.

EXEMESTANE is an irreversible inhibitor

OVARIAN INHIBITOR

DANAZOL

MOA: weak cytochrome P450 inhibitor & partial agonist of progestin & androgen receptors

Uses: endometriosis, fibrocystic dse, hemophilia, angioneurotic edema

SE: acne, hirsutism, weight gain, menstrual disturbances, hepatic dysfunction

Contraindicated during pregnancy & breastfeeding.

May also act on glucocorticoid receptors.

PROGESTINS

AGONIST

NORGESTREL
Norethindrone, Ethylnodiol, Megestrol, Desogestrel, Norelgestromin, Norgestimate, Etonogestrel, Progesterone, Levonorgestrel, Dydrogesterone, Ulipristal, Tibolone, Norethisterone, Dienogest

MOA: activates progesterone receptors; changes rates of trancription of progesterone-regulated genes

Uses: HRT (given together with Estrogen, to prevent Estrogen-induced endometrial cancer), contraception, assisted reproduction (for maintenance of pregnancy), anovulation induction (given in high doses to suppress FDH & LH)

SE: HPN, decreased HDL, weight gain, reversible decrease in bone mineral density, delayed resumption of ovulation after use

MEGESTROL is used as an appetite stimulant.

Given PO or as vaginal cream.

MEDROXYPROGESTERONE has a better oral bioavailability.

L-NORGESTERL & NORETHINDRONE has more androgenic effect.

NORGESTREL undergoes enterohepatic recirculation.

Effects of Progesterone: induces secretory changes in the endometrium, stabilize the endometrium, affect carbohydrate metabolism & stimulate deposition of fat, high doses suppress FSH & LH secretion.

TIBOLONE is a synthetic steroid with weak estrogenic, proestrogenic & androgenic activity, and hence is an agonist of the estrogen, progesterone & androgen receptor. It is primarily used in menopausal hormone therapy, postmenopausal osteoporosis & endometriosis.

ANTAGONIST

MIFEPRISTONE (RU-468)

MOA: pharmacologic antagonist of glucocorticoid & progesterone receptors

Uses: medical abortion, Cushings syndrome

SE: vaginal bleeding, abdl pain, GI upset (vomiting, diarrhea), uterine cramping, nausea, headache, dizziness

Combination with Misoprostol results in abortion of 95% of early pregnancies.

As abortifacient in early pregnancy (may be used up to 49days after menses).

Complication: failure to induce complete abortion. May cause sepsis due to unusual organisms (Clostridium sordelli)

TD

GONADAL HORMONES AND INHIBITORS

PART2

GNRH

AGONIST

LEUPROLIDE Gonadorelin, Goserelin, Histrelin, Nafarelin, Triptorelin

MOA: agonist of GnRH receptors; increased LH & FSH secretion with INTERMITTENT administration; reduced LH & FSH secretion with PROLONGED CONTINUOUS administration (due to downregulation of GnRH receptors in the pituitary cells that normally release LH & FSH)

Uses: ovarian suppression, controlled ovarian hyperstimulation, endometriosis, myoma uteri, central precocious puberty, advanced prostate cancer

SE: hot flushes, sweats, headache, light headedness, injection site rxns, nausea, osteoporosis, gynecomastia, reduced libido, decreased hematocrit

Symptoms of hypogonadism with continuous treatment.

Temporary exacerbation of precocious puberty or prostate cancer.

Apoplexy & blindness during the first few wks of therapy (remedy: co-administer Flutamide, an androgen receptor antagonist)

May be given intranasally, depot formulation also available.

LEUPROLIDE has a long agonist activity.

ANTAGONIST

GANIRELIX Cetrorelix, Abarelix, Degarelix

MOA: blocks GnRH receptors; reduced endogenous production of LH & FSH

Use: prevents premature LH surge during controlled ovarian hyperstimulation, advanced prostate cancer

SE: nausea, headache, hypersensitivity (Abarelix), hot flushes, gynecomastia, decreased libido, decreased hematocrit, osteoporosis

Does not cause a tumor flare-up when used for treatment of advanced prostate cancer

Also less likely to cause ovarian hyperstimulation syndrome

DEGARELIX is used for prostate CA while GANIRELIX prevent LH surge in controlled ovulation.

ANDROGENS

AGONIST

TESTOSTERONE Fluoxymesterone, Methyltestosterone, Testosterone Cypionate, Oxymetholone, Mesterolone

MOA: activates androgen receptors; promotes development of male characteristics; increases body muscle bulk & RBC production

Uses: male hypogonadism, delayed puberty, wasting syndromes, certain types of anemia

SE: virilization & menstrual irregularities in females, paradoxical feminization in males, cholestatic jaundice, elevated LFTs, premature closure of epiphysis

Contraindicated in pregnant women & px with prostate cancer.

Effects of Androgen: secondary sexual characteristics, fertility & libido, male pattern baldness, increases muscle mass, increased RBC production, decreased urea nitrogen excretion, maintains normal bone density

Used illegally by athletes as performance enhancer

OXANDROLONE Nandrolone Deacnoate

MOA: activate androgen receptors; promotes development of male characteristics; increases body muscle bulk & RBC production; increases ratio of anabolic-to-androgenic activity

Uses: illegal performance enhancement drugs in athletes

SE: virilization in females, paradoxical feminization in males, cholestatic jaundice, elevated liver enzymes, HCC

This group is called ANABOLIC STEROIDS

ANTAGONISTS

RECEPTOR ANTAGONISTS

FLUTAMIDE Bicalutamide, Nilutamide

MOA: competitive antagonist androgen receptor

Uses: prostate cancer, surgical castration (Nilutamide)

SE: gynecomastia, hot flushes, impotence, hepatotoxicity

Less hepatotoxicity with Bicalutamide & Nilutamide.

GnRH analogs (Leuprolide) must be co-administered with Flutamide to prevent acute flare-up of prostate cancer

CYPROTERONE Cyproterone Acetate

MOA: antagonist at androgen receptor; marked progestational effect that suppresses the feedback enhancement of LH & FSH

Uses: hirsutism, component of OCPs, decreases sexual drive in men

SE: hepatotoxicity, adrenal suppression, depression, gynecomastia, galactorrhea, thromboembolism

Orphan drug status

SYNTHESIS INHIBITORS

FINASTERIDE Dutasteride

MOA: inhibits 5alpha-reductase enzyme that converts testosterone to dihydrotestosterone

Uses: BPH, male-pattern baldness, hirsutism

SE: impotence (rare), gynecomastia, depression

Controversial use in prevention of prostate cancer.

DUTASTERIDE is newer with longer t1/2

This group is less likely to cause impotence, infertility & decreased libido

OCPS

COMBINED

ESTRADIOL + NORETHINDRONE (Ethinyl Estradiol + Desogestrel/ Norgestrel/ Drospirenone/ Norgestimate/ Norethisterone)

MOA: combined oral contraceptive, activates estrogen & progesteron receptors, inhibits ovulation, effects on cervical mucus gland, uterine tubes & endometrium lead to decreased affinity, inhibit ovulation when given before LH surge

Uses: contraception, hypogonadism, acne, hirsutism, dysmenorrhea, endometriosis

SE: breakthrough bleeding, nausea, breast tenderness, skin pigmentation, thromboembolism (DVTs), breast cancer (earlier onset), headache, depression, weight gain & hirsutism for older OCPs

Lifetime risk of breast cancer is not changed.

Does not protect against STDs

NORETHINDRONE is a testosterone derivative while DROSPIRENONE is a spirinolactone derivative that is anti adrogrenic

NORGESTIMATE & DESOGESTREL are newer progestins

Combined OCPs may be used for androgen-induced hirsutism

MESTRANOL (Estrogen) may also be used in OCPs

PROGESTIN ONLY

MEDROXYPROGESTERONE ACETATE

MOA: activates progesterone receptors; prevents contraception by altering cervical mucus & creating a hostile endometrium

Uses: contraception, HRT

SE: breakthrough bleeding, hair loss, dysmenorrhea, delayed return of fertility, osteoporosis

IM depot preparation (DEPO-PROVERA).

Does not protect against STDs.

POST-COITAL

LEVONORGESTREL Ethinyl Estradiol + Levonorgestrel

MOA: activates estrogen &/or progesterone receptors; thicken cervical mucus; inhibits ovulation

Uses: emergency contraception

SE: severe nausea, vomiting, breast tenderness, irregular bleeding, headache, dizziness (fewer SE compared to estrogen alone & combination contraceptives)

Must be taken within 72hrs of unprotected sexual intercourse (not effective once implantation has occured).

YUZPE regimen for combination emergency contraception.

Doe not protect against STDs

TD

ANTI DIABETIC AGENTS

NON INSULIN

INSULIN SECRETAGOGUES

SULFONYLUREAS

1ST GEN

CHLORPROPRAMIDE Tolbutamide, Tolazamide

MOA: increases insulin secretion from the pancreatic beta cells by closing ATP-sensitive K+ channels

Uses: T2 DM

SE: hypoglycemia, weight gain, disulfiram rxn, hyperemic flush after alcohol ingestion, dilutional hyponatermia, hematologic toxicity

TOLBUTAMIDE & CHLORPROPAMIDE are highly protein bound drugs --> drugs that compete for protein bindng may enhance hypoglycemic effects

Lower potency, greater toxicity.

May also cause allergic rxns & rash

2ND GEN

GLIPIZIDE Glimepiride, Glyburide, Glibenclamide, Gliclazide

MOA: increases insulin secretion from pancreatic beta cells by closing ATP-sensitive Kchannels --> depolarizarion of beta cells of the pancreas

Uses: T2DM, in px with functioning beta cells, reduces circulating glucose, increase glycogen, fat & protein formation, regulates gene expression

SE: hypoglycemia (less), weight gain, photosensitivity, hematologic toxicity, cholestatic jaundice (Glibenclamide)

Contraindicated in px with hepatic impairment & renal insufficiency.

Require islet cell function.

May come in combination with Metformin.

MEGLITINIDES

REPAGLINIDE Nateglinide, Mitiglinide

MOA: increases insulin secretion from pancretic beta cells by closing ATP-sensitive K+ channels; insulin secretagogue, smular to SU with some overlap in binding sites, reduces circulating glucose, increases glycogen, fat & protein formation & gene regulation

Uses: T2DM (postprandial hyperglycemia)

SE: hypoglycemia (least), headache, URTI

Used in diabetics with Sulfa allergies.

NATEGLINIDE has the least incidence of hypoglycemia & may be used in CKD px.

Requires islet cell function.

Very shory DOA (4-8hrs only)

May come in combination with Metformin

INSULIN SENSITIZERS

BIGUANIDES

METFORMIN

MOA: reduced hepatic & renal gluconeogenesis with decreased endogenous glucose production, activates AMP-stimulated protein kinase leading to inhibition of gluconeogenesis/ endogenous glucose production

Uses: T2DM (first line), diabetes prevention, PCOS

SE: GI disturbance, weight loss, lactic acidosis (esp in renally & hepatically impaired px), Vit B12 malabsorption

DOC for obese diabetics.

Contraindicated in px with renal dse, alcoholism, hepatic dse, CHF, or conditions predisposing to tissue anoxia (hypoxic or acidotic states)

May also caused slowing of glucose absorption from GIT, decreased plasma glucagon.

Causes a decrease in endogenous insulin production by increasing insulin sensitivity of tissues "Insulin Sparing Effect" therefore does not have weight gain as SE.

Does not cause hypoglycemia

THIAZOLEDINEDIONES

PIOGLITAZONE Rosiglitazone, Troglitazone

MOA: regulates gene expression by binding to PPAR-gamma & PPAR-alpha --> increases tissue sensitivity, increases glucose uptake in muscle & adipose tissue, inhibits hepatic gluconeogenesis, effects on lipid metabolism & distribution of body fat, conrtol of fasting & postprandial glucose; decreased risk of DM in high rish px

Uses: T2DM, DM prevention

SE: fluid retention, anemia, weight gain, CHF, bone fractures esp in women, CVS events (Rosiglitazone), hepatotoxicity (Troglitazone), macular edema, dyslipidemia, (increase HDL & LDL, decrease TG), incresed risk of MI (Rosiglitazone)

Contraindicated in pregnancy, chronic liver dse & CHF.

PIOGLITAZONE reduces mortality & macrovascular events (MI & stroke) bec of its TG lowering effects.

ROSIGLITAZONE binds to PPAR-gamma only.

PPAR regulates transcription of genes encoding proteins involved in carbohydrate & lipid metabolism.

May increase risk for developing bladder cancer.

ALPHA GLUCOSIDASE INHIBITORS

ACARBOSE Miglitol, Voglibose

MOA: inhibits intestinal alpha glucosidases --> reduce conversion of starch & dissacharides to monosaccharide --> reduce post prandial hyperglycemia

Uses: T2DM, DM prevention

SE: GI disturbance (flatulence, diarrhea, abdl pain), hypoglycemia (when taken with SU), increased liver enzymes

Relatively minor glucose-lowering benefit.

Treat hypoglycemia with oral glucose (Dextrose) NOT Sucrose, bec absorption is impaired.

Impaired absorption of Sucrose.

Taken immediately before a meal.

Contraindicated in px with renal & hepatic impaiement & intestinal disorders

AMYLIN ANALOG

PRAMLINTIDE

MOA: activates amylin receptors; reduce post-meal glucose excursions; suppresses glucagon release; delays gastric emptying; stimulates CNS to reduce appetite (anorectic effect)

Uses: T1 & T2 DM

SE: hypoglycemia, GI disturbances, nausea, anorexia, headache

Administered as an injectable preparation (SC) together with insulin to control post prandial glucose

Short t1/2 of 48 mins

INCRETIN MODULATORS

GLP1 ANALOG

EXENATIDE Liraglutide

MOA: activates GLP-1 receptors --> reduction of post-meal glucose excursoprs; augments glucose-stimulated insulin release from pancreatic B cells; retards gastric emptying; inhibits glucagom secretion; produces satiety

Uses: T2DM

SE: hypoglycemia, acute pancreatitis, nausea, vomiting, headache, anorexia, mild weight loss

Administered as an injectable preparation (SC), used in combination with Metformin or a SU

LIRAGLUTIDE has possible thyroid CA risk

Long actinf injectables

DPP4 INHIBITOR

SITAGLIPTIN Saxagliptin, Linagliptin, Vildagliptin, Tenegliptin

MOA: inhibits dipeptidyl peptidase-4 (DPP4) that degrades GLP-1 & other incretins --> raises circulating GLP-1 levels; augments glucose-stimulated insulin release from pancreatic B cells; retards gastric emptying; inhibits glucagon secretion; produces satiety; reduces post-meal glucose excursions

Uses: T2DM

SE: headache, nasopharyngitis, URTI, hypersensitivity rxns, pancreatitis

Administered orally as monotherapy or in combination with Metformin

SGLT2 INHIBITORS

DAPAGLIFLOZIN Empagliflozin, Canagliflozin

MOA: inhibits SGLT2 transporter --> inhibits reabsorption of glucose in the kidneys back to the blood --> excretion of glucose out in the urine

Uses: T2DM

SE: dizziness, strong smell of urine, edema, weakness, nausea, vomiting, decrease in the amount of urine

Do not use among renally impaired px

BILE ACID SEQUESTRANT

COLESEVELAM

MOA: binds bile acids; lowers glucose through unknown mechanism

Uses: T2DM

SE: constipation, dyspepsia, myalgia, asthenia

TD

PANCREATIC HORMONES AND ANTIOBESITY DRUGS

INSULIN

RAPID: Lispro, Aspart, Glulisine
SHORT: Regular (Humulin R)
INTERMEDIATE: NPH, Lente (Humulin N)
LONG: UltraLente, Glargine, Detemir, Insulin Degludec
PREMIXED INSULIN: Humulin 70NPH/ 30 Regular

MOA: activates insulin receptors --> reduces circulating glucose by increasing glucose uptake; promote glucose transport & oxidation, glycogen lipid & protein synthesis & regulates gene expression

Uses: T1 & T2 DM, diabetic emergencies (DKA, HHS -rapid acting), hyperK

SE: hypoglycemia, insulin allergy, immune insulin resistance, lipodystrophy at injection site, weight gain, increased cancer risk (linked to insulin resistance & hyperinsulinemia in px with prediabetes & T2DM)

Beta blockers may mask signs of hypOglycemia.

All insulin preparations contain Zinc.

Parenteral (IV or SC)

Effects of insulin: increased glycogen & protein synthesis, decreased protein catabolism, increased TG storage

RAPID ACTING INSULINS are injected a few mins prior to meals & they are the preferred insulin for continuous SC infusion devicees.

SHORT ACTING INSULINS are injected more than an hour before a meal

INTERMEDIATE ACTING INSULINS are often combined with regular & rapid acting insulins

LONG ACTING INSULINS are called PEAKLESS insulins

GLUCAGON

MOA: activates glucagon receptors

Uses: severe hypoglycemia, diagnosis of endocrine disorders, beta blocker overdose, radiology of the bowels

SE: nausea, vomiting, hypotension

Glucagon-secreting tumors (Glucagonomas) present with decreased amino acids in blood, anemia, diarrhea, weight loss & necrolytic migratory erythema

MOA of Insulin:

-binds to a tyrosine kinase receptor, which phosphorylayed itself & a variety of intracellular proteins when activated by the hormone
-activation of phosphatidulinositol-3-kinase pathway & MAP kinase pathway
-translocation of glucose transporter (esp GLUT 4) to the cell membrane
-increase in glucose uptake
-increased glycogen synthase activity
-increased glycogen formation

DRUGS FOR OBESITY

ORLISTAT

MOA: inhibits GI & pancreatic lipases; reduces absorption of fats

Uses: obesity, T2DM

SE: weight loss, flatulence, steatorrhea, fecal incontinence, malabsorption of fat-soluble vitamins (A,D,E,L), hepatotoxicity

Rebound weight gain upon discontinuation.

Contraindicated in pregnancy, reduced hepatobiliary function & malabsorption states

SIBUTRAMINE

MOA: inhibits NE & serotonin reuptake in the CNS; reduces appetite (anorectic effect)

Uses: obesity

SE: dry mouth, GI disturbance, tachycardia, HPN, CVS events (MI, arrhythmias), stroke

Withdrawn due to increased risk of CVS events & stroke

RIMONABANT

MOA: selectively blocks cannabinoid-1 (CB-1) receptors; reduces appetite (anorectic effect)

Uses: obesity, smoking cessation, drug addiction

SE: suicidality, depression, nausea

Withdrawn because of increased risk of suicides, depression & other serious psychiatric problems

PHENTERMINE

An appetite suppressant which is an amphetamine derivative

SE: similar with Amphetamine

TRANSPORTER	TISSUES	FUNCTION
GLUT1	All tissues, esp red cells, brain	Basal uptake of glucose; transport across the BBB
GLUT2	Beta cells of pancreas; liver, kidney, gut	Regulation of insulin release, other aspects of glucose homeostasis
GLUT3	Brain, kidney, placenta, other tissues	Uptake in neurons & other tissues
GLUT4	Muscle, adipose	Insulin-mediated uptake of glucose
GLUT5	Gut, kidney	Absorption of Fructose

BONE AND MINERAL HOMEOSTASIS

HORMONAL

PTH

TERIPARATIDE

MOA: act through PTH receptors to produced a net increase in bone formation, stimulates bone turnover

Uses: osteoporosis

SE: hypercalcemia, hypercalciuria, arthralgia, rhinitis, nausea, weakness, dizziness, pharyngitis, dyspepsia, rash

Must be administered in low intermittent doses to stimulate bone formation.

Used IV for osteoporosis.

THYROID HORMONE

CALCITONIN
Salcatonin

MOA: acts through calcitonin receptors to inhibit bone resoprtion

Uses: Pagets dse of bone, hypercalcemia, osteoporosis, tumor marker for thyroid cancer

SE: rhinitis, nausea, vomiting, facial flushing, tingling

Administered as a nasal spray.

Used for osteoporosis but is less effective than Biphosphonates & Teriparatide

VIT D

ERGOCALCIFEROL
Cholecalciferol

MOA: regulates gene transcription via the Vit D receptors; stimulates intestinal Ca absorption, bone resorption, renal Ca & phosphate reabsorption; decrease PTH, promote innate immunity

Uses: Vit D deficiency (rickets, osteomalacia, intestinal ostedystrophy, CKD, chronic liver dse, hypoparathyroidism, nephrotic syndrome), osteoporosis, psoriasis, renal failure, malabsorption

SE: hypercalcemia, hyperphosphatemia, hypercalciuria

Commonly added to dairy products & other food products

Given topically for psoriasis, given with Calcium supplements for osteoporosis

CALCITRIOL
Doxercalciferol, Paricalcitol, Calcipotriene

MOA: regulates gene transcription via the Vit D receptor; stimulates intestinal Ca absorption, bone resorption, renal calcium & phosphate reabsorption, decrease PTH

Uses: secondary hyperparathyroidism in CKD, hypocalcemia in hypoparathyroidism (Calcitriol), psoriasis (Calcipotriene)

SE: hypercalcemia, hyperphosphatemia, hypercalciuria

The active form Calcitriol is preferred in px with CKD, chronic liver dse, & hypoparathyroidism.

DOXERCALCIFEROL is a prodrug that is converted in the liver to 1,25-dihydroxyvitamin D

PARICALCITOL, CALCIPOTRENE are analogs of Calcitriol & are used topically for psoriasis & are being investigated for malignancies & inflammatory disorders.

DOXERCALCIFEROL, PARICALCITOL & CALCIPOTRIENE cause lss hypercalcemia & hypercalciuria

NON HORMONAL

BISPHOSPHONATE

ALENDRONATE
Wtidronate, Ibandronate, Pamidronate, Risedronate, Tiludronate, Zoledronic Acid

MOA: suppresses the activity of osteoclasts in part via inhibition of farnesyl pyrophosphate synthesis; inhibits bone resorption & secondarily, bone formation by acting on the basic hydroxyapatite crystal structure

Uses: Pagets dse of bone, hyoercalcemia esp in malignancies, osteoporosis, bone metastases

SE: adynamic bone, osteonecrosis of the jaw, renal impairment, GI irritation

Take drugs with large quantities of water & avoid situations that permit esophageal reflux.

Remedy for GI irritation & prevent reflux; take lots of water & keep px in an upright position for 30mins after intake of drug.

Contraindicated in those with renal impairment, esophageal motility disorders & peptic ulcers

PHOSPHATE BINDING RESIN

SEVELAMER

MOA: binds to dietary phosphate & prevents its absorption

Uses: hyperphosphatemia in CKD, hypoparathyroidism, vit D intoxication

SE: hypo/hypertension, GI disturbance

Can significantly reduce uric acid levels

Contraindicated in hypophosphatemia & bowel obstruction

SERM

RALOXIFENE

MOA: interacts selectively with estrogen receptors leading to inhibition of bone resorption without stimulating breast or endometrial hyperplasia

Uses: osteoporosis

SE: increased risk of venous thromboembolism

MONOCLONAL ANTIBODY

DENOSUMAB

MOA: binds to RANKL & prevents it from stimulating osteoclast differentiation & function --> inhibit bone resorption

Uses: osteoporosis

SE: increased risk of infection

MINERALS

CALCIUM
Phosphate, Strontium

MOA: multiple physiologic actions through regulation of multiple enzymatic pathways; Sr suppresses bone resorption & increase bone formation; Ca & PO4 are required for bone mineralization

Uses: osteoporosis, osteomlacia, deficiencies in Ca & PO4

SE: ectopic calcification

CALCIUM CONTENT OF DIFFERENT CALCIUM SUPPLEMENTS	
Ca carbonate	40%
Tricalcium phosphate	39%
Ca chloride	27%
Ca acetate	25%
Ca citrate	21%
Ca lactate	13%
Ca gluconate	9%
Ca gluceptate	8%
Ca glubionate	6.5%

Hope this helps you!
This is a tabulated notes of Topnotch Pharmacology.
This is helpful while studying the Pearls ☺
God Bless!

- TD Trix Dones LM Leo Magpantay