

S.E: side effects
Tx: treatment

DOC: Drug of choice

DOA: Duration of action

MOA: Mechanism of action

DOA: oneste // //

∞ → This sign means it's related to or connected

Pharma

Diuretics

→ Osmotic Diuretics

→ Mannitol Tx → ↑ intracranial pressure

⊗ all diuretics cause alkalosis except -CA anhydrase inhibitors

→ Carbonic anhydrase inhibitors (amide)

→ Acetazolamide Tx → glaucoma (↑ intraocular pressure)

→ Dorzolamide, Brinzolamide] ophthalmic drops

other Tx → w/ acute alkalization, acute mountain sickness

→ S.E → Hyperchloremic metabolic acidosis [↓ HCO₃⁻ in H₂O] ↓
Renal stones (sol salts not soluble in alkaline urine)

→ Thiazides (thiazide-like diuretics) (-thiazide, -azone)

- Chlor. thalidone
- Furosemide (direct vasodilating effect)] most used
- Hydrochlorothiazide
- Benz thiazide
- chlor thiazide (can be given IV)
- Poly thiazide
- Bendro flume thiazide
- Hydro flume thiazide
- Methy clo thiazide
- Tri chlor thiazide
- Metal azone
- Quine th azone

⊗ Hyper → calcimim → thiazide
Calcimim → loop diuretics

⊗ DI → thiazide
Inappropriate → loop diuretics
ADH

→ MOA → ⊖ Na-Cl transporter in DCT

- ↑ Ca²⁺ reabsorption
- little CA inhibition
- Direct + indirect vasodilation → ∞ Tx of HTN

→ low ceiling, secreted not filtered, low-moderate efficacy (9-10% of Na⁺)

→ Tx → HTN, Edema of HF, RF, Nephrogenic DI, Hypercalcemia

→ SE → Hyper (calcemia, glycemia, lipidenia) → fatigue, lethargy
Hypo (calcemia, magnesemia) → cardiac arrhythmia → LVH, MI
Uric acid (gout) ∞ Dose dependent → low dose → hyperuricemia
Pancreatitis, ED → high → ↓ uric acid reabsorption → Hypouricemia

→ loop diuretics → High ceiling, secreted + filtered, high efficacy (10-25% of Na⁺), strongest diuretics

rapid DOA, short DOA, all taken O, IV

→ MOA → ⊖ Na-Cl-2Cl transporter in thick segment of loop of henle
effective in Renal failure (GFR < 10, creatinine > 2.5)

→ Furosemide, Ethacrynic acid, Bumetanide, Torsemide

→ Tx → (acute pulmonary edema + edema of HF, renal failure on solids) → DOC

- CHF (DOC)
- HTN
- Hyper calcemia, Hypercalcemia
- Inappropriate ADH secretion

→ SE → Hypo (calcemia, magnesemia, calcemia)

- Irreversible ototoxicity
- Dehydration → ↓ BP → Headache
- allergy, alkalosis

⊖ Lipids → Thiazide → Hyperlipidemic
 ↳ loop → Ca^{2+} sparing → No effect

↳ Ca^{2+} sparing (low efficacy) → diuretic induced hypocalcemia
 ↳ Thiazide or loop diuretic ⊕ → Ca^{2+} supplement
 ↳ Ca^{2+} sparing diuretic

↳ Aldosterone antagonist (competitive) → Spironolactone, Eplerenone

↳ MOA → DCT, collecting duct // ~~+~~ antiandrogenic (More in spironolactone)
 ↳ orally, delayed OOA

↳ TX → Hyperaldosteronism (Ca^{2+} ↓)

↳ Hypokalemic

↳ Hirsutism (antiandrogenic)

↳ HTN + CHF (with other drugs)

↳ hepatic edema

↳ SE → Hyperkalemia → cardiac arrhythmias (More in Eplerenone)

↳ ♂ → Gynecomastia } some use Eplerenone
 ↳ ♀ → Breast tenderness } (More in spironolactone)

↳ Non-steroidal Ca^{2+} sparing ⇒ Amiloride, Triamterene

↳ MOA → Block Na^+ channels → ↓ Na^+ reabsorption, ↓ Ca^{2+} secretion

↳ orally

↳ No antiandrogenic effect

↳ TX → HTN, Hypokalemic

↳ SE → Hyperkalemia, renal tubular damage (Triamterene + Chlorothalidate)
 ↳ Hydro

Drugs

↳ -lamide → Carbonic Anhydrase inhibitor

↳ -thiazide, -azone → thiazide diuretics

↳ ~~ADH~~-vaptan → ADH Antagonist

↳ -pressin → ADH Agonist

↳ -prost → Prostaglandin (uterine stimulant)

↳ -relin → GnRH preparation

↳ -relix → GnRH antagonist

renal excretion
Amphotericin B (for long periods)
Fluconazole
Caspofungin
Terbinafine

liver (bile) fecal excretion
ketoconazole
Caspofungin
Griseofulvin

all are fungistatic
except!
Polyenes

Antifungal drugs

→ Polyenes (Fungicidal) (Polyene Macrolide antibiotics) bind selectively to ergosterol → pores in cell membrane → cell lysis

- Amphotericin B
- Nystatin
- Natamycin

→ Azoles (Fungistatic) (conazole) MOA → ⊖ cytochrome P450 demethylase → no ergosterol formation

→ Imidazole: Ketoconazole, Miconazole, Clotrimazole

→ Triazole: Fluconazole, Itraconazole, Voriiconazole, Isavuconazole

→ Allylamine (Fungistatic) (fine) MOA → ⊖ squalen epoxidase → ↓ ergosterol synthesis → ↑ toxic squalene

selective, BBB → CNS, no embryonic disturbance, ↓ hepatotoxicity, ↓ Tolnaftate

- Terbinafine
- Naftifine
- Butenafine

→ Echinocandins (Fungin) MOA → ⊖ synthesis of β-D-glucan → cell wall synthesis → death & lysis

- Caspofungin
- Micafungin
- Anidulafungin

→ Mitosis inhibitor MOA → ⊖ Mitotic spindle formation → No tubulin, No Microtubule, No mitosis

→ Griseofulvin (Fungistatic)

→ DNA synthesis (RNA) inhibitor (Antimetabolites)

→ Fluorocytosine (5-fluorocytosine) → ⊖ thymidylate synthase → No DNA

Amphotericin B → ⊕

Fluoro deoxy uridine 5'-MP → ⊕ → 5-TTP → ⊖ → RNA synthesis

I ① Amphotericin B

- DOC of systemic infection (IV-infusion)
- orally for Tx of fungal infection of GI (not absorbed orally)
- locally → corneal ulcer, paronychia, bladder irrigation
- No penetration for BBB & vitreous humor & amniotic fluid
- SE → Nephrotoxicity (80%) & Hypokalemia (↑ Hypomagnesemia) {25%}
- to reduce toxicity → liposomal preparation

② Nystatin

- Not used systemically (toxic)
- orally for superficial candidiasis of mouth (esophagus), GI (not absorbed)
- Prescribes for vaginal c.

③ Natamycin

- eye
- Fungal keratitis (eye infection) → ophthalmic eye drops
- Aspergillus & Fusarium & Candida & Cephalosporium & Penicillium

- DOC
- systemic infection → Amphotericin B
 - fungal keratitis → Natamycin
 - seborrheic dermatitis → Icticonazole
 - cryptococcal meningitis → fluconazole
 - dermatophyte → Terbinafine
 - onychomycosis → Icticonazole
 - ~~Vari~~ aspergillosis → Voriconazole

- ⊗ teratogenic drugs
- ↳ ketoconazole
 - ↳ fluconazole
 - ↳ estrogen

II Flucytosine

- with Amphotericin B → cryptococcus
- Itraconazole → Chromo Blastomycosis
- Cryptococcal meningitis in AIDS
 - ↳ penetrates BBB (CSF)
- ↳ SE → reversible (Neuro, Thrombo) cytopenia & reversible ↑ liver enzymes

III Icticonazole

- ↳ 1st oral azole → systemic mycosis
- ↳ only oral, acid → ↑ absorption
- ↳ H₂ Blocker, PPI Inhibitor, antacids, food → ↓ absorption
- ↳ CYP 3A4
 - ↳ cyclosporin, phenytoin → ↑ conc.
 - ↳ warfarin, Ritampin → ↓ conc.
- ↳ Icticonazole inhibits P450 → ↑ conc. of 5
- ↳ No BBB → No CSF
- ↳ ∞ Histoplasma & Blastomycosis & candida & coccidioidosis
- ↳ Not used for aspergillus
- ↳ ∞ Tx of seborrheic dermatitis
- ↳ ∞ endocrine SE → inhibits adrenal, gonada steroidogenesis
- ↳ Cushing syndrome, Prostate CA
- ↳ SE → liver toxicity (min SE) & endocrine abnormality, teratogenic

IV 1

fluconazole

↳ not altered by food or acidity

- ↳ absorbed completely in GI → Bioavailability (0=IV)
- ↳ No drug interactions (P450), NO endocrine SE
- ↳ BBB → CSF → DOC for cryptococcal meningitis + coccidioidomycosis esp. in AIDS
- ↳ Prophylactically in BM transplant
- ↳ ∞ Candidiasis, Histoplasmosis, Blastomycosis, spiridrichosis, ring worm } Itraconazole is better
- ↳ Not effective for Aspergillus
- ↳ SE → Hepatic failure & teratogenic

2 Itraconazole → No endocrine SE

- ↳ oral 100 → for serious cases
- ↳ Food increases absorption
- ↳ ∞ P450 (CYP 3A4)
- ↳ lipid soluble → Bones, Spinal, fat
- ↳ No BBB → NO CSF
- ↳ loading doses → steady state in 4 days
- ↳ SE → Hepatic toxicity, ↑ aminotransferase
- ↳ contraindicated in ventricular dysfunction, HF
- ↳ Rash

3 Voriconazole

- ↳ More potent than Itraconazole
- ↳ ∞ Reversible visual disturbance
- ↳ DOC → aspergillosis

4 Posaconazole

- ↳ ∞ mucor spp. + Zygomycosis
- ↳ candida, aspergillus, parapharyngeal candidiasis
- ↳ ↑ liver fun test
- ↳ ⊖ P450 system
- ↳ Five Apple

V Caspofungin

→ ∞ Candida, Aspergillus

→ IV

→ metabolize (slowly) by hydrolysis + N-acetylation

→ elimination → renal + fecal

VI Cutaneous Mycotic Infection

→ Topical

→ Topical azole

→ (Mico, Clotri, But, ter) Conazole ∞ Imidazole

→ ∞ Contact dermatitis, vulvar irritation, edema

→ Micoconazole (topical) → Bleeding in warfarin treated pts
 ↳ inhibits metabolism → ↑ warfarin conc.

→ Amphotericin B, Nystatin

→ Terbinafine

→ Tolnaftate

→ most cutaneous Mycosis **except candida**

↳ Tinea pedis → 80%

(toothbrush)

→ Oral → oral azole

→ Griseofulvin (keratinolytic)

↳ dermatophyte (hair & skin)

↳ insoluble in water

↳ absorption ↑ by fatty meal

↳ ↓ by Barbiturates

→ Oral not effective topically

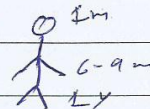
→ resistance P450 system

↳ Mycotic disease (superficial not subcutaneous or deep)

↳ takes time → 1m → scalp

↳ athlete's foot → 6-9m → finger nail

↳ 4-6w → toe nail



↳ SE → Peripheral neuritis

→ Terbinafine → ∞ allylamine

↳ less toxicity & shorter DOA

↳ OOC → dermatophyte

↳ ∞ candida albican

↳ onychomycosis → finger → 6w

↳ toe → 12w

↳ oral → 1st pass metabolism

only

↳ accumulate in skin, nails, Ent

↳ SE → Hepatotoxic

↳ 1/2 half life → 2h → 200-400h

↳ slow release from tissues

↳ conc. ↑ by ritampin Five Apple

↳ ↓ by cimetidine

contraindicated in breast feeding

↳ Breast

Post. Pituitary Hormones (ADH \rightarrow vasopressin)

ADH

- inappropriate ADH secretion

↳ Tx \rightarrow water restriction (Tx of choice)

↳ Hypertonic saline solution

↳ Fludrocortisone \rightarrow \uparrow Na⁺ in blood

↳ ADH Antagonist (**Vaptan**)

↳ Conivaptan \rightarrow V₁, V₂ R antagonist

↳ (Tol, lixi, esaki) vaptan \rightarrow V₂ R antagonist

↳ loop diuretics

DI (ADH deficiency)

↳ ADH preparation (**Pressin**)

↳ DI, Nocturnal enuresis

↳ Hemophilia, esophageal varices bleeding

↳ Pitressin \rightarrow Natural, short half life (15 min)

↳ Lypressin \rightarrow synthetic ADH-like

↳ Desmopressin \rightarrow " " " "] most use

↳ Felypressin \rightarrow vasoconstrictor, dentistry

↳ SE \rightarrow Anginal pain, Gangrene, H₂O intoxication, fallor

↳ stop bleeding

↳ Vasoconstriction

↳ Produce

factor VIII

factor IX

factor VII

↳ V₂ \rightarrow vaso constriction

Drugs acting on Uterus

↳ Uterine stimulus

↳ oxytocin Tx **induction of labor (DOC)**

↳ Post partum hemorrhage

↳ Breast engorgement

↳ Abortification (≥ 20 wks)

↳ SE **rupture of uterus** (Major Most serious)

↳ H₂O intoxication \rightarrow HTN

↳ Antagonist \rightarrow **Atosiban** Tx tocolytic \rightarrow premature delivery

↳ Prostaglandin (**Prost**) \rightarrow less SE than oxytocin (is) for inducing labor

↳ Dinoprostone P6Ez] induce abortification labor

↳ Dinoprost P6Ez] + postpartum hemorrhage

↳ Carb prost P6Ez \rightarrow Prime cervix

↳ Ergot alkaloids \rightarrow Ergonovine & Methyl ergonovine ||| syntometrine = ergometrine

↳ DOC **Postpartum hemorrhage**

↳ contraindication \rightarrow induce delivery \rightarrow fetal distress

oxytocin + fetal distress

↳ Uterine relaxant (Tocolytic) (Tx premature) & Prostaglandin synthase inhibitor

↳ β -adrenergic agonist \rightarrow Ritodrine (most used)

↳ Magnesium sulfate Tx **contraction of pre-eclampsia**

Progestrone (dydrogesterone)
oxytocin competitive with
Atosiban
Prostaglandin synthase inhibitor \rightarrow indomethacin, meloxicam
Mifepristone

E: Estrogen

GnRH (Gonadorelin)

GnRH on Ant. pituitary MOA Ca^{2+} 2nd messenger

LH + FSH on Gonads \rightarrow CAMP 2nd messenger

Synthetic Preparation (relin) \rightarrow SE \rightarrow osteoporosis

(Bus, Tripto, Gose, Hist, Nafa) relin

\rightarrow leuprolide acetate

\rightarrow S.C, IM, IV, Enteral but not oral

\rightarrow Pubertile \rightarrow Kallman's syndrome (GnRH deficiency)

Puberty \rightarrow delayed \rightarrow Pulsatile GnRH
 \rightarrow early \rightarrow Continuous GnRH

\rightarrow Diagnostic use
 \rightarrow β^+ & β^- hypergonadism; induction of ovulation, cryptorchidism

\rightarrow delayed puberty

\rightarrow Continuous (large doses or super agonist)

- \rightarrow (Prostate, Breast) CA
- \rightarrow ~~endometriosis~~ endometriosis, uterine fibroids, uterine leiomyoma
- \rightarrow PCOS (Polycystic ovarian syndrome), uterine
- \rightarrow precocious puberty
- \rightarrow IVF, contraceptive

\rightarrow GnRH antagonist \rightarrow Ganirelix \rightarrow IVF (SC)

* LH + FSH

\rightarrow MOA \rightarrow CAMP 2nd messenger
 \rightarrow LH \rightarrow desmase \rightarrow descent of testis

menotropin
 \rightarrow Contains equal amount of FSH and LH but LH is metabolized more so the main player here is FSH

- \rightarrow Natural \rightarrow Menotropin (AMG, Human menopausal gonadotropin, FSH)
- \rightarrow β -FSH (rDNA) \rightarrow recombinant
- \rightarrow hCG \approx LH \rightarrow from placenta \rightarrow urine of preg ladies

- \rightarrow Tx \rightarrow infertility due to LH, FSH deficiency
 \rightarrow cryptorchidism \approx hCG \approx LH
- \rightarrow SE \rightarrow ovarian hyper stimulation syndrome
 \rightarrow multiple births

⊕ sexual fxn problem \rightarrow E or testosterone

infertility \approx

\rightarrow depend on deficiency

- \rightarrow GnRH (causes)
- \rightarrow LH, FSH, hCG, Menotropin (FSH)
- \rightarrow estrogen (♀), Testosterone (♂)

\rightarrow In case of hyperprolactinemia \rightarrow Bromocriptine (dopamine antagonist inhibit prolactin)
 \rightarrow Clomiphene citrate - Tamoxifen \rightarrow ER antagonist

IVF regulation of ovulation

\rightarrow E antagonist + HMG + hCG

estrogen + Progesterone

⊕ salt + water retention is a side effect of all steroids
↳ ↑ BP

I Estrogen

- ↳ Natural → Estradiol >> Estrone > Estril] in effective orally
- ↳ Transport via SHBG
- ↳ Metabolism → conjugation → enterohepatic circulation
- ↳ Tx
 - ↳ Postmenopausal osteoporosis & prevent heart attack
 - ↳ OCP
 - ↳ Prostate, Breast CA. with progesterone → Estrogenic CA
 - ↳ Infertility
 - ↳ hirsutism acne
- ↳ Preparation
 - ↳ Steroidal → estradiol benzoate, estradiol valerate
 - ↳ Ethinyl estradiol
 - ↳ Mestranol
 - ↳ Non steroidal → DES (diethyl stilbestrol)
 - ↳ conjugated → Estrone sulfate
- ↳ SE
 - ↳ ↑ thromboembolism, ↑ endometrial CA
 - ↳ saltwater retention
 - ↳ teratogenic

Anti-estrogen (all given orally)

- ↳ Tamoxifen, Clomiphene citrate (also they are SERM)
 - ↳ ⊕ → Bone + endometrium ^{cause} → endometrial CA
 - ↳ ⊖ → Breast \xrightarrow{Tx} Breast CA
 - ↳ hypothalamus \xrightarrow{Tx} infertility in ♀, ♂
- ↳ SERM (non hormonal) agonist + antagonist
 - ↳ Raloxifene \xrightarrow{Tx} Osteoporosis (also prophylactic)
- ↳ Aromatase inhibitor \xrightarrow{Tx} Breast CA
 - ↳ Non selective → Amino glutarimide
 - ↳ selective → Anastrozole, Fulvestrant

II Progesterone

- ↳ Preparation Tx
 - ↳ OCP
 - ↳ uterine bleeding
 - ↳ prostate + endometrial CA
 - ↳ endometriosis
- ↳ Dihydroprogesterone \xrightarrow{Tx} IV
- ↳ Cyproterone acetate \xrightarrow{Tx} Prostate CA
- ↳ Norethindrone
- ↳ Norethindrone acetate
- ↳ Medroxy progesterone
- ↳ Hydroxy progesterone caproate
- ↳ Mestranol
- ↳ Mepredrol acetate
- ↳ Anti-progesterone → Mifepristone (RU-486)
- ↳ Abortifacient, induce labor + PG
- ↳ Progesterone dependent CA

Progesterone → stop uterine growth
Bleeding

* Contraception, refer to slides.