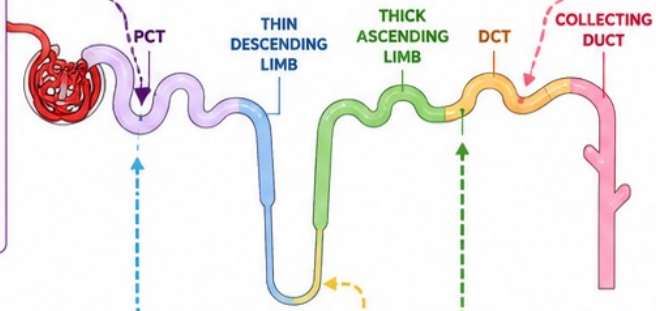
DIURETICS

Increase excretion of sodium (Na^+) and water → ↓ ECF volume → ↓ BP and edema

GENERAL USES

- Edema (CHF, cirrhosis, nephrotic syndrome)
- Hypertension
- Hypercalcemia (loop diuretics)
- Nephrolithiasis (specific types)
- SIADH (ADH antagonists)



1. CARBONIC ANHYDRASE INHIBITORS

DRUG

Acetazolamide (oral, IV)

MECHANISM

Inhibit carbonic anhydrase in PCT → ↓ reabsorption of HCO_3^-, Na^+, and water

EFFECTS

- ↑ Excretion of $NaHCO_3$ → alkaline urine
- Mild diuresis

USES

- Glaucoma
- Acute mountain sickness
- Metabolic alkalosis
- Epilepsy
- Adjunct in heart failure

ADVERSE EFFECTS

- Metabolic acidosis
- Hypokalemia
- Kidney stones (calcium phosphate)
- Paresthesias, drowsiness
- Sulfa allergy (cross-reactivity)

2. LOOP DIURETICS

DRUGS

Furosemide, Bumetanide, Torsemide, Ethacrynic acid

MECHANISM

Inhibit Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) in thick ascending limb → ↓ reabsorption of Na^+, K^+, $2Cl^-$

EFFECTS

- Powerful diuresis
- ↑ Excretion of Na^+, K^+, Ca^{2+}, Mg^{2+}
- Decrease medullary concentration gradient

USES

- Edema (CHF, cirrhosis, nephrotic syndrome)
- Hypertension (especially with renal impairment)
- Hypercalcemia
- Acute pulmonary edema

ADVERSE EFFECTS

- Hypokalemia
- Metabolic alkalosis
- Hypovolemia, hypotension
- Hyperuricemia (gout)
- Ototoxicity (esp. ethacrynic acid, high doses)
- Sulfa allergy (except ethacrynic acid)

3. THIAZIDE DIURETICS

DRUGS

Hydrochlorothiazide, Chlorthalidone, Indapamide, Metolazone

MECHANISM

Inhibit Na^+-Cl^- cotransporter (NCC) in early DCT → ↓ Na^+ reabsorption

EFFECTS

- Moderate diuresis
- ↑ Excretion of Na^+ and water
- ↓ Excretion of Ca^{2+} (increased reabsorption)
- ↑ Excretion of K^+ and H^+

USES

- Hypertension (first-line)
- Mild edema
- Nephrolithiasis (↓ urinary calcium)
- Diabetes insipidus (mild)

ADVERSE EFFECTS

- Hypokalemia
- Metabolic alkalosis
- Hypercalcemia
- Hyperuricemia (gout)
- Hyperglycemia
- Hyperlipidemia
- Hyperlipidemia
- Photosensitivity

4. OSMOTIC DIURETICS

DRUGS

Mannitol (IV)

MECHANISM

Not absorbed; increases osmolarity of filtrate in PCT and loop → ↓ reabsorption of water

EFFECTS

- Increase excretion of water and Na^+
- Diuresis

USES

- Increased intracranial pressure
- Acute glaucoma
- Promote diuresis in AKI
- Rhabdomyolysis, intoxications

ADVERSE EFFECTS

- Fluid overload
- Electrolyte imbalances
- Headache, nausea
- Contraindicated in anuria, heart failure

5. POTASSIUM-SPARING DIURETICS

K^+ CHANNEL BLOCKERS	ALDOSTERONE ANTAGONISTS
Amiloride Triamterene	Spironolactone Eplerenone

MECHANISM

Act on late DCT and collecting duct → ↓ Na^+ reabsorption → ↓ K^+ and H^+ secretion

EFFECTS

- Mild diuresis
- Potassium-sparing

USES

- Hyperaldosteronism
- Heart failure (with other diuretics)
- Prevent hypokalemia

ADVERSE EFFECTS

- Hyperkalemia
- Metabolic acidosis (±)
- Spironolactone: gynecomastia, impotence, menstrual irregularities
- Eplerenone: less endocrine effects

COMPARISON SUMMARY

Class	Diuretic Potency	K^+ Loss	Ca^{2+} Loss	Main Site
CA Inhibitors	Weak	↑	↑	PCT
Loop	Very Strong	↑↑	↑↑	Thick Asc. Limb
Thiazides	Moderate	↑	↓	Early DCT
K^+-Sparing	Weak	↓ (retain)	–	Late DCT / CD
Osmotic	Variable	Variable	Variable	PCT, Loop
ADH Antagonists	Specific (water)	–	–	Collecting Duct

6. ADH ANTAGONISTS (VASOPRESSIN RECEPTOR ANTAGONISTS)

DRUGS

Tolvaptan, Conivaptan

MECHANISM

Block V2 receptors in collecting duct → ↑ excretion of free water (aquaresis) without significant loss of Na^+

USE

- SIADH
- Hyponatremia (euvolemic or hypervolemic)

KEY POINTS

- All diuretics increase Na^+ excretion; the site of action determines potency and electrolyte effects.
- Loop diuretics are most potent; thiazides are first-line for hypertension.
- K^+-sparing diuretics prevent hypokalemia.
- ADH antagonists cause water diuresis without major electrolyte loss.

DRUGS USED IN UTIs

GENERAL PRINCIPLES

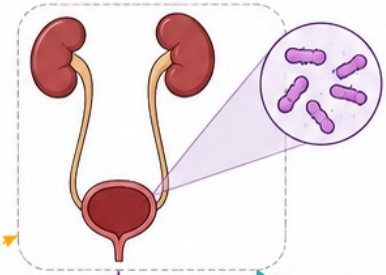
- Choose empiric therapy based on local resistance patterns.
- Adjust therapy based on culture and sensitivity.
- Adequate hydration helps.
- Treat for an appropriate duration to prevent resistance and relapse.

Classification (by site of infection)

- Uncomplicated cystitis
- Complicated UTI
- Pyelonephritis

Goal of therapy

Eradicate the pathogen, relieve symptoms, and prevent complications



Common uropathogens

- *Escherichia coli* (most common)
- *Staphylococcus saprophyticus*
- *Proteus mirabilis*
- *Klebsiella pneumoniae*
- *Enterococcus faecalis*
- *Pseudomonas aeruginosa*

GENERAL ADVERSE EFFECTS

- GI upset (nausea, vomiting, diarrhea)
- Hypersensitivity reactions
- Disruption of normal flora → superinfection (e.g., *C. difficile*)
- Potential for drug interactions
- Use culture results to guide therapy and minimize resistance

1. TRIMETHOPRIM–SULFAMETHOXAZOLE (TMP–SMX)

MECHANISM

Sequential blockade of folate synthesis:

- TMP inhibits dihydrofolate reductase
- SMX inhibits dihydropteroate synthase

USES

- First-line for uncomplicated cystitis (if local resistance <20%)
- Some complicated UTIs
- Prostatitis

ADVERSE EFFECTS

- Rash, hypersensitivity
- GI upset
- Hyperkalemia
- Bone marrow suppression
- Crystalluria
- Hemolysis in G6PD deficiency

NOTES

Avoid in late pregnancy (near term) and in G6PD deficiency.

2. FLUOROQUINOLONES

DRUGS

Ciprofloxacin, Levofloxacin, Norfloxacin, Ofloxacin

MECHANISM

Inhibit DNA gyrase (topoisomerase II) and topoisomerase IV → inhibit DNA replication.

USES

- Complicated UTIs
- Pyelonephritis
- Prostatitis
- Alternative for uncomplicated cystitis (resistance dependent)

ADVERSE EFFECTS

- GI upset, headache, dizziness
- Tendinitis and tendon rupture
- QT prolongation
- CNS effects (insomnia, confusion, seizures)
- Dysglycemia (hypo/hyperglycemia)
- Aortic aneurysm/dissection (rare)
- Photosensitivity

NOTES

Avoid in pregnancy, children, and breastfeeding.

3. NITROFURANTOIN

MECHANISM

Reduced in bacterial cells to reactive intermediates → damage bacterial DNA, RNA, and proteins.

USES

- First-line for uncomplicated cystitis
- Not used for pyelonephritis (does not reach adequate renal tissue levels)

ADVERSE EFFECTS

- GI upset
- Pulmonary toxicity (acute/chronic)
- Hepatotoxicity
- Peripheral neuropathy
- Hemolytic anemia in G6PD deficiency

NOTES

Avoid if CrCl < 30 mL/min.

4. METRONIDAZOLE

MECHANISM

Reduced in anaerobic organisms → free radicals → DNA damage → cell death.

USES

- Not for typical UTIs
- Used for anaerobic infections of the genitourinary tract (e.g., bacterial vaginosis, trichomoniasis)

ADVERSE EFFECTS

- Metallic taste
- Nausea, vomiting
- Disulfiram-like reaction (with alcohol)
- Peripheral neuropathy (with prolonged use)

NOTES

Do not use alcohol during treatment and for 48–72 h after last dose.

5. CLINDAMYCIN

MECHANISM

Inhibits 50S ribosomal subunit → inhibits protein synthesis.

USES

- Not for typical UTIs
- Used for anaerobic infections of the genitourinary tract and pelvis
- Alternative in patients allergic to penicillin

ADVERSE EFFECTS

- GI upset, diarrhea
- *C. difficile*–associated diarrhea
- Rash

NOTES

Given only when anaerobic coverage is required.

COMPARISON SUMMARY

Drug/Class	Typical Use	Covers Gram (–)	Covers Gram (+)	Anaerobes	Good Renal Penetration	Oral Option	Key Limitations
TMP–SMX	Uncomplicated cystitis	Yes	Some (Enterococcus)	No	Good	Yes	Resistance, hyperkalemia, rash
Fluoroquinolones	Complicated UTI, pyelonephritis, prostatitis	Yes	Some	No	Excellent	Yes	Tendon toxicity, QT prolongation, resistance
Nitrofurantoin	Uncomplicated cystitis	Yes	Some (Enterococcus)	No	Poor (renal tissue)	Yes	Not for pyelonephritis, pulmonary/hepatic toxicity
Metronidazole	Anaerobic GU infections	No	No	Yes	Variable	Yes	Metallic taste, alcohol reaction
Clindamycin	Anaerobic GU infections	No	Yes (some)	Yes	Variable	Yes	C. difficile–associated diarrhea

CHOOSING EMPIRIC THERAPY

1. Uncomplicated cystitis (non-pregnant):
   - TMP–SMX or Nitrofurantoin
   - Fosfomycin (single dose) – alternative
2. Pregnancy:
   - Nitrofurantoin (avoid near term)
   - Cephalexin, Amoxicillin–Clavulanate
3. Complicated UTI / Pyelonephritis:
   - Fluoroquinolone or
   - Parenteral β-lactam (e.g., ceftriaxone)
4. Anaerobic GU infections:
   - Metronidazole or Clindamycin

KEY PEARLS

- *E. coli* is the most common cause of community-acquired UTIs.
- Culture and sensitivity guide optimal therapy.
- Avoid overuse to prevent antibiotic resistance.
- Tailor duration: usually 3–5 days for cystitis, 7–14 days for complicated UTIs.

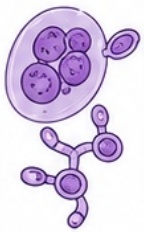
ANTIFUNGAL DRUGS

CLASSIFICATION (BY SITE OF ACTION)

- **Polyenes** — Bind ergosterol → change membrane permeability (fungicidal)
- **Azoles** — Inhibit ergosterol synthesis (fungistatic or fungicidal)
- **Allylamines** — Inhibit ergosterol synthesis (terbinafine)
- **Echinocandins** — Inhibit β-1,3-D-glucan synthesis in cell wall (fungicidal)
- **Antimetabolite** — Inhibits DNA/RNA synthesis (5-Fluorocytosine)

GOAL OF THERAPY

Eradicate fungal infection, relieve symptoms, prevent recurrence, and minimize toxicity.



GENERAL PRINCIPLES

- Fungal cell = eukaryotic → selectivity is harder than antibacterial drugs.
- Therapy depends on site, severity, fungal species, and host factors.
- Prophylaxis is important in immunocompromised patients.

GENERAL ADVERSE EFFECTS

- GI upset (nausea, vomiting, diarrhea)
- Hepatotoxicity (↑ LFTs)
- Hypersensitivity reactions (rash, fever)
- Drug interactions (especially with azoles)
- Nephrotoxicity (mainly with amphotericin B)
- Hematologic toxicity (5-Fluorocytosine)
- Infusion-related reactions (echinocandins)

Always monitor: liver, kidney functions and drug levels when indicated.

1. POLYENES

Binds ergosterol → increases membrane permeability → leakage of intracellular contents

DRUGS

Amphotericin B (IV)
Nystatin (topical/oral)

USES

- **Amphotericin B:** systemic fungal infections (serious)
- **Nystatin:** superficial infections of skin, mucosa, oropharyngeal & esophageal candidiasis

ADVERSE EFFECTS

- **Amphotericin B:**
  - Infusion reactions (fever, chills, rigor)
  - Nephrotoxicity (↓ K^+, Mg^{2+})
  - Anemia
- **Nystatin:** minimal systemic absorption → minimal toxicity (GI upset possible)

NOTES

Amphotericin B = drug of choice for severe systemic mycoses.
Use lipid formulations to ↓ nephrotoxicity.

2. AZOLES

Inhibit 14-α-demethylase (CYP450) → ↓ ergosterol synthesis → defective cell membrane

Squalene → Lanosterol ✕ → Ergosterol

DRUGS

Imidazoles: Ketoconazole, Clotrimazole, Miconazole

Triazoles: Fluconazole, Itraconazole, Voriconazole, Posaconazole, Isavuconazole

USES

- Superficial mycoses (topical azoles)
- Systemic candidiasis (fluconazole)
- Cryptococcosis (fluconazole)
- Histoplasmosis, Blastomycosis (itraconazole)
- Aspergillosis (voriconazole)

ADVERSE EFFECTS

- Hepatotoxicity
- GI upset
- QT prolongation (esp. voriconazole, itraconazole)
- Many drug interactions (CYP450 inhibitors)

NOTES

Fluconazole = good for Candida & Cryptoocccus.
Voriconazole = drug of choice for invasive aspergillosis.

3. ALLYLAMINES

Inhibit squalene epoxidase → ↓ ergosterol synthesis → accumulation of squalene → toxic to fungal cell

DRUG

Terbinafine (oral/topical)

USES

- Dermatophyte infections (tinea: pedis, corporis, cruris)
- Onychomycosis (oral)
- Tinea capitis

ADVERSE EFFECTS

- GI upset
- Headache, rash
- Hepatotoxicity (rare)
- Taste disturbance (oral)

NOTES

Active against dermatophytes.
NOT effective against Candida.

Why Terbinafine?

- Fungicidal for dermatophytes
- Accumulates in skin, nails, hair

4. ECHINOCANDINS

Inhibit β-1,3-D-glucan synthase → inhibit fungal cell wall synthesis → cell lysis (fungicidal)

DRUGS

Caspofungin, Micafungin, Anidulafungin

USES

- Candidemia & invasive candidiasis
- Esophageal candidiasis
- Aspergillosis (salvage therapy)

ADVERSE EFFECTS

- Infusion-related reactions
- ↑ LFTs
- Histamine release (flushing, rash)

NOTES

Poor oral absorption → IV only.
Well tolerated.

5. ANTIFUNGAL ANTIMETABOLITE

Converted to 5-FU in fungal cells → inhibits DNA/RNA synthesis (fungistatic)

DRUG

5-Fluorocytosine (Flucytosine)

USES

- Systemic candidiasis
- Cryptococcal meningitis (always with amphotericin B)

ADVERSE EFFECTS

- Bone marrow suppression (leukopenia, thrombocytopenia)
- GI upset
- Hepatotoxicity

NOTES

Resistance develops rapidly if used alone → always combine with amphotericin B.

COMPARISON SUMMARY

Class	MOA	Spectrum	Route	Key Uses	Key Adverse Effects
Polyenes	Bind ergosterol → ↑ membrane permeability	Broad (fungicidal)	IV (AmB), Topical/Oral (Nystatin)	Severe systemic mycoses (Nystatin: mucocutaneous)	Nephrotoxicity (AmB), infusion: reactions
Azoles	Inhibit 14-α-demethylase → ↓ ergosterol	Broad (fungistatic/ fungicidal)	Oral, IV, Topical	Candidiasis, Cryptococcosis, Histoplasmosis, Aspergillosis	Hepatotoxicity, drug interactions, QT prolongation
Allylamines	Inhibit squalene epoxidase	Narrow (dermatophytes)	Oral, Topical	Dermatophytosis, Onychomycosis	Hepatotoxicity (rare), taste disturbance
Echinocandins	Inhibit β-1,3-D-glucan synthase (cell wall)	Candida, Aspergillus (fungicidal)	IV only	Candidemia, Invasive candidiasis, Aspergillosis (salvage)	Infusion reactions, ↑ LFTs
5-Fluorocytosine	Converted to 5-FU → inhibits DNA/RNA synthesis	Candida, Cryptococcus (fungistatic)	Oral (± IV)	Cryptococcal meningitis (combination therapy)	Bone marrow suppression, GI upset

CLINICAL PEARLS

- Amphotericin B = gold standard for severe, life-threatening fungal infections.
- Nystatin is NOT absorbed → safe for mucosal infections.
- Fluconazole = best choice for candidiasis & cryptococcosis.
- Terbinafine = for dermatophytes only.
- Echinocandins = IV only, safe & effective for candidemia.
- 5-Fluorocytosine = resistance develops fast if used alone.

IMPORTANT REMINDERS

- Assess patient factors: immunity, pregnancy, liver & kidney function.
- Always consider drug interactions with azoles.
- Use appropriate duration to prevent relapse.
- Monitor labs: LFTs, renal function, CBC when needed.

Key Principle
Target the fungus, protect the host, and prevent resistance.

GONADAL HORMONES AND INHIBITORS

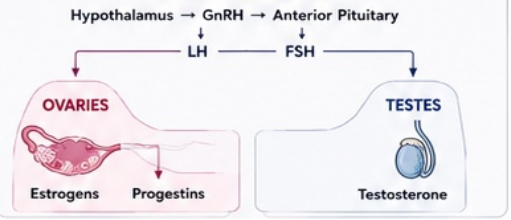
GENERAL PRINCIPLES

- Gonadal hormones exert systemic effects on reproductive organs and secondary sexual characteristics.
- Therapeutic use includes: replacement therapy, contraception, infertility treatment, hormone-dependent cancers, and endometriosis.
- Adverse effects are dose-related and hormone-specific.
- Risk of thromboembolism with estrogens and progestins.
- Contraindicated in pregnancy (except where indicated) and hormone-sensitive cancers.

GOAL OF THERAPY

Modulate the reproductive system by replacing, supplementing, or inhibiting gonadal hormones for therapeutic benefit.

PHYSIOLOGIC BASIS



Regulate: gametogenesis, secondary sexual characteristics, menstrual cycle, fertility, pregnancy

GENERAL ADVERSE EFFECTS

- Thromboembolic events (↑ with estrogens/progestins)
- Nausea, breast tenderness
- Weight gain, edema
- Mood changes, headache
- Hypertension
- Liver dysfunction (especially with androgens)
- Endometrial hyperplasia/cancer (unopposed estrogens)
- Masculinization (with androgens)

Always assess risk factors: age, smoking, obesity, HTN, personal/family history of clots or cancers.

1. ESTROGENS

DRUGS

Estradiol, Ethinyl estradiol, Conjugated equine estrogens

MECHANISM

Bind estrogen receptors (ERα, ERβ) → exert genomic effects on target tissues.

USES

- Menopausal symptoms
- Contraception (in combination)
- HRT (hormone replacement therapy)
- Osteoporosis prevention
- Abnormal uterine bleeding
- Palliative treatment of prostate cancer

ADVERSE EFFECTS

- Thromboembolism
- Nausea, breast tenderness
- Headache, hypertenstion
- Endometrial hyperplasia/cancer (if unopposed)
- Gallbladder disease

NOTES

Always combine with a progestin in women with an intact uterus to prevent endometrial hyperplasia.

2. PROGESTINS

DRUGS

Medroxyprogesterone, Norethindrone, Levonorgestrel, Norgestimate

MECHANISM

Bind progesterone receptors → convert endometrium to secretory phase, thicken cervical mucus, inhibit ovulation (at higher doses).

USES

- Contraception (alone or with estrogen)
- Abnormal uterine bleeding
- Endometriosis
- Menstrual disorders
- Prevention of endometrial hyperplasia
- HRT (with estrogen)

ADVERSE EFFECTS

- Irregular bleeding
- Weight gain, edema, mood changes
- Breast tenderness
- Thromboembolism (↑ with 3rd gen)
- Depression (rare)

NOTES

3rd generation (desogestrel, gestodene) → ↑ risk of thrombosis compared to 2nd generation.

3. SELECTIVE ESTROGEN RECEPTOR MODULATOR (SERM)

DRUG

Tamoxifen

MECHANISM

Antagonist in breast tissue, agonist in bone & endometrium.

USES

- Estrogen receptor–positive breast cancer (treatment & prevention)
- Prevention of osteoporosis in postmenopausal women

ADVERSE EFFECTS

- Hot flashes
- Thromboembolism
- Endometrial hyperplasia/cancer
- Cataracts

NOTES

Do not use in pregnancy. Teratogenic.

4. ANTI-ESTROGENS

DRUG

Clomiphene

MECHANISM

Competitive antagonist at estrogen receptors in hypothalamus → ↑ GnRH → ↑ FSH & LH → ovulation.

USES

- Ovulation induction in anovulatory infertility (e.g., PCOS)

ADVERSE EFFECTS

- Hot flashes
- Visual disturbances
- Nausea
- Multiple pregnancy
- Ovarian hyperstimulation (rare)

NOTES

Monitor ovulation and ovarian response.

5. ANDROGENS

DRUGS

Testosterone, Danazol

MECHANISM

Bind androgen receptors → promote male characteristics and anabolic effects.

USES

- Male hypogonadism
- Delayed puberty
- Some cases of anemia
- Danazol: endometriosis, fibrocystic breast disease

ADVERSE EFFECTS

- Virilization (women)
- Acne, hirsutism
- Hepatotoxicity (danazol)
- Edema
- Aggression, mood changes

NOTES

Danazol suppresses gonadotropins (↓ FSH, LH) → used in endometriosis.

6. ANTI-PROGESTINS

DRUG

Mifepristone (RU-486)

MECHANISM

Competitive antagonist at progesterone receptors → blocks progesterone action on endometrium.

USES

- Medical termination of early pregnancy
- Cushing's syndrome (experimental)

ADVERSE EFFECTS

- Abdominal pain
- Vaginal bleeding
- Nausea

NOTES

Use only under medical supervision. Not for contraception.

COMPARISON SUMMARY

Class	Mechanism	Key Uses	Major Risks
Estrogens	Activate estrogen receptors	Menopause, contraception, HRT, osteoporosis	Thromboembolism, endometrial hyperplasia (unopposed)
Progestins	Activate progesterone receptors	Contraception, AUB, endometriosis, HRT	Irregular bleeding, thrombosis (↑ with 3rd gen)
SERMs	ER antagonist in breast, agonist in bone/uterus	ER+ breast cancer, osteoporosis prevention	Thromboembolism, endometrial effects
Anti-estrogens	Block estrogen receptors (hypothalamus)	Ovulation induction	Hot flashes, visual disturbances, multiple pregnancy
Androgens	Activate androgen receptors	Male hypogonadism, endometriosis (danazol)	Virilization, hepatotoxicity, mood changes
Anti-progestins	Block progesterone receptors	Medical abortion	Bleeding, abdominal pain

CLINICAL PEARLS

- Always combine estrogen with progestin in women with an intact uterus.
- Tamoxifen is NOT a contraceptive.
- Clomiphene is first-line for ovulation induction in PCOS.
- Danazol reduces estrogen levels by suppressing gonadotropins.
- Assess thrombotic risk before prescribing estrogen or progestin-containing therapies.

IMPORTANT REMINDERS

- Use the lowest effective dose for the shortest necessary duration.
- Monitor blood pressure, lipid profile, and liver function when indicated.
- Counsel about signs of DVT/PE: leg pain/swelling, chest pain, shortness of breath.
- Contraindicated in: pregnancy (except mifepristone for termination), hormone-sensitive cancers, active thromboembolic disease.

Understand the hormone, its receptor, and the target tissue → this is the key to remembering uses and adverse effects!

REPRODUCTIVE PHARMACOLOGY – KEY CONCEPTS

1. GONADOTROPINS

A. TYPES
- FSH
- LH
- hCG
- hMG (FSH + LH)

B. AVAILABLE FORMS
- uFSH (from urine of postmenopausal women)
- rFSH (Follitropin)
- rLH (Lutropin)
- rhCG (Choriogonadotropin alfa)

C. THERAPEUTIC USES
1. Induction of ovulation → needs progesterone support of luteal phase.
2. Male infertility → for hypogonadal men.

D. ADVERSE EFFECTS
1. **Ovarian hyperstimulation syndrome (OHSS):**
   - Ovarian enlargement
   - Ascites, hydrothorax
   - Hypovolemia, shock
   - Hemoperitoneum (ruptured ovarian cyst)
   - Fever, arterial thromboembolism
2. Multiple pregnancies (15–20% vs 1%)
3. Headache, depression, edema
4. Production of antibodies against hCG
5. Gynecomastia in males
6. Possible association with ovarian cancer

2. GnRH AGONISTS (GnRH & ANALOGS)

A. PHYSIOLOGY
- GnRH is secreted by neurons in hypothalamus.
- Pulsatile GnRH → stimulates gonadotrophs to release FSH & LH.
- Continuous (nonpulsatile) GnRH → inhibits FSH & LH release → hypogonadism.

B. DRUGS
- Gonadorelin (synthetic GnRH)
- Analogues: Leuprolide, Goserelin
- Preparations with duration from hours to months.

C. PHARMACOLOGIC EFFECTS

Pulsatile (1–4 h)	Continuous
↑ FSH & LH	
First 7–10 days (FLARE): ↑ Gonadal hormones (agonist effect)	After that: ↓ FSH & LH; ↓ Gonadal steroids (antagonist effect); ↓ due to receptor down-regulation

D. THERAPEUTIC USES
1. **STIMULATION** (pulsatile)
   - Female & male infertility
   - "LH responsiveness test" to diagnose delayed puberty
2. **SUPPRESSION** (continuous)
   - Controlled ovarian hyperstimulation (prevent premature LH surge)
   - Endometriosis
   - Uterine leiomyomata (fibroids)
   - Central precocious puberty

E. ADVERSE EFFECTS
1. Headache, light-headedness, nausea, flushing
2. Local swelling at injection site
3. Hypersensitivity reactions (bronchospasm, anaphylaxis)
4. Menopausal symptoms in women
5. Ovarian cysts
6. Sudden pituitary apoplexy
7. Reduced bone density, osteoporosis

3. GnRH ANTAGONISTS

A. DRUGS
- Ganirelix
- Cetrorelix (Synthetic decapeptides)
- Degarelix (used in advanced prostate cancer)

B. MECHANISM
- Competitive inhibition of GnRH receptors in pituitary → ↓ FSH & LH in a dose-dependent manner.

C. THERAPEUTIC USES
1. Prevention of LH surge during controlled ovarian hyperstimulation (IVF).
2. Treatment of advanced prostate cancer (Degarelix) → lowers testosterone without initial flare.

D. ADVANTAGES
- Immediate action
- Shorter duration of therapy
- Can be started day 6–8 of IVF cycle
- More complete suppression of gonadotropins

E. DISADVANTAGES
1. Effect reverses quickly after discontinuation
2. May impair follicular development when used with FSH in IVF
3. Lower pregnancy rate in IVF compared with GnRH agonists

F. ADVERSE EFFECTS
- Nausea
- Headache
- Hot flushes
- Weight gain

4. PROLACTIN & DOPAMINE AGONISTS

A. PROLACTIN
- Secreted by anterior pituitary.
- Main function: lactation.

Hyperprolactinemia

In Women	In Men
• Amenorrhea • Galactorrhea • Infertility	• ↓ Libido • Infertility

→ Causes infertility by inhibiting GnRH release.

B. DOPAMINE EFFECT
- Dopamine inhibits prolactin release.
- Therefore, dopamine agonists are used to treat hyperprolactinemia.

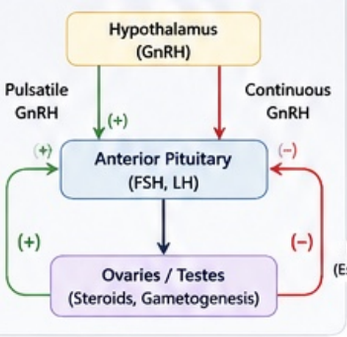
C. DOPAMINE AGONISTS
- Bromocriptine
- Cabergoline

D. MECHANISM
- Stimulate D_2 receptors on lactotrophs → ↓ prolactin secretion.

E. THERAPEUTIC USES
1. Prolactinoma
2. Hyperprolactinemia
3. Acromegaly
4. Parkinson disease

F. ADVERSE EFFECTS
- Nausea, vomiting
- Orthostatic hypotension
- Psychiatric symptoms (hallucinations, confusion)
- Vasospasm (peripheral ischemia)

HYPOTHALAMUS–PITUITARY–GONAD AXIS



QUICK COMPARISON

Feature	Gonadotropins	GnRH Agonists	GnRH Antagonists	Dopamine Agonists
Main action	Directly stimulate gonads	Pulsatile → stimulate Continuous → suppress	Directly block GnRH receptors → suppress	↓ Prolactin
Onset	After several days	Agonist flare then suppression	Immediate	Several days
Used for	Ovulation induction, Male infertility	Endometriosis, Fibroids, Precocious puberty, IVF, Infertility	IVF (prevent LH surge), Prostate cancer	Hyperprolactinemia, Prolactinoma, Acromegaly, Parkinson disease
Key adverse effect	OHSS, Multiple pregnancy	Menopause symptoms, Bone loss	Nausea, Headache	Nausea, Orthostatic hypotension

ORAL CONTRACEPTIVES

1. HORMONAL CONTRACEPTION

A. Combination (Estrogen + Progestin)

- **Monophasic** — Constant dosage of both components during the cycle.
- **Biphasic** — Dosage of one or both components is changed once during the cycle.
- **Triphasic** — Dosage of one or both components is changed twice during the cycle.
- **4-Phasic** — More than two changes in dosage during the cycle.

B. Progestin Alone (Without Estrogen)

Oral tablets, injectable, implantable under the skin.

2. COMPONENTS

Estrogens

- Ethinyl estradiol
- Mestranol

Progestins

- Levonorgestrel
- Drospirenone
- Norethindrone
- Norgestimate
- Ethynodiol diacetate

3. MECHANISM OF ACTION

1. Inhibition of ovulation by inhibiting pituitary function
   - Hypothalamus
   - Pituitary
   - ↓ FSH, ↓ LH
2. Thick cervical mucus
3. Endometrial changes (unsuitable for implantation)
4. Decreased motility and secretions of uterine tubes

→ Decreases the likelihood of fertilization and implantation

4. PHARMACOLOGIC EFFECTS

1. Ovary	• Depression of ovarian function • Ovaries get smaller • Reversible
2. Uterus & Cervix	• Cervical hypertrophy, polyp formation • Cervical mucus thick & less copious • Endometrial changes
3. Breast	• Enlargement • Suppression of lactation • Small amounts cross to breast milk
4. CNS	• Low changes in mood, affect, behavior • Estrogens: useful in PMS, postpartum depression, climacteric depression • Progestins: central thermogenic action
5. Endocrine function	• ↑ Corticosteroid-binding globulin • ↑ Renin activity & aldosterone • ↑ Thyroxine-binding globulin • ↑ SHBG → ↓ free androgens
6. Blood	• Serious thromboembolism • ↑ Clotting factors VII, VIII, IX, X & ↓ Antithrombin III • ↑ Serum iron & TIBC • Possible folic acid deficiency anemia
7. Liver	• ↓ Serum haptoglobins • Cholestasis & cholelithiasis
8. Lipid metabolism	• ↑ Triglycerides, phospholipids, HDL • ↓ Size of LDL particles • Androgenic progestins & synthetic progestins ↓ HDL & blunt benefits
9. Carbohydrate metabolism	• ↓ Absorption of carbohydrate from GIT • ↑ Basal insulin & postprandial insulin • Potent progestins ↓ carbohydrate tolerance (reversible)
10. Cardiovascular system	• ↑ Blood pressure • ↑ Heart rate • Slight ↑ Cardiac output
11. Effects the skin	• ↑ Skin pigmentation (esp. dark complexions) • Androgenic progestins → ↑ sebum → acne • Sequential agents & estrogens alone often ↓ sebum & improve acne

5. THERAPEUTIC USES

1. Oral contraception

- Failure rate of pregnancy ~ 0.5–1 per 100 women-years
- Increased failure with:
  - – Missed doses
  - – Phenytoin
  - – Antibiotics

2. Endometriosis

6. ADVERSE EFFECTS

A. Mild

- Nausea
- Mastalgia
- Breakthrough bleeding
- Edema (↑ with estrogen)
- ↑ ESR (due to ↑ fibrinogen)
- Changes in serum proteins

B. Moderate

- Weight gain
- Acne, hirsutism
- Vaginal infections
- Headache, dizziness
- Amenorrhea

C. Severe / Serious (Contraindications)

- Venous thromboembolism
- Myocardial infarction
- Stroke
- Ischemic bowel disease
- Cholestatic jaundice
- Hepatic adenoma
- Depression

7. PROGESTIN-ONLY CONTRACEPTION

When used?

- When estrogen is contraindicated or not tolerated

A. DMPA (Depot Medroxyprogesterone Acetate) Injection

- Given every 3 months (IM)

Effects

- Irregular spotting
- Amenorrhea

Important

- May prevent ovulation for up to 18 months after last dose

B. Implantable Progestins

- Effective up to 6 years
- Irregular bleeding (common)
- Possible intracranial hypertension

Adverse effects

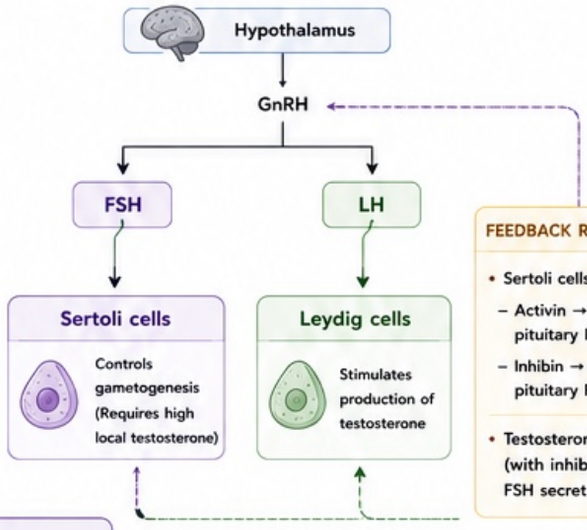
- Headache
- Dizziness
- Weight gain
- ↓ Glucose tolerance

8. SUMMARY – KEY POINTS

Topic	Key Points	High-Yield
Mechanism	Inhibit ovulation + thick mucus + endometrial changes + ↓ tubal motility	Prevents fertilization & implantation
Major Benefits	Highly effective contraception, treats endometriosis, acne (some), PMS symptoms	Failure rate: 0.5–1 per 100 women-years
Major Risks	Thromboembolism, ↑ BP, hepatic complications, lipid & glucose changes	Risk ↑ with estrogen dose, smoking, age > 35
Who should avoid CHCs?	Smokers > 35, thrombosis, CVD, stroke, liver disease, uncontrobled HTN, DM with vascular disease, migraine with aura	Absolute contraindications
Progestin-only options	DMPA (q3 months) – delayed return of fertility Implants – long acting (up to 6 years)	Use when estrogen is contraindicated

MALE HORMONES

HYPOTHALAMIC–PITUITARY–TESTICULAR AXIS



PHYSIOLOGIC EFFECTS

- Responsible for secondary sex characteristics and other changes that occur during puberty in males.

SECONDARY SEX CHARACTERISTICS:

- Deep voice
- Increased body & facial hair
- Increased muscle mass & strength
- Male pattern of fat distribution
- Growth of penis, scrotum & prostate
- Increased libido

FEEDBACK REGULATION

- Sertoli cells secrete:
  - Activin → stimulates pituitary FSH release
  - Inhibin → inhibits pituitary FSH release
- Testosterone & DHT (with inhibin) inhibit FSH secretion

MAJOR ANDROGENS

- Testosterone (major androgen)
- Dihydrotestosterone (DHT)
- Androstenedione
- Dehydroepiandrosterone (DHEA)
- Dehydroepiandrosterone sulfate (DHEAS)

DHEA & DHEAS are produced mainly in the adrenal gland.

- Contribute slightly to maturation
- Improve sense of well-being
- Inhibit atherosclerosis
- DHEA may benefit SLE (immunomodulatory effect; ↓ IL-6, ↑ IL-2)

TESTOSTERONE & DHT: KEY POINTS

65% of circulating testosterone is bound to SHBG, most of the rest bound to albumin (~2% free).

SHBG increased by: estrogen, thyroid hormone, liver cirrhosis

SHBG decreased by: androgens, growth hormone, obesity

- In target tissues: Testosterone → DHT by 5α-reductase (5α-reductase) → **DHT** (Major active androgen)
- Both testosterone & DHT responsible for changes in puberty.
- Testosterone is metabolized by reduction → metabolites excreted in urine as conjugates.

METABOLIC EFFECTS OF ANDROGENS

1. Reduction of sex hormone-binding proteins (SHBG) ↓
2. ↑ Liver synthesis of clotting factors, triglyceride lipase, α1-antitrypsin, haptoglobin, and sialic acid ↑
3. ↑ Renal erythropoietin secretion ↑
4. ↓ HDL levels ↓

SYNTHETIC ANDROGENIC & ANABOLIC STEROIDS

- Testosterone has low oral bioavailability (~15%) → given parenterally.
- 17-alkylated derivatives (e.g., methyltestosterone, fluoxymesterone) are active orally.

Examples:
Oxymetholone | Oxandrolone | Nandrolone decanoate

ACTIONS OF ANABOLIC STEROIDS

1. ↑ Muscle mass & strength; ↑ training intensity
2. Growth & mineralization of bone
3. Improved competitive performance due to increased strength & aggressiveness (seen only in women)

MISUSE IN SPORTS

- Usually used at 10–200 times larger than normal production.
- The adverse effects of these drugs make their use inadvisable.

MISUSE BY
Athletes & body builders

LONG-TERM ADVERSE EFFECTS OF MISUSE

1. Cardiovascular complications
2. Liver disease
3. Reproductive organ toxicity
4. Severe mood swings
5. Aggressiveness

THERAPEUTIC USES

1. Androgen replacement therapy in hypogonadal men. Can be used orally, sublingually, IM, TD, and topical gel.
   - In the presence of pituitary deficiency, androgens are used rather than gonadotropins except when normal spermatogenesis is to be achieved.
2. In conjunction with dietary measures & exercise to reverse protein loss after trauma, surgery, prolonged immobilization and in patients with debilitating diseases.
3. Refractory anemias such as aplastic anemia and others. Recombinant erythropoietin has largely replaced androgens for this purpose.

ADVERSE EFFECTS (THERAPEUTIC DOSES)

1. Masculinizing actions in women: hirsutism, acne, amenorrhea, clitoral enlargement, deepening of voice.
2. Some exert progestational activity → withdrawal endometrial bleeding.
3. May increase susceptibility to atherosclerosis in women.
4. Sodium retention & edema are not common.
5. Masculinization (female fetus) or undermasculinization (male fetus) of external genitalia if given during pregnancy.
6. Administration in early life may affect maturation of CNS centers governing sexual development, especially in females.
7. Hepatic dysfunction (17-alkyl-substituted steroids): cholestatic jaundice, hepatomas and carcinomas.
8. Prostatic hyperplasia.
9. ↑ LDL and ↓ HDL.
10. Acne, sleep apnea, erythrocytosis, gynecomastia, azoospermia & ↓ testicular size. May take months to recover after stopping.
11. Psychologic dependence, increased aggressiveness & psychosis.
12. Hepatocellular carcinoma.

ANTIANDROGENS

	Drug (Class)	Mechanism	Uses	Adverse Effects
1	Finasteride (5α-reductase inhibitors)	Inhibits 5α-reductase → ↓ conversion of testosterone to DHT	• BPH • Male pattern baldness • Hirsutism in women	↓ Libido, erectile dysfunction
	Dutasteride (5α-reductase inhibitors)	Inhibits type I & II 5α-reductase (longer half-life than finasteride)	• BPH	Similar to finasteride
2	Flutamide (Nonsteroidal antiandrogen)	Androgen receptor antagonist	Prostate cancer	Gynecomastia, hepatotoxicity
3	Bicalutamide Enzalutamide (Antiandrogens)	Androgen receptor blockers	Metastatic prostate cancer	Fatigue, hot flashes, diarrhea
4	Spironolactone (Aldosterone antagonist)	Blocks androgen receptors & ↓ testosterone synthesis	Hirsutism in women	Hyperkalemia, menstrual irregularities

KEY TAKE-HOME MESSAGES

- ✓ FSH → Sertoli cells → spermatogenesis
- ✓ LH → Leydig cells → testosterone
- ✓ DHT is the more potent androgen in peripheral tissues
- ✓ Androgens ↑ protein synthesis, EPO, clotting factors, but ↓ HDL
- ✓ Anabolic steroids have important medical uses but significant risks
- ✓ Antiandrogens are crucial in BPH, prostate cancer & hirsutism

IMPORTANT NOTE

Anabolic steroid abuse can cause serious, irreversible health problems. Their use without medical supervision is dangerous and unethical.

ABBREVIATIONS

FSH: Follicle Stimulating Hormone
LH: Luteinizing Hormone
SHBG: Sex Hormone Binding Globulin
DHT: Dihydrotestosterone
BPH: Benign Prostatic Hyperplasia
SLE: Systemic Lupus Erythematosus

DRUGS USED IN NEOPLASMS OF THE UROGENITAL SYSTEM

OVERVIEW – COMMON DRUGS BY CANCER TYPE

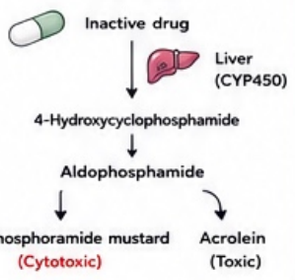
CANCER TYPE	MAIN DRUGS USED
Breast cancer	Cyclophosphamide, Methotrexate, Doxorubicin, Paclitaxel, Bevacizumab, Trastuzumab
Prostate cancer	Antiandrogens (e.g., Flutamide, Bicalutamide), Mitoxantrone
Ovarian cancer	Cisplatin, Carboplatin, Paclitaxel, Topotecan
Testicular cancer	Cisplatin, Etoposide, Bleomycin

GENERAL PRINCIPLES IN CANCER THERAPY

- ✓ Many anticancer drugs are cell-cycle nonspecific (except bleomycin: G_2 phase specific).
- ✓ They target rapidly dividing cells → cancer cells but also affect normal rapidly dividing tissues (bone marrow, GIT, hair follicles, gonads).
- ✓ Toxicity is dose-related and cumulative.
- ✓ Combination therapy improves efficacy and reduces resistance.
- ✓ Adequate hydration and supportive care are essential.

1 CYCLOPHOSPHAMIDE
(Alkylating agent)

MECHANISM



USES
- Breast cancer
- Ovarian cancer
- Wilm's tumor
- Others

TOXICITY (Dose-related)
1. Nausea, vomiting
2. Vesicant → tissue damage at injection site
3. Hemorrhagic cystitis (prevent with hydration, MESNA)
4. Secondary malignancies (e.g., AML)
5. Bone marrow depression → leukopenia, thrombocytopenia, bleeding
6. Alopecia

2 METHOTREXATE (MTX)
(Antimetabolite)

MECHANISM
Folic acid analog → inhibits Dihydrofolate reductase (DHFR)
↓
↓ THF (Tetrahydrofolate)
↓
↓ Synthesis of thymidylate, purines, serine, methionine
↓
↓ DNA & RNA synthesis

LEUCOVORIN (FOLINIC ACID)
Bypasses DHFR block → rescues normal cells from toxicity & used in overdose.

USES
- Breast cancer
- Bladder cancer
- Choriocarcinoma
- Others

TOXICITY
1. Mucositis (GIT), diarrhea
2. Hepatotoxicity
3. Myelosuppression (neutropenia, thrombocytopenia)
4. Neurotoxicity & cognitive impairment
5. Immunoallergic pneumonia → pulmonary fibrosis
6. Chemical pneumonitis
7. Renal dysfunction

3 DOXORUBICIN
(Anthracycline)

MECHANISM
1. Inhibits topoisomerase II
2. Intercalates into DNA
3. Generates free radicals (iron-dependent)

↓
DNA damage & cardiotoxicity

- Given IV
- Extensive liver metabolism
- ~50% excreted in bile → reduce dose in hepatic dysfunction

USES
1. Breast cancer
2. Endometrial cancer
3. Ovarian cancer
4. Testicular cancer
5. Bladder cancer
6. Others

TOXICITY
- Dose-limiting: cardiotoxicity (dose-dependent, cumulative)
- Myelosuppression, N/V, alopecia, mucositis, extravasation injury

4 PACLITAXEL
(Taxane)

MECHANISM
Stabilizes microtubules
↓
Prevents depolymerization
↓
Inhibits mitotic spindle function
↓
Cell cycle arrest in M phase → apoptosis

- Metabolized by CYPs (liver)
- Excreted mostly in feces (≈80%)
- Reduce dose in hepatic dysfunction

USES
1. Ovarian cancer
2. Advanced breast cancer
3. Prostate cancer
4. Bladder cancer
5. Others

TOXICITY
- Dose-limiting: neutropenia, peripheral neuropathy
- N/V, hypotension, arrhythmias
- Hypersensitivity (~5%) → give premedication: dexamethasone + diphenhydramine (H1 blocker) + H2 blocker

5 BEVACIZUMAB
(Anti-VEGF antibody)

MECHANISM
Binds VEGF → prevents binding to VEGF receptors
↓
Inhibits angiogenesis
↓
Inhibits tumor growth & metastasis

USES
- Metastatic colorectal cancer
- Non-small cell lung cancer
- Renal cell carcinoma
- Ovarian cancer, Glioblastoma
- Others

TOXICITY
- Hypertension
- Thromboembolism
- Impaired wound healing
- GI perforation, bleeding
- Proteinuria

6 TRASTUZUMAB
(Anti-HER2 antibody)

MECHANISM
Binds HER2 receptor
↓
Blocks signaling
↓
ADCC (immune-mediated cell killing)

USES
- HER2-positive breast cancer (adjuvant & metastatic)

TOXICITY
- Cardiotoxicity (↓ LVEF, heart failure)
- Infusion reactions
- Fever, chills

7 CISPLATIN
(Platinum compound)

MECHANISM
Forms DNA cross-links
↓
Inhibits DNA replication & transcription
↓
Cell death

- Given IV
- Renal elimination
- Ensure good hydration & diuresis

USES
- Testicular cancer
- Ovarian cancer
- Bladder cancer
- Others

TOXICITY
- Nephrotoxicity
- Ototoxicity (hearing loss)
- Peripheral neuropathy
- N/V (highly emetogenic)
- Myelosuppression

8 TOPOTECAN
(Topoisomerase I inhibitor)

MECHANISM
Inhibits topoisomerase I
↓
Prevents DNA re-ligation
↓
DNA damage → cell death

USES
- Advanced ovarian cancer
- Small cell lung cancer

TOXICITY
- Myelosuppression (neutropenia)
- N/V, diarrhea
- Fatigue

9 ETOPOSIDE
(Topoisomerase II inhibitor)

MECHANISM
Inhibits topoisomerase II
↓
DNA strand breaks
↓
Inhibits DNA replication & cell division

USES
- Testicular cancer
- Small cell lung cancer
- Lymphomas, Leukemias

TOXICITY
- Myelosuppression
- Alopecia
- N/V
- Hypotension (with rapid IV infusion)

10 BLEOMYCIN
(Glycopeptide antibiotic)

MECHANISM
Generates free radicals
↓
Causes DNA strand breaks
↓
Cell death (G_2 phase specific)

USES
- Testicular cancer
- Hodgkin lymphoma
- Head & neck cancers
- Others

TOXICITY
- Pulmonary fibrosis (most serious)

Risk factors: Age >70, high cumulative dose, lung disease, chest radiation

POTENTIALLY OVERLAPPING TOXICITIES

Myelosuppression	Cyclophosphamide, Methotrexate, Doxorubicin, Paclitaxel, Topotecan, Etoposide, Cisplatin
Nephrotoxicity	Cisplatin (>> Carboplatin)
Cardiotoxicity	Doxorubicin, Trastuzumab
Neurotoxicity	Paclitaxel, Cisplatin, Ixabepilone
Pulmonary toxicity	Bleomycin, Methotrexate
Hepatotoxicity	Methotrexate, Doxorubicin
Hypersensitivity	Paclitaxel, Ixabepilone

CHEMO MEMORY TRICKS

- "CYCLOPHOSPHAMIDE → CYSTITIS"
- "MTX → Blocks FOLATE → Give Leucovorin to RESCUE"
- "DOXORUBICIN & TRASTUZUMAB → Heart problem!"
- "CISPLATIN → Kidney & Ear"
- "BLEOMYCIN → Lungs (fibrosis)"

KEY TAKE-HOME POINTS

- ☑ Understand the mechanism → predicts the major toxicity.
- ☑ Supportive care (hydration, antiemetics, growth factors) improves outcomes.
- ☑ Dose adjustment is essential in renal/hepatic dysfunction.
- ☑ Combination therapy improves efficacy but increases toxicity.
- ☑ Monitor patients carefully for early detection of adverse effects.