Pharma. UGS

Pharma1

Introduction to Diuretics

- Diuretics are drugs that increase urine volume by promoting the excretion of water and electrolytes from the body, primarily through their action on various segments of the renal tubule.

➢ **Renal Tubule Transport Mechanisms**

- The **nephron** is divided into **segments**: proximal convoluted tubule (PCT), loop of Henle, distal convoluted tubule (DCT), and collecting duct.
- Each segment has specialized transporters for sodium, potassium, chloride, and other ions, which are targeted by different classes of diuretics.

1. Carbonic Anhydrase Inhibitors (CAIs)

- *Examples*: **Acetazolamide**, **Dichlorphenamide**, **Methazolamide**

- *Mechanism*: Inhibit **carbonic anhydrase** in the **PCT**(proximal convulated tubules), reducing sodium bicarbonate reabsorption (up to **85%** inhibition).

- *Pharmacological Actions:* Cause alkaline diuresis وزيادة حموضة الدم, **reduce** formation of aqueous humor (lowering intraocular pressure), **decrease** cerebrospinal fluid production مفيد لارتفاع ضعف الدماغ ICP, and **induce** metabolic acidosis (raising seizure threshold).

- *Adverse Effects:* Hyperchloremic metabolic acidosis, calcium phosphate renal **stones**, renal potassium loss, hypersensitivity reactions, and hyperammonemia (risk of ١hepatic ٢encephalopathy in **cirrhosis**).

- *Therapeutic Uses*: **Rarely as diuretics**; mainly for glaucoma لتقليل ضغط العين (common), urinary alkalinization ك حالات التسمم, metabolic alkalosis اختلال في حموضة الدم لارتفاع البيكربونات, acute mountain sickness(AMS), and as adjuncts in epilepsy.

✓ AMS—> داء المرتفعات الحاد، عندما يكون الصعود لارتفاع عالي بشكل سريع،ما يُعيق تأقلم الجسمَ،انخفاض الأكسجين واعراض الدوخة،الغثيان،التقيؤ،غيبوبة...

2. Loop Diuretics "الأقوى" غالبا لحالات احتباس السوائل المرتبطة بمرضى الكلى والقلب

- Examples: Furosemide, Bumetanide, Torsemide (sulfonamides); Ethacrynic acid (phenoxyacetic acid)-> ليس من مشتقات السلفوناميد! مناسب للي عندهم حساسية منها ك بديل

- Mechanism: **Inhibit Na+/K+/2Cl–** co-transporterفيمنع إعادة امتصاصها in the thick ascending limb of Henle, abolishing the lumen-positive potential and increasing **ex**cretion ↑ of **Na+, K+, Cl–, Mg2+**, and **Ca2+.**

- Pharmacological Actions: Most efficacious diuretics; increase renal **prostaglandin** synthesis ↑ (blocked by NSAIDs); reduce pulmonary congestion and left ventricular filling pressure; some also inhibit carbonic anhydrase.

- Pharmacokinetics: Rapid absorption, high protein binding, eliminated by secretion and filtration; some are metabolized.

- Adverse Effects: Hypokalemic metabolic alkalosis, ototoxicity (hearing loss أو خاصة جرعات عالية أو عن بالوريد), hypomagnesemia, hyperuricemia (**gout** riskالنقرس), allergic reactions خاصه مع أدويه السلفا, dehydration, hyponatremia, possible hypocalcemia, hyperglycemia.

- Therapeutic Uses: Acute pulmonary edema, heart failure, hypercalcemia, hyperkalemia, acute renal failure, forced diuresis for toxin elimination.

3. Thiazide Diuretics

•Examples: Hydrochlorothiazide, Chlorthiazide, Chlorthalidone, Indapamide, Metolazone-> في حالات الفشل الكلوي هو الأنسب لأنه لا يُخرج كليا عن طريق الكلى

✓ All have unsubstituted sulfonamide group.

- Mechanism: Inhibit NaCl reabsorption in the **DCT**(distal convoluted tubules)via the Na+/Cl− co-transporter; enhance Ca2+ reabsorption.

- Pharmacological Actions: Cause volume depletion, significant carbonic anhydrase inhibition, and depend partially on prostaglandin synthesis.

- Pharmacokinetics: Oral use; differences in metabolism and excretion (some via biliary system); compete with uric acid for secretion.

- Adverse Effects: Hypokalemic metabolic alkalosis, hyperuricemia(النقرس), hyperglycemia, hyperlipidemia, weakness, impotence, hyponatremia, allergic reactions, photosensitivity حساسية ضد الضوء.

- Therapeutic Uses: Hypertension, edema (heart failure, hepatic/renal insufficiency), nephrolithiasis تكون الحصى خاصه عند ارتفاع الكالسيوم بالبول (due to hypercalciuria), nephrogenic diabetes insipidus.

4. Potassium-Sparing Diuretics المحافظ على البوتاسيوم

❖ **Aldosterone Antagonists:** Spironolactone, Eplerenone

- Mechanism: Block aldosterone receptors(التي توسع الأوعية)in the **collecting tubule**, reducing sodium reabsorption and potassium excretion.

- Adverse Effects: Hyperkalemia, metabolic acidosis, **gynecomastia** تضخم حجم الثدي لدى الذكور (*not with eplerenone*), GI upset.

- Therapeutic Uses: Mineralocorticoid excess-لما يزيد الالدوستيرون, adjunct to other diuretics to prevent hypokalemia.

❖ **Sodium Channel Blockers:** Amiloride, Triamterene

- Mechanism: Block epithelial sodium channels (ENaC) in the collecting tubule, sparing potassium.
- Adverse Effects: Hyperkalemia ارتفاع البوتاسيوم بالدم, nausea, metabolic acidosis, leg cramps تقلصات عضلية (triamterene خاصه مع), nephrolithiasis, interstitial nephritis.

- Therapeutic Uses: Same as above; also for hypokalemia.

5. Osmotic Diuretics

- Examples: Mannitol, Urea, Glycerin, Isosorbide
- Mechanism: Filtered but not reabsorbed; act in **PCT** and **descending limb of Henle,** increasing urine volume by attracting water into the lumen; oppose ADH in the collecting tubule.

- Pharmacokinetics: **Not** orally absorbed, not metabolized, excreted via glomerular filtration.
- Adverse Effects: Extracellular volume expansion, hyponatremia, pulmonary edema, headache, dehydration, hypernatremia, hyperkalemia.

- Therapeutic Uses: Prevent acute renal failure, reduce intracranial and intraocular pressure, increase water excretion when sodium retention limits response to other diuretics.

  - The nonreabsorbable osmotic diuretic prevents the normal absorption of water, thus reducing Na + as well as water reabsorption.
  - The resulting natriuresis is of lesser magnitude than the water diuresis, leading eventually to excessive water loss and hypernatremia.

6. Antidiuretic Hormone (ADH) Antagonists

- Examples: 1Conivaptan (nonpeptide), 2Nonselective agents: demeclocycline"tetracycline", lithium (**not** commonly used)

- Mechanism: Block ADH receptors in the collecting tubule, reducing cAMP formation and water reabsorption.

- Pharmacokinetics: Conivaptan used **IV**, with a half-life of 5–10 hours.
- Adverse Effects: Nephrogenic diabetes insipidus, severe hypernatremia, dry mouth, thirst, hypotension.

- Therapeutic Uses: Syndrome of Inappropriate ADH Secretion (**SIADH**) and other causes of elevated ADH.

Summary ❗

Class	Main Site of Action	Key Examples	Main Adverse Effects	Main Uses
Carbonic Anhydrase Inhibitors	Proximal tubule	Acetazolamide	Metabolic acidosis, renal stones	Glaucoma, alkalinization, mountain sickness
Loop Diuretics	Thick ascending limb	Furosemide, Bumetanide	Hypokalemia, ototoxicity, dehydration	Edema, heart failure, hypercalcemia
Thiazide Diuretics	Distal convoluted tubule	Hydrochlorothiazide, Chlorthalidone	Hypokalemia, hyperuricemia, hyponatremia	Hypertension, nephrolithiasis
Potassium-Sparing Diuretics	Collecting tubule	Spironolactone, Amiloride	Hyperkalemia, gynecomastia (spironolactone)	Mineralocorticoid excess, adjunct
Osmotic Diuretics	PCT, loop of Henle	Mannitol	Volume expansion, hyponatremia	Intracranial/intraocular pressure
ADH Antagonists	Collecting duct	Conivaptan, demeclocycline	Hypernatremia, nephrogenic DI	SIADH

Pharma2 *Fungal Infections*

Superficial Infections:

- Dermatomycosis (caused by Trichophyton, Microsporum, Epidermophyton; affects skin, nails, hair)
- Candidiasis (affects skin, mucous membranes)

Systemic Infections:

- Affect deeper tissues/organs
- Incidence/severity increased *due to* broad-spectrum antibiotics, immunosuppression (AIDS, drugs, chemotherapy), aging, diabetes, and advanced surgery.

➢ Amphotericin B

General Properties

- Polyene macrolide antibiotic, broad-spectrum **fungicidal** agent.
- Binds **ergosterol** in fungal membranes, forming pores or transmembrane ion channels by the hydrophilic core of the molecule. → cell death.

✓ Binding is relatively specific to fungi and the protozoan parasite Leishmania spp.

Resistance

- Caused by modifications to sterol target, reducing drug affinity.

Pharmacokinetics

- Poor oral absorption; used orally for GI infections, **IV** for systemic use (complexed with **deoxycholate**لتحسين الذائبية).
- **Liposomal formulations** reduce toxicity, allow higher dosing.آمنة
- Highly protein-bound 90%, poor BBB penetration unless meninges inflamed❗; long half-life (~15 days يعتبر طويل جدا).

Adverse Effects

Infusion-related(IV): Fever, chills, muscle spasm, vomiting, headache, hypotension (mitigated by slow infusionقبله هيستامين مضاد أو ببطء بإعطاؤه الأعراض نخفف).

Cumulative toxicity:

- Nephrotoxicity "common 80%" (reversible prerenal failure, irreversible tubular damage❗ with prolonged use على المدى الطويل, electrolyte wasting, elevated urea/creatinineبالدم).
- Anemia (↓ **erythropoietin**), hepatic dysfunction, thrombocytopeniaقلة الصفائح, anaphylaxisفرط التحسس, seizures, chemical arachnoiditis (intrathecal useعند إعطاؤه بالسائل الشوكيّ).

Antifungal Activity ->

- Broad spectrum: yeasts (Candida, Cryptococcus), endemic mycoses (Histoplasma, Blastomyces, Coccidioides), molds (Aspergillus, Mucor).

➢ **Nystatin**

- Similar to amphotericin B->polyene, but **more toxic**لذلك يستخدم موضعياً.
- Used **topically** for skin/mucous membrane infections (creams, ointments, suppositories).

➢ **Flucytosine**

- **Pyrimidine analog**, oral/IV use, narrow spectrum (yeasts:candida,cryptococcus).
- Synergistic with amphotericin B for cryptococcal meningitis.

Mechanism

•Taken up by fungal **cytosine permease**, converted to **5-fluorouracil**سامة للفطر then to 5-FdUMP and FUTP in fungal cells, → inhibits DNA/RNA synthesis respectively .

•Resistance develops rapidly with monotherapyإذا استخدم لوحده،لذلك غالبا ما يترافق مع أدوية اخرى.

Pharmacokinetics

•Well absorbed orally>90%, distributes widely (including CNSلالتهاب السحايا), 90%excreted unchanged by kidneys, short half-life (3–4 hours).

Adverse Effects

- Narrow therapeutic window: toxicity at high levels, resistance at low levels.
- Side Effects: GIT disturbances, bone marrow suppression (anemia, neutropenia ↓ WBCs, thrombocytopenia), alopecia تساقط الشعر.

➢ **Azole Antifungals**

Classification

- **Imidazoles:** Ketoconazole, Miconazole, Clotrimazoleموضعيه غالبا
- **Triazoles:** Itraconazole, Fluconazole, Voriconazole فموي وريدي

Spectrum

•Broad: Candida, Cryptococcus(**yeasts**),**endemic mycoses**, **dermatophytes**.

->**Itraconazole/voriconazole** cover Aspergillus, Pseudallescheria هذه الفطريات لا تستجيب لأي دواء عادةً

Mechanism

- Inhibit **fungal cytochrome P450** (ergosterol synthesis), altering membrane fluidity and inhibiting growth.
- **Imidazoles** also inhibit human P450 (more drug interactions/adverse effects).

Fluconazole

- High oral/IV bioavailability, penetrates CSF/ocular fluid.
- Drug of choice for fungal meningitis (cryptococcalالتهاب السحايا الفطريّ, coccidioidal), candidemia, mucocutaneous candidiasis.
- **No** activity against Aspergillus/filamentous fungi.
- Prophylactic use in immunosuppressed (risk of resistanceلكن يزيد خير المقاومة).

- Excreted unchanged in urine.

•Adverse Effects: Nausea, headache, abdominal pain, Exfoliative skin lesions (Steven-Johnson syndrome) have been seen in AIDS patients، hepatitis; fewer drug interactions than ketoconazole.

Itraconazole

- Extensive first-pass metabolism يقلل تركيزه بالدم; absorption increased by food/low pH.
- IV/ lipid-soluble forms available; reduced bioavailability with rifamycins.

الريفاميسينات تُحفز إنزيمات الكبد التي تُسرّع استقلاب itraconazole، هذا يؤدي إلى تقليل تركيز الدواء في الدم، مما يُضعف فعاليته

- **Does not cross BBB.**
- Uses: **Di**morphic fungi (Histoplasma, Blastomyces, Sporothrix), dermatophytosis, onychomycosis, aspergillosis..يستهدف الرئة وينتشر (now replaced by **voriconazole**).

•Adverse Effects: GIT, headache, hepatitis, hypokalemia, Interacts with P450s (but less than ketoconazole): Impotence, and sexual dysfunction، allergic reactions.

Voriconazole

- Broad spectrum, oral/IV, well absorbed, hepatic metabolism, low P450 inhibition.

•Adverse Effects: Transient **v**isual disturbances,common (30% of patients, resolve in 30 min).

- Uses: Candida, fluconazole-resistant fungi, dimorphic fungi, invasive aspergillosis هو الخيارالأول (as or more effective than amphotericin B).

Topical Azoles

- Clotrimazole, Miconazole, Econazole: Vulvovaginal candidiasis, oral thrush, dermatophyte infections (creams for tineaجلدية), ketoconazole for seborrheic dermatitisللشعر/pityriasis طفح.

➢ **Terbinafine**

- Synthetic **allylamine**, oral/topical, accumulates in skin/nails/adipose. فهو فعال بالفطريات بهذه الأماكن
- Inhibits **squalene epoxidase** (ergosterol synthesisيصنعه), causing toxic squalene accumulation. نقص الارجوستيرول بالخلية الفطرية يؤدي لتراكم مادة سكوالين السامة وموتها
- Uses: Onychomycosis بالأظافر, tinea cruris/corporis (naftifine similarله دواء مشابه, topical only).
- Adverse Effects: GIT, rash, headache, joint/muscle pain, hepatitisنادرا.

➢ **Echinocandins**

•**Newest** class: **Caspofungin**, **Micafungin**, **Anidulafungin**.

•Large cyclic peptides, **IV only(**slow**),** water soluble, protein bound, require loading doses لتسريع فعاليه الدواء بوقت أقصر.

✓ t½ : caspofungin ~ 10 hours, micafungin ~ 13 hours, anidulafungin ~ 36 hours.

•Mechanism: Inhibit **β(1,3)-glucan** synthesis (cell wallمهم لجدار الفطر), causing lysis/death.

•Uses: Candidiasis (mucocutaneous, septicemia), esophageal candidiasis, empiric therapy in (febrileحرارة neutropenia), salvage for invasive aspergillosis عندما تفشل الأدوية الأخرى.

•Adverse Effects: Generally well tolerated; GIT irritation, liver enzyme elevation (esp. with cyclosporine بعد زراعه عضو او لأمراض مناعية), drug interactions (micafungin), histamine release (anidulafungin)حكة وطفح موقت, fever, headache, phlebitisالتهاب الوريد مكان الحق/thrombophlebitis .

Drug/Class	Mechanism	Spectrum	Route(s)	Key Points / Adverse Effects
Amphotericin B	Binds ergosterol → pore formation	Broad: Candida, Cryptococcus, molds	IV, oral (GI only)	Nephrotoxicity, infusion reactions; liposomal form less toxic
Nystatin	Similar to Amphotericin B	Candida (superficial)	Topical, oral	Too toxic systemically; used topically
Flucytosine	Inhibits DNA/RNA synthesis	Yeasts (Candida, Cryptococcus)	Oral, IV	Bone marrow suppression, resistance with monotherapy
Azoles	Inhibit fungal cytochrome P450	Broad: Candida, Cryptococcus, molds	Oral, IV, topical	Drug interactions; hepatotoxicity; varies by agent
– Fluconazole	Good CNS penetration	Candida, Cryptococcus	Oral, IV	Used for cryptococcal meningitis; fewer interactions
– Itraconazole	Poor CNS penetration	Dimorphic fungi, dermatophytes	Oral, IV	Hepatitis, GI side effects
– Voriconazole	Broad, including Aspergillus	Candida, Aspergillus, molds	Oral, IV	Visual disturbances, hepatotoxicity
Terbinafine	Inhibits squalene epoxidase	Dermatophytes	Oral, topical	Used for onychomycosis; hepatotoxicity
Echinocandins	Inhibit β-(1,3)-D-glucan synthase	Candida, Aspergillus	IV only	Well tolerated; liver enzyme elevation, histamine reactions

Pharma3. "Drugs Used in Urinary Tract Infections"

Drugs used in UTIs include penicillins, 2nd and 3rd generation cephalosporins (e.g., cefuroxime, ceftriaxone), ampicillin + gentamicinحالات معقدة, ampicillin-sulbactam, and amoxicillin/clavulanateعند المقاومة.

➢ **Trimethoprim and Co-trimoxazole** (**Trimethoprim - Sulfamethoxazole**)

•Mechanism of Action: Trimethoprim inhibits bacterial dihydrofolate reductase, blocking folic acid synthesis required for DNA production. When combined with sulfamethoxazole, it blocks sequential steps in folate synthesis, resulting in a bactericidal effect.

•*Resistance Mechanisms:* Reduced cell permeability, overproduction of the target enzyme, and altered enzyme with low drug bindingمهم عمليا.

•*Pharmacokinetics*: Well absorbed orally, can be given **IV** with sulfamethoxazole, widely distributed, excreted in urine, dose reduction needed in renal failure, concentrates in prostatic and vaginal fluids.لذا يعالج التهاب بهذه المناطق

•*Therapeutic Uses:* Acute UTI (oral, alone or in combination), prostatitis, salmonellosis, shigellosis, Pneumocystis jiroveci infections(most common in AIDS patients)-(**IV**).

•*Adverse Effects:* Megaloblastic anemia, leukopenia ↓, granulocytopenia ↓, sulfonamide-related side effects كالطفح الجلدي،حساسية, high frequency of adverse reactions in AIDS

patients, **hyper**kalemia, and hyponatremia (by blocking amiloride-sensitive sodium channels in the cortical collecting duct)

- **Fluoroquinolones**

•Mechanism of Action: Inhibit bacterial DNA synthesis by blocking DNA gyrase (١topoisomerase II) and ٢topoisomerase IV, preventing DNA replication and cell divisionقتل للبكتيريا.

•Resistance Mechanisms: Point mutations in target enzymes or altered cell permeability يمنع وصول الدواء للبكتيريا.

✓ (Point Mutations): هي تغيّرات صغيرة جدًا في الشيفرة الوراثية (DNA) للبكتيريا. تحديدًا، يُستبدل حرف واحد فقط (نيوكليوتيد واحد) في سلسلة الـDNA بآخر، فتُنتج إنزيمًا معدلًا في تركيبه،هذا التغيير يجعل الإنزيم لا يرتبط جيدًا بالدواء

Antibacterial Spectrum:

•Norfloxacin: Least active.

•Ciprofloxacin, levofloxacin, ofloxacin: Excellent gram-negative coverage (Enterobacteriaceae, Pseudomonas, Neisseria, Haemophilus, Campylobacter), moderate gram-positive, some activity against staphylococci (not MRSA), less active against streptococci and enterococci.

•Gemifloxacin, moxifloxacin: Improved gram-positive activity, moxifloxacin also covers anaerobes.

•*Pharmacokinetics*: Well absorbed orally, impaired by divalent cations and dairy الامتصاص يقل مع منتجات الألبان والمعادن الثنائية كلكالسيوم والمغنيسيوم, widely distributed, mostly renal elimination (except moxifloxacin), dose reduction in renal failure except for moxifloxacin.

Therapeutic Uses:

•UTI (except moxifloxacin) by multidrug-resistant gram-negatives.

•Bacterial diarrhea, soft tissue, bone/joint, intra-abdominal, respiratory infections (except norfloxacin), anthrax prophylaxis/treatment, gonococcal infections, tuberculosis (second-line), meningococcal eradication, neutropenic prophylaxisالوقاية عند نقص المناعه, upper/lower respiratory tract infections.

•*Adverse Effects:* Nausea, vomiting, diarrhea, headache, dizziness, insomnia, rash, liver enzyme elevation ↑, photosensitivity, QTc prolongationخطورة عالقلب, hyperglycemia (especially gatifloxacin), cartilage damage (contraindicated in <18 years), tendonitis/rupture, contraindicated in pregnancy.

- **Nitrofurantoin**

•Mechanism of Action: Prodrug(يُفعّل داخل الجسم تحديدا داخل البكتيريا)activated to metabolites that damage bacterial DNA; bacteriostatic.

- *Spectrum*: Active against E. coli and enterococci(Gram-positive bacteria) ; not effective against Pseudomonas, Proteus, Enterobacter, Klebsiella—> (These are more resistant Gram-negative pathogens that often cause complicated UTIs.)

•*Clinical Use*: Only for lower UTIs; **not** for pyelonephritis or patients with impaired renal function or infants <1 month.

•Adverse Effects: Nausea, vomiting, diarrhea, hypersensitivity, acute pneumonitis التهاب رئوي حاد <—— قد يتحول إلى interstitial pulmonary fibrosis عند الاستخدام المزمن, hemolysis in G6PD deficiency, megaloblastic anemia, polyneuropathies, brown urine discoloration.

Key Clinical Considerations

•Trimethoprim-Sulfamethoxazole: First-line if local resistance <20%; avoid in sulfa allergy.

•Nitrofurantoin: Preferred for uncomplicated lower UTIs, contraindicated in renal failure and for upper UTI.

•Fluoroquinolones: Reserved for complicated or resistant infections due to safety concerns and resistance; avoid in pregnancy and children.

✓ General: Dose adjustments required in renal impairment for most agents.لتفادي السّمية

Drug/Class	Mechanism	Spectrum	Key Uses	Major Adverse Effects	Contraindications
Trimethoprim/SMX	Folate synthesis block	Broad (esp. E. coli)	UTI, prostatitis	Hematologic, hypersensitivity, hyperkalemia	Sulfa allergy, renal failure
Fluoroquinolones	DNA gyrase/topoisomerase	Broad (esp. gram-negatives)	UTI, GI, RTI, etc.	GI, CNS, QTc, tendinopathy, cartilage damage	Pregnancy, children <18 y
Nitrofurantoin	DNA damage (prodrug)	E. coli, enterococci	Lower UTI	GI, pulmonary, hemolysis, neuropathy, brown urine	Renal failure, infants <1 mo

Pharma4

Metronidazole & Tinidazole (Nitroimidazoles)

Mechanism of Action

- Both drugs are activated in anaerobic bacteria and sensitive protozoa via reduction of their nitro group, producing reactive products responsible for antimicrobial activity.

Pharmacokinetics

- Rapid oral absorption and wide tissue distribution, including equal concentrations in plasma and intracellular compartments.
- Peak plasma levels in 1–3 hours.fast
- *Half-life:* Metronidazole (7.5 hrs), Tinidazole (12–14 hrs).
- Can be administered orally, rectally, topically, or intravenously.
- Mainly excreted in urine.
- Dose reduction required in hepatic impairment; adjustments may also be needed in renal impairment.

Therapeutic Uses

- Bacterial vaginosis (caused by anaerobic bacteria replacing normal lactobacilli)
- Trichomoniasis (sexually transmitted; both partners should be treated)
- Invasive amebiasis (kills trophozoites, not cysts)
- Giardiasis
- Anaerobic bacterial infections (e.g., Bacteroides fragilis, Clostridium spp.), intra-abdominal infections, antibiotic-associated enterocolitis, brain abscess

Adverse Effects

- Metallic/bitter taste, nausea, dry mouth, vomiting, diarrhea
- Mucous membrane irritation, dysuria, dark urine
- Rash, neutropenia ↓, pancreatitis
- Disulfiram دواء لعلاج ادمان الكحول-like reaction with alcohol (inhibits acetaldehyde dehydrogenase)

فعند شرب أي نوع من الكحول(بعض غسولات الفم والأدوية)يسبب تراكم لل acetaldehydeوتسبب هذه الأعراض

- CNS effects: dizziness, insomnia, neuropathy, seizures (especially with **IV**)
- Teratogenicتشوهات; avoid in pregnancy and lactation

✓ Dose adjustment needed in severe hepatic/renal disease

Drug Interactions

- Potentiates ↑ warfarin's anticoagulant effect خطر النزيف
- Elimination increased by phenobarbital/phenytoin, decreased by cimetidine
- May increase lithium toxicity due to decreased excretion

Clindamycin

Mechanism of Action

- Inhibits protein synthesis by binding to the 50S ribosomal subunit, interfering with initiation and translocation يعيق بداية تصنيع البروتين ونقله(similar to macrolides).

Mechanisms of Resistance

- Mutation in ribosomal receptor site تمنع الدواء يرتبط
- Methylase-mediated modification of the receptor تمنعه يرتبط
- Enzymatic inactivation تفرز البكتيريا إنزيمات تثبط الدواء
- Gram-positive aerobes are often resistant due to poor permeability
- Resistance can be acquired or constitutive دائمة موجودة بتركيب البكتيريا

Antibacterial Spectrum

- Effective against anaerobic bacteria (both Gram-positive and Gram-negative), including those causing bacterial vaginosis
- Many Gram-positive cocci (streptococci, staphylococci, pneumococci), but not first-line for Staphylococcus
- Not effective against enterococci, aerobic Gram-negatives, some Group B Streptococci, and some Bacteroides fragilis strains

Pharmacokinetics

- Widely distributed, including bone(osteomyelitis), placenta, breast milk, and abscesses (not brain/CSF) لذلك لا يستخد مثلا للالتهاب السحايا
- Concentrated in phagocytic cells-للالتهابات
- Highly protein-bound (~90%)
- Metabolized in liver, excreted in bile and urine
- Half-life: ~2.5 hrs (normal), ~6 hrs (anuria); **no** renal dose adjustment required but accumulates in severe liver dysfunction

Therapeutic Uses

- Female genital tract infections (bacterial vaginosis, septic abortion, pelvic abscess)
- Anaerobic infections
- Osteomyelitis (previously drug of choiceكان استخدامه شائع)
- Lung abscess
- Infections from fecal spillage (GI surgery, trauma)تسريب العدوى من الأمعاء للبطن
- Aspiration pneumonia (used with aminoglycosides/cephalosporins for mixed infections)

Adverse Effects

- GI irritation: nausea, vomiting, diarrhea
- Superinfection عدوى ثانوية: pseudomembranous colitis (Clostridium difficile), which can be severe/fatal

✓ عند استخدام Clindamycinلا يقتل فقط البكتيريا الضارة بل قد يقتل البكتيريا النافعة في الأمعاء،فيسمح لنوع خطير من البكتيريا Clostridium difficile بالتكاثرويُسبب التهاب القولون .

- Thrombophlebitisالتهاب بالأوردة, thrombocytopeniaنقص الصفائح, neutropenia, allergic reactions

Antiherpes Agents (Acyclovir)

General Information

- Used for herpes simplex virus (HSV-**1**(oral cold sores), HSV-**2**(genital herpes)) and varicella-zoster virus (VZV)

- Acyclovir is an acyclic guanosine derivative, ~**10x** more potent against **HSV** than **VZV**

Mechanism of Action

- Requires three phosphorylation steps: first by viral thymidine kinase, then by host cell enzymes
- Selectively activated in infected cells
- Acyclovir triphosphate الشكل النشط inhibits viral DNA synthesis **by**:

1. Competing with deoxy-GTP for viral DNA polymerase
2. Causing chain termination after incorporation into viral DNA

1. التنافس مع deoxy-GTP (وهو جزء طبيعي من الـDNA) للارتباط بإنزيم DNA polymerase الفيروسي.
2. إيقاف بناء الحمض النووي للفيروس بعد دمجه في سلسلة DNA، مما يؤدي إلى انقطاع السلسلة وعدم استكمال تكاثر الفيروس

✓ This selective activation means it only works in infected cells, reducing damage to healthy cells

Mechanism of Resistance

- Alterations in viral thymidine kinase or DNA polymerase

Pharmacokinetics

- Low oral bioavailability (15–20%), unaffected by food; available orally, IV, topically
- Cleared by glomerular filtration and tubular secretion
- Half-life: ~3 hrs (normal), ~20 hrs (anuria)

- Widely distributed in tissues/fluids

Therapeutic Uses

- Genital herpes (mainly HSV-2)
- Herpes labialis -lip(cold sores)
- Herpes zoster (shingles)
- Herpes encephalitis
- Neonatal herpes (from infected mothers)

Adverse Effects

- Nausea, diarrhea, headache (can be distressing and affect daily activities)
- IV administration may be associated with reversible crystalline nephropathy (drug precipitation in kidney tissues as crystals, leading to crystalluria) or interstitial nephritis (allergy in kidney); or neurologic toxicity (tremors, delirium, seizures). These are uncommon with adequate hydration and avoidance of rapid infusion rates.

✓ Very important.! So, in patients with low blood volume or dehydration, intravenous fluids should be administered before initiating acyclovir therapy. This preventive approach is also commonly applied with several chemotherapeutic agents, where adequate hydration is essential to minimize toxicities.

Drug Interactions:

Probenecid and cimetidine decrease acyclovir clearance and increase exposure, by inhibiting renal tubular secretion, which is one of the main pathways for acyclovir clearance. As a result, co-administration of these drugs can reduce acyclovir elimination and lead to its accumulation in the body.

Pharma5"The Gonadal Hormones & Inhibitors"

Estrogens

- *Types and Sources:*

The main estrogens in women are **estradiol** (the primary ovarian product), **estrone**, and **estriol**. Estrone and estriol are mainly formed from estradiol in the liver or from androgens in peripheral tissues.

- Synthetic Estrogens:

These include **steroidal** (ethinyl estradiol, mestranol) and **nonsteroidal** compounds, which are orally effective.

- *Pharmacokinetics*:

Estradiol binds to sex hormone-binding globulin (**SHBG**) and albumin in circulation. Estrogen metabolites are excreted in bile, reabsorbed in the gut, and present in small amounts in breast milk.

Therapeutic Uses:

- Primary hypogonadism: Replacement therapy in young girls to induce secondary sex characteristics, menses, growth, and prevent osteoporosis.

- Postmenopausal hormone therapy (HRT): Benefits lipids يحسن مستوى الدهون بالدم but increases breast cancer risk and does not reduce cardiovascular events. Routine HRT is **not** recommended except possibly in young women with premature menopause.

- Osteoporosis prevention: Estrogen with calcium may help, but increases endometrial carcinoma risk unless progestin is added.
- Other uses: Combined with progestins to suppress ovulation (dysmenorrhea عسر الطمث), ovarian function (hirsutism شعر زائد, amenorrhea انقطاع الطمث).

- Hirsutism—>Cause: Often due to excess androgens (male hormones) produced by the ovaries.
  ✔ Estrogens (with progestins) reduce ovarian androgen production.

How is the therapy given? Usually as combined oral contraceptives (COCs), which contain both estrogen and progestin.

- *Adverse Effects:*

- Uterine bleeding, breast/endometrial cancer, infertility, ectopic pregnancy, breast tenderness, hyperpigmentation(Estrogen stimulates melanocytes (pigment-producing cells) to make more melanin), migraine(severe headache), cholestasis(Estrogen may impair the liver's ability to excrete bile, which can cause:

Itching (pruritus), especially at night,Jaundice (yellowing of the skin and eyes), gallbladder disease, hypertension.

- *Contraindications*:
Estrogen-dependent tumors, undiagnosed vaginal bleeding, liver disease, thromboembolic جلطات disorders, heavy smokers٣٥ خاصه بعمر فوق.

Progestins

Types:

- Natural: Progesterone
- Derivatives: Hydroxyprogesterone caproate, medroxyprogesterone acetate, megestrol acetate
- Synthetic: 17-ethinyl testosterone derivatives (dimethisterone), 19-nortestosterone derivatives (desogestrel, norethynodrel, norethindrone, L-norgestrel)

- *Pharmacokinetics*:
Rapid absorption, extensive first-pass metabolism, short plasma half-life (~5 min), excreted in urine. Some have **no** androgenic activity"do not produce male hormone-like effects"(progesterone, dimethisterone, desogestrel, norgestimate, gestodene, norethynodrel).

- *Therapeutic Uses:*

Hormone Replacement Therapy (**HRT**)"Used along with estrogen to reduce the risk of endometrial cancer" , contraception"combined oral pills or progestin-only pills", long-term ovarian suppression (treating dysmenorrhea, endometriosis, bleeding disorders when estrogens are contraindicated).

- *Adverse Effects*:

Elevated blood pressure, reduced HDL(especially with androgenic progestins), increased breast cancer risk in postmenopausal women.

TABLE 40–2 Properties of some progestational agents.

	Route	Duration of Action	Activities[1]				
			Estrogenic	*Androgenic*	*Antiestrogenic*	*Antiandrogenic*	*Anabolic*
Progesterone and derivatives							
Progesterone	IM	1 day	–	–	+	–	–
Hydroxyprogesterone caproate	IM	8–14 days	sl	sl	–	–	–
Medroxyprogesterone acetate	IM, PO	Tabs: 1–3 days; injection: 4–12 weeks	–	+	+	–	–
Megestrol acetate	PO	1–3 days	–	+	–	+	–
17-Ethinyl testosterone derivatives							
Dimethisterone	PO	1–3 days	–	–	sl	–	–
19-Nortestosterone derivatives							
Desogestrel	PO	1–3 days	–	–	–	–	–
Norethynodrel[2]	PO	1–3 days	+	–	–	–	–
Lynestrenol[3]	PO	1–3 days	+	+	–	–	+
Norethindrone[2]	PO	1–3 days	sl	+	+	–	+
Norethindrone acetate[2]	PO	1–3 days	sl	+	+	–	+
Ethynodiol diacetate[2]	PO	1–3 days	sl	+	+	–	–
L-Norgestrel[2]	PO	1–3 days	–	+	+	–	+

[1]**Interpretation:** + = active; – = inactive; sl = slightly active. Activities have been reported in various species using various end points and may not apply to humans.

Estrogen and Progesterone Inhibitors & Antagonists

Tamoxifen & Related Drugs:

- **Tamoxifen**: SERM" Selective Estrogen Receptor Modulator", partial agonist/antagonist at estrogen receptors, used for breast cancer in postmenopausal women, prevents bone loss and lipid changes but increases endometrial cancer risk❗. Adverse effects include hot flushes and nausea.
- **Toremifene**: Similar to tamoxifen.
- **Raloxifene**: SERM, affects bone/lipids but not endometrium/breast, used for osteoporosis prevention.

✓ A **SERM** is a drug that binds to estrogen receptors (ERs) and acts differently in different tissues: It can act as an agonist (activator) in some tissues like bone. And as an antagonist (blocker) in others like the breast or uterus.

Mifepristone:

Progesterone receptor blocker, emergency contraceptive, also blocks glucocorticoid receptors. **Used for** endometriosis, Cushing's syndrome, some tumors. **Adverse effects:** prolonged bleeding, abdominal pain, nausea, vomiting.

Danazol:

Weak progestational, androgenic, glucocorticoid activities. Suppresses ovarian function, **used for** endometriosis and fibrocystic breast disease. **Adverse effects:** weight gain, edema, acne, hirsutism, voice deepening, hot flushes, libido changes. **Contraindicated in** pregnancy/breastfeeding❗

Aromatase Inhibitors:

(Anastrozole, Fadrozole) Used in breast cancer resistant to tamoxifen, precocious puberty بلوغ مبكر, excessive aromatase syndrome.

Fulvestrant:

Pure estrogen receptor antagonist, used in tamoxifen-resistant breast cancer.

Ovulation-Inducing Agents (Clomiphene)

Pharmacology:

Partial estrogen agonist, increases gonadotropin secretion by blocking estradiol's negative feedback, stimulating ovulation in women with ovulatory dysfunction.

- ✓ يعمل عن طريق منع تأثير (Estradiol) على (hypothalamus) والغدة النخاميةpituitary. هذا يؤدي إلى: منع (Negative feedback) التي يمنع بها الإستروجين إفراز الهرمونات المحفزة للتبويض، فينتج عن ذلك زيادة إفراز FSH وLH → مما يُحفّز الإباضة لدى النساء اللاتي لديهن خلل في التبويض

Therapeutic Uses:

Treats ovulatory dysfunction in women desiring pregnancy. Ineffective in ovarian or pituitary failure.❗

Adverse Effects:

Hot flushes (most common)❗, visual disturbances, headache, constipation, allergy, hair loss, ovarian enlargement, multiple pregnancies (10%), nausea, vomiting, mood changes, breast soreness, weight gain, urinary frequency, heavy menses.

Contraindications/Cautions:

Use small doses in women with enlarged ovaries; caution with visual symptoms.❗

Pharma6 Gonadotropins

The main gonadotropins are: مجموعة من الهرمونات التي تُفرز من الغدة النخامية أو تُعطى دوائيًا لتحفيز نشاط الغدد التناسلية (المبيضين في الإناث والخصيتين في الذكور).

- Follicle-stimulating hormone (**FSH**)
- Luteinizing hormone (**LH**)
- Human chorionic gonadotropin (**hCG**)
- Human menopausal gonadotropins (**hMG**)

Feature	GnRH (Gonadotropin-Releasing Hormone)	Gonadotropins
Full Name	Gonadotropin-Releasing Hormone	Gonadotropins
Source	Hypothalamus	Anterior Pituitary gland (or placenta for hCG)
Main Function	Stimulates the pituitary to release gonadotropins	Stimulate the gonads (ovaries/testes) to produce sex hormones or gametes
Hormone Type	Regulatory hormone (Releasing hormone)	Effector hormones
Examples	GnRH	FSH, LH, hCG, hMG
Therapeutic Use	Used to either stimulate or suppress the reproductive axis (depending on dosing)	Used directly to induce ovulation or spermatogenesis

- ✓ Hypothalamus → GnRH → Pituitary → FSH & LH (Gonadotropins) → Gonads → Sex hormones (Estrogen, Testosterone…)

Gonadotropins Available for Clinical Use

- **Urofollitropin** (**uFSH**): Extracted from urine of postmenopausal women.
- **Recombinant FSH** (**rFSH**), known as follitropin.
- **Recombinant human LH** (**rLH**), or Lutropin.
- **Choriogonadotropin alfa:** Recombinant hCG (rhCG), a combination of FSH and LH.

Therapeutic Uses of Gonadotropins

- Induction of ovulation (requires progesterone support for luteal phase).
- Treatment of male infertility علاج العقم, especially in hypogonadal men.

Adverse Effects of Gonadotropins

- Ovarian hyper-stimulation syndrome(OHSS): Can include ovarian enlargement, ascites, hydrothorax, hypovolemia, shock, hemoperitoneum, fever, and arterial thromboembolism.
- Increased risk of multiple pregnancies (15–20% vs. 1% baseline).
- Headache, depression, edema.
- Antibody production against hCG.

- Gynecomastia in males." enlargement of male breast tissue"
  - Possible association with ovarian cancer.

Gonadotropin-Releasing Hormone (GnRH) & Analogs

- Secreted by hypothalamic neurons; pulsatile secretion stimulates FSH and LH release.
- Sustained, **non**pulsatile administration inhibits FSH and LH, causing hypogonadism.
- Synthetic analogs: Gonadorelin, Goserelin, Leuprolide.

✓ Lower pulse frequencies favor FSH secretion, while higher pulse frequencies favor LH secretion.

Pharmacologic Use

- Pulsatile **IV** administration stimulates FSH and LH.
- Continuous administration causes a **biphasic response:**
  - Initial "flare" (7–10 days): ↑ Increased gonadal hormones. زيادة مؤقتة
  - Subsequent inhibition: ↓ Decreased gonadotropins and gonadal steroids due to receptor downregulation and changes in the signaling pathway

✓ Gonadal hormones: Hormones produced by the ovaries or testes, including both steroid and non-steroid types.

✓ Gonadotropins: Hormones from the pituitary (like FSH and LH) or placenta (like hCG) that stimulate the gonads.

✓ Gonadal steroids: Steroid hormones (derived from cholesterol) produced by the gonads — such as estrogen, progesterone, and testosterone.

Term	Source	Includes	Main Function
Gonadal hormones	Gonads (ovaries or testes)	All hormones secreted by the gonads	Regulate reproductive and sexual functions
Gonadotropins	Pituitary gland or placenta	FSH, LH, hCG, hMG	Stimulate the gonads to produce hormones or gametes
Gonadal steroids	Gonads	Estrogens, progesterone, and androgens	Control puberty, menstrual cycle, pregnancy, spermatogenesis

Therapeutic Uses of GnRH & Analogs

Stimulation:

- **Infertility** in men and women (less common than gonadotropins)-> Gonadotropins (FSH & LH directly) are more commonly used in fertility treatments.
- LH responsiveness test for delayed puberty. البلوغ المتأخر

Suppression:

- Controlled ovarian hyperstimulation (assisted reproduction).
- Endometriosis (reduces pain by suppressing cyclical hormone changes).
- Uterine leiomyomata (fibroids).
- Central(pituitary or hypothalamic) precocious puberty. البلوغ المبكّر (onset of secondary sex characteristics before 8 years in girls and 9 years in boys).

Adverse Effects of GnRH & Analogs

- Headache, light-headedness, nausea, flushing.
- Local injection site reactions.
- Hypersensitivity (bronchospasm, anaphylaxis). خطيرة

- Menopausal symptoms in women-> Hot flashes, mood swings, vaginal dryness due to reduced estrogen.

- Ovarian cysts.

- Sudden pituitary apoplexy.-> Rare but life-threatening event, especially in patients with undiagnosed pituitary tumors. leading to abrupt onset of severe headache, neck stiffness, visual disturbances, and oculomotor palsies.

- Reduced bone density, osteoporosis. نتيجة الانخفاض طويل الأمد للأستروجين أو التستوستيرون

✓ مثال عملي للفهم: امرأة عمرها 38 سنة،تعاني من نزيف رحمي غزير وألم في الحوض، (ultrasound) أظهرت وجود ورم ليفي في الرحمuterine fibroid بدأ الطبيب بإعطاء Leuprolide (GnRH agonist)،الهدف: إيقاف تحفيز المبيض لإنتاج الإستروجين، تقليل مستويات الإستروجين → لأن الورم الليفي يعتمد على الإستروجين في نموه،بالتالي: ينكمش الورم الليفي و يتحسن النزيف، اليه عمله: في أول أسبوع يحصل "flare effect" (زيادة مؤقتة في الهرمونات، بعد ذلك ينخفض FSH وLH بسبب توقف حساسية المستقبلات في الغدة النخامية، هذا يؤدي إلى حالة مؤقتة تشبه سن اليأس ، وبالتالي نقص في الإستروجين.

GnRH Receptor Antagonists

•Examples: Ganirelix, Cetrorelix, Degarelix

Mechanism of Action:

- Directly block GnRH receptors in the pituitary → suppress FSH & LH release in a dose-dependent way.
- **No** initial "flare" effect like GnRH agonists.تأثير فوري وسريع
-

Therapeutic Uses

•Prevention of LH surge during controlled ovarian hyperstimulation (IVF).

•Advanced prostate cancer (Degarelix): Rapidly reduces gonadotropins and androgens, avoiding testosterone surge.

✓ Adherence to treatment regimen is more critical because effect reverses quickly after discontinuation.

❖ ***Advantages*** Over *GnRH Agonists*

•Immediate action, shorter administration."تأثير فوري" جرعة أقل وفترة علاج أقصر

•Can be started later in IVF cycle (day 6–8). IVF = In Vitro Fertilization = الجسم التلقيح الصناعي خارج

❖ ***Disadvantages***

- Requires strict adherence; effects reverse quickly after discontinuation.
- More complete suppression of gonadotropins.
- May impair follicular development when used with FSH.
- Lower pregnancy rates in IVF compared to GnRH agonists.

✓ حالة للفهم: امرأة عمرها 33 عامًا، تعاني من عقم غير مفسر منذ 3 سنوات. قرر الطبيب إجراء IVF لها. بدأ الطبيب تحفيز المبيض باستخدام FSH لتحفيز نمو أكثر من بويضة، في اليوم السادس من التنشيط، قرر البدء باستخدام GnRH antagonist (مثل Cetrorelix)، الهدف ؟ منع حدوث اندفاع مفاجئ لهرمون LH الذي قد يؤدي إلى إباضة قبل أن يستطيع الطبيب سحب البويضات، بعد 2–3 أيام، يقوم الطبيب بمتابعة النمو ثم يحدد موعد سحب البويضات. تُخصب البويضات في المختبر وتُعاد إلى الرحم لاحقًا.

Adverse Effects

- Nausea, headache.
- Injection-site reactions, increased liver enzymes (in prostate cancer treatment).
- Signs of androgen deprivation ↓ (hot flushes, weight gain).

Prolactin

- 198 amino acid peptide, structurally similar to growth hormone.
- **Main hormone for lactation.** It is secreted by the anterior pituitary gland.
- Hyperprolactinemia causes amenorrhea, galactorrhea, infertility in women; loss of libido and infertility in men (due to GnRH inhibition).

✓ Amenorrhea (absence of menstruation)،Galactorrhea (milk discharge without pregnancy or breastfeeding) ،Infertility (because high prolactin inhibits GnRH → reduced FSH and LH)

Regulation

- Inhibited by dopamine (prolactin-inhibiting hormone),It is released from the hypothalamus and binds to D2 receptors on pituitary cells.
- Dopamine agonists treat hyperprolactinemia.
- Prolactin-secreting adenomas remain sensitive to dopamine.

✓ على الرغم من أن الورم يُفرز البرولاكتين بشكل مفرط، إلا أن خلاياه ما زالت تحتوي على مستقبلات للدوبامين (D2 receptors)، وما زالت تستجيب لتأثير الدوبامين أو الأدوية التي تنشط مستقبله.

Dopamine Agonists العلاج لتقليل إفراز البرولاكتين

D2 receptor agonists:

- Ergot derivatives: Bromocriptine, cabergoline(most effective, fewer side effects), pergolide.
  •Nonergot: Quinagolide.

Pharmacodynamics

- Suppress prolactin release (hyperprolactinemia).
- Suppress **GH** in acromegaly.
- Improve motor function in Parkinsonism.

Therapeutic Uses

- Hyperprolactinemia: Shrink tumors, lower prolactin, restore ovulation in many women.
- Restore ovulation in ~ **70%** of women with microadenomas and ~ **30%** of those with macroadenomas.
- Acromegaly.
- Parkinsonism.

Adverse Effects

- Nausea, vomiting, headache, fatigue, lightheadedness.
- Orthostatic hypotension انخفاض الضغط عند الوقوف.
- Psychiatric symptoms.
- Erythromelalgia. الم واحمرار بالأطراف
- Ergot derivatives: Cold-induced vasospasm تشنج الأوعية عند البرد, pulmonary infiltrates with high doses.
- Rare: Stroke or coronary thrombosis in postpartum women taking bromocriptine for lactation suppression.

Pharma7

Regulation of Male Hormones

- FSH (Follicle-Stimulating Hormone): Controls gametogenesis, requiring high local testosterone ليعمل بكفاءة. **Stimulated by** activin, **inhibited by** inhibin, testosterone, and dihydrotestosterone.
- LH (Luteinizing Hormone): Stimulates Leydig cells to produce testosterone.
- Sertoli Cells: Secrete inhibin (inhibits FSH) and activin (stimulates FSH).

Androgens and Anabolic Steroids

Testosterone and Dihydrotestosterone (DHT)

- Binding: **65%** bound to SHBG, most of the rest to albumin, only ~2% is free (biologically active).
- SHBG (Sex Hormone-Binding Globulin): Increased ↑ by estrogen, thyroid hormone, and liver cirrhosis; ↓ decreased by androgens, growth hormone, and obesity.
- ***Conversion***: In target tissues (not testis), testosterone is converted to DHT by 5α-reductase❗. DHT is the major active androgen in peripheral tissues.❗
- Metabolism: Excreted as glucuronide and sulfate conjugates in urine.

Other Androgens

- Androstenedione, DHEA Dehydroepiandrosterone, DHEAS Dehydroepiandrosterone Sulfate: Produced mainly in adrenal glands, contribute to maturation, well-being, and inhibit atherosclerosis.
- •**DHEA** in **SLE**Systemic Lupus Erythematosus : Immunomodulatory, shifts balance toward anti-inflammatory interleukins.-> such as Interleukin-6 and upregulates the anti-inflammatory interleukin, interleukin-2

Physiological and Metabolic Effects

•Secondary Sex Characteristics: Responsible for puberty changes in males.physiological

Metabolic Effects:

1. Reduces sex hormone-binding proteins. بالتالي زيادة الهرمونات الحرة بالدم(الفعّالة)
2. Increases liver synthesis of clotting factors, triglyceride lipase, α1-antitrypsin حماية للأنسجة, haptoglobin يربط الهيموغلوبين الحر, sialic acid.
3. Increases renal erythropoietin secretion (previously used to treat anemia).
4. ↓ Reduces HDL High-Density Lipoprotein (risk for atherosclerosis).

Synthetic Androgenic and Anabolic Steroids

- Testosterone: Low oral bioavailability, given parenterally.
- 17-Alkylated Derivatives: Methyltestosterone, fluoxymesterone (orally active).
- Other Synthetics: Oxymetholone, oxandrolone, nandrolone decanoate (varying anabolic:androgenic ratios, higher anabolic activity, commonly misused by athletes).

Anabolic Steroid Misuse

- Abuse in Sports: Doses 10-200x normal; adverse effects outweigh benefits.
- Actions: Increased muscle mass/strength, bone growth, Growth and mineralization of bone, improved performance (notably in women❗).

•Long Term Adverse Effects: Cardiovascular issues, liver disease, reproductive toxicity, mood swings, aggressiveness.

➢ Synthetic Androgens & Anabolic Activity Androgens have anabolic effects, which help build muscle mass and strength. They are often misused by athletes (both men and women) for performance enhancement.

✓ Activity Ratio = Androgenic : Anabolic❗

- Testosterone = 1:1 (equal masculinizing and muscle-building effects)
- Fluoxymesterone = 1:2 (more anabolic)

TABLE 40–5 Androgens: Preparations available and relative androgenic:anabolic activity in animals.

Drug	Androgenic Anabolic Activity
Testosterone	1:1
Testosterone cypionate	1:1
Testosterone enanthate	1:1
Methyltestosterone	1:1
Fluoxymesterone	1:2
Oxymetholone	1:3
Oxandrolone	1:3–1:13
Nandrolone decanoate	1:2.5–1:4

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✓ Drugs with higher anabolic effect (commonly misused):

Oxymetholone.	1:3
Oxandrolone	1:3 to 1:13
Nandrolone decanoate	1:2.5 to 1:4

Therapeutic Uses

1.Androgen Replacement: For hypogonadal men (various administration routes) 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. In this case, the goal is not only to correct hypogonadal dysfunction but also to achieve normal spermatogenesis, which requires FSH (gonadotropin). However, if spermatogenesis is not desired, androgen therapy is given

2.Protein Loss Reversal: After trauma, surgery, immobilization, or debilitating diseases.

3.Refractory Anemias: or any anemia that's associated with bone marrow suppression, Now largely replaced by recombinant erythropoietin.

Adverse Effects

- Women: Masculinization ظهور صفات ذكرية (hirsutism, acne, amenorrhea, clitoral enlargement, deep voice).
- Progestational Activity: Withdrawal endometrial bleeding.
- Atherosclerosis: Increased risk in women. ↓ HDL
- Pregnancy: Can cause genital malformations in fetuses-> Masculinization or undermasculinization of the external genitalia of the female and male fetuses , respectively, if given during pregnancy.
- Sodium retention and edema are not common.
- CNS Effects: Early-life administration can affect sexual development centers.
- Hepatic Dysfunction: Especially with 17-alkyl-substituted steroids (cholestatic jaundice, hepatomas, carcinomas).

- Prostatic Hyperplasia, Lipid Changes: Increased LDL, decreased HDL.
- Other: Acne, sleep apneaتوقف النفس, erythrocytosis ↑ RBCs, gynecomastia, azoospermia ↓ sperms, testicular atrophy, psychological dependence(not physical, nor physiological) ,hepatocellular carcinoma.

Contraindications and Cautions❗

- Pregnancy, Prostate/Breast Cancer in Males, Children (growth concernsنمو العظام), Patients with Renal/Cardiac Disease (edema risk).

✓ Infants and young children: special caution is required in giving them To produce a growth spurt (However, somatotropin is more appropriate). If they have a short stature and are predicted not to grow further, it's better to give them somatotropins rather than androgenic and anabolic steroids.

Antiandrogens تعارض تأثير الهرمونات الذكر

علاج :تضخم البروستاتا (BPH)،سرطان البروستاتا، الشعرانية (لدى النساء)،الصلع الذكوري المبكر...

5α-Reductase Inhibitors

They inhibit the conversion of testosterone to DHT, which is active in tissues, stimulates the prostate.

•Finasteride: Reduces DHT, treats BPH, hirsutism in women, early male pattern baldness❗.

•Dutasteride: Similar, longer half-life, mainly for BPH, **Not** approved to be used against hirsutism in women or male-pattern baldness in men.

Androgen Receptor Blockers

1.Cyproterone/Acetate: Inhibits androgen action, "acetate" has progestational effect, treats hirsutism❗, reduces sexual drive in men.

2.Flutamide: Nonsteroidal,potent , treats prostatic carcinoma, can cause gynecomastia and hepatic toxicity, also used in women for excess androgen.

3.Bicalutamide, Enzalutamide, Nilutamide: Potent, orally active, used for metastatic prostate cancer, often with GnRH analogs to reduce tumor flare.

4.Spironolactone: Potassium-sparing diuretic, blocks androgen receptors can cause gynecomastia in males , inhibits 17α-hydroxylase يقلل تصنيع الاندروجين, used for hirsutism ❗in women

Pharma8 ***"Drugs Used in Neoplasms of the Urogenital System"***

Drugs for Breast Cancer

Cyclophosphamide

- Alkylating agent, prodrug activated in the liver, It is inactive and needs activation by microsomal enzymes to 4-hydroxycyclophosphamide and aldophosphamide.
- Used for breast, ovarian, Wilm's tumor عند الأطفال, and other cancers.
- Adverse effects: dose-related toxicity in rapidly dividing tissues كالشعر, nausea, vomiting, tissue damage at injection site, hemorrhagic cystitis (preventable by hydration), carcinogenicity especially acute myelogenous leukaemia, bone marrow depression, alopecia تساقط الشعر.

Methotrexate (MTX)

•Folic acid analog; inhibits dihydrofolate reductase, blocking DNA/RNA synthesis.

•Intracellular formation of polyglutamate metabolites by folylpolyglutamate synthase, with the addition of up to 5-7 glutamate residues, is needed for the therapeutic action of MTX.

- MTX polyglutamates are selectively retained within cancer cells.

- *Resistance mechanisms:* decreased drug transport, reduced polyglutamate formation, increased(through gene amplification) /altered DHFR , activation of drug efflux pumps اخراج للدواء. Activation of the multidrug resistance transporter P170-glycoprotein.

- Administered orally, IV, or intrathecally; renal elimination (dose adjust in renal dysfunction), Its renal excretion is inhibited by aspirin, other NSAIDs, penicillins, and cephalosporins.
- Leucovorin"5- formyltetrahydrofolate"(folinic acid) rescue reverses toxicity. لحمايه الخلايا الطبيعية
- *Used for* breast, bladder cancer, choriocarcinoma, others.
- *Toxicity*: mucositis, diarrhea, hepatotoxicity, myelosuppression, neurotoxicity, pulmonary toxicity, renal dysfunction.

Doxorubicin (Anthracyclines)

•Inhibits topoisomerase II, intercalates DNA, generates free radicals (cardiotoxicity).

•Alters membrane fluidity and ion transport.

•IV administration, hepatic metabolism, biliary excretion50% (dose adjust in liver dysfunction).

•Used for breast, endometrial, ovarian, testicular, bladder cancers.

Paclitaxel (Taxanes)

- Derived from yew trees صنوبريات; inhibits mitosis by stabilizing microtubules.
- Metabolized by **CYPs**,80% fecal excretion (dose adjust in hepatic dysfunction).
- Used for ovarian, advanced breast, prostate, bladder cancers.
- Adverse effects: nausea, vomiting, hypotension, arrhythmias, myelosuppression, neuropathy, hypersensitivity 5%(premedication required with dexamethasone, diphenhydramine (H1-blocker) and an H2-blocker), albumin-bound formulation has milder side effects.

Ixabepilone

- Microtubule inhibitor (**not a taxane**: Paclitaxel, Docetaxel).
- Used for **metastatic breast cancer.**

- Adverse effects: hypersensitivity, myelosuppression, neurotoxicity.

Bevacizumab

•Monoclonal antibody targeting **VEGF-A**, inhibits tumor angiogenesis.

✓ Bevacizumab is a recombinant humanized monoclonal antibody that targets all forms of VEGFs particularly VEGF-A.❗

•Toxicity: hypertension, arterial thromboembolism, impaired wound healing, GI perforations, proteinuria.

Trastuzumab

- Monoclonal antibody against HER-2/neu receptor.على سطح الخلايا السرطانية
- Used in **HER-2 positive metastatic breast cancer**.❗
- Cardiotoxicity (reduced ejection fraction) is a key adverse effect.❗

Drug	Mechanism of Action	Main Use	Key Side Effect
Cyclophosphamide	DNA alkylation	Breast cancer + others	Hemorrhagic cystitis, myelosuppression
Methotrexate	Inhibits DHFR (folate analog)	Breast cancer, choriocarcinoma	Hepato- and nephrotoxicity
Doxorubicin	Free radicals, Topoisomerase II inhibition	Breast, ovarian cancer	**Cardiotoxicity** (heart failure)
Paclitaxel	Microtubule stabilization	Breast, ovarian, prostate	Neuropathy, hypersensitivity
Ixabepilone	Microtubule inhibitor (not a taxane)	Metastatic breast cancer	Neurotoxicity, myelosuppression
Bevacizumab	Anti-VEGF-A (angiogenesis inhibitor)	Advanced breast cancer	Hypertension, GI perforation, proteinuria
Trastuzumab	HER2 receptor blocker	HER2+ breast cancer	**Cardiotoxicity** (↓ejection fraction)

Drugs for Prostate Cancer

Hormonal Therapy

Mainstay is elimination of testosterone (surgical or pharmacological castration).

Mitoxantrone

•Anthracycline antibiotic, intercalates DNA, inhibits topoisomerase II. بشبه الdoxorubicin

•Used for advanced, hormone-refractory prostate cancer.❗

•Toxicity: myelosuppression (dose-limiting), thrombocytopenia, nausea, alopecia, mucositis, blue discoloration of nails, sclera, urine.

Drugs for Ovarian Cancer

Common Agents

Cisplatin, Carboplatin, Cyclophosphamide, Paclitaxel, Topotecan, Doxorubicin, Altretamine.

Platinum Analogs (Cisplatin, Carboplatin)

•Act like alkylating agents, bind DNA, inhibit synthesis/function, active in all cell cycle stages.

•Used for breast, testicular, ovarian, bladder cancers.

•Cisplatin: nephrotoxicity❗, neuropathy, ototoxicity, nausea; dose adjust in renal dysfunction.

•Carboplatin: less nephrotoxic, main issue is myelosuppression.

Camptothecins (Topotecan)

- Inhibit topoisomerase I, causing DNA damage.
- Used as second-line for **advanced ovarian cancer**. following platinum-based chemotnerapy. – (Cisplatin, Carboplatin)
- Toxicity: nausea, vomiting, myelosuppression; dose adjust in renal dysfunction.

Altretamine

- Alkylating agent, forms DNA cross-links.
- Toxicity: nausea, myelosuppression, neuropathy, flu-like syndrome كالانفلونزا.

Drugs for Testicular Cancer

Common Agents

Cisplatin, Etoposide, Bleomycin, Ifosfamide (similar to cyclophosphamide).

Etoposide

- Semisynthetic podophyllotoxin derivative, inhibits topoisomerase II.
- Teniposide is a related drug.
- IV and oral forms; dose adjust in renal dysfunction.
- Toxicity: nausea, hypotension, myelosuppression, alopecia.

Bleomycin

- Anticancer antibiotic, binds DNA, causes strand breaks via free radicals, inhibits DNA synthesis.
- Cell cycle-specific (**G2** phase).
- Used for testicular, **cervical**, **vulvar** cancers; dose adjust in renal dysfunction.
- Dose-limiting toxicity: pulmonary (pneumonitis, fibrosis); risk higher with age>70, high dose>400 units, prior lung disease, or chest radiation.
- Other toxicities: allergic reactions, fever, hypotension, dermatotoxicity, alopecia, mucositis التهاب وتقرحات فموية.

Pharma9 ***Oral Contraceptives***

Hormonal Contraception:

Combined Estrogen-Progestin Forms:

- **Monophasic**: Constant dosage of both hormones throughout the cycle.
- **Biphasic**: Dosage of one or both hormones changes once during the cycle.
- **Triphasic**: Dosage changes twice during the cycle.

Progestin-Only Therapy:

Continuous progestin without estrogen, administered orally or via subcutaneous implants.

Common Hormonal Agents:

- Estrogens: Ethinyl estradiol, mestranol.

- Progestins: *L-Norgestrel*, drospirenone, *norethindrone*, norgestimate, ethynodiol diacetate.

Mechanism of Action

- Inhibit ovulation by suppressing pituitary function.
- Alter cervical mucus, endometrium, and uterine tube motility to reduce conception and implantation likelihood.

Pharmacologic Effects

- **Ovary**: Chronic use depresses ovarian function and reduces size (reversible).
- **Uterus**: May cause cervical hypertrophy and polyp formation.
- **Cervical Mucus:** Becomes thicker and less abundant.
- **Endometrium**: Effects depend on hormonal content.
- **Breast**: Enlargement, lactation suppression, small hormone transfer to breast milk.
- **CNS**: Minimal mood/behavior changes; estrogens may help premenstrual/postpartum/climacteric depression; progestins have thermogenic effects رفع للحرارة

- **Endocrine**: Estrogens increase corticosteroid-binding globulin يقلل الهرمونات الحرة, renin activity, aldosterone, thyroxine-binding globulin, and SHBG (reducing free androgens).
- **Blood:** Increased clotting factors, VII, VIII, IX, and X and decrease antithrombin III. risk of thromboembolism, higher serum iron ↑, possible folic acid deficiency anemia.
- **Liver**: Reduced serum haptoglobins, risk of cholestasis and gallstones.
- **Lipid Metabolism:** Estrogens raise triglycerides, phospholipids, HDL (lower LDL size); progestins, especially androgenic types, may counteract these benefits.
- **Carbohydrate Metabolism:** Reduced absorption, increased basal insulin, possible decrease in tolerance with potent progestins.
- **Cardiovascular**: Increased blood pressure, heart rate, and cardiac output.
- **Skin:** Increased pigmentation, acne risk with androgenic progestins, but sequential agents/estrogens may reduce sebum and acne.

Therapeutic Uses

- Primary: Oral contraception فعاليه عاليه (failure rate ~0.5–1 per 100 women-years).
- Other: Endometriosis treatment.

Adverse Effects

- ***Mild***: Nausea, breast tenderness, breakthrough bleeding أي خارج وقت الطمث, edema, ↑ increased **ESR** "Erythrocyte Sedimentation Rate" due to increased fibrinogen, headaches (may worsen migraines), failure of withdrawal bleeding خلل بالرجوع للوضع الطبيعي.

- ***Moderate*** (may require discontinuation): Frequent breakthrough bleeding (common 25%) (especially with progestin-only), weight gain (androgenic progestins), Increased skin pigmentation exacerbated by vitamin B12 and folic acid deficiency" It is slowly reversible" , acne, hirsutism "may be aggravated by 19-nortestosterone derivatives", ureteral dilation, more

frequent/difficult vaginal infections(more common), amenorrhea (sometimes with galactorrhea, possible prolactinoma).

•***Severe*** (Contraindications): Venous thromboembolism, myocardial infarction, cerebrovascular/ischemic bowel disease, cholestatic jaundice"17-alkyl substituted agents", cholecystitis, cholangitis, hepatic adenomas, depression6%, increased risk of cervical cancer (with HPV Human Papilloma Virus).

Special Considerations

- Cardiovascular Risk: Increased risk is mainly due to thromboembolic events, not atherosclerosis. Women with controlled dyslipidemia may use low-dose CHCs with monitoring; those with **un**controlled dyslipidemia or additional risk factors should avoid CHCs.

- Diabetes: Non-smoking women under 35 with diabetes but no vascular disease can use CHCs; those with vascular complications or long-standing diabetes should not.

Progestin-Only Contraception

Suitable for those who cannot take estrogens.

Depot Medroxyprogesterone Acetate (DMPA): Injected every 3 months, suppresses ovulation for 14 weeks, common side effects include irregular bleeding and amenorrhea.

•Not ideal for women planning pregnancy soon, as ovulation may be suppressed for up to 18 months after last dose.

- All users experience episodes of spotting and bleeding.
- Amenorrhea is common.

•Long-term DMPA reduces menstrual blood loss and lowers endometrial cancer risk, but may decrease bone density and adversely affect lipids.

Progestin Implants: Subcutaneous, effective up to 6 years, cause irregular bleeding.
Other adverse effects: headache, dizziness, bloating, weight gain, reversible reduction in glucose tolerance, possible intracranial hypertension and papilledemaتورم العصب البصري.

تمّ بحمد الله تعالى

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