YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 6 - Pharmacology

Lec. Title : Androgens & Antagonists

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تفريغ الريكورد عسلايد نفسو

اخر 7 سلايدات مكتوب عليهم اكسترا هدول مش من الريكورد ولا السلايد للي حاب يفهم شغله او يستزيد

Androgens and antagonists

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Objectives

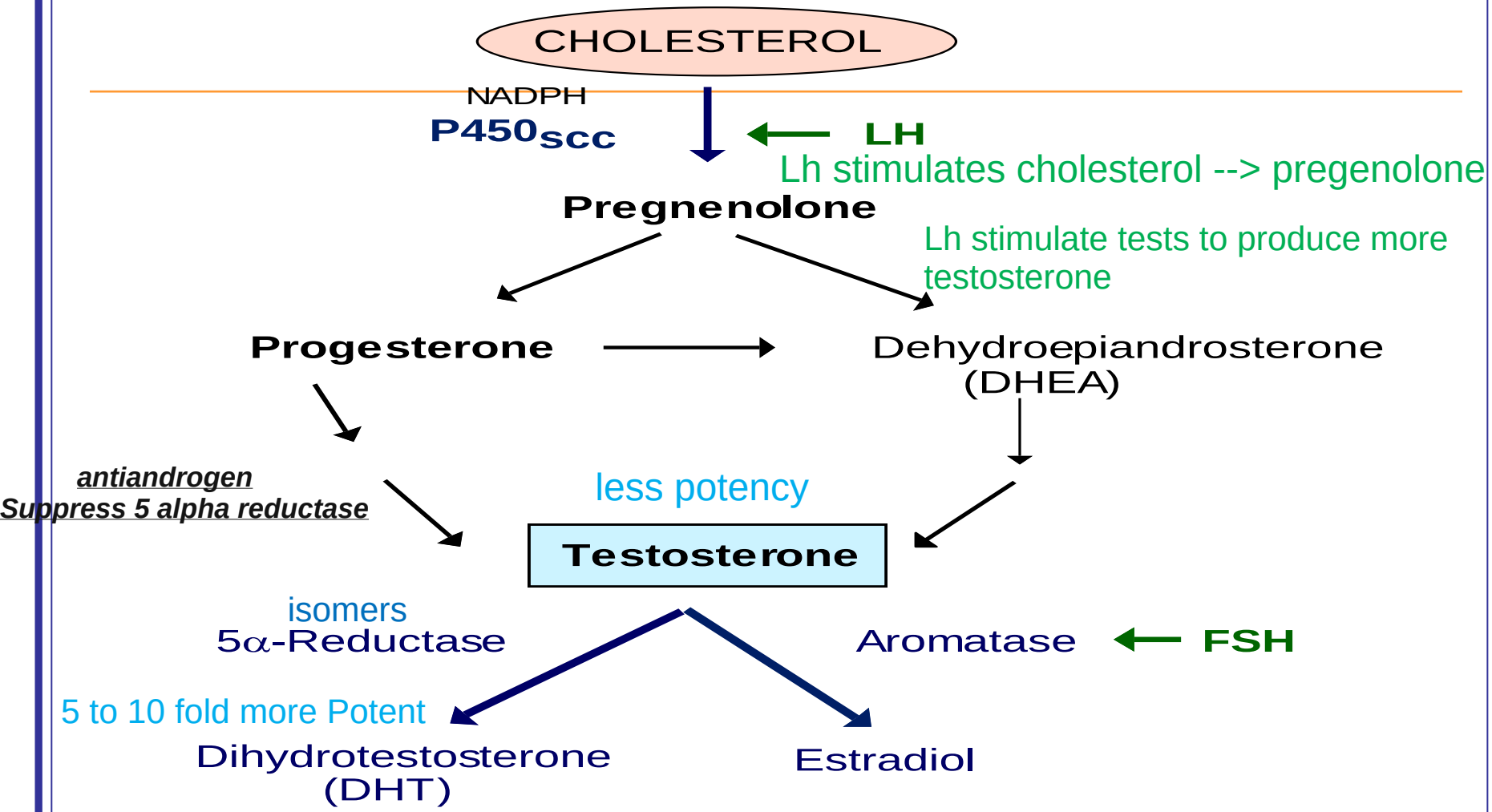
- 1. Classify and understand the nature and the mechanism of action of androgens and androgen antagonists.
- 2.Discuss the therapeutic uses of androgens and their abuse potential.

Prostate hypertrophy: تضخم البروستات
بفرق عن ال prostate cancer

hirsutism: نمو زائد للشعر عند النساء
بنعالجه ب androgen antagonist

Androgens : Synthesis

cholesterol مصدرهم steroid hormones كل ال



Androgens and Anabolic Steroids

1. *Testosterone* The main Male hormone
It's responsible for secondary Male Manifestation

a. **Testosterone is synthesized primarily in the Leydig cells of the testis under the influence of LH.**

b. Testosterone is metabolized to the more potent 5α-dihydrotestosterone (DHT) by **5 α-reductase.**

- **There are two isoforms of this enzyme:**
  - **Type I**, which is expressed in skin and liver; more
  - **Type II,** which is expressed in prostate, seminal vesicles, and hair follicles.

a. **Testosterone is extensively bound (98%), mostly to SSBG and also to albumin.**
Serum steroid bending protein

b. **Natural testosterone can be administered transdermally or intramuscularly**
Not taking orally because it's exposed to first pass metabolism extensively

Synthetic androgens

1. **Testosterone esters :**
    1. **testosterone propionate,**
    2. **testosterone enanthate,**
    3. **testosterone cypionate,** بستعملوه لتكبير العضلات athletes
    - administered by injection, usually as a depot in oil. ***and Im***
2. **17-Alkyl testosterone derivatives include**
    - **methyltestosterone,**
    - **fluoxymesterone,**
    - **oxymetholone**.
    - administered sublingually, thus avoiding the large hepatic first-pass effect.
3. **Nandrolone and oxandrolone are** testosterone derivatives with about a **5- to 10-fold higher anabolic-to-androgenic ratio** than testosterone itself.
    - Nandrolone is administered parenterally; oxandrolone is an **oral agent**

الوحيد الي بنسعمله orally

Actions.

hormone - receptor complex

MOA: Androgens form a complex with a specific intracellular receptor and interact with specific genes to modulate differentiation, development, and growth.

بنفرز وقت البلوغ 12-13 سنه

a. Androgenic and Anabolic actions بنائي

(1) Androgens stimulate the differentiation and development of Wolffian structures, including the epididymis, seminal vesicles, prostate, and penis.

(2) Androgens stimulate the development and maintenance of male secondary sexual characteristics

(3) Anabolic steroids cause linear growth at puberty.

↑bone dinsity
↑voice course

(4) Anabolic steroids cause an increase in muscle mass

(5) Behavioral effects of anabolic steroids include aggressiveness and increased libido

بشبه ال estrogen عند الانثى

Uses

افضل وقت للعلاج اعطائه بسن 13-14

a. **Hypogonadism.** Secondary characters يعني ما عنده Hypogonadism وعندو male وصل لعمر 16-17 سنه

   a. **Androgens promote linear growth and sexual maturation and maintain male secondary sexual characteristics, libido, and potency.**

Chemotherapy patient او Chronic renal failure بستخدمها للناس الي عندهم

Erythropoietin بكون ال عندهم منخفض طبعا هاض الحكي كلو قديما لنو حاليا مع تطور تكنولوجيا ال

b. **Anemia** Recombinant صرنا نعمل erythropoietin recombinant

(1) Androgens stimulate secretion of erythropoietin. normaly secreted by kidney

(2) Androgens have largely been replaced by recombinant erythropoietin (epoetin) for anemia, but they may be effective in some cases of bone marrow hypoplasia.

c. Estrogen-dependent breast cancers 1male hormone 2anti estrogen

d. Wasting disorders in AIDS or after severe burns

بالامراض الي بتقل فيها الكتله العضليه زي الايدز او بحالات الحروق الشديده الي حتقل الكتله العضليه فيها بعطيهم اندروجين عشان ازيد من الكتله العضليه عندهم طبعا بالاشراف الطبي

Uses

e. illegal use by athletes. Large doses of androgens increase the extent and rate of muscle formation and may increase the intensity of training.

f. Hereditary angioedema. ***allergic reaction***

Androgens are used to treat hereditary angioedema based on androgen-dependent increases in **C1 complement inhibitor.**

لما اعطي هرمون خارجي ← بعملي نيجاتيف فيد باك انهيبشن ← for LH and FSH ← infertility

Adverse effects and contraindications

خصائصه عكس الايستروجين

infertility ممكن يعملي

a. **Androgens and anabolic steroids produce decreased testicular function, edema**
b. **altered plasma lipids (increased LDL and decreased HDL levels).**
c. **These agents cause masculinization in women.** hirsutism خصوصا
d. **Androgens increase plasma fibrinolytic activity, causing severe bleeding with concomitant anticoagulant therapy.** خصوصا الي بوخذو مميع
e. **17-Alkyl substituted androgens (but not testosterone ester preparations) are associated with increases in hepatic enzymes, hyperbilirubinemia, and cholestatic hepatitis, which may result in jaundice. Long-term use is associated with liver tumors.** بأثر علكبد

e. Androgens and anabolic steroids are contraindicated:

- **in pregnant women**
- **in patients with carcinoma of the prostate or hepatic, renal, cardiovascular disease**

Androgen very rarly used

Antiandrogens

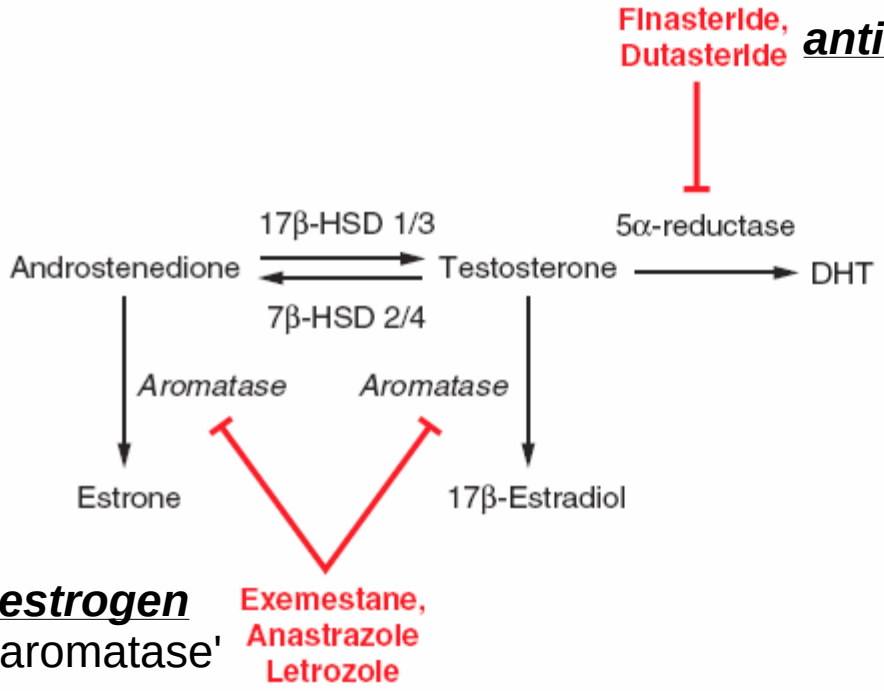


FIGURE 10.4. Enzymatic conversion of androgens to estrogens and dihydrotestosterone. 17β-HSD is hydroxysteroid dehydrogenase. There are multiple isoforms of this enzyme: types 1 and 3 catalyze reactions that make more-active steroids; types 2 and 4 make less active metabolites.

1- may block the androgen receptor
2- or inhibit androgen synthesis by blocking 5 alpha reductase isomers

Antiandrogens

I. Antiandrogens are agents that impair the action or synthesis of endogenous androgens.

1. Flutamide and nilutamide

a. **Flutamide is a steroidal oral antiandrogen that acts as a competitive androgen-receptor antagonist.**

b. **Nilutamide is nonsteroidal androgen-receptor antagonists** with better specificity for the androgen receptor and have a **longer half-life** that permits once-a-day dosing

ما الهم اي استعمال اخر

c. **These drugs are useful in the treatment of prostatic carcinoma**

for male

c. Adverse effects include: gynecomastia, elevation in liver enzymes, chest pain, and GI disturbances.

- **These agents are highly teratogenic**

Orally no tropical application

2. *Finasteride (Proscar)* معظم ادويه الرجال الكبار في العمر

a. Finasteride inhibits type II 5α-reductase, thereby reducing the production of the potent androgen 5α-dihydrotestosterone.

b. Finasteride is used to treat benign prostatic hypertrophy (BPH) and male pattern baldness.

بقلل من حجم البروتسات وبزيد كميه البول الخارجه

c. Finasteride decreases prostate volume and increases urine flow.

baldness الصلع الوراثي

It's gene influenced by the androgen hormone so using antiandrogen ↓baldness

3. *Dutasteride* ***more potent than Proscar***

a. **Dutasteride inhibits both type I and II 5α-reductase and is more potent than finasteride.**
b. Serum dihydrotachysterol (DHT) levels can be reduced by more than 90% in 2 weeks.
c. **Dutasteride is used to treat BPH and baldness**

4. *Ketoconazole*

كان يستخدم ل Cushing syndrome

حيمنع تكوين التستوستيرون اساسا في ال Adrenal cortex

a. Ketoconazole is an antifungal agent that blocks multiple P-450-dependent steps in steroidogenesis

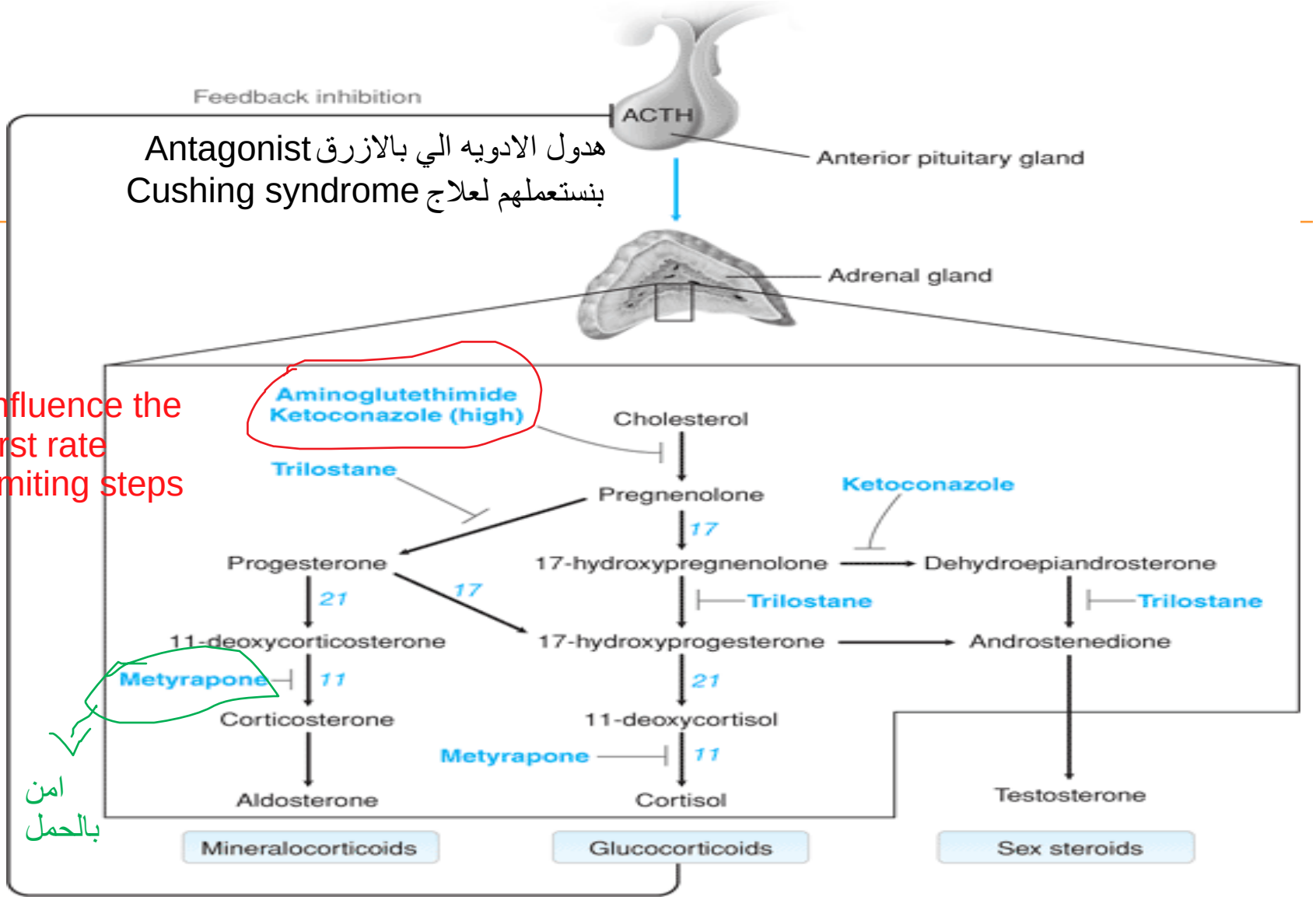
Influence the synthesis of glucocorticoid and minercorticosteroids

b. Ketoconazole can be used to treat precocious puberty and is used to treat hirsutism in female.

بلوغ مبكر

بتبدأ Sexual Characteristics تظهر من عمر ٩ ل ١١ سنه

Antagonist هدول الادويه الي بالازرق
Cushing syndrome بنستعملهم لعلاج



Influence the first rate limiting steps

امن بالحمل

ضعيف لازم ادمجه مع estrogen

5. *Spironolactone*

a. Spironolactone antagonizes the binding of both androgen and aldosterone at their respective receptors; it also decreases the activity of the steroidogenic enzyme 17-hydroxylase.

b. Spironolactone is used as a potassium-sparing diuretic and to treat hirsutism in women (usually in combination with estrogen).

علاجها بكون يا
1: بقلل من الهرمون الذكري
2: بزيد الهرمون الانثوي

Potassium sparing drugs can act as ***testesteron receptor blockers***

بس ضعيفه وبتسببلنا Gynecomastia

Anti testosterone can cuze infertility

hirsutism

The following medications can cause hirsutism:

- Testosterone
- Glucocorticoids
- Cyclosporine
- Phenytoin

Medical treatments

Oral contraceptives
Spiranolactone
Finasteride
Flutamide
Ketoconazole

extra

- The **androgens** are a group of steroid hormones that have **anabolic** and **androgenic** effects → the development and maintenance of the male sex organs and secondary sex characteristics.

Testosterone:

- It is the most important androgen
- It is synthesized by Leydig cells in the testes -

Smaller amounts are synthesized by the ovary of the female and by the adrenal gland in both sexes.

- Its secretion by is controlled by gonadotropin-releasing hormone from the hypothalamus → stimulates the anterior pituitary gland → secrete:

1. FSH→ necessary for spermatogenesis
2. LH → stimulates steroidogenesis (testosterone) in the Leydig cells -

Testosterone or its active metabolite dihydrotestosterone (DHT) → a negative feedback on trophic hormones → regulates testosterone production.

extra

Mechanism of action:

Just like other lipophilic hormones, it binds to a specific intracellular androgen receptors in a target cell to make the hormone-receptor complex then binds to DNA and affects gene expression & protein synthesis

- In ***muscle*** and ***liver:*** testosterone is the active ligand.
- In the ***prostate, seminal vesicles, epididymis, and skin:*** testosterone is converted by 5-a reductase enzyme to dihydrotestosterone (DHT), which binds to the receptor.
- In the ***brain, liver, and adipose tissue:*** testosterone is biotransformed by cytochrome P450 aromatase enzyme to estradiol.

Actions:

A. Androgenic:

1. Male sex organs development (penile & scrotal development)
2. 2 ry sex characters (hair growth, thickening of vocal cords)
3. Testosterone + FSH → spermatogenesis
4. ↑ libido in males & females (increase sexual desire)
5. Large doses for prolonged time → feedback inhibition of Gns → testicular atrophy.

That's why some body builders develop infertility after a period of prolonged intake of external testosterone due to negative feedback

B. Anabolic:

1. ↑ protein synthesis
2. ↑ bone density and closure of epiphyseal ends of long bone

So bones stop developing in length after puberty or if a child had precocious puberty they'll be shorter

3. ↑ muscle development.
4. ↑ Erythropoiesis and coagulation

Uses:

extra

A. For its Androgenic effects:

1. Replacement therapy in Male hypogonadism:

- If the problem was primarily in the testes themselves it is called primary hypogonadism, due to testicular dysfunction they're unable to produce testosterone although (GnRH,FSH,LH) are normal or even high → give testosterone
- Secondary ry hypogonadism (due to failure of the hypothalamus or pituitarynot the testes themselves) → give L.H + F.S.H if normal and functioning testes

2. Adjuvant in the treatment of Cancer breast:

To get benefit from the negative feedback mechanism produced by testosterone on GnRH, it is as adjuvent (which means not the primary drug) in treating breast cancer to decrease the levels of estrogen
↓release of gonadotropins (+ anti-estrogen)

B. For its anabolic effect

1. Growth stimulant in debilitating conditions e.g. after major surgery.
2. Senile osteoporosis: ↑ protein formation and calcium deposition in bones.
Senile means due to old age, so here it's used to make bones healthier
3. Aplastic anemia: ↑ erythropoietin synthesis

Adverse Effects: ***extra***

1. In female: Virilization: masculinization – acne - growth of facial hair deepening of the voice - menstrual irregularities - clitorial enlargement.

CI: pregnant women → virilization of the female fetus (the clitorial enalrgement will make it looks like penis so they'll think that the baby is boy when it's a girl actually)

2. In males: Azospermia(no sperms in the semen at all while oligospermia means little sperms) - decreased libido – priapism (painful erection due to VD and blockage of venous drainage for more than 4 hours treated by aspiration of the corpora cavernosa and injection of alpha agonist).

- Behavioral effects: increased aggressiveness, and psychotic symptoms.

3. In children: Short stature due to premature closure of epiphysis

4. Methyl-testosterone causes reversible cholestatic jaundice.

5. Increase incidence of cancer prostate (basically it grows due to high levels of DHT) so it's CI in cancer prostate

ANTIANDROGENS **extra**

(it's the opposite of the uses cases)

A. Inhibitors of testosterone secretion:

Analogs of GnRH as Leuprolide when are given continuously → inhibit LH secretion → inhibit testosterone production.
Used to - suppress precocious puberty - treat prostate cancer.

B. Inhibitors of testosterone synthesis:

Some antifungal drugs such as ketoconazole inhibit CYPs → block the synthesis ofsteroid hormones, including testosterone and cortisol.
Remember: In the brain, liver, and adipose tissue: testosterone is biotransformed by cytochrome P450 aromatase enzyme to estradiol.
They are not used to inhibit androgen synthesis because they may induce adrenal insufficiency and are associated with hepatotoxicity (non specific).

May used in cases of glucocorticoid excess.

C. Inhibitors of androgen action:

1) 5-a reductase inhibitors: Finasteride & Dutasteride: they block the conversion of testosterone to dihydrotestosterone, especially in the male external genitalia.

Used in Benign Prostatic Hyperplasia (BPH).

extra

2) Androgen receptor (AR) antagonists: Flutamide - Bicalutamide &Cyproterone: Competitive antagonist at androgen receptors.

Used in
- Cancer prostate
- Acne & hirsutism in females.

Spironolactone: aldosterone antagonist that also is a weak AR antagonist and a weak inhibitor of testosterone synthesis (by inhibiting CYP)

** Common adverse effects of antiandrogens:
1. Gynecomastia
2. ↓ libido (sexual desire)
3. Erectile dysfunction (impotence): inability to obtain or maintain erection of
penis for sexual intercourse.

BENIGN PROSTATIC HYPERPLASIA (BPH)

extra

The prostate gland is formed of:

- capsular & stromal tissue rich in alpha adrenoreceptors.
- Glandular tissue under the influence of androgens.

Both alpha adrenoreceptors and androgens are targets for drug therapy.

1.Alpha1-adrenoceptors blockers e.g. prozosin, terazosin

- ↓ prostatic congestion → ↑ the maximal urine flow rate.
- Additional effect → ↓ BP in hypertensive patients. (effective for old patients who usually have hypertension along with BPH)

Major adverse effect:

1st dose hypotension & postural hypotension (avoided by starting with low doses and taking the dose while setting)

Tamsulosin doesn't block vascular α1-adrenoceptors → avoid undesirable side effects of other alpha-blockers so it's used in normotensive patients.

2. Antiandrogen: Finasteride - Dutasteride which might cause erectile dysfunction so combined with 3. Phosphodiestrase type-5 inhibitor: (if ED developed due to antiandrogen)