ANDROGENS & THEIR ANTAGONISTS

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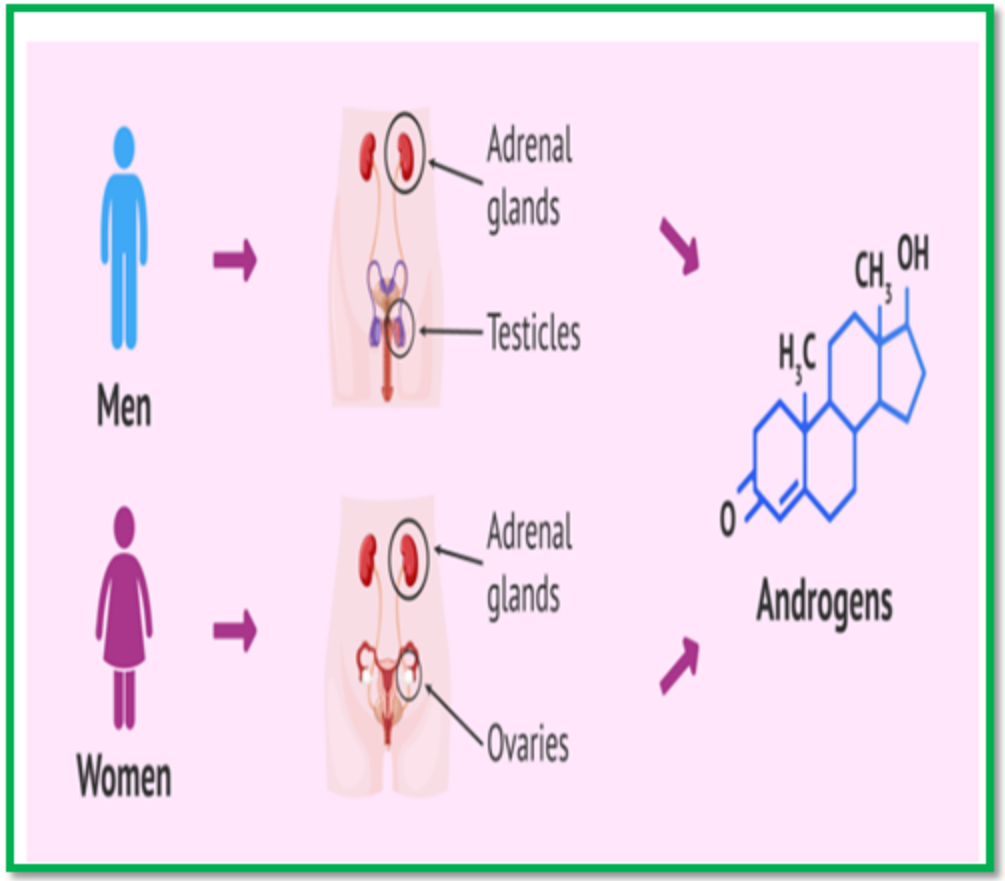
Mu'tah University- Faculty of Medicine-JORDAN 2025/2026

Objectives

- **Androgens**: synthesis, regulation of secretions, fate, metabolism
- Physiological functions of androgens
- **Testosterone**: preparations, indications, adverse effects and contraindications
- Anabolic Androgenic Steroids
- Anti-androgenic drugs
- GnRH analogues (Antigonadotropins)
- Androgen Receptor (AR) Antagonists: steroidal and non-steroidal
- Androgen Synthesis Inhibitors
- 5-alpha-reductase Inhibitors

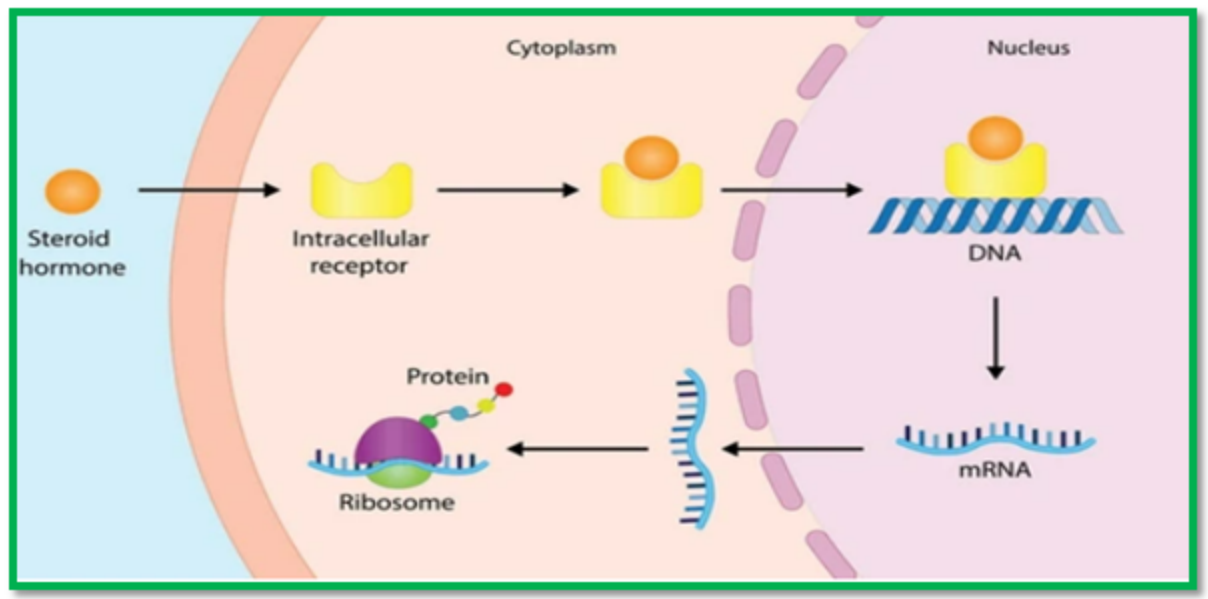
Androgens

- Androgens are the male sex hormones and include **testosterone**, **androsterone** and **androstenedione**.
- **The main function** of these hormones is **to promote the development of sexual characteristics in male, such as beard and voice tone.**
- **Other Androgens functions :**
- The human metabolism.
- Insulin sensitivity.
- Regulation of the amount and distribution of body fat and muscle tissue.

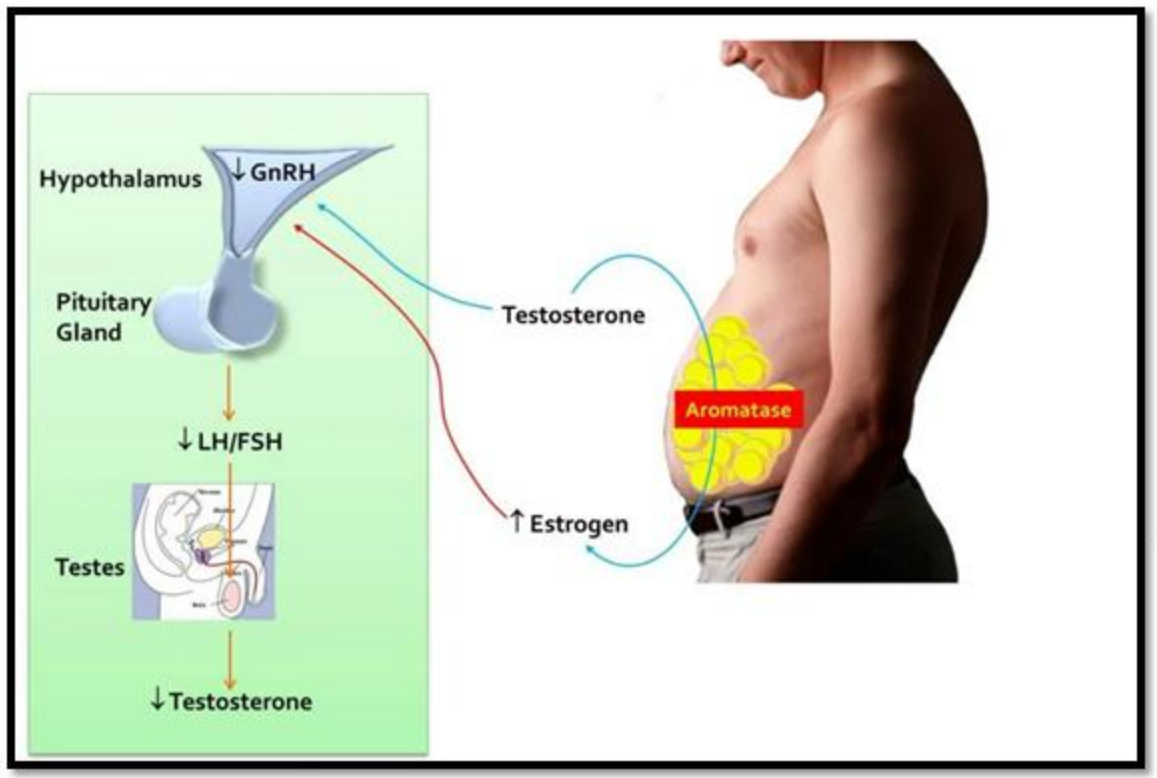


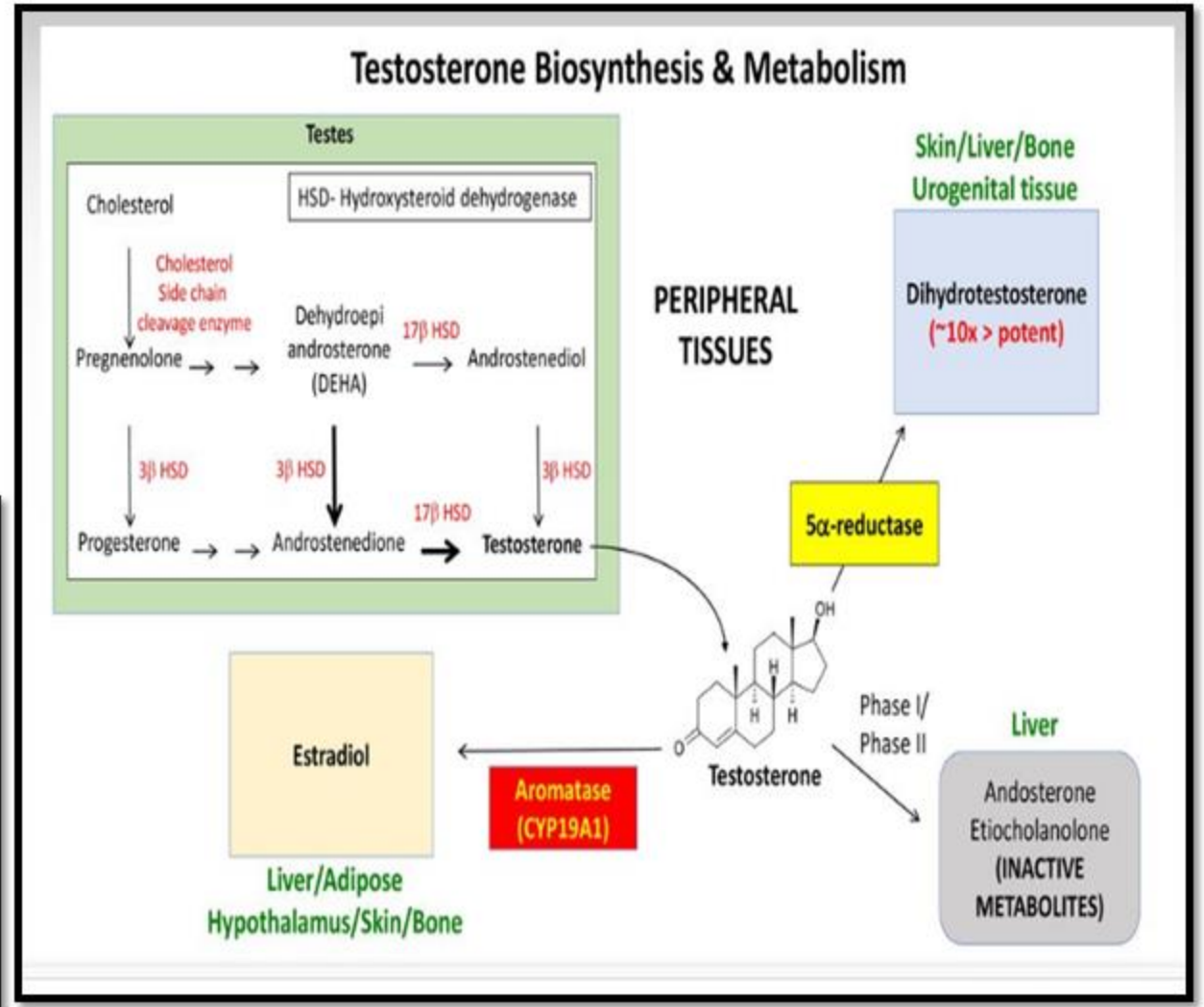
Testosterone

- Testosterone is the main androgen produced in testis by interstitial cells of Leydig under influence of (LH).
- There are specific androgen receptors (AR) in cytoplasm of target cell.
- **Androgen receptor**: ligand-dependent nuclear transcription factor and member of the steroid hormone nuclear receptor family.
- Testosterone has androgenic and anabolic actions.

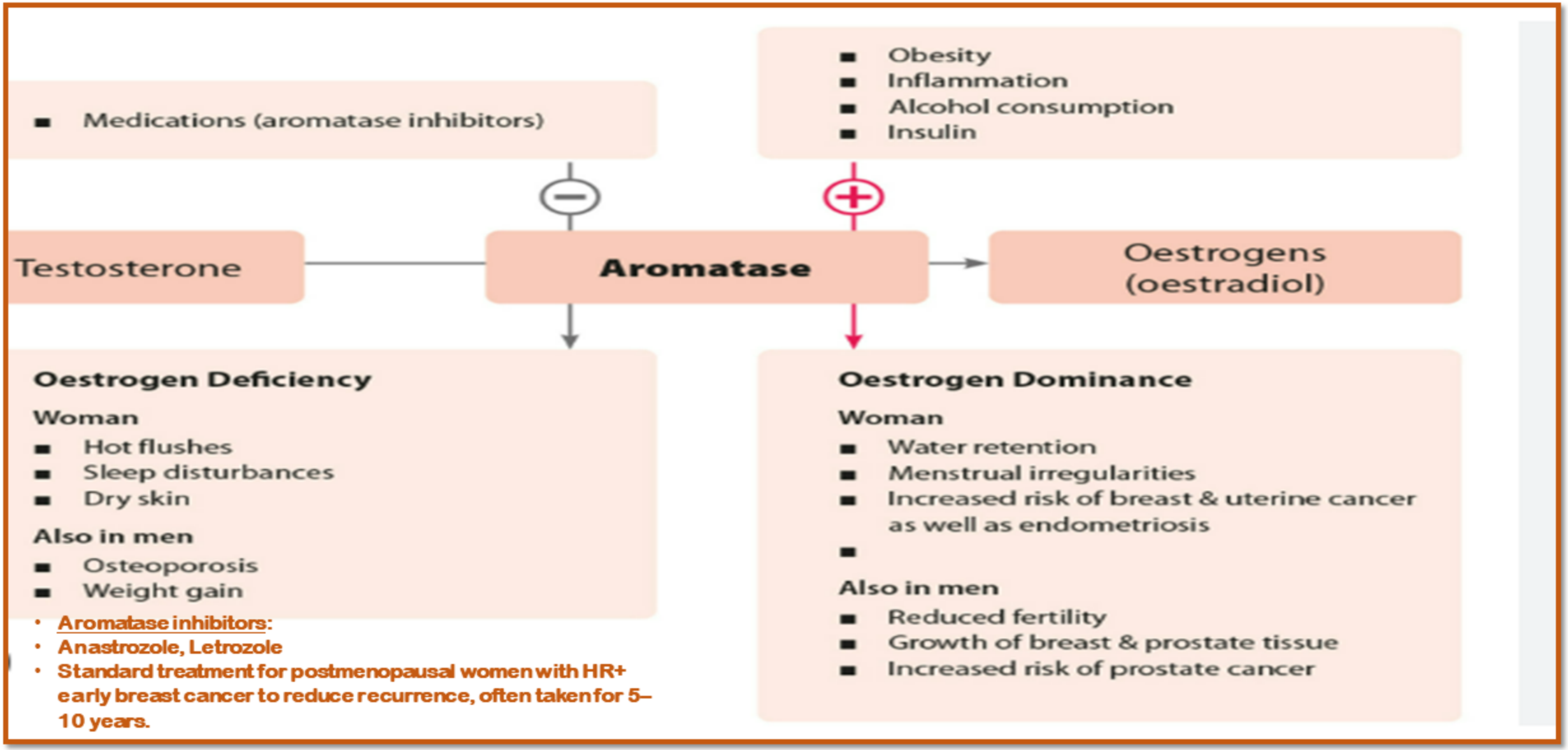


Fate of testosterone

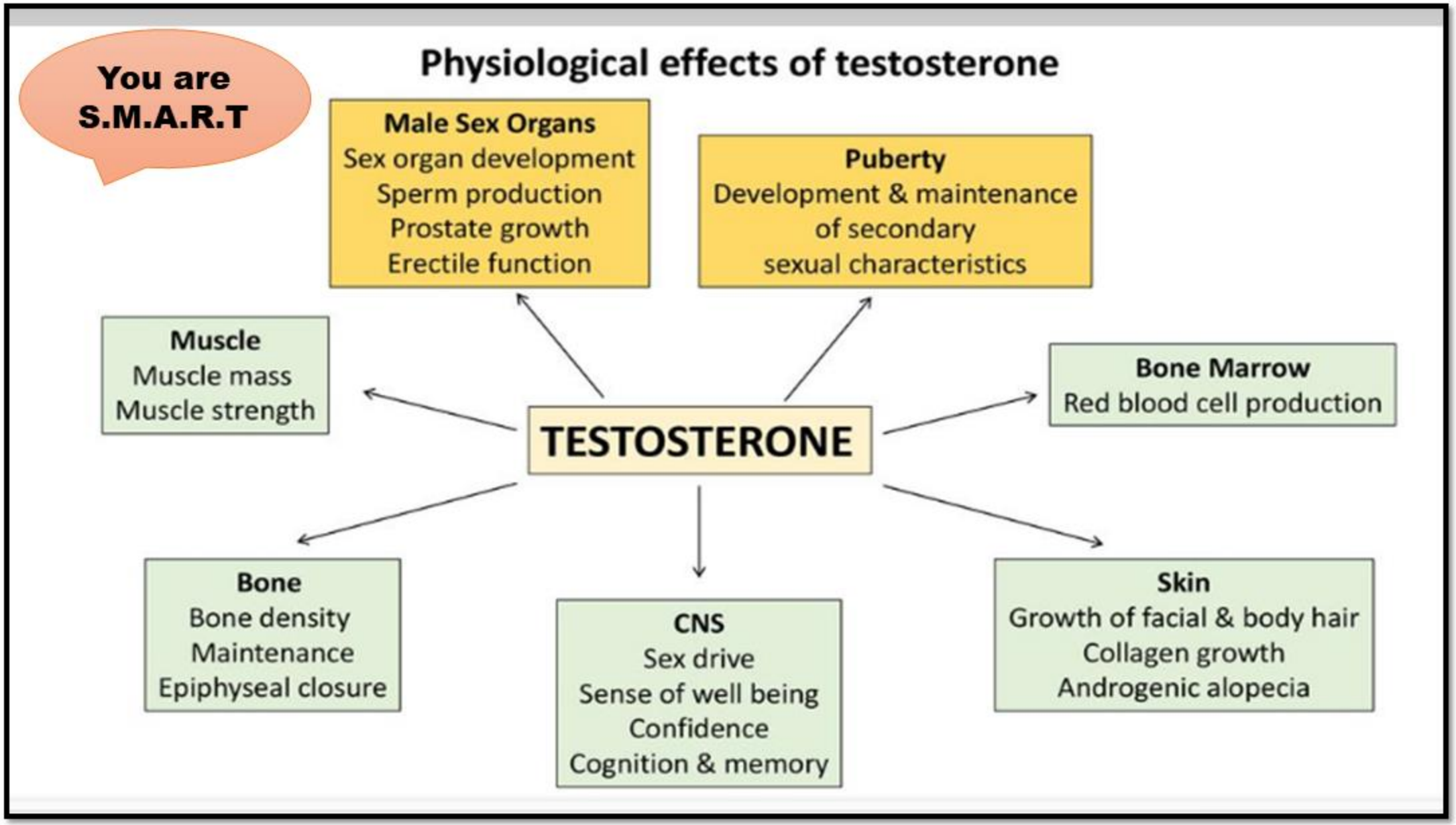




Aromatase pathway: estrogenic pathway of testosterone

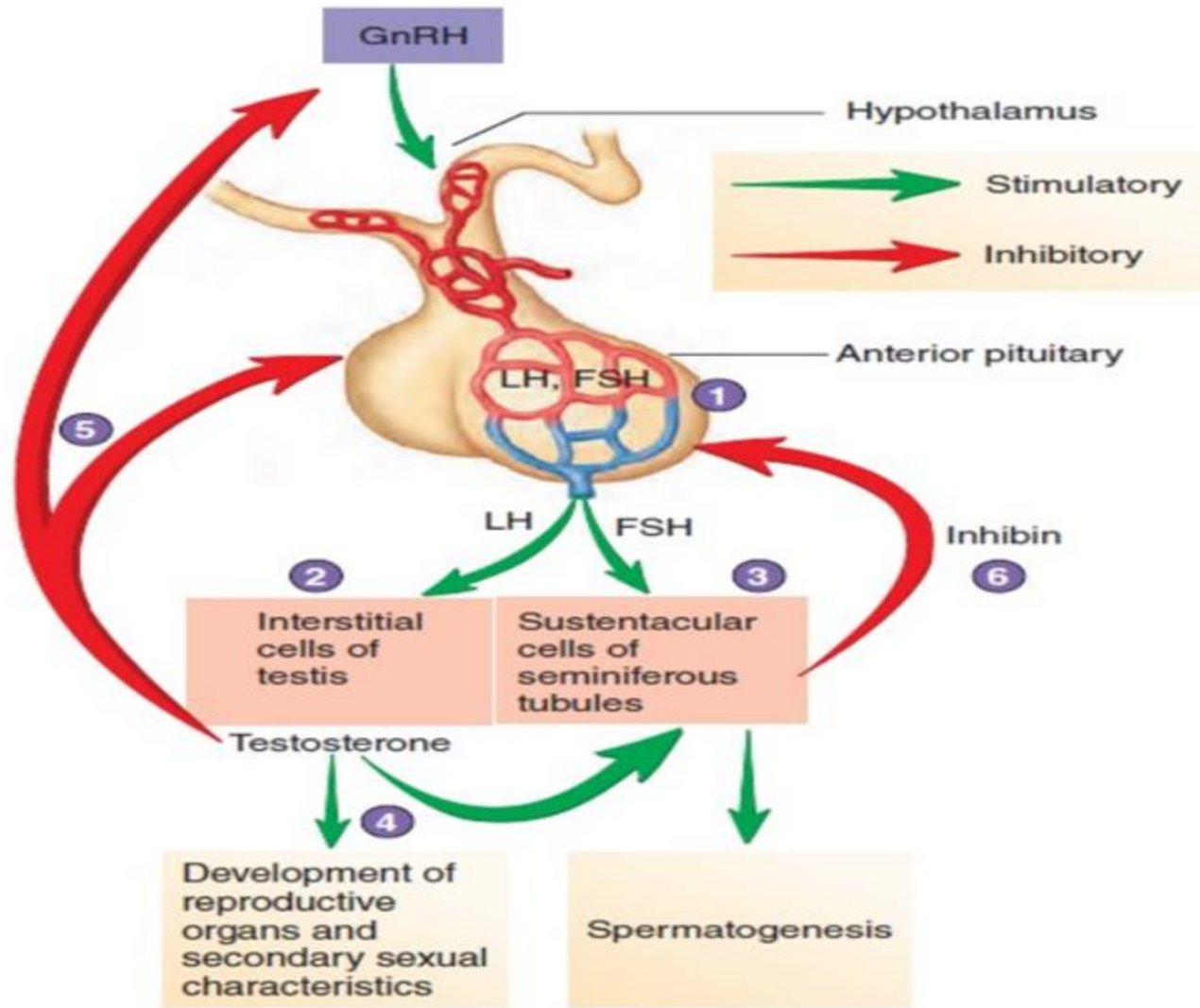


- Aromatase inhibitors:
- Anastrozole, Letrozole
- Standard treatment for postmenopausal women with HR+ early breast cancer to reduce recurrence, often taken for 5–10 years.


You are S.M.A.R.T
Physiological effects of testosterone
Male Sex Organs
Sex organ development
Sperm production
Prostate growth
Erectile function
Puberty
Development & maintenance of secondary sexual characteristics
Muscle
Muscle mass
Muscle strength
Bone Marrow
Red blood cell production
TESTOSTERONE
Bone
Bone density
Maintenance
Epiphyseal closure
CNS
Sex drive
Sense of well being
Confidence
Cognition & memory
Skin
Growth of facial & body hair
Collagen growth
Androgenic alopecia

Regulation of testosterone synthesis and secretion

1. Gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary.
2. LH stimulates testosterone secretion from the interstitial cells.
3. FSH stimulates sustentacular cells of the seminiferous tubules to increase spermatogenesis and to secrete inhibin.
4. Testosterone has a stimulatory effect on the sustentacular cells of the seminiferous tubules, as well as on the development of reproductive organs and secondary sexual characteristics.
5. Testosterone has a negative-feedback effect on the hypothalamus and pituitary to reduce GnRH, LH, and FSH secretion.
6. Inhibin has a negative-feedback effect on the anterior pituitary to reduce FSH secretion.



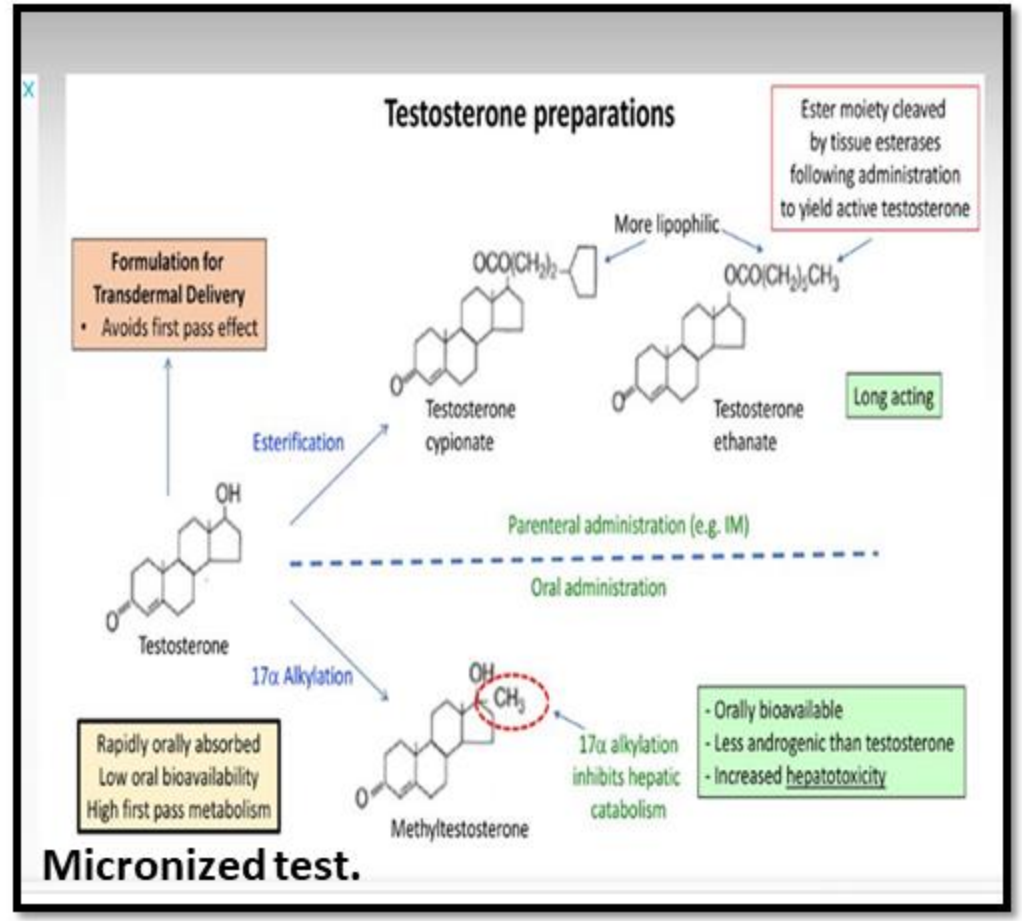
Testosterone preparations

- Testosterone preparations are available in various forms: injections, gels, solutions, patches, pellets, and oral
- Are designed to normalize serum testosterone levels.
- **Injectable Testosterone (Most Common):**Testosterone **Cypionate/Enanthate**:
- Short-acting, often injected every 1–2 weeks.
- Testosterone **Undecanoate:** Long-acting, typically injected every 10–14 weeks.
- **Topical Gels/Solutions**: Applied daily to shoulders, upper arms, or abdomen.
- **Transdermal Patches**: Applied daily to the skin, providing continuous delivery.
- **Subcutaneous Pellets**: Surgically implanted under the skin, lasting 3–6 months.
- **Intranasal Gel**: Applied to the nasal mucosa, usually 2-3 times daily.
- **Oral Testosterone Undecanoate (TU):**
- A long-chain fatty acid ester of testosterone.
- Its high lipophilicity allows it to be absorbed via the intestinal lymphatic system rather than the portal vein, bypassing liver degradation.
- Orally twice daily

Oral Testosterone preparations

- **17-alpha Alkylation (Historical):** Early oral formulations like methyltestosterone were modified at the (17)-(alpha) position to prevent liver inactivation.
- While effective, this structure caused significant hepatotoxicity.
- **Micronized Testosterone**: Oral native testosterone that is micronized (reduced in size)
- Disadvantages: very low and variable bioavailability
- **Modified Release**: Some newer formulations are designed with lipids to create a slow-release effect, aimed at reducing the high fluctuations characteristic of older oral preparations.

Testosterone preparations



Indications of androgen therapy

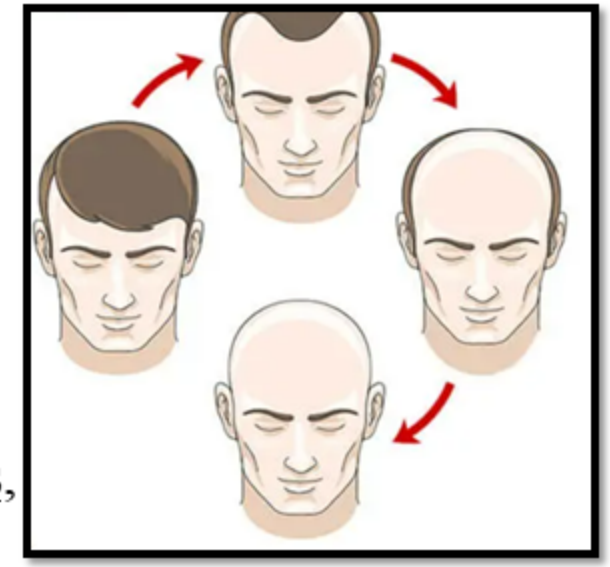
- **Testosterone replacement therapy TRT:**
- Primarily indicated for treating symptomatic, biochemically confirmed **hypogonadism in men**.
- Low serum testosterone (<250-300 ng/dL) and clinical symptoms.
- **Male Hypogonadism (Primary/Secondary):** testicular failure (primary) or pituitary/hypothalamic dysfunction (secondary)
- **Symptoms of Testosterone Deficiency**: as reduced libido, erectile dysfunction, low energy, loss of muscle mass, or sparse beard growth.
- **Delayed Puberty:** Used in adolescent boys to induce sexual maturation and pubertal development.
- **Cachexia/Wasting States**: sever weight loss, often associated with HIV/AIDS or chronic illnesses.
- **Refractory Anemias:** (e.g., aplastic anemia) due to erythropoiesis stimulation

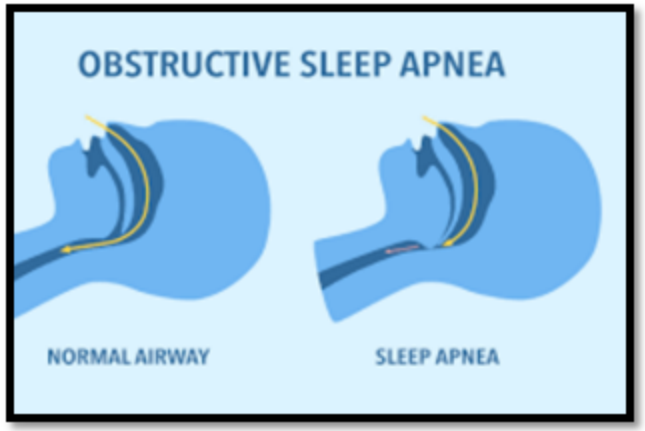
Testosterone indications and therapeutic uses

Male hypogonadism		
Primary	Disease of testes	- Sperm & testosterone < normal - LH & FSH > normal (no negative feedback)
Secondary	Hypothalamus/ Pituitary Disease	- Sperm & Testosterone < normal - LH & FSH < normal

Adverse effects of androgen therapy

- **Common Physical and Emotional Effects**
- **Skin and Hair:** Acne, oily skin, and increased male pattern baldness (androgenetic alopecia).
- **Body Changes:** Fluid retention (edema), weight gain, (gynecomastia).
- **Sexual Function:** Potential for painful or prolonged erections (priapism).
- **Emotional/Cognitive:** Irritability, mood swings, increased aggression.
- **Serious Potential Risks**
- **Cardiovascular Risks:** Possible increased risk of stroke, MI, and blood clots, especially in older men or those with existing cardiovascular disease.
- **Blood Disorders:** High red blood cell count (erythrocytosis), which requires monitoring to avoid increased blood viscosity and thrombosis.
- **Sleep Apnea:** Worsening of existing sleep apnea or development of new breathing disorders during sleep.
- **Prostate cancer:** higher PSA levels (prostate-specific antigen) or exacerbating existing prostate problems.
- **Fertility:** Lowered sperm count, which can lead to infertility.





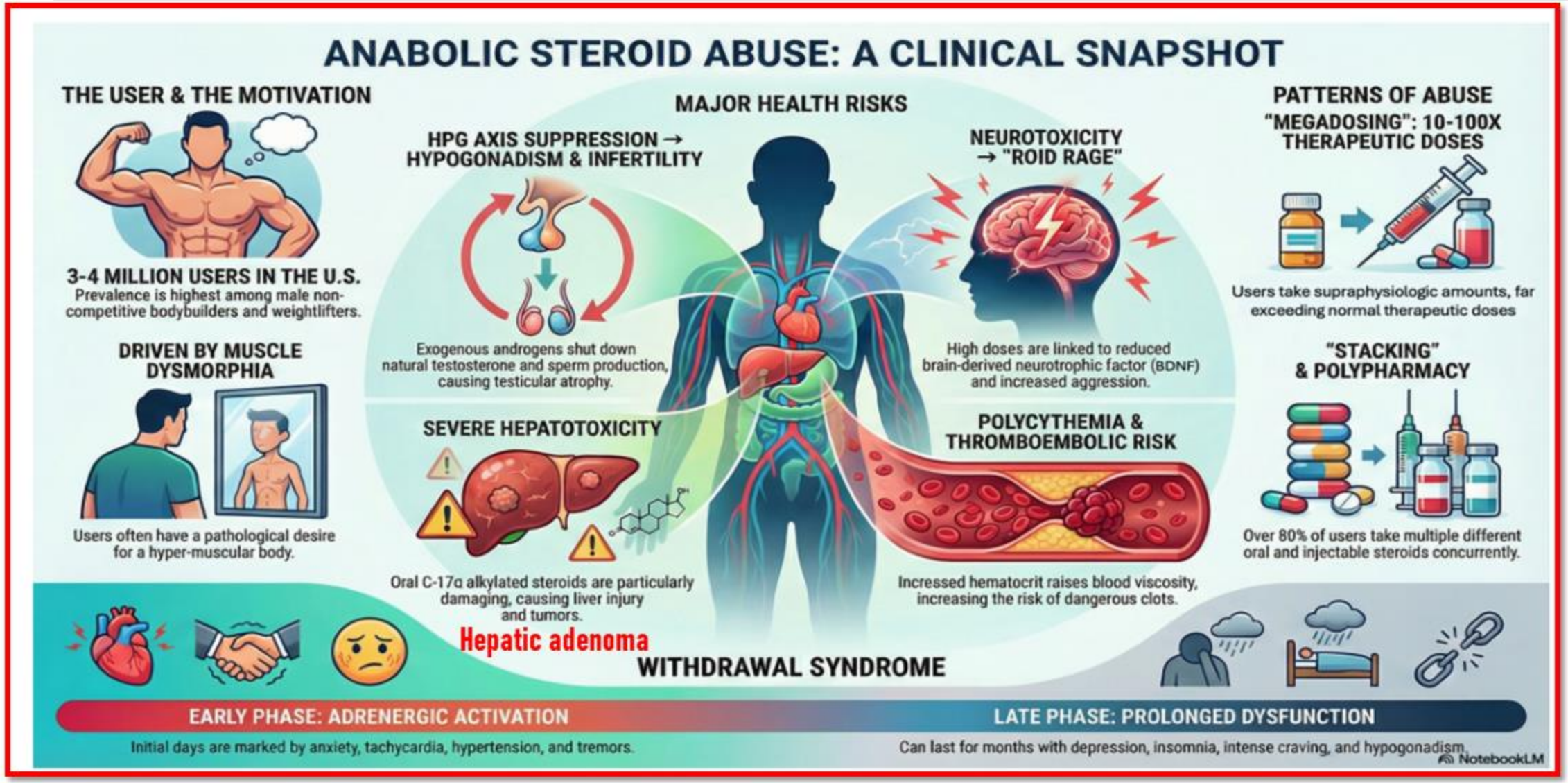
Contraindications of testosterone therapy

- **Cancer:** Prostate cancer and breast cancer.
- **Hematological:** Elevated hematocrit >54% or hemoglobin >17 g/L, due to risks of polycythemia.
- **Cardiovascular:** Uncontrolled or sever heart failure (NYHA Class IV).
- **Respiratory:** Untreated or severe obstructive sleep apnea.
- **Urological:** Palpable, undiagnosed prostate nodule or prostate-specific antigen (PSA) >4 ng/mL without investigation.
- **Infertility**

Androgens as performance enhancing drugs

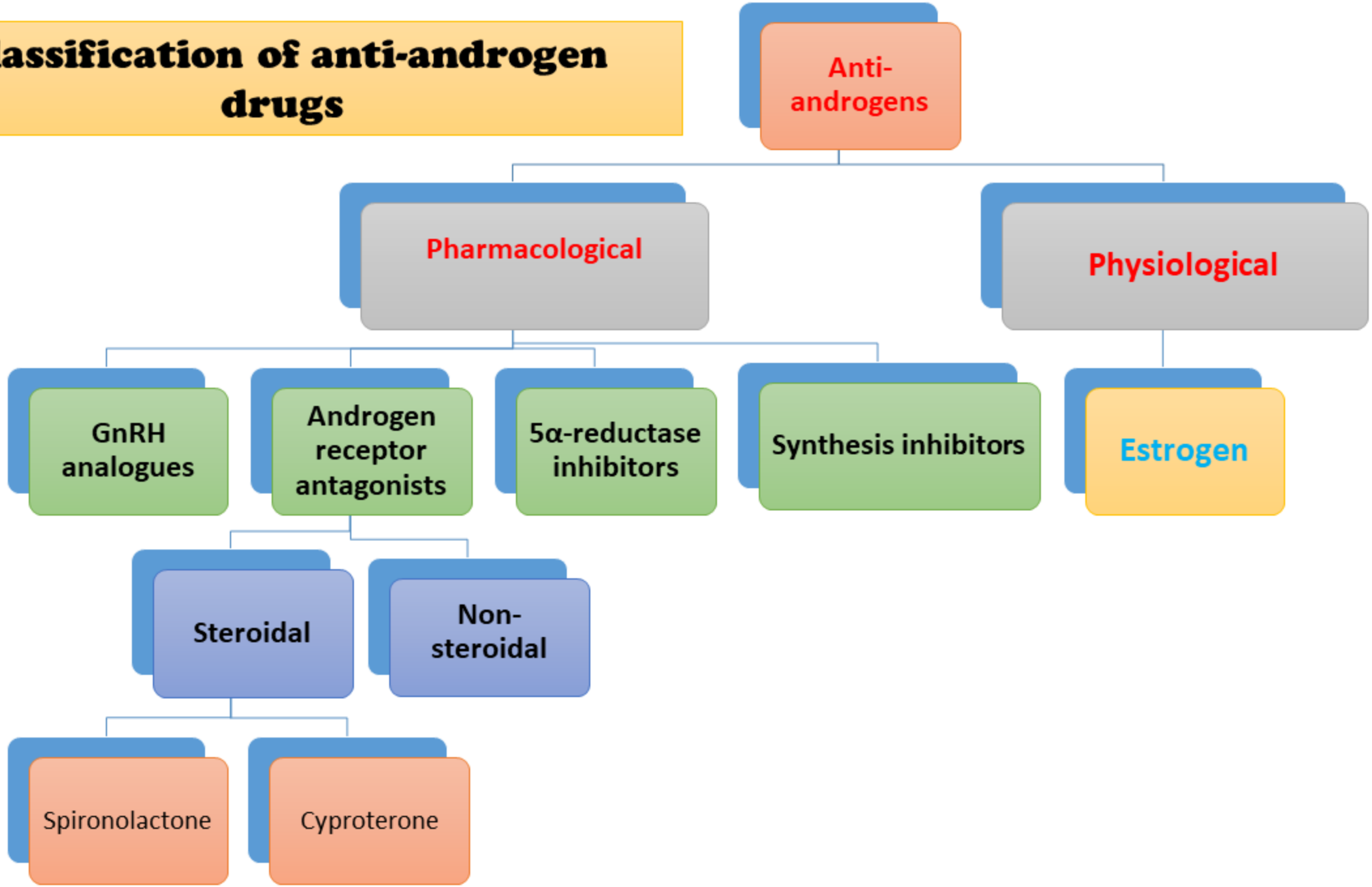
- **Anabolic Androgenic Steroids (AASs)** –(**naturally** occurring or **synthetic**) hormones **increase lean body mass** and **decrease fat mass** and are the most frequently used class of **performance-enhancing drugs**.
- They can also have **significant adverse effects**, especially when used incorrectly.
- **Long-term**, **non-medical** uses are linked to heart problems, unwanted physical changes, and aggression.
- **Doping**: refers to the **use of banned substances** in competitive sports.

Androgens as performance enhancing drugs



Androgen antagonists (Anti-androgens)

Classification of anti-androgen drugs



1. GnRH analogues (Antigonadotropins)

- **Leuprolide**
- **Mechanism of action:** lower androgen levels by inhibiting the release of gonadotropins (LH/FSH), reducing overall sex hormone production
- Higher affinity for GnRH receptor in pituitary than endogenous GnRH.
- **Administration:** SC or IM of leuprolide (DEPOT FORM) every 1-4 months
- At first it will stimulate, then desensitizes GnRH receptor causing ↓ secretion of FSH & LH, so ↓ testosterone secretion in male or estrogen secretion in female.
- **Indications:**
- **1- Palliative treatment of prostate cancer** (androgen-dependent), usually with androgen receptor antagonist
- **2- Ovarian hyper-stimulation programs** for an-ovulatory infertility:
- to suppress endogenous Gn production: allows fertility specialists to use exogenous gonadotropins to stimulate multiple follicles to grow uniformly
- but pure GnRH competitive antagonists like Ganirelix are preferred for this suppression since they act rapidly.
- **Adverse effects:**
- Prolonged use of GnRH analogues may produce menopausal symptoms, and osteoporosis in females (if used longer than 6 months).

2. Androgen Receptor (AR) Antagonists: steroidal

- **Examples**: Cyproterone acetate, Megestrol
- **Cyproterone acetate :**
- **Mechanism of action**: blocks androgen receptors
- **Uses:** 1- Hirsutism.
- 2- Prostate cancer palliation
- **Dianette contains**: 2 mg cyproterone acetate (anti-androgen) and 35 ug ethinylestradiol (oestrogen). (**combined hormonal contraceptive pill**)
- **Uses:** skin conditions such as acne, very oily skin and excessive hair growth in females of reproductive age.
- **Administration:** One pill daily for 21 days, followed by a 7-day break (withdrawal bleeding).
- **Risk:** Higher risk of venous thromboembolism (blood clots) than some other contraceptive pills.
- **Spironolactone** :
- **Mechanism of action**:
- Competitive antagonist of AR
- Decreasing testosterone synthesis by inhibiting 17α-hydroxylase.
- **Uses:** Hirsutism, alopecia, acne

2. Androgen Receptor (AR) Antagonists: non-steroidal

- **Flutamide :**
- Used for palliation of prostate cancer.
- Its continued use may lead to ↑ LH secretion which ↑ testosterone synthesis, and may thus cause therapeutic failure.
- So usually it is combined with GnRH antagonist or replaced by cyproterone.
- **Adverse effects:**
- loss of libido, impotence, gynecomastia, reversible hepatic dysfunction, GI upset.
- **Bicalutamide**
- 1- Fewer GI side effects
- 2- No liver toxicity

3. Androgen Synthesis Inhibitors

- **CYP17A1 Inhibitors**: Block enzymes involved in testosterone production.
- **Example: Abiraterone acetate**
- **Mechanism**: Abiraterone acetate is a prodrug that is converted in the body to abiraterone, which acts as a potent, irreversible, and selective inhibitor of the CYP17 enzyme, blocking both 17 alpha-hydroxylase and 17,20-lyase activity.
- **Action**: It prevents the conversion of pregnenolone and progesterone into DHEA and androstenedione—the precursors required for testosterone and dihydrotestosterone (DHT) synthesis.
- **Clinical Use:** It is approved for the treatment of metastatic castration-resistant prostate cancer (CRPC)
- **Ketoconazole :**
- **Mechanism of action:**
- An antifungal agent that also acts as a non-selective, competitive inhibitor of **CYP17A1**.
- Found to be less effective than anti-androgens in prostate cancer.
- **Adverse effects**: gynecomastia- liver toxicity

3. Androgen Synthesis Inhibitors

- Prostate cancer often progresses by producing its own testosterone even when the testes are removed or suppressed (**castration resistance**).
- **CYP17A1 inhibitors**: blocking androgen production from both the adrenal glands and within the tumor itself, offering significant survival benefits in clinical trials

4-
5-alpha-reductase Inhibitors

- Prevent the conversion of testosterone to dihydrotestosterone (DHT).
- **Finasteride** : blocks synthesis of Dihydrotestosterone from testosterone in prostate and hair follicles by inhibiting the enzyme 5α-reductase type 2.
- **Indications:** **oral** in:
- **1- Benign prostatic hyperplasia in elderly**: (20% reduction in prostate size after 1 year of use)
- **2- Male pattern of baldness**
- **3- Hirsutism**
- Finasteride is **NOT useful** in prostate cancer since 5α-reductase 1 is still intact in other tissues e.g. liver, skin fibroblasts
- **Advantages of finasteride**:
- less likely to cause ↓ libido or impotence than androgen receptor antagonist

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THANK YOU