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Androgens and androgen antagonists

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Introduction

The **androgens** are a group of steroids that have **anabolic and/or masculinizing effects** in both males and females.

1-Testosterone is the most important androgen in humans, it is synthesized by Leydig cells in the testes and, in smaller amounts, by thecal cells in the ovaries and by the adrenal gland in both sexes.

2-Other androgens secreted in small amounts by the **testes:**

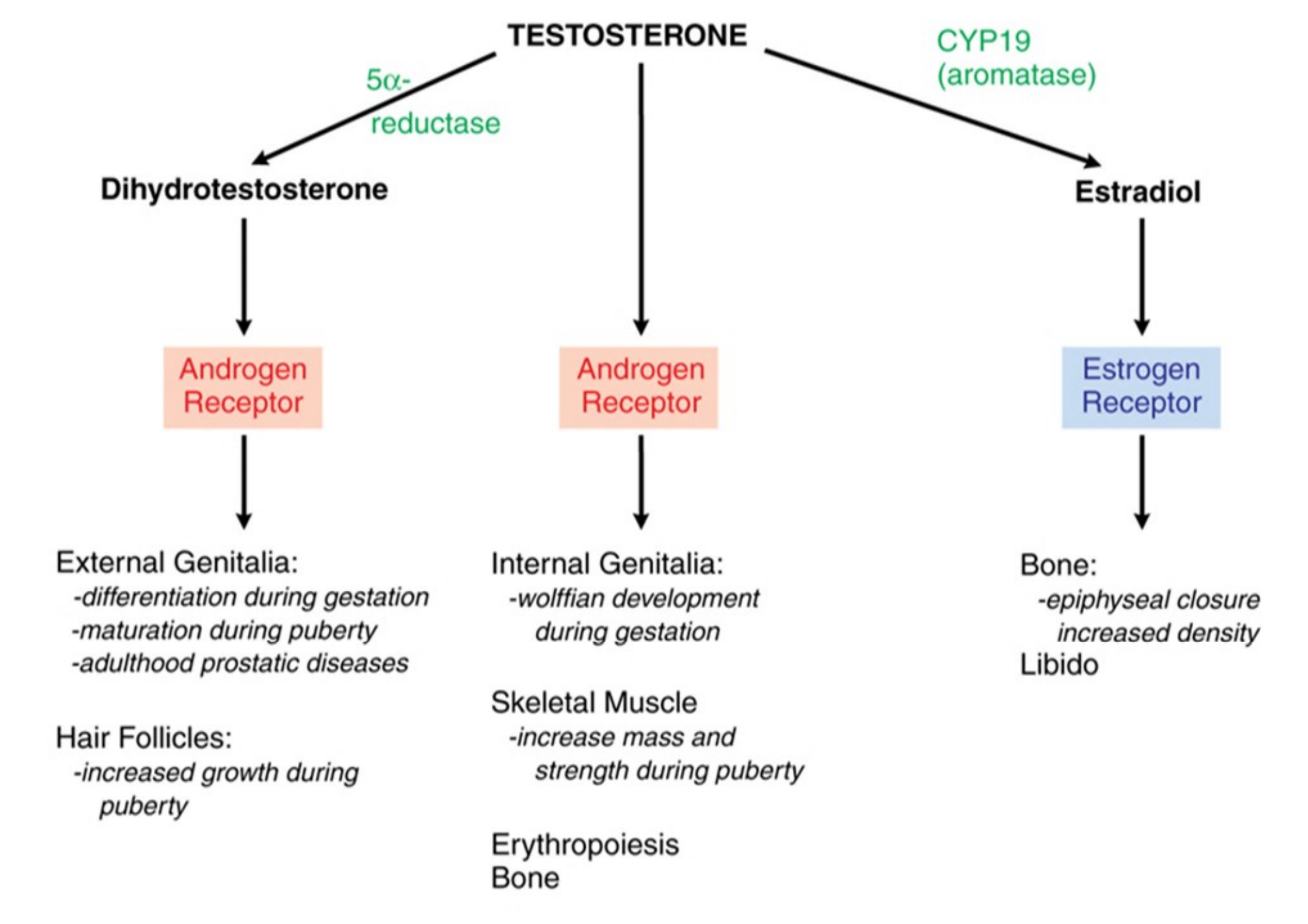
- ❑ 5α-dihydrotestosterone (**DHT**)
- ❑ androstenedione
- ❑ dehydroepiandrosterone (**DHEA**)

➢ In adult males, testosterone secretion by Leydig cells is controlled by gonadotropin-releasing hormone (**GnRH**) from the hypothalamus, which stimulates the anterior pituitary gland to secrete **FSH and LH**.

Testosterone or its active metabolite, **DHT,** inhibits production of these specific trophic hormones through a negative feedback loop and, thus, regulates testosterone production.

Mechanism of action of androgens

- Like other steroid hormones; androgens bind to a **specific nuclear receptor** in a target cell.
- Testosterone itself is the active ligand in skeletal muscles and the liver.
- However, in other tissues **(prostate**, **seminal vesicles**, **epididymis**, and **skin) ; Testosterone** must be metabolized by 5α-reductase to DHT which binds and activates androgen receptors.


TESTOSTERONE
5α-
reductase
CYP19
(aromatase)
Dihydrotestosterone
Estradiol
Androgen Receptor
Androgen Receptor
Estrogen Receptor
External Genitalia:
-differentiation during gestation
-maturation during puberty
-adulthood prostatic diseases
Hair Follicles:
-increased growth during puberty
Internal Genitalia:
-wolffian development during gestation
Skeletal Muscle
-increase mass and strength during puberty
Erythropoiesis
Bone
Bone:
-epiphyseal closure
increased density
Libido

Pharmacokinetics of androgens

1. Testosterone:

-It is **ineffective orally** because of inactivation by first-pass metabolism.

-C17-esters of testosterone (for example, **testosterone cypionate** or **enanthate**) are administered **intramuscularly**. [Note: The addition of the esterified lipid makes the hormone more lipid soluble, thereby increasing its duration of action.]

-**Transdermal patches or implants**, topical gels, and buccal tablets of testosterone are also available.

-Testosterone and its esters demonstrate a 1:1 relative ratio of androgenic to anabolic activity.

-As with the other sex steroids, **testosterone is rapidly absorbed** and is **metabolized** to relatively or completely inactive compounds that are excreted primarily in the urine.

2. Testosterone derivatives:

-Alkylation of the 17α position of testosterone **allows oral administration of the hormone.**

-**Fluoxymesterone** has a longer half-life in the body than that of the naturally occurring androgen. It is **effective orally**, and it has 1:2 androgenic-to-anabolic ratio.

-**Oxandrolone** is another **orally active testosterone derivative** with anabolic activity 3 to 13 times that of testosterone (that could be an explanation for its current status of the most popular A in sports doping and bodybuilding).

N.B: **Hepatic adverse effects have been associated with the 17α-alkylated androgens.**

3- Danazol

Danazol, a weak androgen, which is used in women mainly.

Physiological actions of androgens

1-Reproductive actions:

- **Growth**, **development** and **maintenance** of **primary** (genitalia and genital tract) and **secondary** sex characteristics in men.
- Early stages of **breast** and **pubertal** development in girls (**adrenarche**).
- Promote **spermatogenesis** (with **FSH**).
- **Neuroendocrine** regulation of gonadotropin secretion.
- **Stimulate libido**.

2-Anabolic actions:

- Increase protein synthesis.
- Increased lean body mass and body growth.
- Skeletal growth and closure of epiphyses of long bones at puberty and adolescence.
- Growth of larynx and voice deepening at puberty.

3-Metabolic/hematologic actions:

- Erythropoiesis (increase the production and effects of erythropoietin).
- Decreased synthesis of several clotting factors.
- Increased sebum production in skin.
- Decrease synthesis of HDL cholesterol, increase synthesis of LDL-cholesterol
- Androgenic alopecia (male pattern baldness)
- Increases bone density (direct and indirect after conversion to estrogen).

Therapeutic uses of androgens

1.Hormone replacement therapy (HRT) in primary or secondary hypogonadism in males.

N.B. Androgen replacement alone can't restore fertility in males.

2. **Induction of puberty in delayed maturation**.

3. To help enlargement of a **micropenis** (systemic or topical testosterone).

4. Treatment of **osteoporosis in males.**

5. Treatment of **Hereditary Angioneurotic Edema**: the 17a-Alkylated androgens stimulate the production of C1 esterase inhibitor and can therefore be used to prevent angioedema (e.g. danazol)

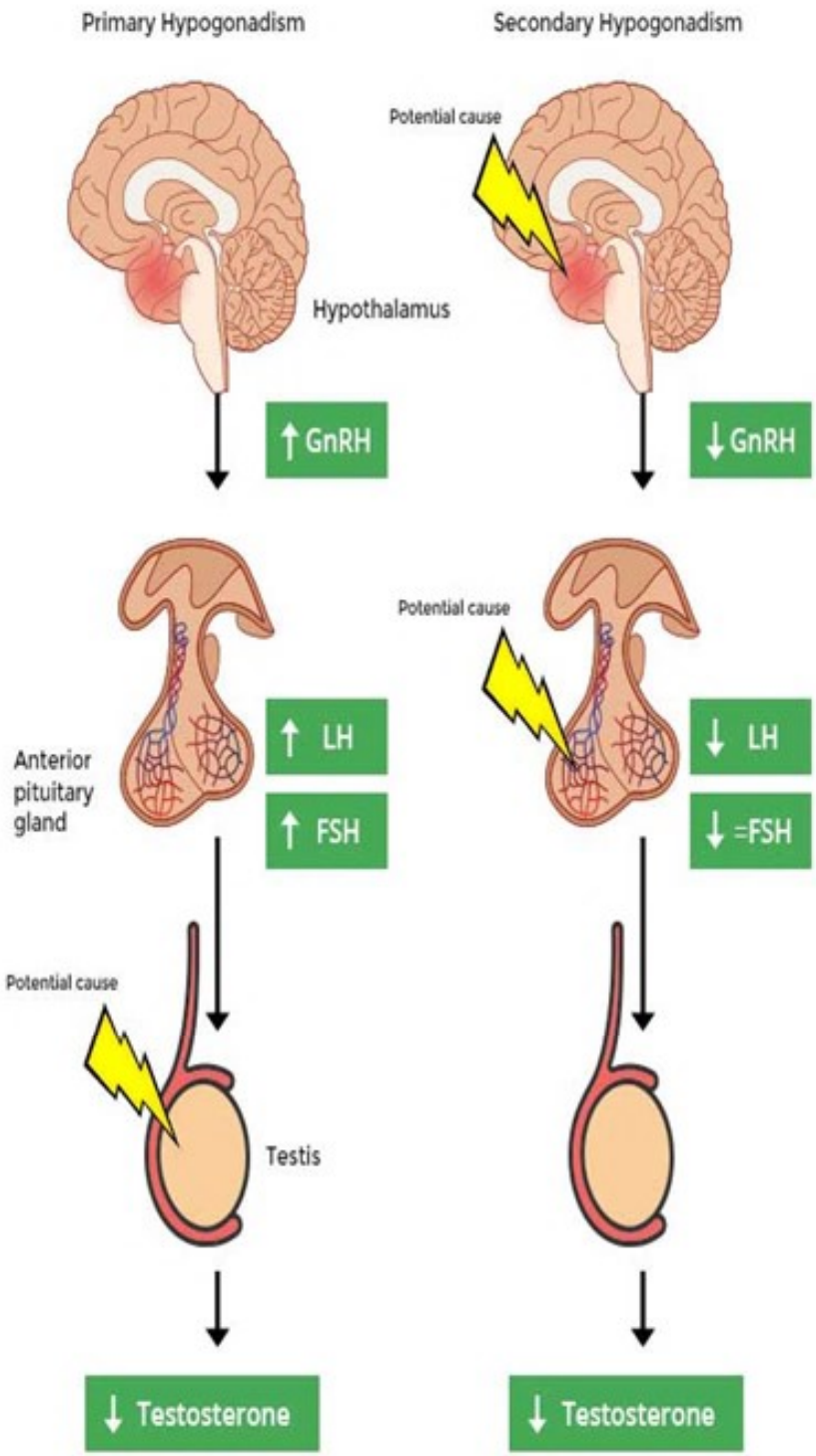
6. Treatment of **Hematological Disorders**

Androgens can also be beneficial to treat patients with anemia due to chronic renal failure (erythropoietin is very expensive and androgens can be used alone or in combination with erythropoietin), aplastic anemia, Fanconi's anemia, hemolytic anemia, and sickle cell anemia.

- Primary hypogonadism (low testosterone & elevated LH and FSH).
- Secondary hypogonadism (low testosterone & low LH and FSH).

➢In males with primary hypogonadism, androgen-dependent processes can be stimulated and maintained by exogenous hormone replacement; however, **fertility cannot be induced by hormonal therapy**.

➢For secondary hypogonadism in males who are potentially fertile, there are two treatment options, exogenous testosterone (without achieving fertility) or **exogenous gonadotropins**, which can stimulate endogenous secretion and spermatogenesis until paternity is achieved.



Experimental and other Uses of Androgens

1- Male Contraception (exogenous large doses of androgen can inhibit Gonadotropin secretion, resulting in **inhibition of spermatogenesis**).

2- Treatment of Wasting Syndromes: Androgens increases skeletal muscle mass and can prevent or reverse the **sarcopenia** associated with aging, human immune deficiency virus (HIV) infection, cancer, chronic illness, major surgery, or burns could result in an improved quality of life.

✓**N.B. Androgens are used to improve muscle wasting in AIDSA patients.**

3- Treating constitutional tall stature in boys (predicted adult height of 205 cm) in some European countries. Supra-physiological doses of testosterone are given until epiphyseal closure occur. Because tall stature is often desirable, this treatment is very rarely indicated.

Androgen therapy in women

1-Adrenal insufficiency.

2- **Benign fibrocystic breasts** (**danazol**) to decrease pain and tenderness.

3- Advanced ER-positive **breast cancer.**

4- **Endometriosis** (**Danazol** is given)

5- Premature ovarian failure (e.g., Turner's syndrome, surgical menopause, chemotherapy, irradiation).

6- Symptomatic deficiency following **natural menopause**.

- **Estrogen replacement** therapy further **reduces free testosterone levels** and thereby may enhance the symptoms of androgen deficiency.
- Testosterone is usually recommended in combination with estrogen (this will increase bone density more than estrogen alone; however, the risk of fractures is not affected).

Misuse of androgens

❑Androgens (DHEA for example) promote nitrogen retention, muscle mass, & hematopoiesis. This led to their use to improve physical performance by both male and female athletes (**weightlifters, bodybuilders,** and others).

❑Athletes obtain the anabolic steroids from "**black market**s" on the Internet and non-medical sources. These anabolic steroids are consumed in **extremely high doses** and along **with other drugs.**

➢Because the misuse of androgens is clearly an escalating problem, urine and blood testing prior to many athletic events is needed.

The toxic effects of anabolic steroids include:

1-Cardiovascular : **Cardiomyopathy**, **acute myocardial infarction**, pulmonary embolism, **arrhythmia**, and possible sudden death.

2- **Decreased testicular size**, and decreased spermatogenesis.

3- Hepato-renal (cholestatic **jaundice**, **tumors**, and kidney failure).

3- Psychological (increased aggression, dysphoria, **psychosis**, **addiction**, **withdrawal-like symptoms**, and depression).

4- Needle sharing may transmit hepatitis and HIV infection.

✓There is no evidence that anabolic steroids cause breast cancer.

Adverse effects of androgens

1. In females:

Androgens can cause masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development. **Menstrual irregularities** may also occur.

Testosterone should not be used by pregnant women because of possible virilization of the female fetus.

The effects on body composition, lipids, risk of coronary heart disease, and hormone-dependent cancers (breast, uterus, ovary) remain unclear.

2. In males:

Excess androgens can cause **priapism**, **impotence**, **decreased spermatogenesis**, **gynecomastia** and **acne**.

Androgens can also stimulate growth of the prostate and can cause prostatic hyperplasia, increasing risk of cancer prostate.

3. In children:

Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.

4. General effects:

Androgens can cause disturbed lipid profile (increase serum LDL and lower serum high-density lipoprotein levels). **Androgens can also cause fluid retention, leading to edema.**

Contraindication of androgen

1. Breast cancer in men
2. Prostate cancer
3. Pregnancy when used in women
4. Heart failure
5. Diabetes

Androgen Antagonists

For women

1- Women with polycystic ovary syndrome (PCOS) often have higher androgen levels (which cause excess hair growth, acne, and ovulation problems). Anti-androgens can help reduce these symptoms in women.

2- Other conditions that cause high levels of androgens in women include:

A. Adrenal hyperplasia and adrenal gland tumors.

B. Some ovarian tumors.

Anti-androgens can help manage these conditions and prevent complications caused by high androgen levels in women (**diabetes, hyperlipidemia, CV diseases).**

For men

In its early stages, prostate cancer cells rely on androgens to feed their growth. **Anti-androgens work by blocking androgens** from binding to androgen receptors in prostate cancer cells.

However, anti-androgens don't stop androgen production. **Surgical or chemical castration may be needed to achieve complete androgenic inhibition.**

Androgen receptor blockers

1-Flutamide

Mechanism : Competitive inhibition of androgen receptors and used in:

1. Metastatic prostate cancer.
2. Benign prostatic hypertrophy.

Side Effects: Hepatotoxicity, Diarrhea and Nausea, Rash, Hot Flashes, Hematopoietic disorders.

Contraindication: Severe hepatic impairment.

2-Spironolactone

- Spironolactone blocks androgen receptors and used as anti-androgen that to treat hormonal acne and excessive body hair.
- Hyperkalemia and gynecomastia are common adverse effects.

3- Cyproterone acetate

- It blocks androgen receptors in women to treat hirsutism and in men to decrease excessive sexual drive.
- It is rarely used now.
- It produces **oligospermia**

Inhibitors of Peripheral Testosterone Conversion to DHT

Finasteride and dutasteride

Mechanism of Action: Selective inhibition of type II 5 α-reductase; the enzyme responsible for conversion of testosterone to dihydrotestosterone in prostate, liver and skin.

Indications:

1. Benign prostatic hyperplasia.
2. Androgenic alopecia (But; dutasteride is more effective than finasteride for treating male pattern baldness).

Side Effects:

1. **Neoplasm of male breast** (rare and not yet investigated).
2. Breast tenderness.
3. Decreased libido.
4. Erectile dysfunction.
5. Ejaculatory disorder.
6- The use of 5α reductase inhibitors may increase the risk of type 2 diabetes.

17 alpha-hydroxylase inhibitor

- Abiraterone has been approved for use in metastatic prostate cancer.

Ketoconazole

Ketoconazole, used primarily in the treatment of fungal disease, is an inhibitor of adrenal and gonadal steroid synthesis,

It displaces estradiol and dihydrotestosterone from sex hormone binding protein in vitro and increases the estradiol: testosterone ratio in plasma in vivo by a different mechanism.

It can be used topically for treating hormonal acne.


Thank You!