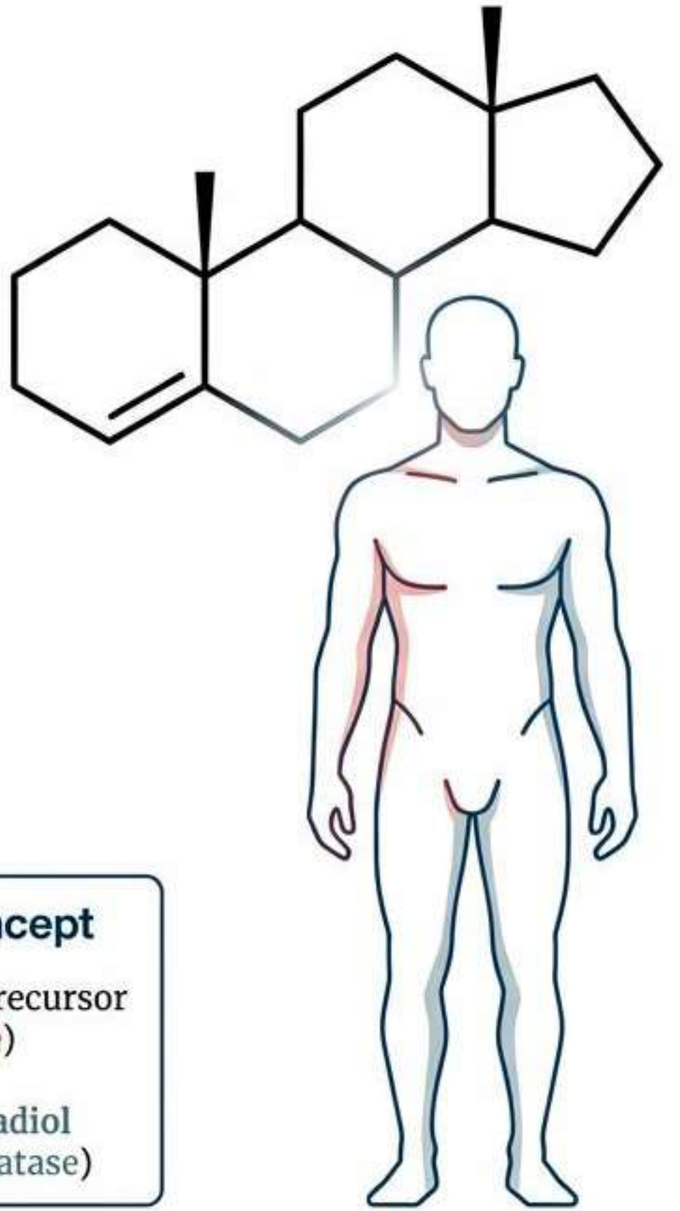
Androgens, Anti-Androgens & GnRH Modulators

Pharmacology, Mechanisms, and Clinical Applications of the Hypothalamic-Pituitary-Gonadal Axis



Definition: Androgens

A generic term for natural and synthetic steroidal drugs causing the development of secondary sexual characteristics (SSC) in the male.

Testosterone • Dihydrotestosterone (DHT) • Androstenedione

The Prohormone Concept

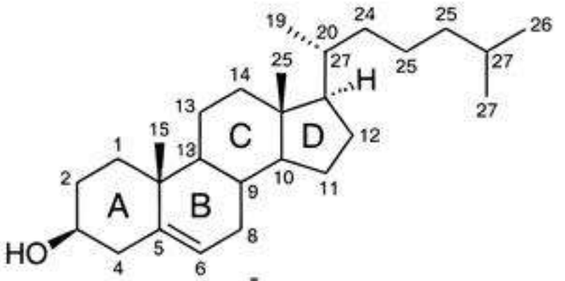
Testosterone serves as a precursor for DHT (via 5α-reductase)

↓ ↙

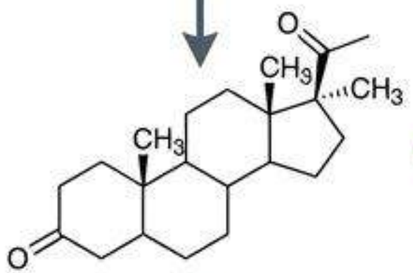
and Oestradiol ⟶ Oestradiol (via Aromatase)

Biosynthesis: The Steroid Cascade

Cholesterol
(27 carbons)

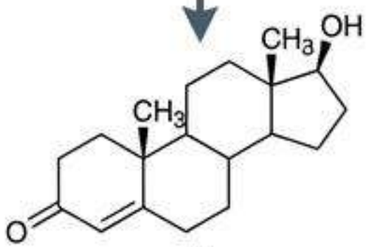


Pregnane derivatives
(21 carbons)



→ Progesterone / Corticoids

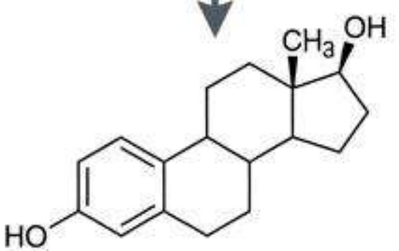
Androstane derivatives
(19 carbons)



→ Androgens

Synthesized primarily by
Leydig cells in the testes.

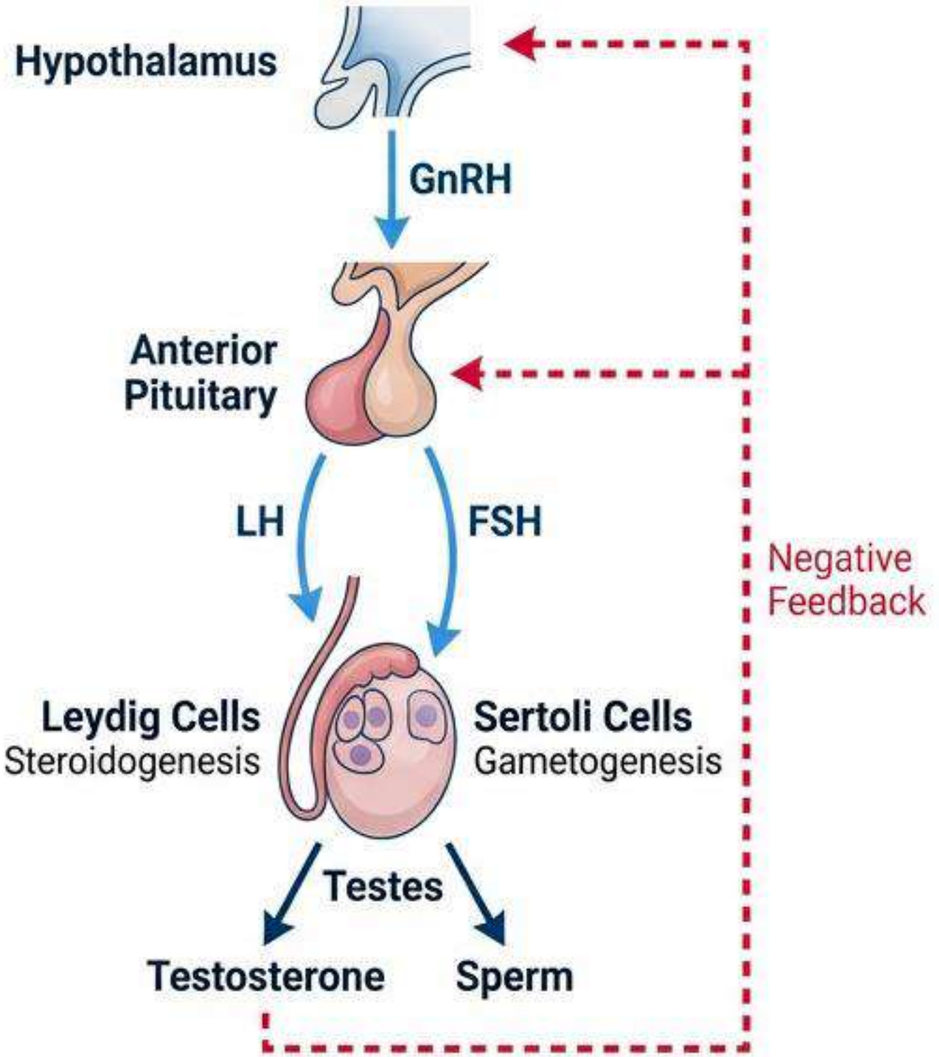
Estrane derivatives
(18 carbons)



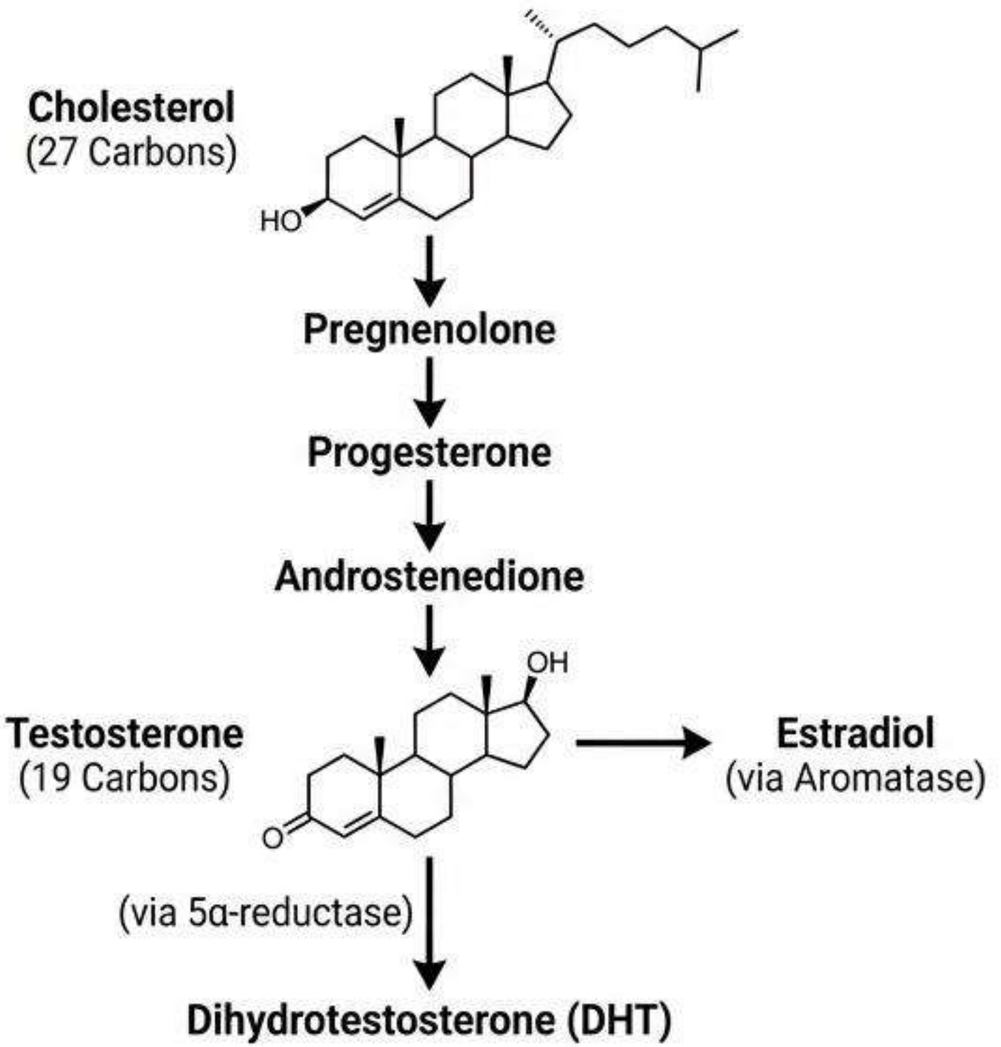
→ Estrogens

The Hypothalamic-Pituitary-Gonadal (HPG) Axis & Biosynthesis

Regulation of Secretion



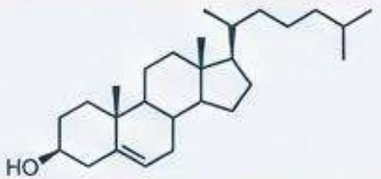
Steroidogenesis Cascade



Excretion: Metabolized by liver into androsterone; excreted in urine.

The Biosynthetic Pathway: Chemical Degradation

Cholesterol
(27 Carbons)



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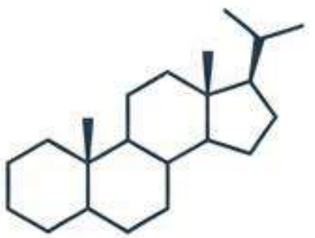
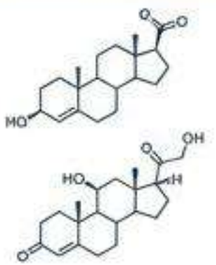
(21 Carbons)→ Progesterone / Corticoids





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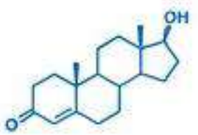
(19 Carbons) → Androgens



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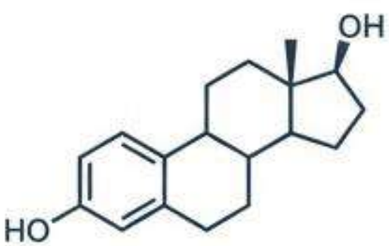
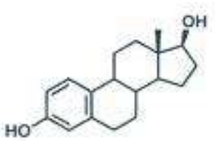
(18 Carbons) → Estrogens



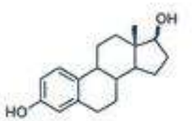


Key Insight

Testosterone is a Prohormone. It serves as a precursor for:

1. Dihydrotestosterone (DHT) - More potent androgen.

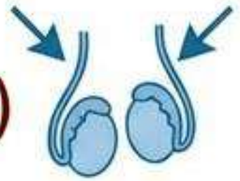
2. Estradiol - Via aromatization.



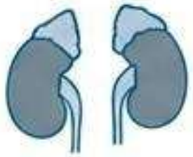
Secretion & Transport

Secretion Source

- 95% Leydig Cells (Testes)

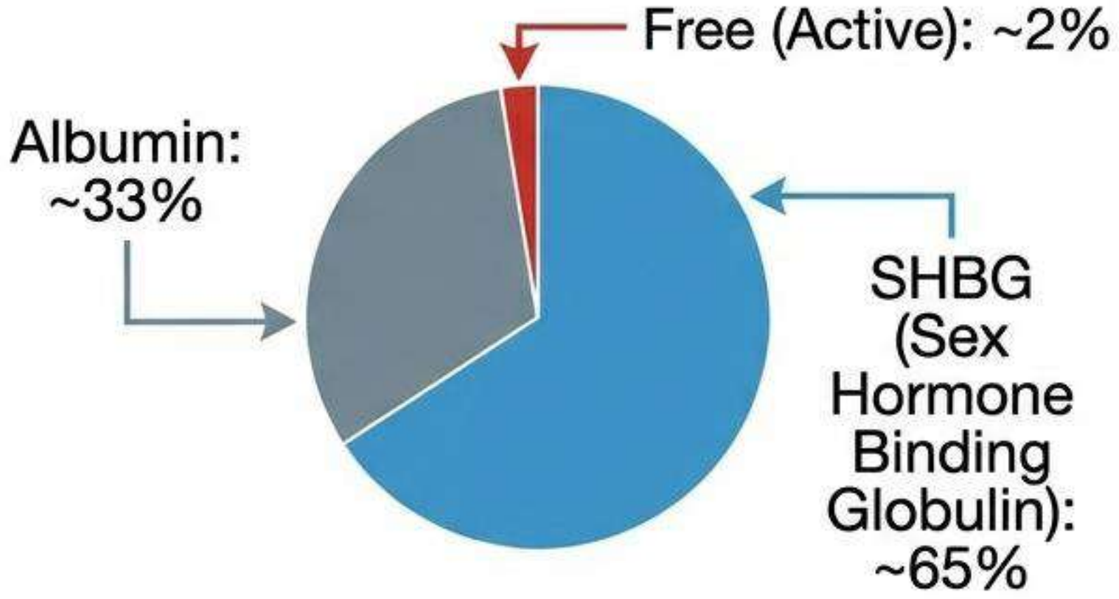


- 5% Adrenal Cortex



Note: Women produce small quantities in the ovary.

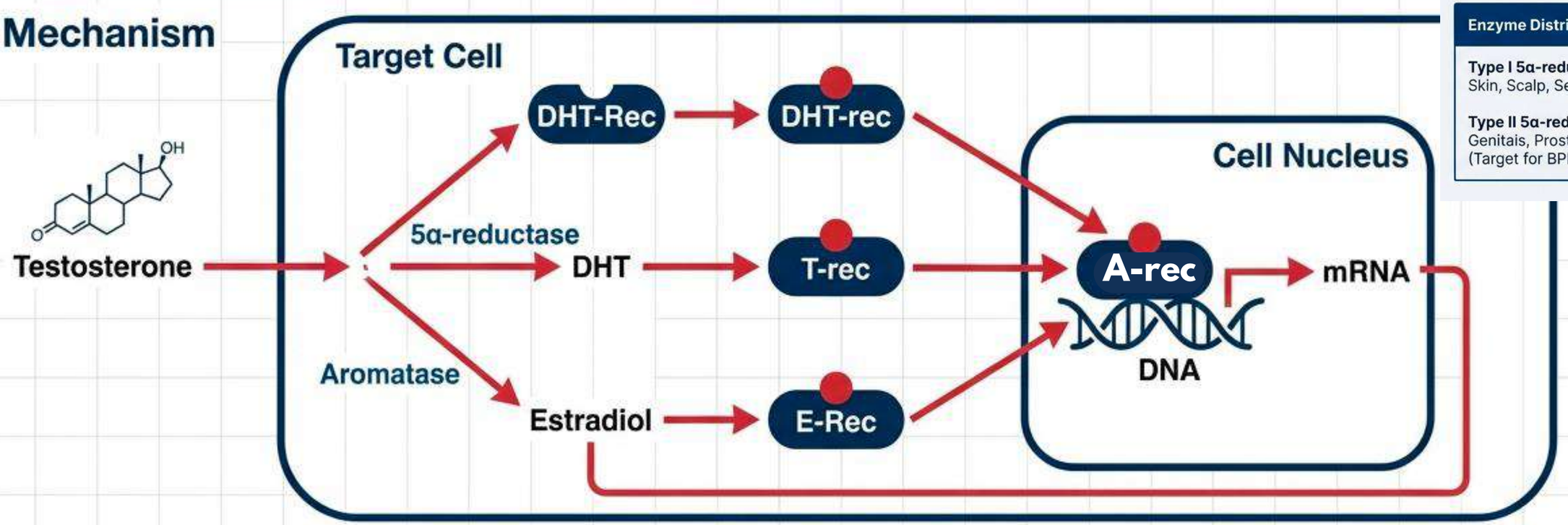
Transport in Plasma



Metabolism: Degraded in the liver into Androsterone and Etiocholanolone (excreted in urine).

Intracellular Mechanisms & Physiological Effects

The Mechanism



Enzyme Distribution

Type I 5α-reductase:
Skin, Scalp, Sebaceous Glands

Type II 5α-reductase:
Genitals, Prostate
(Target for BPH therapy)

The Effects

Testosterone (Direct Effects)

- Internal Genitalia
- Muscle Mass
- Erythropoietin (RBCs)
- Lipid Profile (↑ LDL, ↓ HDL)

DHT (External Virilization)

- External Genitals
- Prostate Growth
- Facial/Body Hair
- Acne / Sebaceous Glands

Oestradiol (Aromatization)

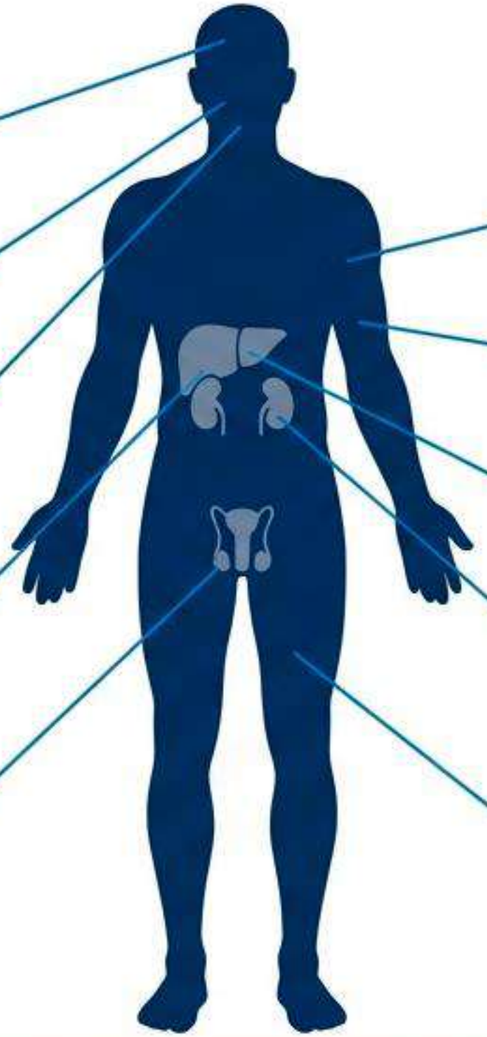
- Bone Density (Epiphyseal closure)
- Libido

General Anabolic Effects: Nitrogen retention, laryngeal growth (voice deepening), loss of subcutaneous fat.

Physiological Actions: The Androgenic vs. Anabolic Spectrum

Androgenic/Virilizing ♂

- Libido & Behavioral changes
- Facial hair growth
- Voice deepening (Larynx growth)
- Sebaceous gland secretion (Acne)
- Spermatogenesis, Prostate growth



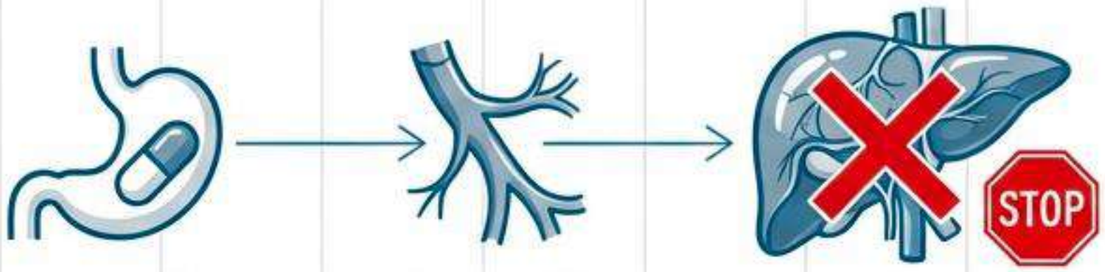
Anabolic/Metabolic

- Skeletal muscle hypertrophy
- Increased density, Epiphyseal closure
- Increased Erythropoietin (EPO)
- ↑ Increased LDL, ↓ Decreased HDL
- Sodium & Water retention (Edema)

Differentiation: Synthetic AAS aim to maximize Anabolic effects (Right) while minimizing Androgenic effects (Left).

Pharmacokinetics: The First-Pass Barrier

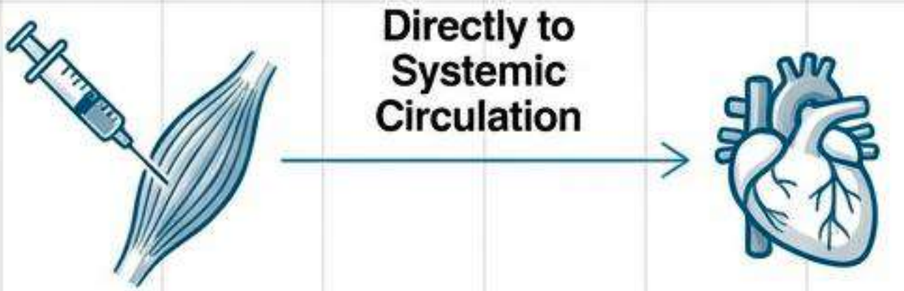
Oral Path



Oral Pill → Portal Vein → Liver

High first-pass metabolism renders natural testosterone ineffective orally.

Injection Path

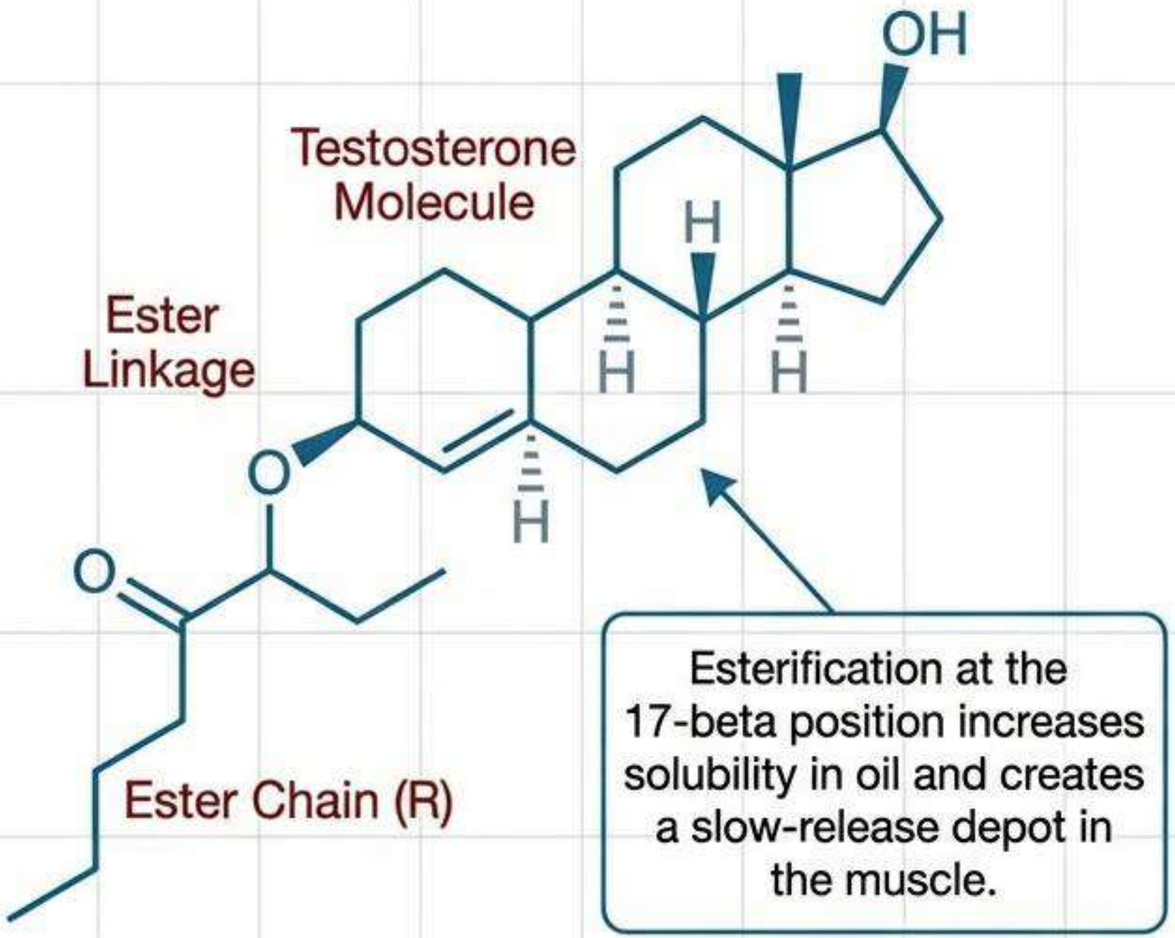


IM Injection → Directly to Systemic Circulation → Systemic Circulation

Solution Strategy

- 1. Parenteral Esters (IM Injection) – Avoids liver initially.
- 2. 17-alpha-Alkylation (Oral) – Resists hepatic breakdown.
- 3. Transdermal/Lymphatic – Bypasses portal circulation.

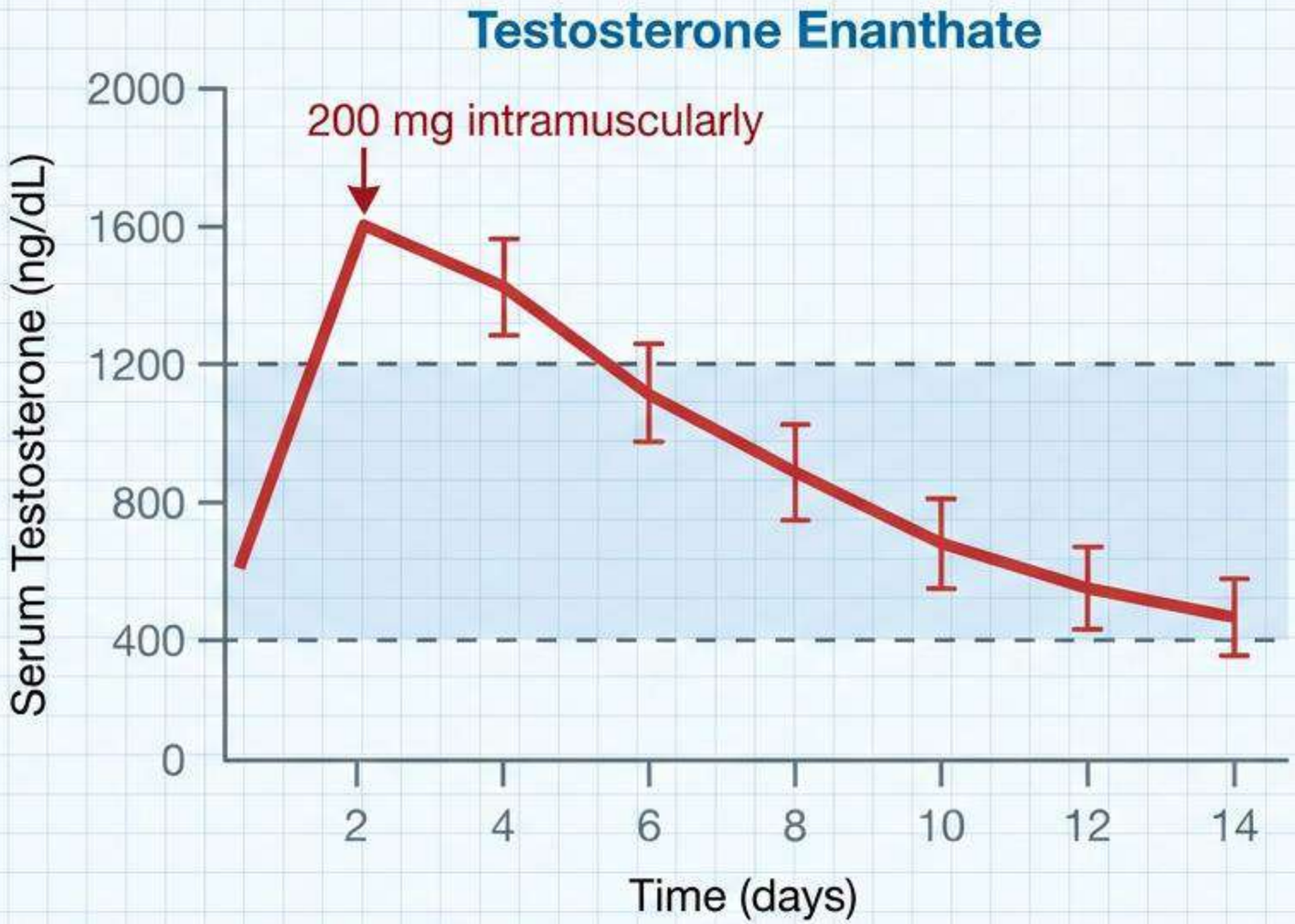
Formulation 1: Parenteral Esters



Common Esters & Durations

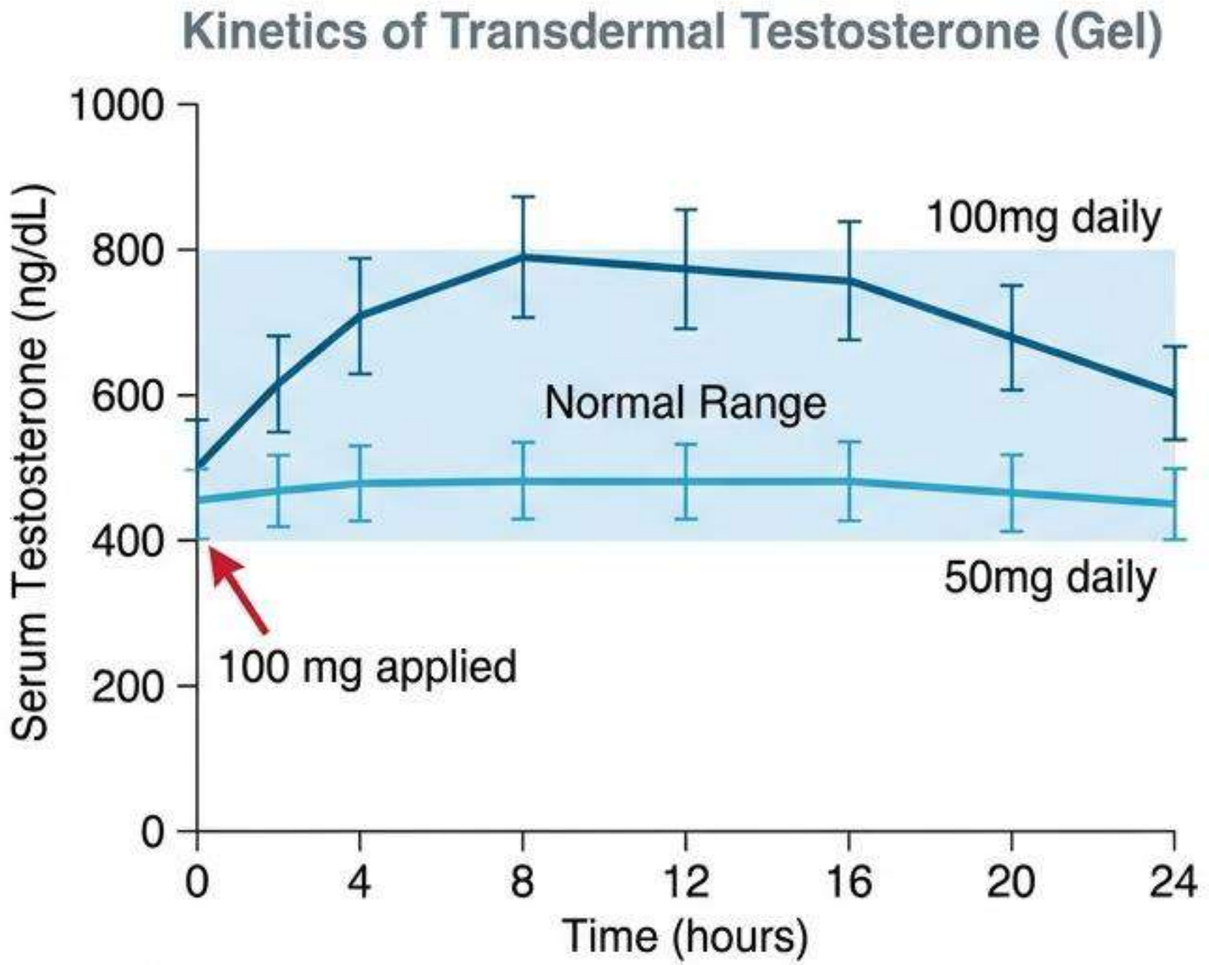
- **Propionate**
  Short-acting
  (25-50 mg, 3x/week).
- **Phenylpropionate**
  Medium-acting
  (40-60 mg, 1-2 weeks).
- **Enanthate / Cypionate**
  Long-acting
  (100-200 mg, every 2 weeks).

Kinetics of Injectable Esters



Supraphysiological peaks followed by sub-therapeutic troughs can cause fluctuations in mood, energy, and libido.

Formulation 2: Transdermal Systems

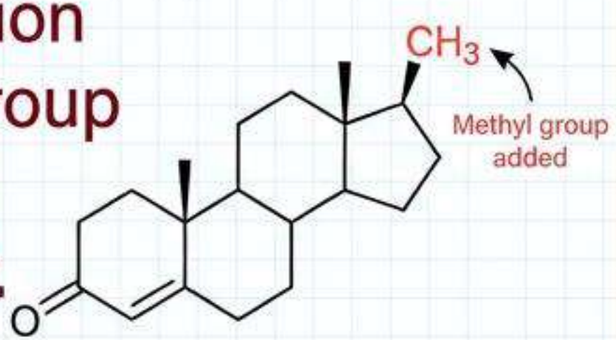


- Applied once daily (Back, Abdomen, Thigh).
- Provides steady-state serum concentrations.
- Avoids the “rollercoaster” effect of injections.
- Risk: Secondary transfer to women/children via skin contact.

Formulation 3: Oral & Alkylated Agents

The Chemistry

17-alpha-Alkylation adds a methyl group to allow survival through the liver.



Agents

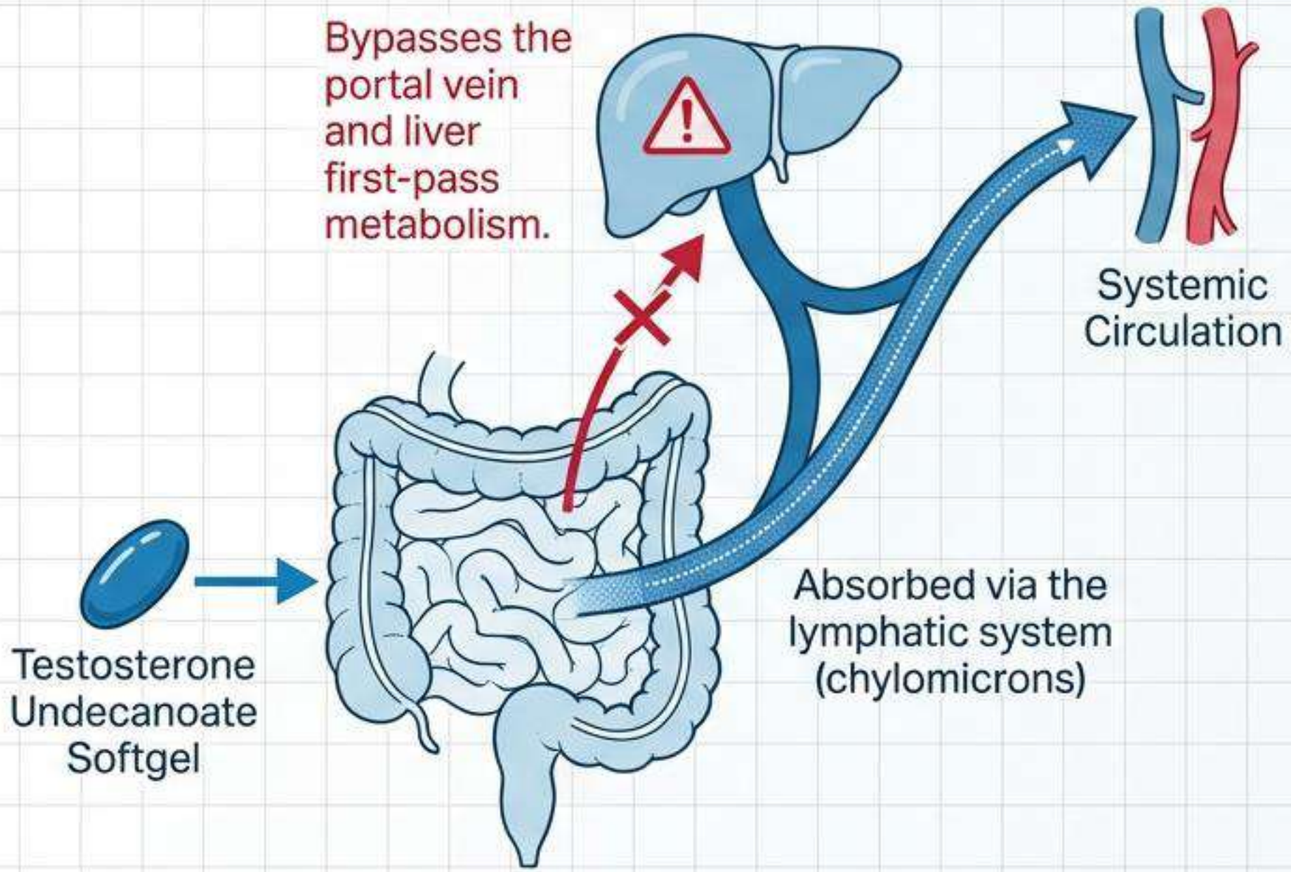
- Methyltestosterone
- Fluoxymesterone

The Risk

High potential for Hepatotoxicity and Cholestatic Jaundice.

Note: Submaximal androgenic efficacy. Rarely used for replacement therapy today.

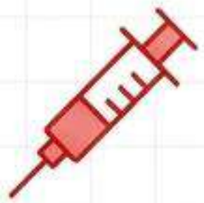
Testosterone Undecanoate: The Exception



- **Path:** Absorbed via the lymphatic system (chylomicrons).
- **Outcome:** Bypasses the portal vein and liver first-pass metabolism.
- **Benefit:** Avoids the hepatotoxicity of alkylated androgens.

Clinical Indications for Androgen Agonists

Primary Indication: Replacement Therapy



Restoring Physiological Levels

- **Testicular Failure** (Primary & Secondary Hypogonadism)
- **Hypopituitarism**
- **Ageing** (Andropause)

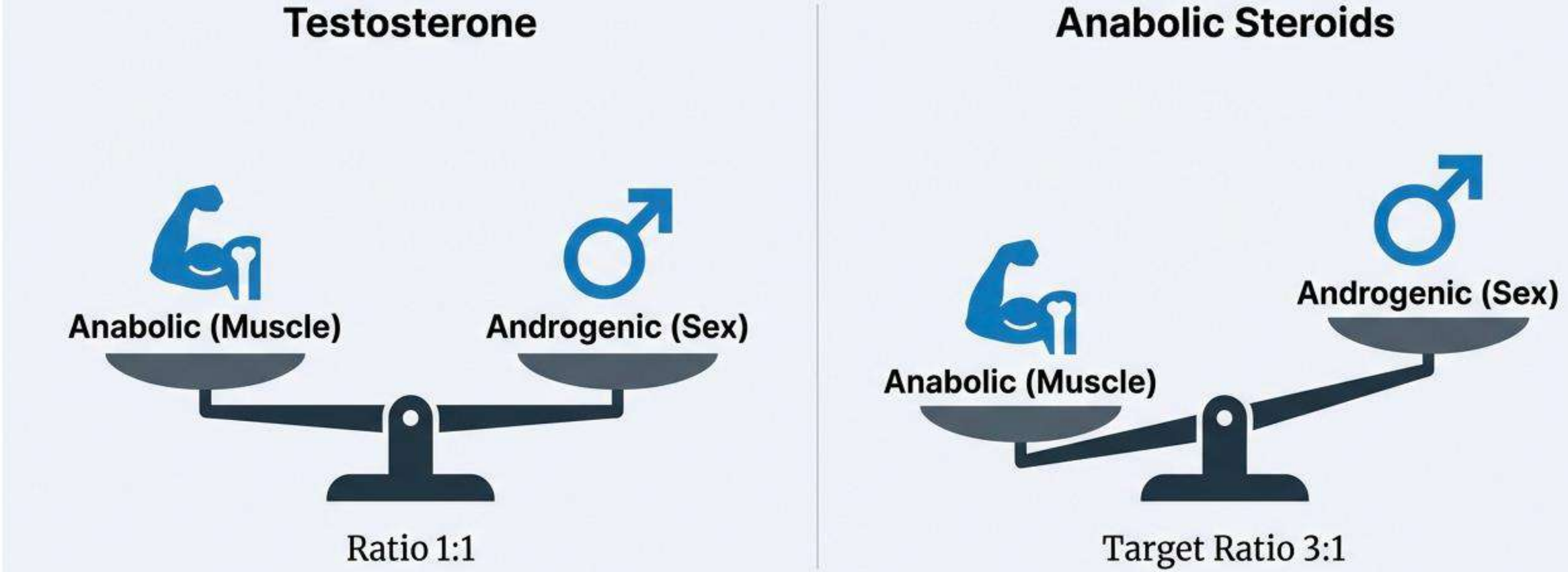
Pharmacological Indications

Therapeutic Exploitation of Effects

- **Senile Osteoporosis:** In elderly males (often combined with oestrogen).
- **Refractory Anaemia:** Stimulation of erythropoietin.
- **Catabolic States:** Reversing negative Nitrogen balance (burns, chronic illness, corticosteroid therapy).
- **Hereditary Angioneurotic Oedema.**
- **Palliative Care:** In specific cases of breast carcinoma.

Clinical Pearl:
Merriweather Regular
Goal of therapy is to mimic the circadian rhythm of natural testosterone secretion.

Anabolic Steroids: The Dissociation of Effects



Goal: Maximize anabolic activity (positive Nitrogen balance) while minimizing androgenic side effects.
Reality: Complete separation is impossible. All anabolics retain some androgenic activity.

Swiss Medical Editorial

Adverse Effects & Contraindications

Systemic impact of hormonal manipulation.

Gender-Specific Effects

- **Female:**
  - Virilization (Deepening voice, hirsutism), frontal baldness, shrunken breasts, acne, menstrual irregularities.
- **Male:**
  - Feminization (Gynaecomastia due to aromatization), testicular atrophy, frequent/painful erections.

Systemic & Metabolic

- **Liver:**
  - Cholestatic Jaundice (specifically with 17-alkylated orals: Stanozolol, Oxymetholone). Long-term risk of Hepatic Carcinoma.
- **Cardiovascular:**
  - Atherosclerosis, increased LDL, oedema.
- **Growth:**
  - Precocious puberty, stunted growth via premature epiphyseal closure.

Contraindications

- Carcinoma of the Prostate
- Carcinoma of the Male Breast
- Liver or Kidney Disease
- Pregnancy (Category X)

Anabolic-Androgenic Steroids (AAS)

Synthetic derivatives maximizing the Anabolic:Androgenic Ratio

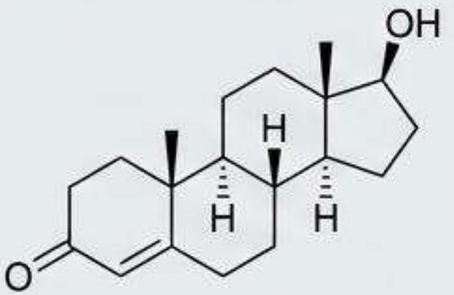
	Drug Name	Route	Ratio (Anabolic:Androgenic)	Characteristics
1	**Testosterone**	IM	1:1	Reference Standard.
2	**Nandrolone** (Deca-Durabolin)	IM	3:1	High anabolic selectivity. Low virilization.
3	**Stanozolol**	Oral	3:1	High potency. 17-alkylated.
4	**Methandienone**	Oral	3:1	Historic athletic abuse.
5	**Oxymetholone**	Oral	High	Hepatotoxic risk.

Design Goals

- Dissociate anabolic effects (muscle growth) from androgenic effects (virilization).
- Improve oral bioavailability (17α-alkylation).
- Slow absorption (Esterification).

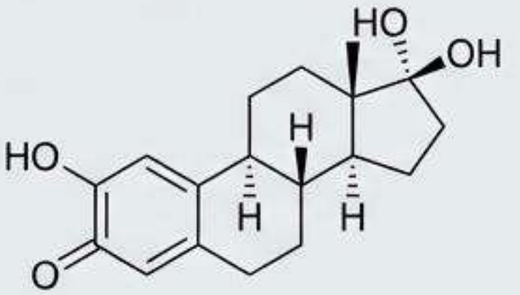
Modern Clinical Editorial

Anabolic Steroids: Use vs. Abuse



Legitimate Medical Uses

- Osteoporosis (Elderly males)
- Catabolic States (Trauma, Burns, Negative Nitrogen Balance)
- Bone Marrow Failure (Aplastic/Hemolytic Anemia)



Performance Enhancement (Abuse)

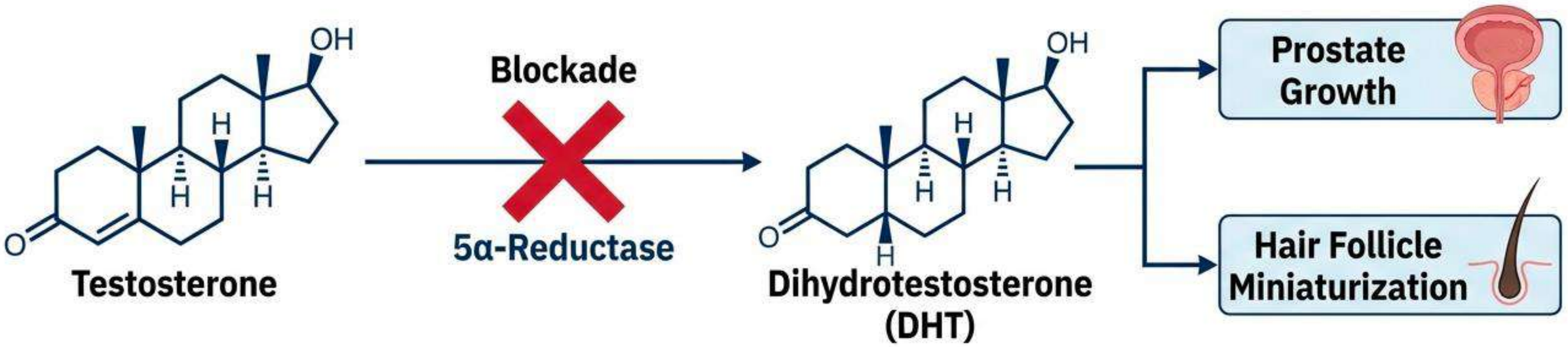
Use by athletes to increase muscle mass and recovery.

Specific Risks of Abuse:

- Cholestatic Jaundice (Oxymetholone/Stanozolol)
- Severe Lipid Profile Worsening
- Psychological effects (“Roid Rage”)

Source: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e.

Anti-Androgens I: 5α-Reductase Inhibitors



Finasteride	Dutasteride
Selectivity: Inhibits Type II 5α-reductase.	***Selectivity:*** Inhibits Type I & Type II 5α-reductase.
Indications: Benign Prostatic Hyperplasia (BPH), Male Pattern Baldness (Alopecia).	***Potency:*** Greater reduction in serum DHT.
Dosing: 5mg (BPH) vs 1mg (Alopecia).	

Prostate Volume: Decreases ~20-25% with treatment

Flow Rate: Improves significantly in BPH patients.

Adverse Effects Box:
Sexual Side Effects: Decreased libido, erectile dysfunction, ejaculation disorders (reversible).
Teratogenic risk (avoid contact in pregnancy).

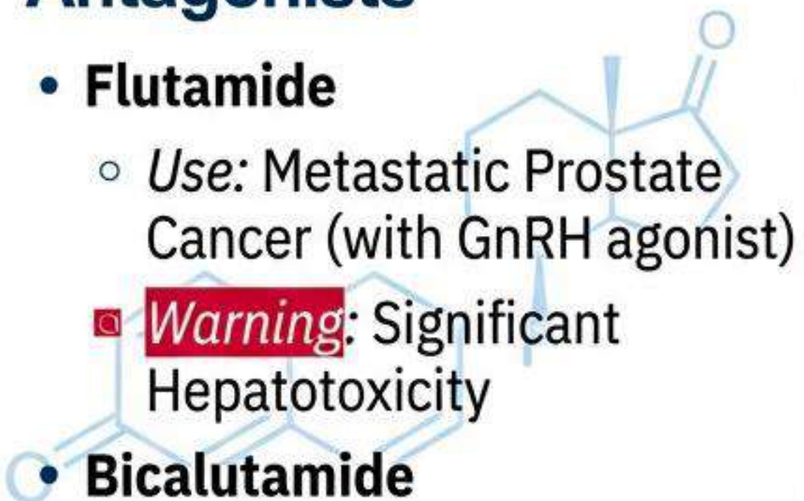
Anti-Androgens II: Receptor Antagonists

Competitive blockade at the Androgen Receptor (AR)

Steroidal Antagonists

- **Cyproterone Acetate**
  - *Mechanism:* Blocks AR + Progestational effect (inhibits gonadotropins)
  - *Uses:* Severe hirsutism
  - Precocious puberty
  - Acne

Non-Steroidal (Pure) Antagonists



- **Flutamide**
  - *Use:* Metastatic Prostate Cancer (with GnRH agonist)
  - *Warning:* Significant Hepatotoxicity
- **Bicalutamide**
  - *Status:* Standard of care
  - *Benefit:* Long half-life (OD dosing)
  - Less hepatotoxic

Clinical Pearl

Reflex Rise: Pure antagonists block feedback, causing LH/Testosterone surge. Must combine with GnRH agonist ('Chemical Castration') to prevent this.

Miscellaneous Modulators & Synthesis Inhibitors

Impeded Androgen

Danazol

- **Mechanism:** Weak androgen agonist / Inhibits pituitary gonadotropins & steroid enzymes.
- **Uses:** Endometriosis (atrophies ectopic tissue), Fibrocystic breast disease, Hereditary Angioedema.
- **Adverse Effects:** Mild virilization, amenorrhea, weight gain.

Synthesis Inhibitor

Ketoconazole

- **Mechanism:** Antifungal (high dose) inhibits CYP450 steroid synthesis enzymes.
- **Uses:** Prostate Cancer (2nd line rapid suppression), Cushing's Syndrome.

Aldosterone Antagonist

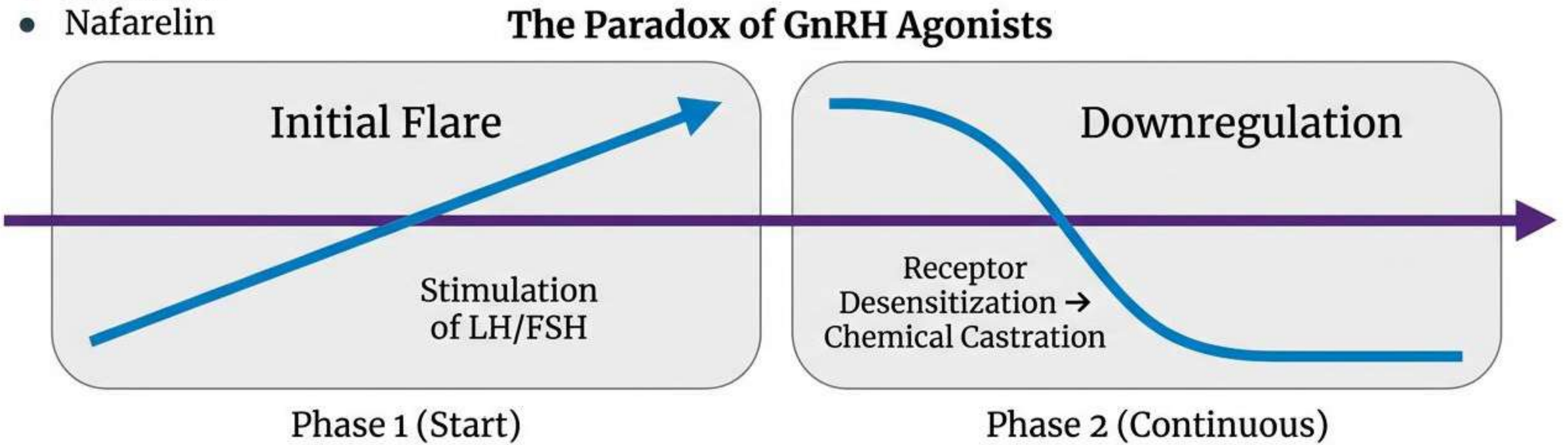
Spironolactone

- **Mechanism:** Competes for Androgen Receptor + Inhibits synthesis.
- **Uses:** Female Hirsutism (Off-label), PCOS.

GnRH Agonists (Superagonists)

Agents

- Leuprolide
- Goserelin
- Nafarelin



Uses

- 🥊 Prostate Cancer
- 🩳 Endometriosis
- 👩‍🦱 Precocious Puberty

Adverse Effects (Menopausal Symptoms)

- Hot flushes
- Osteoporosis
- Vaginal dryness

GnRH Antagonists

Agents and Clinical Advantages

Agents

Ganirelix
(IVF use, prevents ovulation)

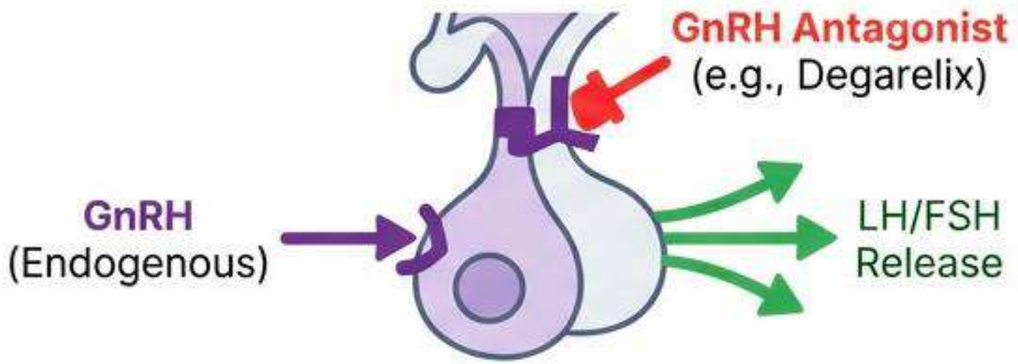
Cetrorelix
(IVF use, similar mechanism)

Degarelix
(Prostate cancer treatment)

Advantages over Agonists

✅ **Immediate Suppression**: No initial "Flare" (Safer for cancer).

- **Mechanism**: Competitive antagonism of GnRH receptors.
- **IVF Use**: Prevents premature ovulation.
- **Safety**: Lower risk of Ovarian Hyperstimulation Syndrome (OHSS).



Mechanism of Action: Receptor Blockade

Emerging Therapies & Safety Summary

Future: SARMs (Selective Androgen Receptor Modulators)

- Goal: Tissue-selective anabolism (Bone/Muscle) without prostate/skin effects.
- Agents: Ostarine, Ligandrol.
- Status: Investigational / Not FDA Approved.

Absolute Contraindications for Androgens

- Pregnancy (Fetal Masculinization)
- Carcinoma of Prostate / Male Breast
- Liver & Kidney Disease


THANK
YOU!