الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

السنة الثالثة

تأثير الأدوية2

د.رامز ونوس

م5

150

Sex hormones and drugs

Androgens

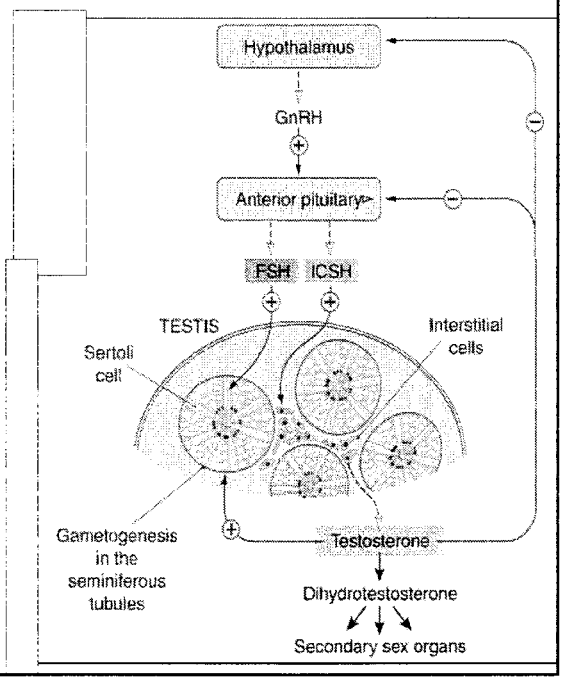
Pharmacology II
Dr. Ramez WANNOUS
2017

Introduction

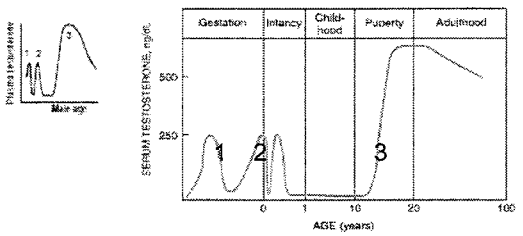
- **Natural Androgens:**
  - From Testes:
    - Testosterone
    - Dihydrotestosterone (more active) by 5 α-reductase
  - From Adrenal cortex: (weak androgens)
    - Dehydroepiandrosterone (DHEA)
    - Androstenedione
  - Androsterone – metabolite of testosterone
- **Synthetic androgens:**
  - Methyltestosterone, Fluoxymesterone
  - Testosterone esters (propionate and enanthate)

Regulation of Secretion

- LH/ICSH – Testosterone secretion
- FSH – Spermatogenesis
- High testosterone – inhibits LH
-
- Plasma level of Testosterone:
0.3 to 1 mcg/dl (male)
20 to 60 ng/dl (female)

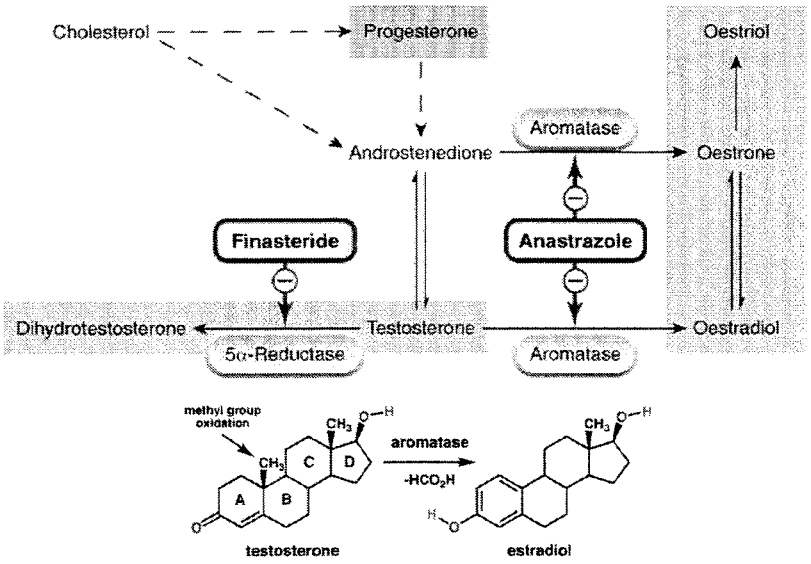


Testosterone



- Produced from cholesterol primarily by Leydig cells in testes
- Secreted at adult levels during 1st trimester 1, during neonatal life 2, continually after puberty 3
- Testosterone is responsible primarily for the development of male primary sexual characteristics, whereas dihydrotestosterone is responsible for secondary male characteristics.
- Can be converted to the more potent, 5α-dihydrotestosterone (DHT), which is responsible for many of the responses to testosterone in the urogenital tract (e.g. prostate, testes) and hair follicles.
- Androgen receptors are present in many tissues including reproductive tissue, skeletal muscle, brain, kidney etc.

Biosynthetic pathway for the androgens



Biological Effects - Testosterone

Androgenic Effects:

- In the foetus, testosterone promotes development of male reproductive tract – internal genitalia, vas deferens, epididymis and external genitalia (sex differentiation)
- During puberty, testosterone promotes development of :
  - primary sexual characteristics (e.g. enlargement of penis, scrotum and testes)
  - secondary sexual characteristics (e.g. male body shape, facial/pubic hair, deeper pitch of voice)
- Adulthood: Baldness, BHP, Prostatic cancer

Biological Effects - Testosterone

anabolic effects

- Pubertal spurt of growth at puberty – both boy and girl
- Bone growth – thickness and length
- Oestrogen from testosterone – fuse of bones and mineralization
- Increase in appetite
- Positive nitrogen, minerals and water balance – increase in weight
- Muscle building – if aided by exercise
- Acceleration of erythropoiesis

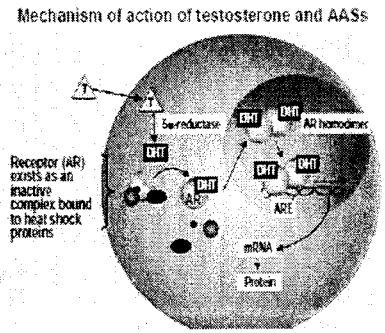
Mechanism of Action

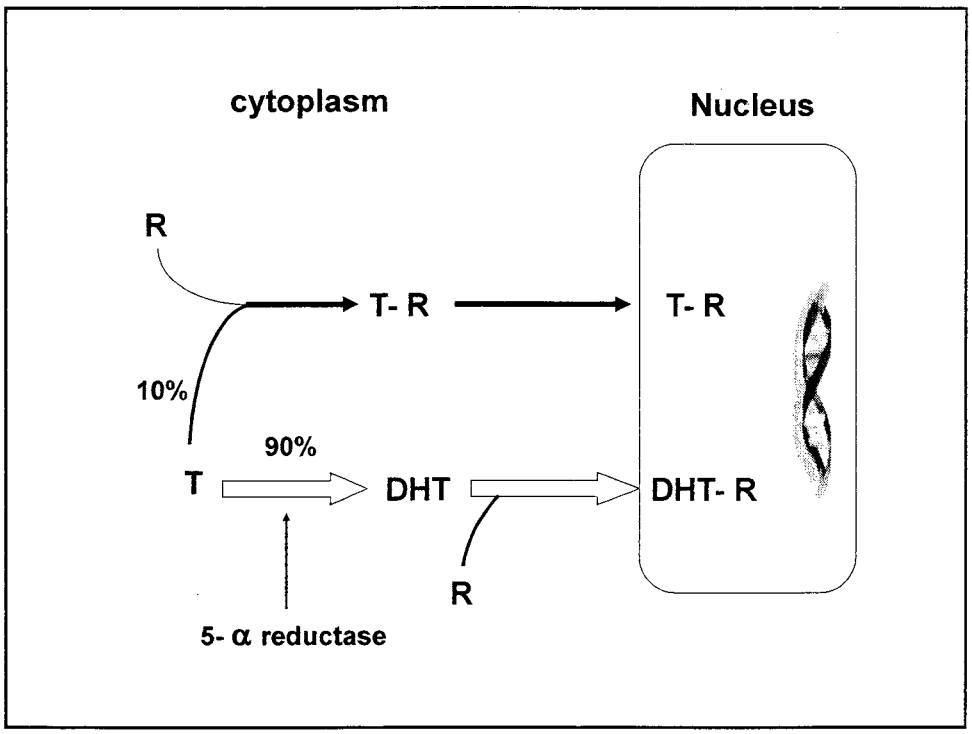
Androgen receptor:

- Both, testosterone and DH testosterone – act via Androgen receptors (AR) – nuclear receptor super family
- 5 α-reductase 1 and 2
- Ligand binding and DNA binding domains

Estrogen Receptor:

- Teststerone converts to estrogen by CYP19
- Deficiency of CYP19 and estrogen receptor – failure to fuse long bones, osteoporosis etc.





Androgen - Pharmacokinetics

- Absorption: undergoes high first pass metabolism. Therefore IM injections or synthetic preparations are used
- Metabolism:
  - by liver enzymes : androsterone & etiocholanolone
  - excretion by urine after conjugation
  - small quantity of oestrogen also produced from testosterone

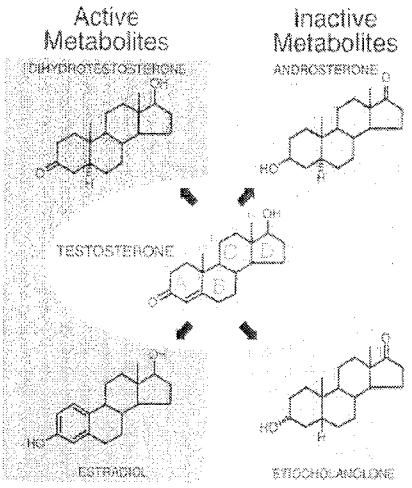
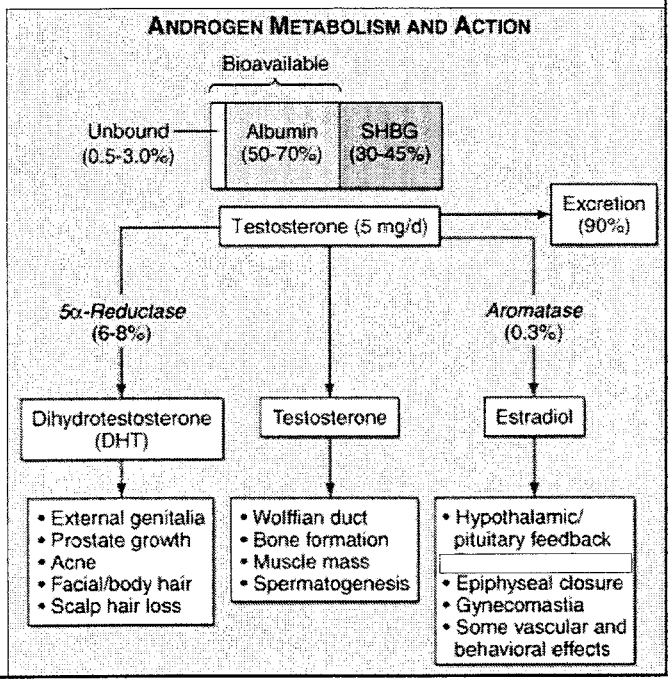


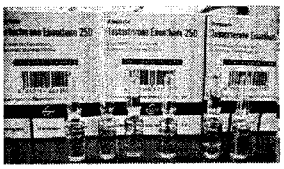
Figure 58–1. Metabolism of androgens.

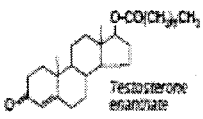
Transport:

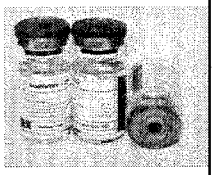
highly protein bound (98%, SHBG, albumin)



Therapeutic Androgen Preparations





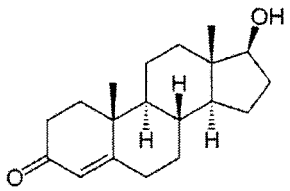


- Testosterone is ineffective orally (inactivated by liver),
  Testosterone undecanoate in oil – and Mesterolone orally.
- Usually given as i.m. injections of testosterone esters
  - Esterification of fatty acid at 17-hydroxyl group
  - Examples- propionate (25-50 mg), enanthate (100 mg depot preparations)
  - effects last for 2-3 weeks
- Transdermal preparations:
  - Implants, capsules and patches may improve compliance
  - more stable levels and symptoms, effects last for months

Therapeutic Androgen Preparations

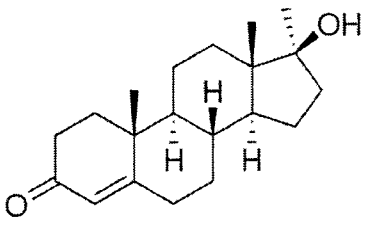
Androgen preparations for replacement therapy.

Drug	Route of Administration	Dosage
Methyltestosterone	Oral	25–50 mg/d
	Sublingual (buccal)	5–10 mg/d
Fluoxymesterone	Oral	2–10 mg/d
Testosterone enanthate	Intramuscular	See text
Testosterone cypionate	Intramuscular	See text
Testosterone	Transdermal	2.5–10 mg/d
	Topical gel (1%)	5–10 g/d

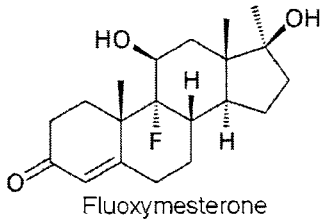


Testosterone

17-alkyl substitution



Methyltestosterone



Fluoxymesterone

Therapeutic Uses of Androgens

- **Androgen replacement therapy (ART)**
- **Anabolic effect**

1. **Androgen deficiency:** clinical diagnosis confirmed by hormone assays
   - is usually caused by
     - underlying testicular disorders (high LH, but low testosterone levels)
     - hypothalamic-pituitary disorders (low LH and low testosterone levels)

- Goal: Mimic the normal testosterone concentration as closely as possible (serum concentration monitoring)
- If untreated, does not shorten life expectancy, but is associated with significant morbidity (ambiguous genitalia, delayed puberty & infertility)
- Treated by androgen replacement therapy (ART), usually for the remainder of life. The aim is to restore tissue androgen exposure by using the natural androgen testosterone

Uses – contd.

Misuse:

involves prescription with no acceptable medical indication

- Examples of misuse include:
  - male infertility
  - male sexual dysfunction or impotence
  - "male menopause" (andropause)
- no convincing evidence that androgen therapy is either effective treatment or safe for older men unless there is frank androgen deficiency

Androgens – Adverse Effects

- Virilization:
  - may occur in women receiving relatively high doses for prolonged periods, such as for estrogen-dependent mammary carcinoma
- Infertility (decreased gonadotrophins)
- Priapism (sustained erection)
- Oligospermia
- Precocious puberty and short stature
- Acne
- Edema--via promotion of salt and water retention.
- Gynaecomastia – children and liver disease
- Edema--via promotion of salt and water retention.
- Cholestatic Jaundice
  - may be produced by steroids possessing a 17-alpha methyl group – oral Vs parenteral
- Hepatic carcinoma – oral

Androgens - contraindications

- Carcinoma of Prostate and male Breast
- Liver and Kidney diseases
- Pregnancy
- Congestive heart failure
- Epilepsy and migraine

Anabolic Steroids

- Synthetic analogues – higher anabolic but lower androgenic activity (1: 3 ratio)
- Examples;
  - Nandrolone propionate 10-25 mg/ml (10 – 50 mg IM/week) – inj. Durabolin
  - Nandrolone decanoate 25-100 mg/ml (25-100mg/week) – inj. Decadurabolin
  - Stanazolol (2mg tablets (2-6 mg/day)

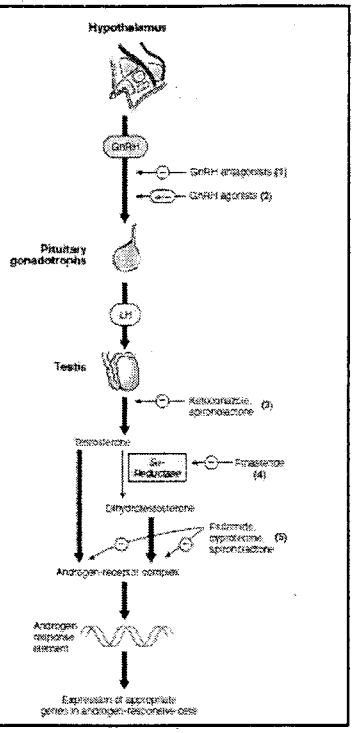
Androgens: Preparations available and relative androgenic:anabolic activity in animals.

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

Anabolic Steroids – Therapeutic uses

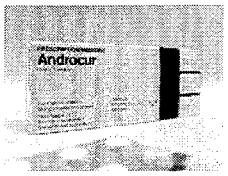
1. Catabolic states: Acute illness, severe trauma, major surgery
2. Renal insufficiency – frequency of dialysis
3. Osteoporosis – elderly males
4. Suboptimal growth in boys
5. Anaemia
6. Perfomance enhancement
7. AIDS (related muscle wasting)

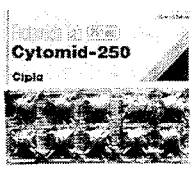
Anti-androgens



Anti-androgens

- Cyproterone acetate
- Flutamide
- Finasteride





Cyproterone acetate

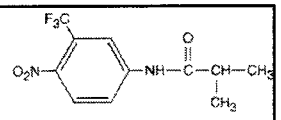
- Progesterone like activity – inhibits LH causing antiandrogenic action
- Competes with dihydroteststerone for intracellular receptor

Uses:

- Acne
- Hirsutism
- Virilizing syndrome
- Male pattern of baldness
- Cancer of prostate
- Precocious puberty
- Inappropriate behaviour

- A formulation of cyproterone plus ethinylestradiol (Diane®) is offered for the treatment of severe female hirsutism as well as for severe acne in women; this preparation acts as an oral contraceptive too.
- Cyproterone causes hepatomas in rats.

Flutamide



Flutamide

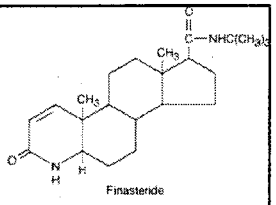
- Non-steroidal and no hormonal activity but specific antiandrogenic action
- Antagonise androgens

Uses:

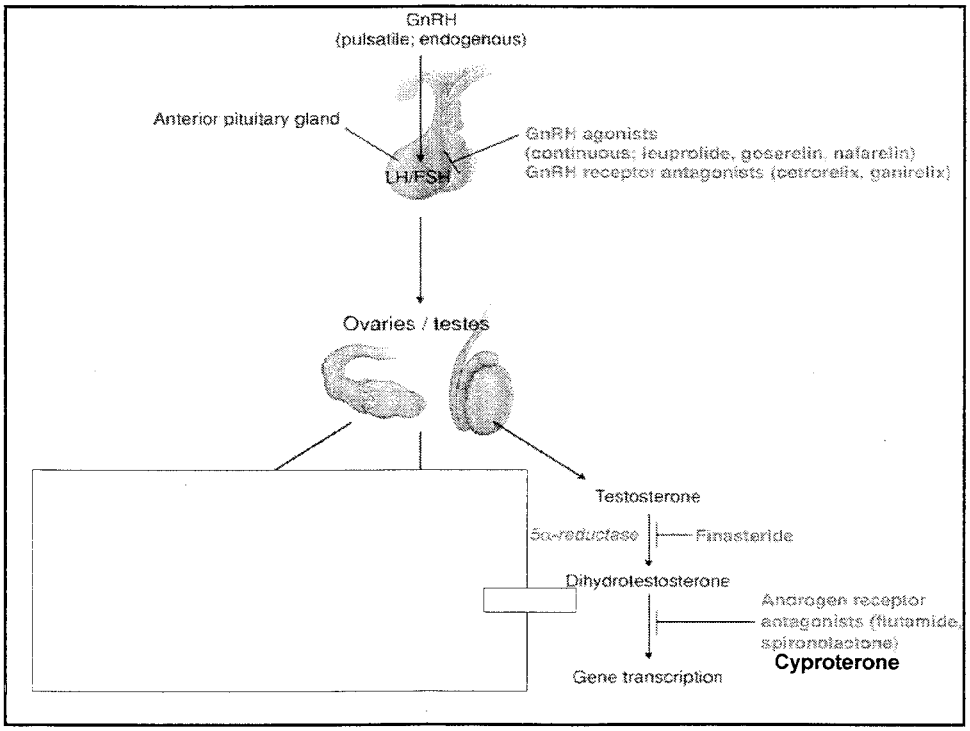
- Cancer of prostate along with GnRH agonist
- Female hirsutism

Dose: 250 mg tds.

Finasteride



- MOA: Competitive inhibitor of 5 α-reductase
  - Selective of 5 α-reductase type-2 isoenzyme
  - Mainly acts on urogenital tract (prostate) – DHT level lowered but not plasma Testosterone level
- Uses:
  1. Benign prostatic hypertrophy – decrease in prostate volume, improved urinary flow, reversion of disease progression
     - Withdrawal results in regrowth – prolonged therapy
  2. Male pattern baldness
- Kinetics: effective orally, metabolized in liver (t1/2 – 4-6 hrs)
- Side effects: loss of libido, impotence, decreased ejaculation
- Doses: 5 mg OD (BHP) Proscar®, or 1 mg OD in Male pattern baldness Propecia®



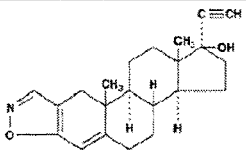
GnRH agonist
Leuprolide (+ Flutamide) used in prostatic cancer.

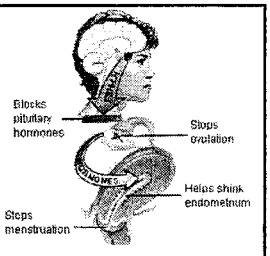
Spironolactone
Has antiandrogen activity and may help hirsutism in women.

Ketoconazole (antifungal drug)
Inhibits androgen synthesis and may be used in *prostatic cancer.*

.

Danazol





- FSH & LH release in both sexes decrease – inhibition of testicular/ovarian function
- Binding of steroids to receptors decrease
- Weak partial androgenic, anabolic, progestational & glucocorticoid action

Uses:

- Endometriosis
- Menorrhagia
- Fibrocystic breast disease
- Hereditary angioneurotic oedema
- Gynecomastia

Preparations:

- 50,100 and 200 mg. tablets
- Dose is 200 – 600 mg/day

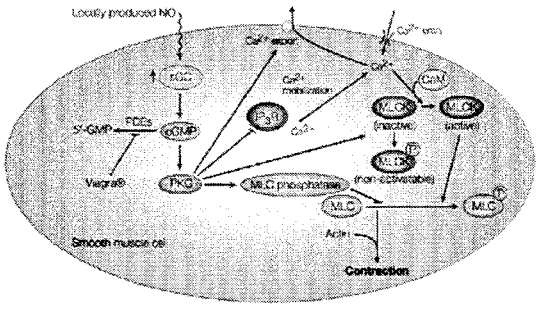
Side effects: Dose related

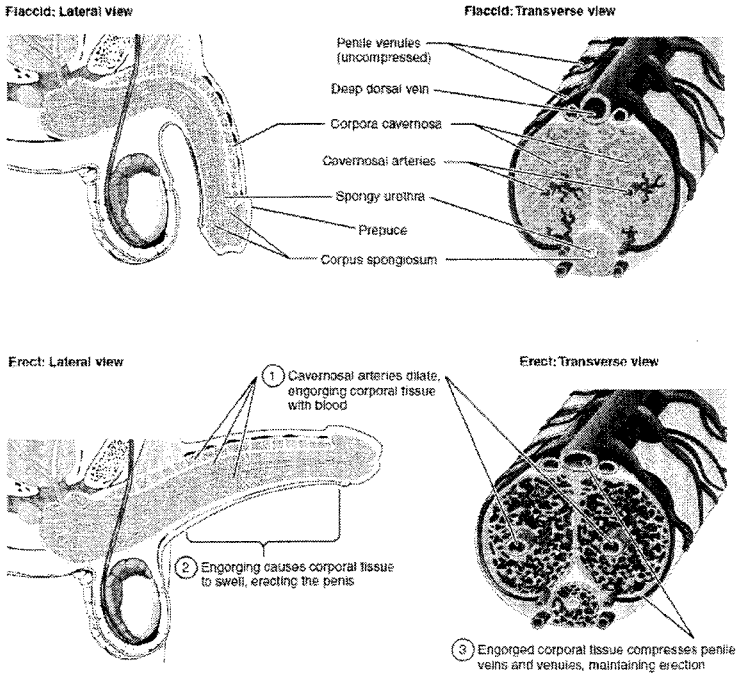
- Amenorrhea (High doses)
- Androgenic effects - Decreased breast size, hirsutism, weight gain etc.
- Hot flashes, night sweating, cramps

Erectile Dysfunction Drugs

PDE-5 Inhibitors: Sildenafil, tadalafil

– Nitric oxide (NO) pathway





Sildenafil

- Absorbed orally and half-life is 4 Hrs
- Inhibits PDE5 in the corpus cavernosa of the penis
- 50mg 1 h before sexual activity
- Potentiate nitrate's hypotension activity
- Ketoconazole, erythromycin, Verapamil increases its level – due to CYP3A4 inhibition
- Renal & hepatic disease increases its level
- Side effects:
  headache, flushing, dyspepsia, myalgia
- Other Uses: Pulmonary hypertension

Tadalafil

- The effects on erectile dysfunction last for 24 hours and the onset of effects take approximately 16 minutes.

  - The IC50 ratios for:
    PDE 5 vs. PDE 1 = 10,000
    PDE 5 vs. PDE 7 = 10,000
    PDE 5 vs. PDE 6 = 780

  So, there are no serious cardiovascular adverse effects nor color vision disturbances.

Male Contraceptives

- **Gossypol:**
  - Is a phenolic compound present in cotton seed oil.
  - Decrease number of sperms and impairs their motility.
  - It effect is reversible.
  - Side Effects:
    - Hypokalemia, weakness, diarrhea and edema.