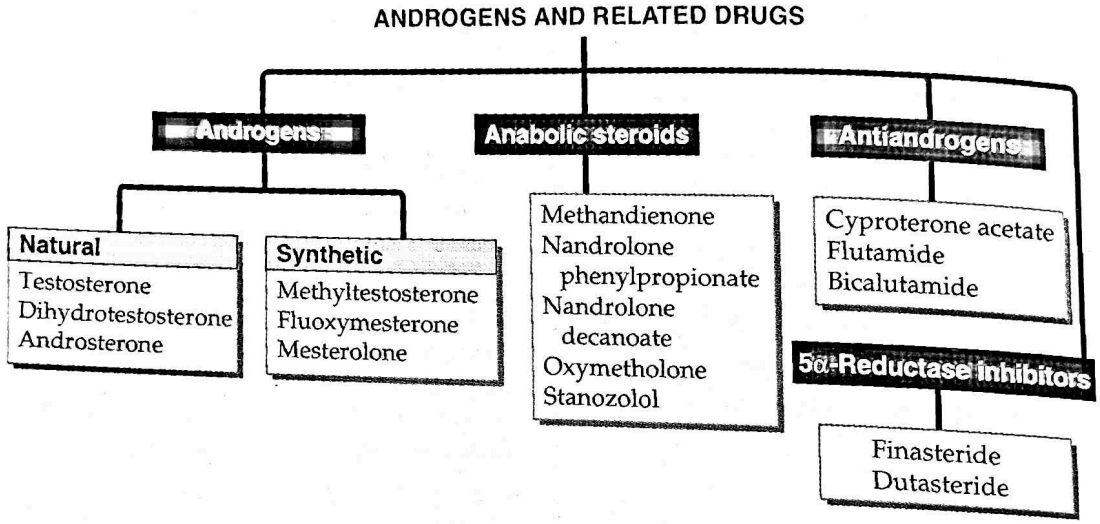
Chapter 21 | Androgens and Related Drugs, Drugs for Erectile Dysfunction

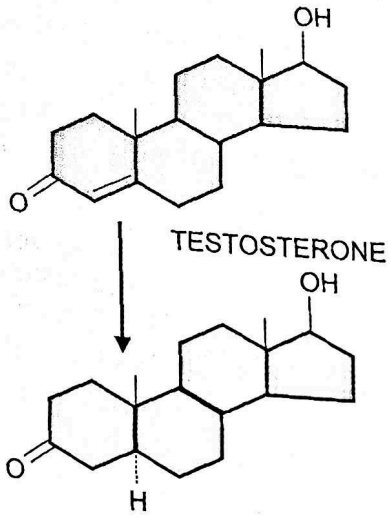
Drugs that have androgenic action or that modify androgen function can be grouped as follows:



ANDROGENS
(Male Sex Hormones)

These are substances which cause development of secondary sex characters in the castrated male. That testes are responsible for the male characters is known since prehistoric times. Its endocrine function was established by Berthold in 1849. *Testosterone* was isolated as the testicular hormone, its structure was worked out and it was synthetically prepared by the year 1935.

Natural androgens Testes of adult male produce 5–12 mg of *testosterone* daily, a part of which is converted in extraglandular tissues to the more active *dihydrotestosterone* (DHT); by the enzyme steroid 5 α-reductase; cholesterol is the starting material and the same pathway depicted in Fig. 20.1 is utilized. Adrenal cortex produces small quantities of *dehydroepiandrosterone* and *androstenedione* which are called 'weak androgens' (potency 1/20 to 1/30), but are infact inactive as such, and derive their weak activity from partial conversion to testosterone



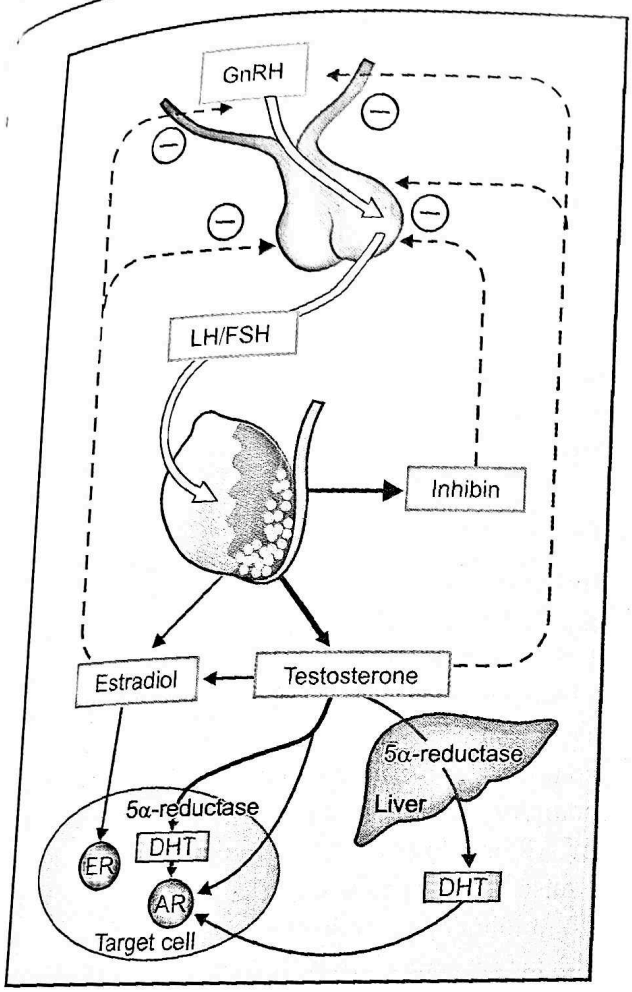


Fig. 21.1: Production of sex steroids and their regulation in the male
In liver and many target cells the 5α-reductase enzyme converts testosterone to the more potent androgen dihydrotestosterone (DHT) which combines more avidly with the androgen receptor (AR). The aromatase enzyme in testes, liver and adipose tissue converts some testosterone into estradiol which exerts certain actions in male target cells by combining with estrogen receptor (ER) and is probably important for feedback inhibition of gonadotropins (LH/FSH) as well as that of gonadotropin releasing hormone (GnRH) from hypothalamus.

in peripheral tissues. Adrenals themselves do not produce significant quantity of testosterone. In women ovary produces small quantity of testosterone; this together with that derived indirectly from adrenals amounts to 0.25–0.5 mg/day.

Androsterone It is a metabolite of testosterone which is excreted in urine. It has 1/10 the activity of testosterone.

Synthetic androgens *Methyltestosterone* and *fluoxymesterone* are 17-alkyl substituted derivatives of testosterone which are orally active because of resistance to first pass metabolism, but have submaximal androgenic efficacy and potential to cause cholestatic jaundice. Other orally active compounds are *testosterone undecanoate* which is administered as oily solution to be absorbed through lymphatics bypassing the liver, and *mesterolone.* A number of lipid-soluble esters of testosterone have been produced, suitable for injection in oily vehicle, from which they are absorbed slowly and exert prolonged action after deesterification in the body.

Regulation of secretion

Testosterone is secreted by the interstitial (Leydig) cells of the testes under the influence of pulsatile secretion of LH from pituitary. FSH is mainly responsible for promotion of spermatogenesis in tubular (Sertoli) cells. The mediator of feedback relationship with pituitary is uncertain. While relatively high concentration of testosterone inhibits LH secretion and in time causes atrophy of interstitial cells, it has only weak inhibitory action on FSH secretion. Estrogens are more potent inhibitors of Gn secretion even in males, and it is believed that the small amount of estradiol produced by testes as well as that generated from conversion of testosterone to estradiol in liver and fat plays a role in the feedback inhibition. *Inhibin* (a protein), produced by Sertoli cells, has strong FSH inhibitory action and may be mediating the feedback inhibition. Testosterone and estradiol act on hypothalamus to reduce GnRH as well as act directly on pituitary. The plasma level of testosterone in adult males ranges from 0.3 to 1 μg/dl. In women, small amounts of testosterone are produced by corpus luteum and adrenal cortex; blood levels remain low (20–60 ng/dl).

ACTIONS

1. Sex organs and secondary sex characters (Androgenic) Testosterone is responsible for all the changes that occur in a boy at puberty:

Growth of genitals—penis, scrotum, seminal vesicles, prostate.
Growth of hair—pubic, axillary, beard, moustache, body hair and male pattern of its distribution.
Thickening of skin which becomes greasy due to proliferation and increased activity of sebaceous glands—especially on the face. The duct often gets blocked and infection occurs resulting in acne. Subcutaneous fat is lost and veins look prominent.
Larynx grows and voice deepens.
Behavioural effects are—increased physical vigour, aggressiveness, penile erections. Male libido appears to be activated by testosterone directly, and probably to a greater extent by estradiol produced from testosterone.
Testosterone is also important for the intrauterine development of the male phenotype. Relatively large amounts of testosterone are produced by the foetal testes during the first half of intrauterine life.

2. Testes Moderately large doses cause testicular atrophy by inhibiting Gn secretion from pituitary. Still larger doses have a direct sustaining effect and atrophy is less marked. Testosterone is needed for normal spermatogenesis and maturation of spermatozoa. High concentration of testosterone is attained locally in the spermatogenic tubules by diffusion from the neighbouring Leydig cells and stimulates spermatogenesis.

3. Skeleton and skeletal muscles (Anabolic) Testosterone is responsible for the pubertal spurt of growth in boys and to a smaller extent in girls. There is rapid bone growth, both in thickness as well as in length. After puberty, the epiphyses fuse and linear growth comes to a halt. Estradiol produced from testosterone, and not testosterone itself, is responsible for fusion of epiphyses in boys as well as in girls. Moreover, estradiol largely mediates the effect of testosterone on bone mineralization. Testosterone also promotes muscle building, especially if aided by exercise. There is accretion of nitrogen, minerals (Na, K, Ca, P, S) and water—body weight increases rapidly, more protoplasm is built. Appetite is improved and a sense of well being prevails. The nitrogen retaining and muscle building effect of exogenous androgens is more marked in women and children than in adult men. Testosterone given to patients prone to salt and water retention may develop edema.

4. Erythropoiesis Testosterone accelerates erythropoiesis by increasing erythropoietin production and probably direct action on haeme synthesis. Men have higher hematocrit than women.

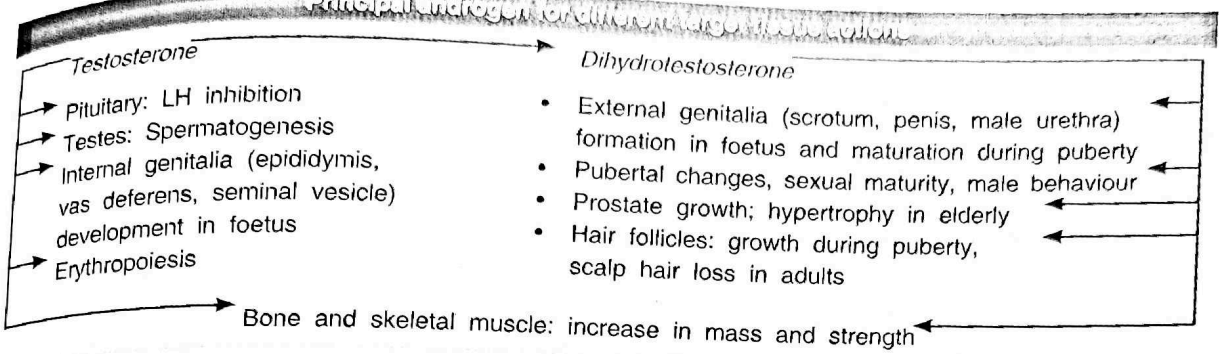
Mechanism of action

Testosterone can largely be regarded as the circulating prohormone. In most target cells, the 4–5 double bond is reduced producing *dihydrotestosterone*—which binds more avidly with the cytoplasmic androgen receptor (AR), and this complex is more active than testosterone-receptor complex in combining with DNA. No subtypes of AR are known; both genital and nongenital (muscle, bone) cells express the same AR. After combining with androgen response elements of the target genes, DNA transcription is enhanced/repressed with the help of coactivators or corepressors, which may be tissue specific. The effects are expressed through modification of protein synthesis.

The 5α-reductase enzyme exists in two isoforms: 5α-reductase-1 and 5α-reductase-2. The genital skin of both sexes and urogenital tract of male contains 5α-reductase-2 which is more sensitive to inhibition by finasteride. Genetic deficiency of this isoenzyme causes male pseudohermaphroditism because of inability of male genitalia to produce the active hormone dihydrotestosterone from circulating testosterone. 5α-reductase-1 has a wider distribution in the body including nongenital skin and liver; and is inhibited by finasteride to a lesser extent.

Testosterone itself appears to be the active hormone at certain sites, such as—

- foetal genital rudiments
- hypothalamus/pituitary site involved in feed back regulation
- erythropoietic cells
- spermatogenic cells in testes.



PHARMACOKINETICS

Testosterone is inactive orally due to high first pass metabolism in liver. The duration of action after i.m. injection is also very short. Therefore, slowly absorbed esters of testosterone are used by this route; they are hydrolysed to the active free form. While testosterone propionate is short acting, and needs daily injections, the enanthate, cypionate, isocaproate and decanoate esters are long acting; can be injected every 2–4 weeks depending on the dose. The latter are preferred for long term replacement therapy. Testosterone in circulation is 98% bound to sex hormone binding globulin (SHBG) and to albumin. The SHBG bound testosterone is unavailable for action due to tight binding.

The major metabolic products of testosterone are androsterone and etiocholanolone which are excreted in urine, mostly as conjugates with glucuronic acid and sulfate. Small quantities of estradiol are also produced from testosterone by aromatization of A ring in extraglandular tissues (liver, fat, hypothalamus). Plasma t½ of testosterone is 10–20 min.

Methyltestosterone and fluoxymesterone are metabolized slowly and have a longer duration of action, but are weaker androgens. Estrogens are not produced from fluoxymesterone and dihydrotestosterone.

Preparations and Dose

1. Testosterone (free): 25 mg i.m. daily to twice weekly; AQUAVIRON 25 mg in 1 ml inj.

2. Testosterone propionate: 25–50 mg i.m. daily to twice weekly: TESTOVIRON, PARENDREN, TESTANON 25, 50 mg/ml inj.

3. TESTOVIRON DEPOT 100: testo. propionate 25 mg + testo. enanthate 100 mg in 1 ml amp; 1 ml i.m. weekly.

4. TESTOVIRON DEPOT 250: testo. propionate 250 mg + testo. enanthate 250 mg in 1 ml amp; i.m. every 2–4 weeks.

5. SUSTANON '100': testo. propionate 20 mg + testo. phenyl propionate 40 mg + testo. isocaproate 40 mg in 1 ml amp; 1 ml i.m. every 2–3 weeks.

6. SUSTANON '250': testo. propionate 30 mg + testo. phenylpropionate 60 mg + testo. isocaproate 60 mg + testo. decanoate 100 mg in 1 ml amp; 1 ml i.m. every 3–4 weeks.

7. NUVIR, ANDRIOL; Testosterone undecanoate 40 mg cap, 1–3 cap daily for male hypogonadism, osteoporosis.

8. Mesterolone: Causes less feedback inhibition of Gn secretion and spermatogenesis, and has been promoted for treatment of male infertility PROVIRONUM, RESTORE, MESTILON 25 mg tab; 1–3 tab daily for androgen deficiency, oligozoospermia and male infertility.

Transdermal androgen Delivery of androgen across skin has been achieved by developing suitable solvents and absorption facilitators. By cutaneous delivery, testosterone/dihydrotestosterone circumvent hepatic first pass metabolism and uniform blood levels are produced round the clock. A gel formulation has been marketed for once daily application which has become the preferred method of androgen replacement for hypogonadism and impotence.

ANDRACTIM: Dihydrotestosterone 25 mg/g gel (100 g tube); 5–10 g gel to be applied over nonscrotal skin once daily.

Fixed dose combinations of testosterone with yohimbine, strychnine and vitamins are banned in India.

SIDE EFFECTS

1. Administered to women, androgens can cause virilization, excess body hair and menstrual irregularities. Many effects, e.g. voice change may be permanent after prolonged therapy.
2. Acne: in both males and females.
3. Frequent, sustained and often painful erections in males in the beginning of therapy; subside spontaneously after sometime.
4. Oligozoospermia can occur with moderate doses given for a few weeks to men with normal testosterone levels. Prolonged use may produce testicular atrophy.
5. Precocious puberty, premature sexual behaviour, and stunting of stature due to early closure of epiphysis—if testosterone is given continuously to young boys for increasing stature.
6. Salt retention and edema: especially when large doses are given to patients with heart or kidney disease. This is rare with the doses used for hypogonadism.
7. Cholestatic jaundice: occurs with methyltestosterone and other 17-alkyl substituted derivatives (fluoxymesterone and some anabolic steroids like oxymetholone, stanozolol) in a dose dependent manner, but not with parenterally used esters of testosterone. For this reason, the latter are preferred. However, the jaundice is reversible on discontinuation.
8. Hepatic carcinoma: incidence is higher in patients who have received long-term methyltestosterone or other oral androgens.
9. Gynaecomastia: may occur, especially in children and in patients with liver disease. This is due to peripheral conversion of testosterone to estrogens. Dihydrotestosterone does not cause gynaecomastia because it is not converted to estradiol.
10. Lowering of HDL and rise in LDL levels, especially with 17α-alkylated analogues.

Contraindications Androgens are contraindicated in carcinoma of prostate and carcinoma of male breast, as well as in liver and kidney disease and during pregnancy (masculinization of female foetus). They should not be given to men aged >65 years, and to those with coronary artery disease or CHF. Androgen therapy can worsen sleep apnoea, migraine and epilepsy.

USES

1. *Testicular failure* It may be primary, which is noticed during childhood, and results in delayed puberty. Treatment with parenteral testosterone esters or transdermal testosterone/dihydrotestosterone in courses of 4–6 months at a time may achieve satisfactory results/normal adult stature if administered judiciously to avoid acceleration of epiphyseal closure which occurs if the dose is high. Secondary testicular failure (hypogonadism) occurring later in life manifests mainly as loss of libido, muscle mass and energy, feminization, mild anaemia and impotence. These are corrected gradually over months by androgen treatment. However, impotence due to psychological and other factors, and not testosterone deficiency, does not respond.

2. *Hypopituitarism* Hypogonadism is one of the features of hypopituitarism. Androgens are added at the time of puberty in boys to other hormonal replacement.

3. *AIDS related muscle wasting* Testosterone therapy has been shown to improve weakness and muscle wasting in AIDS patients with low testosterone levels.

4. *Hereditary angioneurotic edema* This is a genetic disorder. The attacks can be prevented by 17α-alkylated androgens (methyltestosterone, stanozolol, danazol) but not by testosterone. These drugs act by increasing the synthesis of complement (C1) esterase inhibitor.

5. *Ageing* Because testosterone levels decline in old age, it has been administered to elderly males with the aim of improving bone mineralization and muscle mass. However, safety of such therapy in terms of metabolic, cardiovascular and prostatic complications is not known.

Occasionally small amount of androgen is added to postmenopausal hormone replacement.

6. *Idiopathic male infertility* Since high intratesticular level of testosterone is essential for spermatogenesis, it is presumed that exogenous androgens will stimulate spermatogenesis or improve sperm maturation in epididymis. On the other hand, androgens can adversely affect spermatogenesis by suppressing Gn secretion. Since mesterolone causes less feedback inhibition of Gn (probably due to restricted entry into brain) it is believed that moderate doses will predominantly stimulate testis directly.

A recent metaanalysis of 11 clinical trials has found that oral androgens (mesterolone and testosterone undecanoate) had no effect on sperm count or sperm motility as well as on subsequent pregnancy rate when given to oligo-astheno-spermic subfertile men. As such, use of these androgens for improving male fertility is not backed by objective evidence.

ANABOLIC STEROIDS

These are synthetic androgens with supposedly higher anabolic and lower androgenic activity. Drugs are *Nandrolone, Oxymetholone, Stanozolol* and *Methandienone.*

The anabolic: androgenic activity ratio is determined by injecting the drug in castrated rats and measuring the increase in weight of levator ani muscles to that of ventral prostate. The anabolic: androgenic ratio of testosterone is considered as 1; The anabolic selectivity of these steroids is modest with ratios between 1 to 3 in the rat model, and probably still lower in man. The anabolic effects are similar to that of testosterone and are mediated through the same receptor as the androgenic effects. For all practical purposes, they are androgens.

Preparations and dose

1. Methandienone: 2–5 mg OD–BD oral; children 0.04 mg/kg/day, 25 mg i.m. weekly; ANABOLEX 2, 5 mg tab, 2 mg/ml drops, 25 mg/ml inj.
2. Nandrolone phenyl propionate: 10–50 mg; children 10 mg; i.m. once or twice weekly; DURABOLIN 10, 25 mg/ml inj.
3. Nandrolone decanoate: 25–100 mg i.m. every 3 weeks, DECADURABOLIN, 25, 100 mg/ml inj.
4. Oxymetholone: 5–10 mg, children 0.1 mg/kg, OD; ADROYD 5 mg tab.
5. Stanozolol: 2–6 mg/day, MENABOL, NEURABOL, TANZOL 2 mg tab.

Combination of anabolic steroids with any other drug is banned in India.

Side effects Anabolic steroids were developed with the idea of avoiding the virilizing side effects of androgens while retaining the anabolic effects. But the same adverse effect profile applies to these compounds.

The 17-alkyl substituted compounds oxymetholone, stanozolol, can produce jaundice and worsen lipid profile.

Contraindications are same as for testosterone.

Uses

1. *Catabolic states* Acute illness, severe trauma, major surgery, etc. are attended by negative N balance. Anabolic steroids can reduce N_2 loss over short periods, but long-term benefits are questionable. They may cause a transient response in the elderly, under-nourished or debilitated individuals, but controlled studies have failed to demonstrate a difference in the total weight gained. However, short-term use may be made during convalescence for the sense of wellbeing and improvement in appetite caused by such treatment.
2. *Osteoporosis* In elderly males and that occurring due to prolonged immobilization may respond to anabolic steroids, but bisphosphonates are more effective and are the preferred drugs.
3. *Suboptimal growth in boys* Use of anabolic steroids for accelerating the growth rate is controversial; somatropin is a better option. Brief spurts in linear growth can be induced by anabolic steroids, but this probably does not make a difference in the final stature, except in hypogonadism. Use for more than 6 months is not recommended—premature closure of epiphyses and shortening of ultimate stature may result.
4. *Hypoplastic, haemolytic and malignancy associated anaemia* Majority of properly selected patients respond to anabolic steroids/androgens by an increase in RBC count and Hb%. However, erythropoietin therapy is more effective.
5. *To enhance physical ability in athletes* When administered during the period of training androgens/anabolic steroids can increase the strength of exercised muscles. However, effects are mostly short-lived and the magnitude of improvement in performance is uncertain except in women who may gain substantially. However, such use is considered illegal, and anabolic steroids are included in the list of 'dope test' performed on athletes before competitive games.

ANTIANDROGENS

Superactive GnRH agonists are the most potent inhibitors of gonadal function. Administered over a few days, they markedly inhibit LH and FSH release, resulting in loss of androgen secretion (*see* Ch. 17).

Ketoconazole at high doses inhibits steroidogenic CYP 450 enzymes: testosterone as well as adrenal steroid production is interfered. Plasma protein binding of testosterone is also reduced. However, toxicity of high doses precludes its use to suppress androgens.

Cimetidine and *spironolactone* have weak antiandrogenic action which manifests as side effects. *Progesterone* has weak androgen receptor blocking action.

Drugs that have been clinically used as antiandrogens are:

Cyproterone acetate This relatively weak AR antagonist is chemically related to progesterone. In contrast to flutamide which increases LH release by blocking feedback inhibition, cyproterone acetate inhibits LH release by its progestational activity. Lowering of serum testosterone (consequent to LH inhibition) supplements its direct antiandrogenic action.

Given to boys in relatively higher doses, it prevents pubertal changes, while in adult men libido and androgenic anabolism are suppressed. Its clinical indications are— precocious puberty in boys, inappropriate sexual behaviour in men, acne and hirsutism in women (in combination with an estrogen). Combined with ethinylestradiol (35 µg) cyclic (3 weeks on–1 week off) treatment with cyproterone has also been used as a contraceptive in women. Efficacy of cyproterone in metastatic prostate carcinoma is inferior to other forms of androgen deprivation. Hepatotoxicity limits its use.

Dose: 2 mg OD; GINETTE-35, DINAC-35; cyproterone acetate 2 mg + ethinyl estradiol 35 µg tab.

Flutamide A nonsteroidal AR antagonist with no other hormonal activity. Its active metabolite 2-hydroxyflutamide competitively blocks androgen action on accessory sex organs as well as on pituitary. Thus, it increases LH secretion by blocking feedback inhibition. Plasma testosterone levels increase in males which partially overcome the direct antiandrogenic action. This limits utility of monotherapy with antiandrogens in carcinoma prostate. They are now used only in conjunction with a GnRH agonist (to suppress LH and testosterone secretion) or after castration to block the residual action of adrenal androgens as *combined androgen blockade (CAB)* therapy of metastatic carcinoma prostate (also *see* p. 264). It is preferably started 3 days before the GnRH agonist to block the initial flare up that may occur due to excess release of LH and testosterone in the beginning (before GnRH receptors are desensitized). However, long-term benefit of CAB over GnRH agonist alone is not established. Along with oral contraceptives it has been tried in female hirsutism, but its hepatotoxic potential may not justify such use. Though gynaecomastia and breast tenderness occur frequently, libido and potency are largely preserved during flutamide treatment. Reports of liver damage have restricted its use.

Dose: 250 mg TDS
PROSTAMID, FLUTIDE, CYTOMID 250 mg tab.

Bicalutamide This more potent and longer acting (t½ 6 days) congener of flutamide is suitable for once daily administration in metastatic carcinoma of prostate as a component of CAB therapy. When used along with a GnRH agonist or castration, 50 mg OD affords marked relief in bone pain and other symptoms due to the metastasis. Side effects are hot flashes, chills, edema and loose stools, but it is better tolerated and less hepatotoxic than flutamide. Elevation of hepatic transaminase above twice normal is a signal for stopping the drug.
BIPROSTA, CALUTIDE, TABI 50 mg tab.

Nilutamide is another potent and long acting antiandrogen.

5 α-REDUCTASE INHIBITOR

Finasteride A competitive inhibitor of the enzyme 5 α-reductase which converts testosterone into the more active DHT responsible for androgen action in many tissues including the prostate gland and hair follicles. It is relatively selective for 5 α-reductase type 2 isoenzyme which predominates in male urogenital tract. Circulating and prostatic DHT concentration are lowered, but plasma LH and testosterone levels remain unchanged because testosterone itself mediates feedback pituitary LH inhibition.

Treatment with finasteride has resulted in decreased prostate size and increased peak urinary flow rate in ~50% patients with symptomatic benign hypertrophy of prostate (BHP). The beneficial effects are typically delayed needing ~6 months for maximum symptomatic relief. Patients with large prostate (volume > 40 ml) obtain greater relief than those with smaller gland. Upto 20% reduction in prostate size may be obtained.

Withdrawal of the drug results in regrowth of prostate, but with continued therapy benefit is maintained for 3 years or more. The relief of obstructive symptoms, however, is less marked compared to surgery and adrenergic α_1 blockers (*see* p. 157). It primarily reduces the static component of obstruction, while α_1 blockers overcome the dynamic component.

Concurrent treatment with both produces greater symptomatic relief.

Finasteride has also been found effective in male pattern baldness, though hair follicles have primarily type 1 enzyme. In such subjects it promotes hair growth and prevents further hair loss. Observable response takes 3 or more months therapy and benefit is reversed within 1 year of treatment cessation. However, 20–30% cases do not improve.

Finasteride is effective orally, extensively metabolized in liver—metabolites are excreted in urine and faeces; plasma t½ 4–8 hours (elderly 6–15 hours). It is well tolerated by most patients; side effects are decreased libido, impotence and decreased volume of ejaculate (each in 3–4% patients). Gynaecomastia, skin rashes, swelling of lips are rare.

Dose for BHP 5 mg OD, review after 6 months;
for male pattern baldness 1 mg/day.
FINCAR, FINAST, FINARA 5 mg tab; FINPECIA, ASTIFINE 1 mg tab.

Dutasteride This newer congener of finasteride inhibits both type 1 and type 2 5α-reductase and reduces DHT levels. It is metabolized by CYP3A4 and is very long-acting (t½ is ~ 9 weeks). It is approved for use in BHP and can benefit male pattern baldness. In clinical trias, both finasteride and dutasteride have been found to reduce the risk of developing carcinoma prostate by upto 25%. Interactions with CYP3A4 inducers and inhibitors are possible.

Dose: 0.5 mg OD; DUPROST, DURIZE 0.5 mg tab.

DRUGS FOR ERECTILE DYSFUNCTION

Erectile dysfunction (ED) refers to the inability of men to attain and maintain an erect penis with sufficient rigidity to allow sexual intercourse. It occurs mainly past middle-age and is common after the age of 65 years. A variety of vascular, neurogenic, hormonal, pharmacologic or psychogenic causes may underlie the disorder.

Sexual arousal increases blood flow to the penis and relaxes the cavernosal sinusoids so that they fill up with blood, making the penis rigid, elongated and erect. Nitric oxide (NO) released from parasympathetic nonadrenergic noncholinergic (NANC) nerves and vascular endothelium is the major transmitter causing relaxation of smooth muscle in corpus cavernosum and the blood vessels supplying it; ACh and PGs also play a role. A variety of mechanical/prosthetic devices and surgery have been used for ED, but drug therapy has made a big impact now.

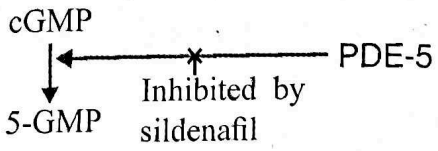
1. Androgens

Hypogonadism is an infrequent cause of ED. Parenteral testosterone esters or transdermal testosterone therapy is effective only when androgen deficiency is proven to be responsible for the loss of libido and ED.

2. Phosphodiesterase-5 (PDE-5) inhibitors

This class of drugs have become the first line therapy for ED.

Nitric oxide causes smooth muscle relaxation by generating cGMP intracellularly which then promotes dephosphorylation of myosin light chain kinase (MLCK) so that myosin fails to interact with actin (*see* Fig. 40.3). Inhibition of PDE-5, the cGMP degrading isoenzyme in cavernosal and vascular smooth muscle, results in accumulation of cGMP and marked potentiation of NO action. *Sildenafil, Tadalafil* and *vardenafil* are selective PDE-5 inhibitors found effective in a majority of patients with ED.



Sildenafil It is an orally active drug, marketed in the USA in 1998 and 2 years later in India, for treatment of ED. It became an instant hit, and evoked worldwide response. Sildenafil acts by selectively inhibiting PDE-5 and enhancing NO action in corpus cavernosum. Penile tumescence during sexual arousal is improved, but it has no such effect in the

absence of sexual activity. It does not cause priapism in most recipients.

Oral bioavailability of sildenafil is ~40%, peak blood levels are attained in 1–2 hr; it is metabolized largely by CYP3A4 and an active metabolite is produced; t½ in men <65 years averages 4 hours. It is recommended in a dose of 50 mg (for men > 65 years 25 mg), if not effective then 100 mg 1 hour before intercourse. Duration and degree of penile erection is increased in 74–82% men with ED including diabetic neuropathy cases. Over 20 controlled trials have confirmed its efficacy. However, sildenafil is ineffective in men who have lost libido or when ED is due to spinal injury or damaged nervi eregantes.

Adverse effects Side effects are mainly due to PDE-5 inhibition related vasodilatation—headache, nasal congestion, dizziness, facial flushing and fall in BP, loose motions. Relaxation of lower esophageal sphincter may cause gastric reflux and dyspepsia. Sildenafil, in addition, weakly inhibits the isoenzyme PDE-6 which is involved in photoreceptor transduction in the retina. As such, impairment of colour vision, especially blue-green discrimination, occurs in some recipients. Few cases of sudden loss of vision due to nonarteritic ischaemic optic neuropathy (NAION) among users of PDE-5 inhibitors have been reported.

Sildenafil markedly potentiates the vasodilator action of nitrates; precipitous fall in BP; MI can occur. After >6 million prescriptions dispensed in USA, the FDA received reports of 130 deaths related to sildenafil use by the year 2002. Most deaths occurred in patients with known risk factors, drug interactions or contraindications, and were timed either during or within 4–5 hours of sex. Sildenafil is contraindicated in patients of coronary heart disease and those taking nitrates. Though sildenafil remains effective for <8 hours, it is advised that nitrates be avoided for 24 hours. Caution is advised in presence of liver or kidney disease, peptic ulcer and bleeding disorders. Inhibitors of CYP3A4 like erythromycin, ketoconazole, verapamil, cimetidine potentiate its action. Caution is required also in patients of leukaemia, sickle cell anaemia or myeloma which predispose to priapism.

Sildenafil is erroneously perceived as an aphrodisiac. Men even without ED are going for it to enhance sexual satisfaction/pleasure.

PENEGRA, CAVERTA, EDEGRA 25, 50, 100 mg tabs.

Pulmonary arterial hypertension (PAH) Since NO is an important regulator of pulmonary vascular resistance, PDE-5 inhibitors lower pulmonary arterial pressure (*see* p. 547). Sildenafil is more selective for pulmonary circulation than vardenafil. Sildenafil has been shown to improve arterial oxygenation in pulmonary hypertension; exercise capacity is significantly imporved. Sildenafil 20 mg TDS has now become one of the drugs of choice for PAH.

Ambrisentan This endothelin receptor antagonist is a new drug for PAH.

Tadalafil It is a more potent and longer acting congener of sildenafil; t½ 18 hours and duration of action 24–36 hours. Peak plasma levels are attained between 30–120 min. Consequently time to onset of action may be longer. Side effects, risks, contraindications and drug interactions are similar to sildenafil. In addition, back pain is reported, which has been ascribed to some degree of PDE-2 inhibition by tadalafil. Because of its longer lasting action, nitrates are contraindicated for upto 3 days after tadalafil. Due to its lower affinity for PDE-6, visual disturbances occur less frequently. Tadalafil is also approved for use in PAH.

Dose: 10 mg at least 30 min before intercourse (max. 20 mg)

MEGALIS, TADARICH, TADALIS 10, 20 mg tabs, MANFORCE 10 mg tab.

Vardenafil Another congener of sildenafil with similar time-course of action; peak levels in 30–120 min and t½ 4–5 hours. Side effects, contraindications and interactions are also the same. It prolongs Q-T interval; should be avoided in hyperkalaemia and in patients with long Q-T or those receiving class IA and class III antiarrhythmics.

Dose: 10 mg (elderly 5 mg), max 20 mg.

3. Papaverine/Phentolamine induced penile erection (PIPE) therapy

Injection of papaverine (3–20 mg) with or without phentolamine (0.5–1 mg) in the corpus cavernosum produces penile tumescence to permit intercourse. However, the procedure requires skill and training. Priapism occurs in 2–15% cases, which if not promptly treated leads to permanent damage. This is reversed by aspirating blood from the corpus cavernosum or by injecting phenylephrine locally. Repeated injections can cause penile fibrosis. Other complications are—local haematoma, infection, paresthesia and penile deviation. In view of the availability of PDE-5 inhibitors, it is rarely used now; only in cases not responding to sildenafil and alprostadil.

4. Prostaglandin E_1

Alprostadil (PGE_1) injected directly into the corpus cavernosum using a fine needle produces erection lasting 1–2 hours to permit intercourse. Alprostadil injections are less painful than papaverine, but local tenderness may occur. Penile fibrosis and priapism are rare. It is now the most commonly used drug in patients not responding to PDE-5 inhibitors, such as neurogenic and psychogenic ED.

A transurethral pellet termed 'medicated urethral system for erection' (MUSE) has been developed which avoids intracavernosal injection, but is less effective and may cause urethral burning.

PROBLEM DIRECTED STUDY

21.1 A 65-year-old man presented with severe pain in the left shoulder region. The pain has progressively increased over the last 4 weeks, is not relieved by analgesics or NSAIDs and is worsened by pressure or movement. He also has increasing micturition difficulty for the last 6 months. Shoulder X-ray showed osteolytic lesion in the head of humerus. Rectal examination was consistent with prostate cancer which was confirmed by needle biopsy and raised serum PSA level (30 ng/ml). He refused orchidectomy and was prescribed injection triptorelin 3.75 mg i.m. to be repeated after one week and then every 4 weeks. After 1 week of 1st injection, he reported increased bone pain and greater bladder voiding difficulty. The serum PSA level was 34 ng/ml.

(a) What is the cause of the increase in bone pain and urinary obstructive symptoms? Is the choice of the drug incorrect?

(b) Could this flaring of symptoms be avoided; if so how?

(c) Can any other drug be given to relieve the bone pain?

(see Appendix-1 for solution)