Chapter

Steroidal 5α-Reductase: A Therapeutic Target for Prostate Disorders

Neelima Dhingra

Abstract

Steroidal 5α-reductase is a system of NADPH dependent enzyme that catalyzes the irreversible conversion of Δ^4–3-ketosteroid precursor (testosterone) to its corresponding 5α-reduced metabolite (dihydrotestosterone). Initial role of DHT was discovered through males pseudohermaphroditism, a genetic disorder with complete or partial 5α-reductase deficiency accompanied with features at critical juncture of fetal and postnatal development. However, excessive DHT production, has brought a revolution in revealing the etiology of complications like prostate cancer and benign prostatic hyperplasia. Over the last two decades, converging lines of evidences have highlighted the role of 5α-reductase inhibitors in the treatment of these androgen dependent disorders. Finasteride and Dutasteride, are the two clinically approved inhibitors available in the market, that helps in reducing the prostate volume by blocking the 5a-reductase enzyme.

Keywords: androgen, isozymes, prostate, genetic disorder, benign prostatic hyperplasia

1. Introduction

The prostate gland located between the bladder and the rectum is an heterogeneous organ, and wraps around the urethra. It is considered to be consisted of central, peripheral or transitional zone and composed of three different types of cells: glandular epithelial cells, smooth muscle cells and stromal cells (**Figure 1**). At the time of birth, prostate is about the size of a pea and undergoes many changes during the course of man's life. It grows only slightly until puberty, then it begins to enlarge rapidly attaining normal adult size and shape [1].

The gland generally remains stable until about the mid 40s, and in most men over the age of 60, the prostate begins to enlarge. The dense capsule surrounding the enlarging prostate prevents it from further expansion outward, which in turn forces the prostate to press against the urethra, and partially block urine flow (**Figure 2**). This apparent increase in number of stromal and epithelial cells results in obstruction of the proximal urethera and condition is called as benign prostatic hyperplasia (BPH). This obstruction, in turn causes bladder irritation and contraction, even for small amount of urine. Eventually the bladder weakens and does not completely empty through urination [2].

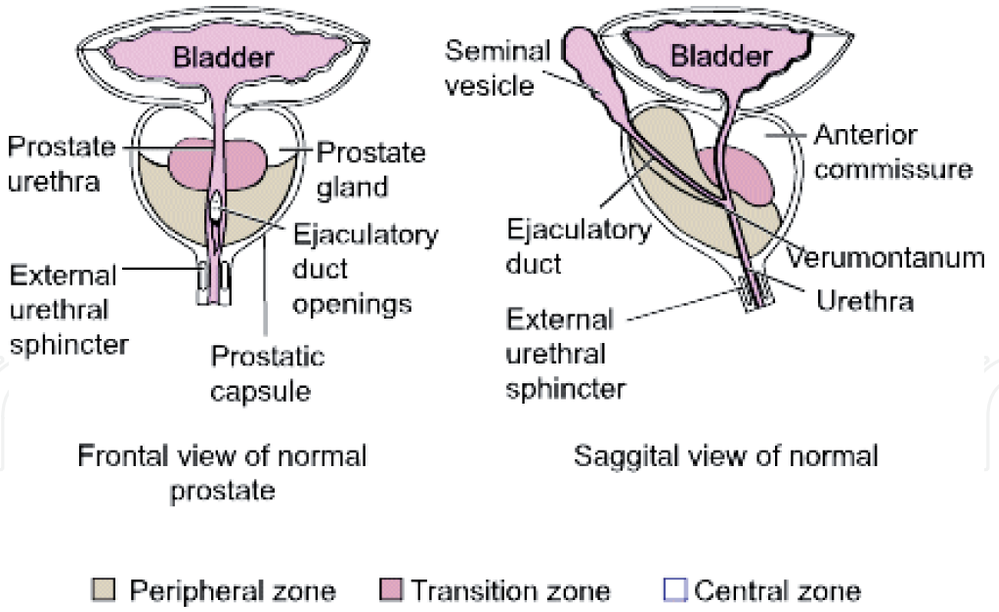


Figure 1.
Location and different sections of prostate gland.

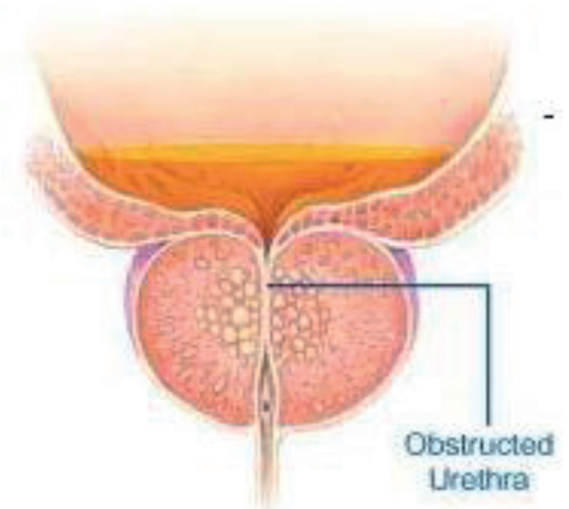


Figure 2.
Enlarged prostate gland.

Clinically BPH is manifested as lower urinary tract symptoms (LUTS) and consisting of voiding and storage symptoms such as slow urinary stream, splitting or spraying of urinary stream, recurrent urinary stream, straining to void and terminal dribbling, hesitancy, urgency, increased frequency, and incontinence. Although urge incontinence is an irritative symptom, it may indicate the presence of obstruction [3, 4].

BPH is also described as quality of life disorder, as its affects man's ability to initiate or terminate urine flow stream (the symptoms interfere with the normal activities) and reduces the feeling of well being. Though the etiology of hyerplastic process of BPH is clearly not known, but many partially overlapping and complementary theories have been proposed for the overgrowth of smooth muscle tissue and glandular epithelial tissue like aging: late activation of cell growth [5], defective cell death and hormonal changes. According to the most widely accepted hypothesis i.e. androgen (dihydrotestosterone hypothesis) BPH occurs due to an age related changes in prostate androgen metabolism that favors the accumulation of DHT and responsible for cell growth in the tissues that lines the prostate gland thus rapid prostate enlargement [6, 7].

2. Treatment options for BPH

During the last two decades, it has become clear that the management of LUTS associated with BPH is much more than just treating symptoms. It is a progressive disease and defined as worsening of symptoms, increase in prostate volume (PV), deterioration of urinary flow rate, inability to void i.e. acute urinary retention (AUR) and the need for surgery either for AUR or deteriorating symptoms [8]. Further, AUR with an annual risk of less than 1% is found to be uncommon, but requires urgent bladder catheterization. Therefore, diagnosis, monitoring, frequency, severity and assessment of the prognosis for disease progression should be assessed before management decisions. EAU guidelines have recommended a series of evaluation as a routine part of the initial assessment of men with LUTS, that includes clinical history, a validated questionnaire to assess symptoms, physical examination, creatinine measurement, urinalysis, flow rates, postvoid residual (PVR) volume and serum prostate-specific antigen (PSA) measurement especially when a diagnosis of prostatic carcinoma is required [9]. A more profound knowledge on the pathogenesis, the natural history and risk of the progression, has enabled more differentiated therapy of elderly men with lower urinary tract symptoms due to benign prostatic hyperplasia as follows (**Figure 3**) [10, 11].

2.1 Watchful waiting

Watchful waiting is a well known approach to treat BPH where men are asymptomatic or with mild to moderate symptoms without causing no serious health. It is generally considered as the first tier in the therapeutic cascade and patients are

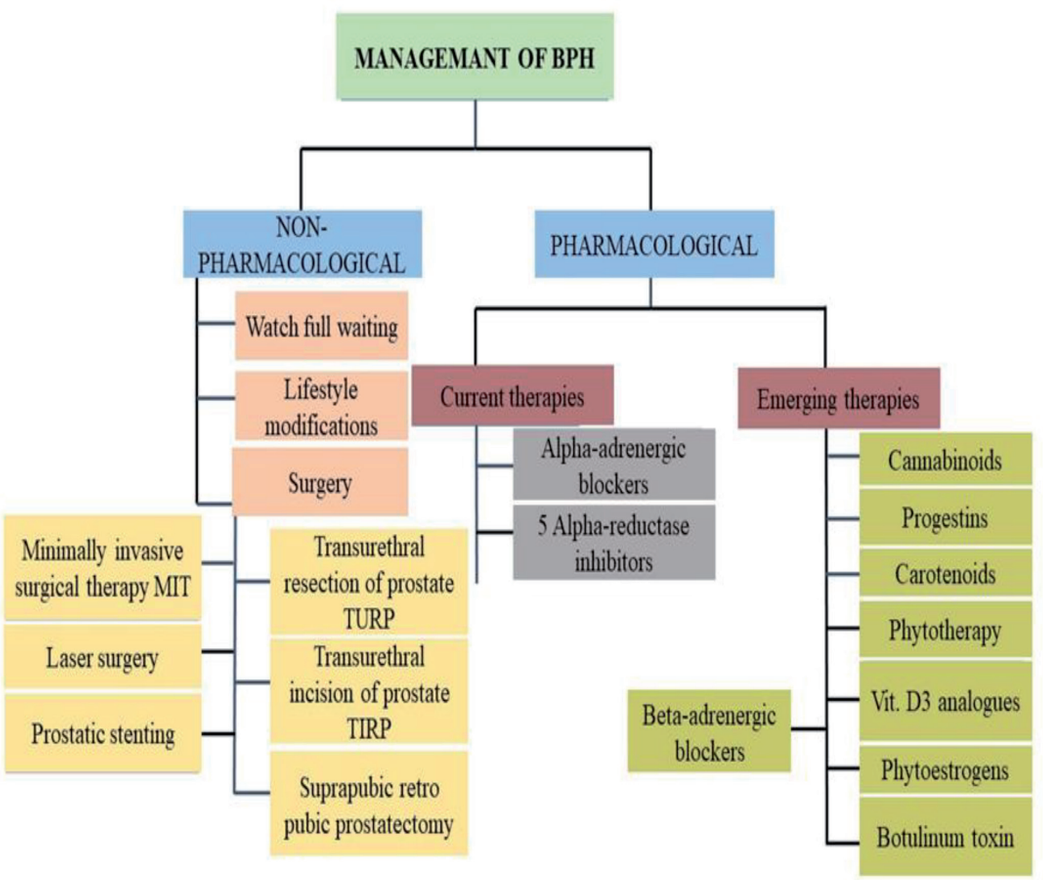


Figure 3.
Management options.

monitored by his physician without receiving any active intervention. Untreated BPH will progress to AUR and other complications such as renal insufficiency and stones. Thus regular check up along with continual education is recommended to avoid chances of occurrence of serious complications [12, 13]. Further, optimization can be achieved by including certain lifestyle or dietary changes as recommend in EAU guidelines, to prevent the deterioration requiring medical or surgical treatment [9].

2.2 Surgical treatment

Surgical interventions are often endorsed for patients with complications of LUTS such as AUR, renal insufficiency, bladder calculi or .recurrent urinary tract infections, persistent gross hematuria secondary to BPH [14]. Further, other candidates for surgery includes the patients refractory to other medical management, or men with unacceptable side-effects following drug therapies and requested for active treatment [15].

Open prostatectomy, transurethral resection of the prostate (TURP), and transurethral incision of the prostate (TUIP) are some of the conventional surgical treatment options for symptomatic BPH. The removal of obstructing tissue was first achieved by open prostatectomy in early 1900s [16] and considered as gold standard for the surgical treatment, but later replaced by TURP. Significant improvement in LUTS were observed with TURP, and it takes only 20–30 min, to resect an average gland weighing 30 g. Though TURP is considered to be as the hallmark by the urologist, the one against which other surgical options are compared, but it carry the complications of excessive bleeding and longer hospital stay [16, 17]. TUIP a comparative less invasive technique than TURP and with similar improvements in symptoms is recommended for prostate gland weighing <25 g of the prostate [18]. An electrosurgical modification of the TURP and TUIP technique i.e. transurethral vaporization (TUVP), is reserved particularly for the patients with a small prostate and bleeding disorders. Its long term efficiency has been found to be comparable with that of TURP, but number of patients reported for irritative symptoms as side effects [19].

Raising the temperature of the cells through the use of low level radiofrequency (microwave) in prostate to 40-45°C (hyperthermia), 46-60°C (thermotherapy) and 61-75°C (transrectal thermal ablation) are found to be more specific techniques for the necrosis of obstructive tissue without affecting normal cells [16]. In comparison to high-energy TUMT with increased morbidity, low range TUMT has been found to well tolerated in patients with reasonable improvement in flow rate and less effect on sexual function [20]. Another simple, safe and relatively inexpensive technique to deliver high frequency radiowaves (temperature range 90-100°c) to produce localized necrotic lesions in hyperplastic tissue is Transurethral needle ablation (TUNA). Its a method of choice over TURP in younger men and with small sized gland, wishing to preserve sexual function, as it poses a low or no risk for incontinence and impotence [21, 22].

Laser vaporization or prostectomy, has been found to be another safe, effective and widely used form of MIT technique with significant improvement in urinary flow rates and symptoms. Light at different wavelength is being generated using four types of lasers, namely potassium titanyl phosphate (KTP) diode laser; neodymium: yttrium-aluminum-garnet (Nd: YAG) laser, and holmium YAG laser (Ho:YAG), that cause irreversible cellular damage, followed by their coagulation necrosis and ultimately vaporization of tissues. Further, evolution in holium laser prostatectomy i.e. Holmium laser enucleation of the prostate (HoLEP) is being used for prostate of all sizes at considerable faster rate than TURP and now considered to be as new gold standard for the treatment of BPH. HoLEP relieves the pressure on the urethra tube by anatomically enucleating the majority of excess benign prostate tissue. Short operative time & hospital stay, minimal blood loss and fluid

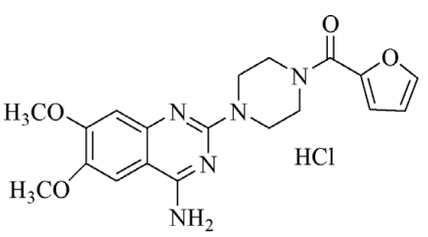
absorption, and bladder neck contractures are some of the advantages of laser prostatectomy over the TURP and other conventional techniques [23–25].

2.3 Pharmacological treatment

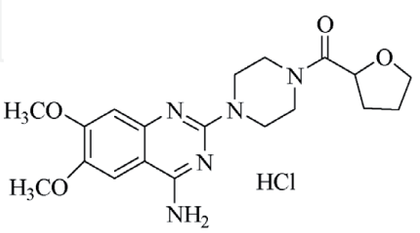
The clinical manifestations of BPH are primarily precipitated by increased resistance to the flow of urine through the bladder neck and/or compressed prostatic urethra. Thereby, the treatment strategies are targeted to decrease the urinary resistance by reducing the prostatic volume. A number of strategies are available but great strides in the development of alpha-adrenergic blockers and anti-androgen (androgen deprivation therapy) have fueled this evolution.

2.3.1 Alpha adrenergic blockers

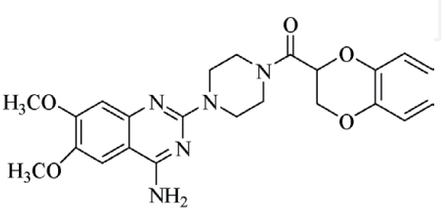
Alpha adrenergic blockers relaxes the smooth muscle in and around the prostate and bladder neck without affecting the detrusor muscle of the bladder wall thus relieve the obstruction due to dynamic component of LUTS. The rationale for this approach is based on that noradrenaline (NA) acts at alpha-1 adrenergic receptors (α_1-AR) in the neck and sphincter of the urinary bladder to promote contraction and urinary retention. NA also acts at alpha-1 adrenergic receptors to control the smooth muscles in the prostate capsule and urethra [26]. Prazosin with a piperazinyl quinazoline nucleus, was the first clinically investigated selective α_1-adrenergic receptor antagonist for BPH with 1000-fold greater affinity than that for α_2-receptor. But, because of associated important adverse effects like postural hypotension and retrograde ejaculation, soon it was withdrawn from market [27]. The next advancement in drug therapy was the advent of selective α_1-drugs, Terazosin and Doxazosin, structurally close analogs of Prazosin [28].



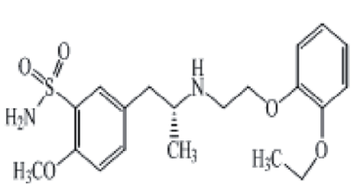
Prazosin



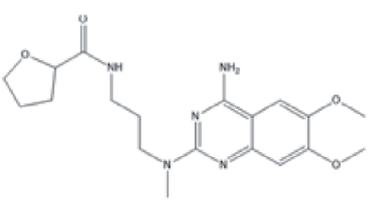
Terazosin



Doxazosin



Tamsulosin



Alfuzosin

Molecular studies have further identified three subtypes α_{1A}, α_{1B} and α_{1D} of the α_1-AR. The α_{1A} is predominant in prostate, whereas α_{1B} subtype has been found to be predominant in blood vessels [29]. Their relative distribution and concentration in the bladder, prostate, neck, brain and vascular smooth muscle have been exploited to develop uroselective α_1-adrenergic antagonists with reduced side-effects. Tamsulosin was launched as the first subtype selective α_1-AR antagonist, but third uroselective α_1-AR antagonist with ten fold more selectivity for α_{1A}-receptor subtype compared to α_{1B}-receptor subtype. Whereas, Alfuzosin, with comparable clinical efficacy to that of tamsulosin was the fourth uroselective α_1-AR antagonist with almost similar affinity for all of the α_1 receptor subtypes and [12, 30]. Currently, Tamsulosin and Alfuzosin are the most widely prescribed medications as selective α_1-AR antagonists for the LUTS associated with BPH.

2.3.2 Androgen deprivation therapy

The biological basis of this therapy lies in the observation that the androgens (dihydrotestosterone). plays a crucial role in the development and maturation of prostate gland. Furthermore, BPH does not develop in the patient who are castrated prior to the puberty [31, 32]. Androgen suppression causes reduction in prostatic volume which is believed to decrease the considerable responsible static component of bladder outlet obstruction resulting from benign prostatic hyperplasia [33].

Progestational agents like medogesterone, and hydroxyprogesterone acetate, acts in reversible manner and are capable of decreasing testosterone level in the serum by inhibiting the release of luteinising hormone (LH) [34]. Further, desensitization and down regulation of pituitary gonadotropin releasing hormone (GnRH) receptors by agonistic GnRH analogues is well established approach in the clinical treatment of BPH [35]. These agents (leuprolide, and Nafarelin acetate) [36], results in the blockage of gonadotropin release from the anterior pituitary gland followed by the suppression of steroidal sex hormones production. Antiandrogens like flutamide, cyproterone acetate, curcumin analogues bicalutamide, 16 substituted/non-substituted D-homo-pregnane derivatives) compete for androgen receptor with the natural ligand (DHT) binding and are used therapeutically in BPH patients [37–41].

Plethora of the evidences has indicated the role of estrogen along with male androgens in the aging men with BPH condition. Estradiol is the product of the peripheral conversion of testicular and adrenal androgen in man under the influence of enzyme aromatase. Under the estrogenic effect, stromal and epithelial interactions presumably mediate and regulate the proliferative activity of the prostate [42]. Testolactone, atermestone, TZA-2237, and abiraterone are some of the aromatase inhibitors and found application in non-surgical treatment of BPH by blocking this peripheral conversion [43–45].

The importance of androgendeprivation by the use of antiandrogen agents was underscored by the fact that these centrally acting drugs decrease the testosterone level, and cause complications like erectile dysfunction and loss of libido [45, 46]. Therefore, search for the new drugs with more efficacies, selectivity and relative broader therapeutic index was being pursued and continued accrual resulted in the development of 5α-reductase inhibitors.

3. 5α-reductase inhibitors

5α-reductase (5AR) is a nuclear membrane bound enzyme that converts testicular endogenous testosterone T to dihydrotestosterone DHT in the presence of

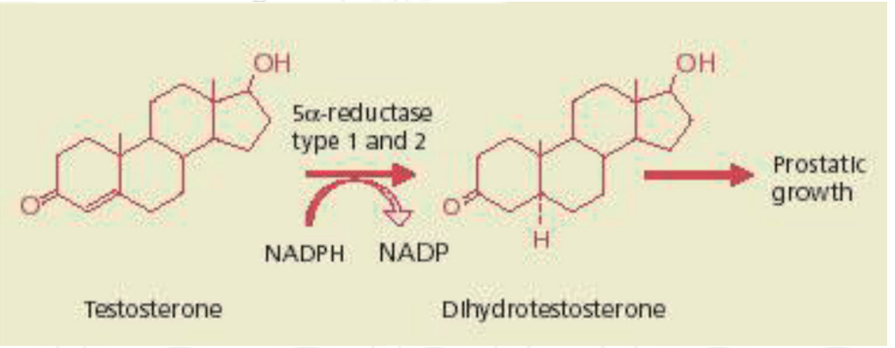


Figure 4.
5α-reductase enzymatic action.

cofactor NADPH. Thus 5AR dictates the cellular availability of DHT to prostatic epithelial cells and consequently modulate its growth as shown in **Figure 4** [47].

Thus, inhibiton of androgen action by 5α-reductase represents a logical treatment of 5α-reductase activity disorder i.e. BPH. 5ARI decreases the dihydrotestosterone concentration by blocking the enzyme and, provide relief from the symptoms related to the static mechanical obstruction caused by BPH by shrinking the size of prostate [48]. Further, the rationale for use of 5ARI is rooted in the observation that these agents are more specific to DHT action without affecting/lowering T level, thus capable of decreasing long term side effect of castration associated with loss of testosterone, without compromising the efficacy of hormonal therapy [49, 50].

3.1 Physiology of androgens release

Figure 5 indicating the control of testicular androgen production by hypothalamus and the pituitary gland. Neurons in preoptic area of the hypothalamus secrete the decapeptide lutenizing hormone releasing hormone (LHTH), in a pulsatile fashion, which in turn stimulates the release of lutenizing hormone (LH) from the pituitary. After reaches to the testies, LH binds to the high affinity receptor present on the surface of leydig cells and stimulate them to produce testosterone. Released T travels in the blood either in the free state or after binding with protein [43]. Circulating testosterone levels in a negative feed back mechanism regulates the secretion of hypothalamus and pituitary.

Major androgen in the adult male is Testosterone (T) and 98% of all T in the prostate is of testicular origin, whereas only 5–10% being produced by adrenal gland [51]. The unbound T diffuses into the prostate cell (target organ), where most of it gets converted to dihydrotestosterone (DHT) by the membrane bound NADPH dependent enzyme 5α-reductase. Within prostate, DHT binds to cytosol androgen receptor protein (AR) followed by entry of DHT-AR complex into the nucleus, where it stimulates the RNA synthesis after interacting with DNA binding sites (**Figure 6**) [52].

T and DHT differ in their physiological action and T also binds to androgen receptor but with lesser affinity to that of DHT [53]. According to Burckovsky and Wilson postulation T acts as a prohormone and DHT is found to be the main active hormone in androgen sensitive tissue [47]. With in embryo, T is responsible for the transformation of Wollffian ducts in epididymis, seminal vesicle & differential ducts & and responsible for production of DHT after activating the expression of 5AR. On the other hand, DHT in embryo is found to be crucial for the sexual differentiation of male foetus organ, formation of external genitilia, like urethera and prostate. After puberty, it's the T that determines the modification of external

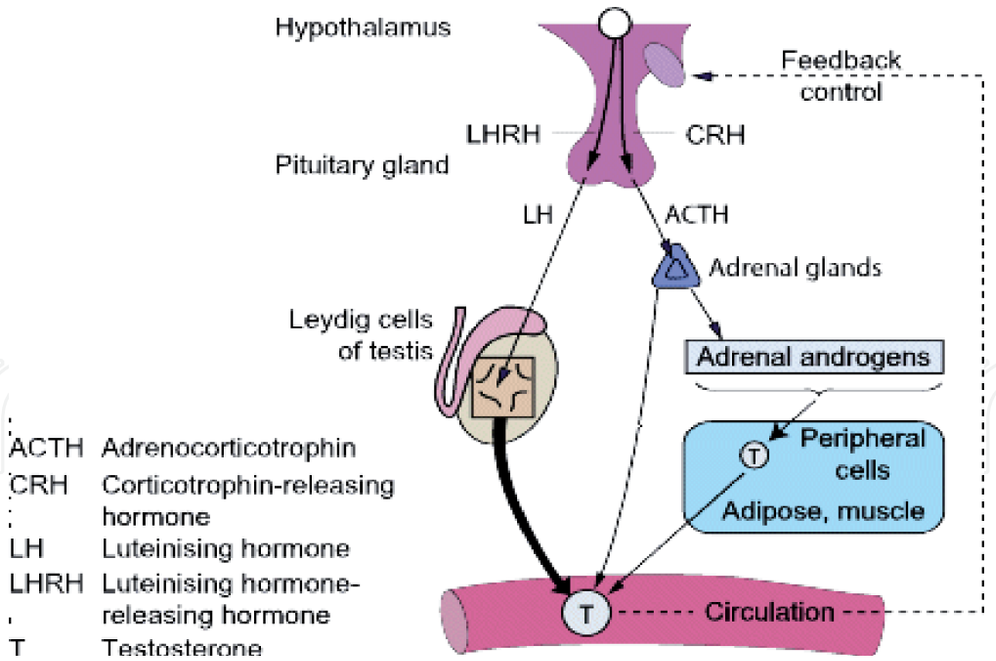


Figure 5.
Physiology of androgen release.

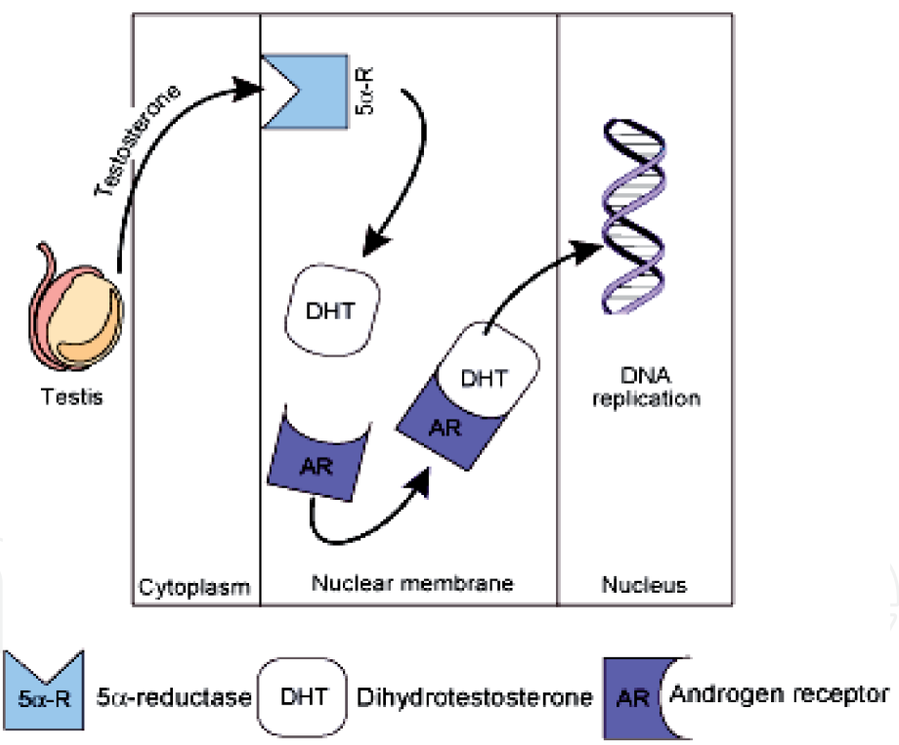


Figure 6.
Interaction of androgen within prostate cell.

genitilia, deeping of voice, increase of muscle mass, spermatogenesis, and male sexual behavior. In contrary to that DHT formation in male puberty is related with the increase of facial & body hair,r and the enlargement of prostate [32, 37, 54, 55].

Further crucial role of DHT was discovered through male pseudohermaphroditism, a genetic disorder with complete or partial 5α-reductase deficiency. Decreased 5AR activity not only resulted in low level of DHT [56, 57], but also accompanied by several distinguished features at the critical juncture of foetal and postnatal development [58]. Male with such condition showed ambiguous external genitilia

at-birth [59], often raised as girls, little facial hairs as adults, no temporal receding hairline, small prostate no acne and normal libido. Whereas, female with 5AR deficiency did not show any clinical symptoms.

Excessive production of DHT is associated with development of several endocrine diseases such as acne, alopecia in men, male pattern baldness, hirusitism in women, prostatic carcinoma and benign prostatic hyperplasia [7]. In BPH, concentration of DHT is found to 2.5 fold higher than in normal prostate.

3.2 Isozyme of 5α-reductase

The family of 5AR is composed of three known isoenzymes with the types I and II being the most known. Steroidal 5α-reductase is a system of NADPH dependent enzymes that catalyzes the irreversible conversion of 4-en-3-oxo-steroid to the corresponding 5α-H-3-oxo-steroid [60–62]. Based on the anatomical location, biochemical properties, and tissue expression pattern three different isozymes of 5AR have been isolated, expressed and characterized (**Table 1**). The type 2 isozyme is predominantly present in the prostate, seminal vesicle, epididymis, genital skin, and liver. It has been found to be essential for differentiation of male external genitilia during foetal life, and its deficiency leads to the condition known as male pseudohermaphroditisms [63, 64]. Whereas, type 1 is not the major species expressed in the prostate and exhibit only micromolar affinities for steroidal natural substrate (T) [65, 66].

Both the isoforms have optimal activity at different pH range as type 1 is active at alkaline pH of 8.5, while type 2 is active at pH 4.7–5.5. Studies have shown that the activity of type I enzyme is several times higher in PC than in BPH. Whereas the 5AR type II (5AR-2) isoenzyme with higher affinity for T at the optimum pH 5.5 predominates in the prostate and other genital tissues and plays a major role in BPH [67, 68].

	5AR-1	**5AR-2**	**5AR-3**
Gene	SRD5A1	SRD5A2	SRD5A3
Location	5p15	2p23	4q12
Length (b)	36,173	56,385	25,458
Protein size	259	254	319
Transmembrane helices	5	4	6
Protein weight (Da)	29,459	28,393	36,521
Optimal pH	6–8.5	5–5.5	6.9
Affinity for testosterone	Km = 1.7 μM	Km = 0.2 μM	—
In vitro inhibition	$K_i \geq 300$ nM	K_i = 3–5 nM	—
Localization (in tissues)	Sebaceous glands of skin, sweat glands, dermal papilla cells, fibroblasts from all areas	Prostate, genital skin, epididymis, seminal vesicles	Hormone refractory prostate cancer cells, pancreas, brain, skin, adipose tissue
Selectivity to the inhibitors	Inhibitors with 4-methyl-4-aza functionality are very potent	4-aza, 6-aza and charged 3-substitutents derivatives are highly selective.	—

Table 1.
5AR isozymes and their characteristic features.

A new isoenzyme of 5AR, type III (5AR-3) have been identified recentlyin castration resistant prostate cancer (CRPC) cells as well as in other tissues such as pancreas, brain, skin and adipose tissues [69, 70]. The length, location and other characteristics of these isoenzymes have been presented in **Table 1** [71].

3.3 Mechanism of 5α-reductase action

The detailed chemical and kinetic mechanisms of conversion of T into DHT by 5AR have been investigated as follows:

3.3.1 Chemical mechanism

Figure 7 is indicating the proposed mechanism of T reduction to DHT under the influence of 5α-reductase. It is based on the known regio and stereoselectivity of the reduction that involves the formation of binary complex between the enzyme and NADPH, followed by formation of ternary complex with the substrate [72, 73]. Binary complex formation follows the activation of the enone system by based on its strong interaction with commonly present electrophilic residue (E^+) (proton, +ve charged group, proton donor) in the active site. Enone activation gives the delocalized carbocation which is being reduced selectively at C-5, on the α-face, by a direct hydride transfer from NADPH and lead to the formation of the enolate of DHT [74]. Generated intermediate duly coordinated with $NADP^+$ on the α- face, is further attacked by a proton on the β-face at C-4 and results into the formation of

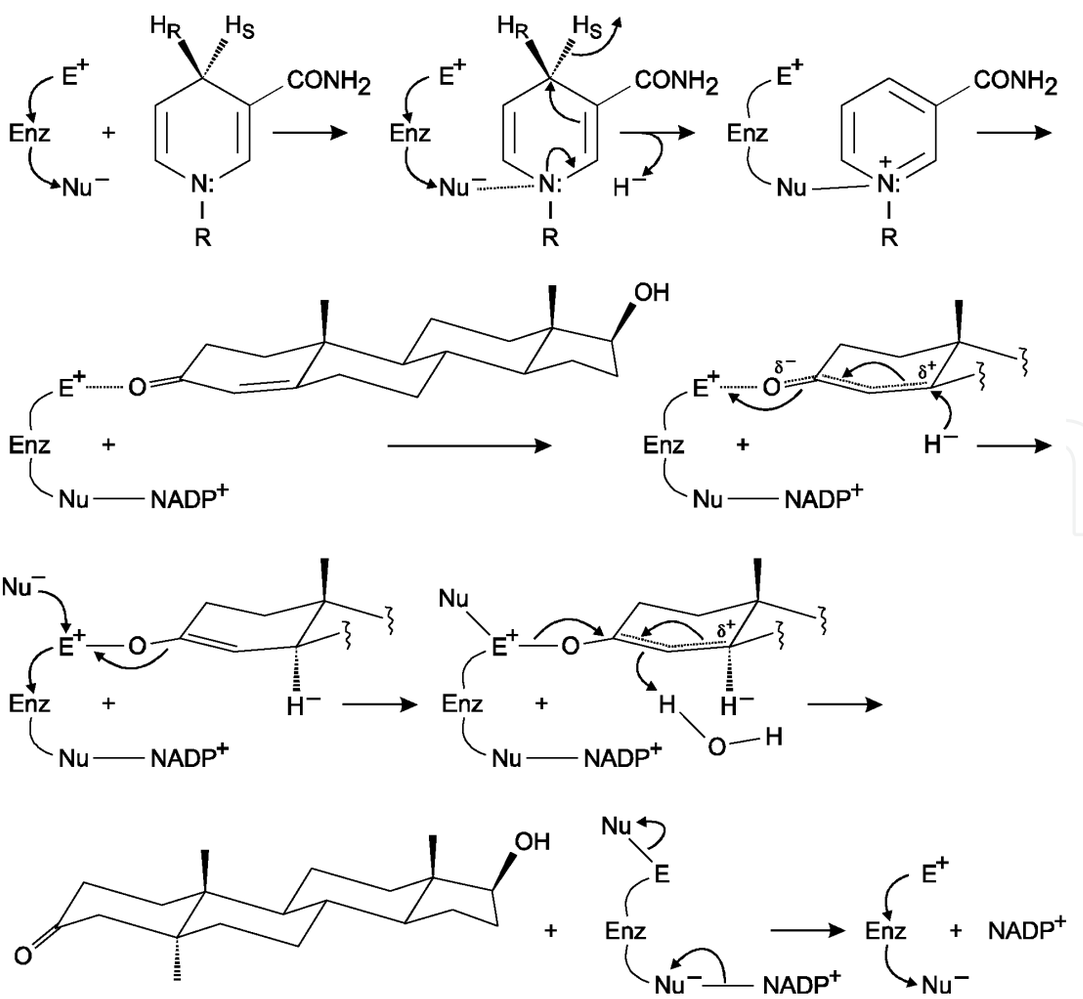


Figure 7.
Chemical mechanism of action of 5α-reductase.

ternary complex E-$NADP^+$–DHT. Towards the end of reaction, release of DHT gives the binary $NADP^+$-enzyme complex, followed by the release of $NADP^+$ leaving the enzyme free for further catalytic reactions.

3.3.2 Kinetic mechanism

The kinetic mechanism was studied for the natural substrate T using rat and human prostatic 5α-reductase and both the models showed similar kinetic mechanism as shown in **Figure 8.** 1,4-reduction of the substrate (T) depends on the initial velocity data from progesterone and 5α-reductase, wherein $NADP^+$ is found to be competitive versus NADPH but non-competitive versus progesterone. Further catalysis occurs with the initial release of DHT followed by $NADP^+$.

3.4 Classification of 5α-reductase inhibitors

The control of the physiological action of major androgen DHT, without significant change in the overall profile of other hormones especially (T), through the inhibition of specific enzyme 5AR involved in its synthesis and metabolism, plays an important role in the design of ARIs, mimicking the electronic and steric properties of the enolate [75].

The identification of different isozymes of 5AR, their specific role in physiological and pathological developments of BPH has opened the door for more specific and selective inhibitors of this enzyme [76]. Broadly 5α-reductase inhibitors have been divided into following major groups a) Transition state analogues b) Mechanism based inhibitors c) Structure based.

3.4.1 Transition state analogues

Based on chemical mechanism of 5AR, two possible transition states (**Figure 9**) have been postulated substrate like and product like. [77, 78]. The 'substrate like' transition state is the one in which the C-5 has not yet changed it sp^2-hybridization and the structure of C-3, C-4, and C-5 are similar to those of intermediate carbonation. On other hand in 'product like' TS C-5 has assumed its final sp^3 hybridization and structure of C-3, C-4 and C-5 are similar to those of enol form of DHT.

Transition state analogue states that the binding to the enzyme and thus its inhibition could be greater for molecules being mimic of the transition of the enzymatic process [77].

3.4.2 Mechanism based analogues

According to the kinetic mechanism of T reduction to DHT, three different types (Type A, B and C) of inhibitors have been identified [79, 80]:

a. Type A: Inhibitors compete with substrate testosterone and cofactor NADPH i.e. bisubstrate.

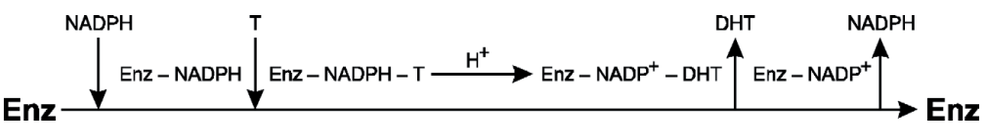


Figure 8.
Kinetic mechanism.

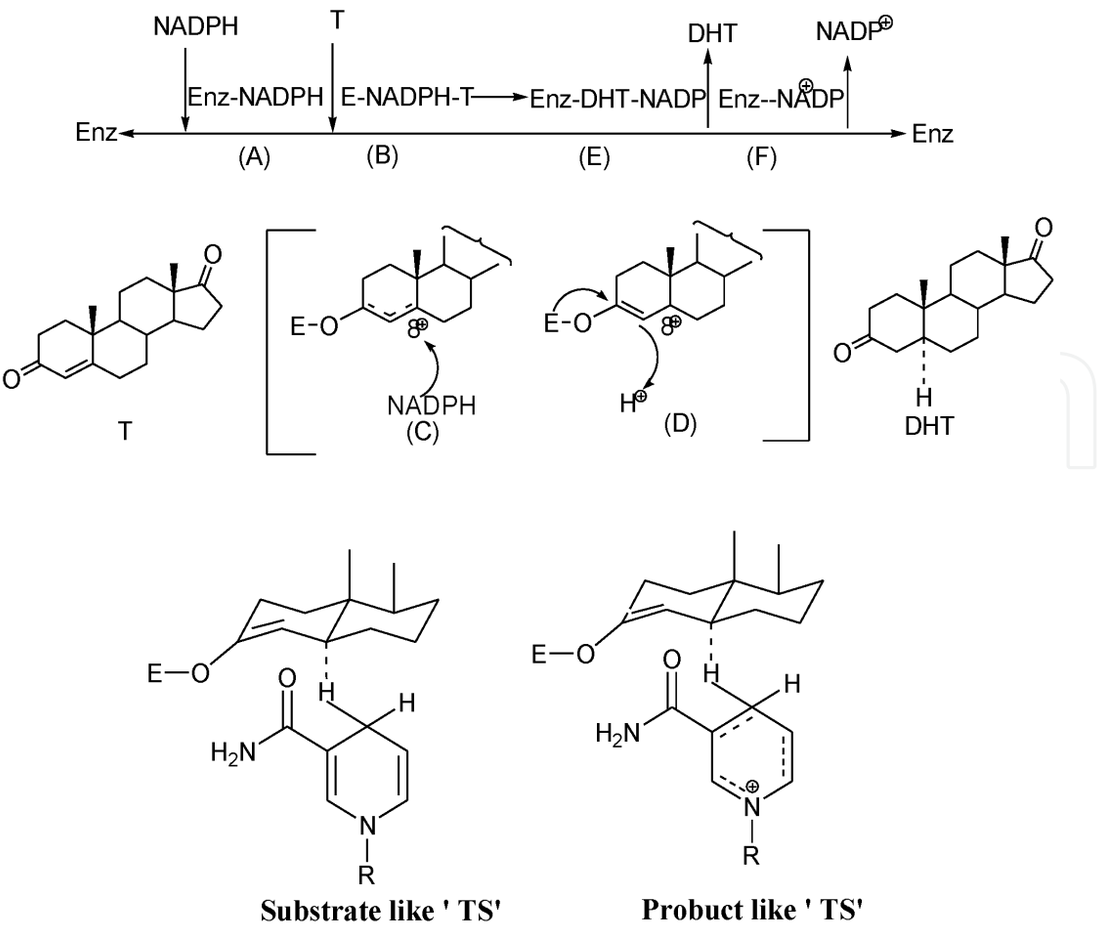


Figure 9.
Transition states of the enzyme (5AR).

b. Type B: These are the compounds that got the potential to bind reversibly to NADPH-enzyme complex and competitive with natural substrate T thus competitive inhibitors.

c. Type C: Such inhibitors fit the enzyme- NADP complex and are uncompetitive versus the substrates.

Number of steroidal and non-steroidal analogs ranging from classical, reversible and irreversible inhibitors, and transition state analogues to mechanism-based analogues have been synthesized and evaluated during last two decades as shown in **Figure 10**.

Biological basis for the steroidal inhibitors lies in the observation that enzyme could be best inhibited by the compounds having structural similarities to natural substrate i.e. T. One of the earlier report in 1970 by Voigt and Hsia, indicate the ability of 23 steroidal hormones to inhibit 5AR in human skin thus the efficacy of steroidal derivatives in BPH [81]. Progesterone, a competitive substrate of T, restrained transformation by upto 93.3% and was converted to 5-pregnane-3, 20-dione. Great affinity of progesterone for 5AR was further indicated by its high value of inhibitory constant (K_i = 700 nm). Other potent inhibitors were deoxycortisone, deoxycortisone acetate and dehydroepiandrosterone [82]. In 1973, synthesis and evaluation of series of 5ARI, indicated the key structural requirements for the 5ARI activity i.e. presence of 4-en-3-one function and 17β-side chain having one or more oxygen functionalities. Molecules possessing these features act as competitive inhibitors of 5AR, therefore, all of them could be regarded as a substrate of the enzyme 4-en-3-one steroids [83]. The clinically approved first inhibitor was

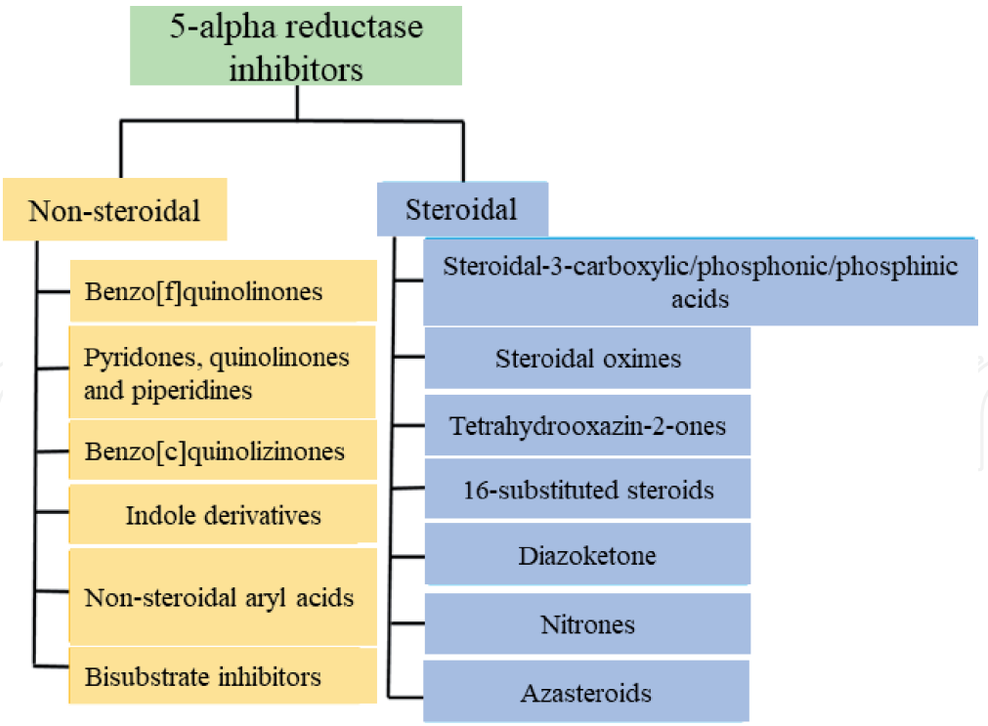
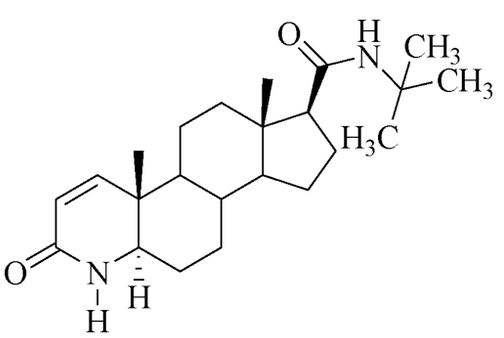


Figure 10.
Chemical classes of 5AR inhibitors.

prepared by modification of the structure of naturally existing substrates. This modification included the substitution of various hetero atom such as nitrogen, by forming the azasteroids by replacing carbon atom of the ring with nitrogen in the steroidal moieties.

Finasteride.

Chemically Finasteride (MK-906) is 17β-(N-tert-butyl-carbamoyl)-4-aza-5α-androst-1-en-3-one. It was synthesized in 1984, and got clinical approval in 1992 in the United States as the first 5α-reductase inhibitor for the treatment of BPH [84]. It is a competitive inhibitor of 5α-reductase type 2 with 10-fold high affinity than type 1 and forms a stable complex with enzyme. Clinical doses of 5 mg/day has been found to decrease the prostatic DHT level by 70 to 90%, in human beings, thus decreases prostate volume or size followed by improvement in urinary flow rate [85, 86]. It has neither any other hormone (androgenic, antiandrogenic) related properties, nor it interferes with the binding of T or DHT to the androgen receptor [87]. Though significant improvement in term of increased flow rates and decreased prostate-specific antigen level has been observed in finasteride-treated group. But, its long term usage results in common side effects like decreased libido, ejaculatory dysfunction, or impotence, while rashes and breast enlargement have also been observed in some of the patients.

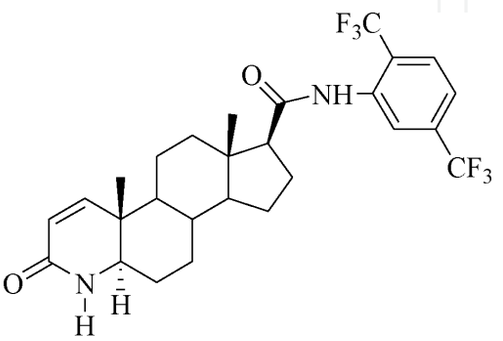


Finasteride

Dutasteride.

Chemically dutasteride is 17β-N-{2, 5-bis (trifluoromethyl) phenyl)} -3- oxo- 4-aza- 5α- androst - 1- ene - 17-carboxamide and belongs 4-aza-steroids [86] It was approved in 2002 by the US FDA for the symptomatic treatment of BPH. Unlike finasteride, dutasteride is a nonselective competitive inhibitor of both isozymes. 5α-reductase type 1 and type 2.

At clinical dose of 0.5 mg/day, it decreases DHT levels >90%, by forming a stable complex with a slow rate of dissociation constant. Dutasteride has been found to improve urinary flow rate, decrease the risk of AUR and need for surgery by reducing the size of enlarged prostate [88–90]. Dutasteride is found to be 60 times more active than finasteride and efficacy has been improved in terms of symptom score, maximal urinary flow rate, and quality of life [86].



Dutasteride

These two drugs have been found to display competitive blocking effect in short-term kinetic, whereas long-term reaction analysis revealed their irreversible inhibitory effect by forming a stable complex of enzyme-bound intermediates [91]. The binding affinity between 5α-R isoenzyme and 4-azasteroids can be described in the two step mechanism:

$$E + I \underset{}{\overset{K_i}{\rightleftharpoons}} EI \xrightarrow{K_3} EI^*$$

Where K_i is the inhibition constant for the first step equilibrium and K_3 is the rate constant for the time-dependent second step [92]. Mechanistically, finasteride has been proven to be 5α-R2 inhibitor by acting on alternative substrate for 5α-R2 which is initially bound to highly stable complex of enzyme-bound NADP-dihydrofinasteride. The resulting adduct is finally processed to form dihydrofinasteride [93]. The bisubstrate complex of NADP-dihydrofinasteride is a potent inhibitor with dissociation constant k_i1x 10^{-31} M that makes it as one of the extremely potent known non-covalently bound complexes.[180,183] Finasteride is also

	K_3 (s^{-1})	K_1 ($IC_{50,}$ nM)	K_3/K_1 (M^{-1} s^{-1})
5α-R 1			
Finasteride inhibition	1.4×10^{-3}	360	4×10^3
Dutasteride inhibition	1.1×10^{-3}	6	1.8×10^5
5α-R 2			
Finasteride inhibition	2.2×10^{-2}	69	3.2×10^5
Dutasteride inhibition	4.9×10^{-3}	7	6.8×10^5

Table 2.
Inhibition of 5α-R isozymes by clinically approved drugs.

known for its inhibitory effect on 5α-R1. However, the resultant dihydrofinasteride complex has comparatively lower rate constant **(Table 2)**.

4. Combination therapy

The scientific rationale for combining 5ARIs and α_1-AR antagonists is based on their different and complementary modes of action, that help in managing static and dynamic component responsible for of an enlarged prostate gland and symptoms of LUTS. The rationale for this combination was further recommended on account of rapid relief of symptoms by the α_1-AR antagonists, without targeting the underlying disease process along with mid or more sustained relief of symptoms by the 5ARIs [94]. The efficacy and safety of the treatment with different combinations versus treatment with either agent alone has been investigated by different groups in large mulitcentral trials [95, 96].

Veterans Affairs Cooperative Study and Prospective European Doxazosin group evaluated the combination of finasteride with terazosin & doxazosin, respectively for one year. Significant improvement in the symptom score and flow rate was observed with α_1-AR antagonists alone or combination therapy as compared to placebo or finasteride alone, but there was no significant difference observed for combination therapy over α_1-AR antagonists alone. Short term successful trials were followed by studying the combination of finasteride and doxazosin for a period of 4.5 years as Medical therapy for Prostate Symptoms. Finasteride alone and this particular combination reduced the risk of AUR and need for BPH-related surgery versus placebo, whereas none of these outcomes were reduced significantly in patients consuming doxazosin alone.

Outcomes of another long term study examining the role of combination of dutasteride and tamsulosin (CombAT) over the α_1-AR antagonists (tamsulosin) alone would be a major step in assessing the combination therapy and treatment decision [97]. Though present observations demonstrated a higher incidence of impotence with combination therapy compared with 5ARIS, in addition to higher incidence of α_1-AR antagonists-mediated dizziness, hypotension [93]. Cost-effectiveness studies by Nickel suggest that the combination therapy is more suitable for men at high risk for BPH progression, patients with high symptom score, large prostate volume and low q_{max} value.

Author details

Neelima Dhingra
Pharmaceutical Chemistry, MNASc, MPASc, MIABMS, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India

*Address all correspondence to: neelimad08@gmail.com

IntechOpen

References

[1] Kenny, B.; Ballard, S.; Blagg, J.; Fox, D.Pharmacological Options in the Treatment of Benign Prostatic Hyperplasia. *J. Med. Chem.* **1997**, *40*, 1293-1315

[2] Arora RP, Nayak RL, Malhotra V, Mohanty NK, Kulkarni SK. Role of herbal drugs in the management of benign prostatic hyperplasia: Clinical trial to evaluate the efficacy and safety of Himplasia. *Med Update* **2003**;11:55-58.

[3] Thorpe A, Neal D. Benign prostatic hyperplasia. Lancet **2003**; 361: 1359-1367.

[4] Djavan B, Remzi M, Erne B, Marberger M. The pathophysiology of benign prostatic hyperplasia. *Drugs Today* **2002**; 38: 867-870.

[5] Culig Z, Hobisch A, Cronauer MV, Radmayr C, Hittmair A, Zhang J, et al. Regulation of prostatic growth and function by peptide growth factors. *Prostate* **1996**; 28: 392-405.

[6] Geller, J. Benign prostatic hyperplasia: pathogenesis and medical therapy*J. Am. Geriatr. Soc.* **1991**, *39*, 1208-1216.

[7] Jenkins EP, Andersson S, Imperato-McGinley J, Wilson JD, Russell DW. Genetic and pharmacological evidence for more than one human steroid 5-alpha-reductase. J Clin Invest **1992**; 89: 293-300.

[8] Giacomo, N.; Antonio, G.; Mario, G.; Vincenzo, F. Critical review of guidelines for BPH diagnosis and treatment strategy. *Europ. Urol. Suppl.*, **2006**, 5(4), 418-429.

[9] Rosette, J.; De, L.; Alivizatos, G.; Madersbacher, S.; Rioja Sanz, C.; Nordling, J.; Emberton M. Guidelines on benign Prostatic hyperplasia. *Europ. Assoc. Urol.*, **2002**, 5-54.

[10] Ziada, A.; Rosenblum, M.; Crawford, E.D. Benign prostatic hyperplasia: An overview. *Urology,* 1999, 53(3), 1-6.

[11] Madsen, F.A.; Rhodes, P.R.; Bruskewitz, R.C. Reproducibility of pressure-flow variables in patients with symptomatic benign prostatic hyperplasia. Urology, **1995**, 46(6), 816-820

[12] Griffiths, D.J. Pressure-flow studies of micturition. *Urol. Clin. North. Am.*, **1996**, 23(2), 279-297.

[13] Eri, L.M.; Tveter, K.J. Treatment of benign prostatic hyperplasia. a pharmacoeconomic perspective. Drugs Aging**, 1997**, 10(2), 107118

[14] Orandi, A. transurethral resection versus transurethral incision of the prostate. *Urol. Clin. Am.*, **1990**, 17(3), 601-612.

[15] Curtis Nickel, J.; Carlos, E.; Thomas, F.; Whelan Ryan, F. Paterson, Hassan Razvi. 2010 Update: Guidelines for the management of benign prostatic hyperplasia. *Can. Urol. Assoc.* J., **2010**, 4, 310-316.

[16] Garg, G.; Singh, D.; Saraf, S. Management of benign prostate hyperplasia: An overview of α-adrenergic antagonist. *Biol. Pharm. Bull.*, **2006**, 29, 1554-1558.

[17] Blohm, T.R.; Laughlin, M.E.; Benson, H.D.; Johnston, J.O.; Wright, C.L.; Schatzman, G.L. Pharmacological induction of 5-alpha reductase deiciency in rats: Separation of testosterone-mediated and 5-alpha-dihydrotestosterone-mediated effects. *Endocrinology*, **1986**, 119, 959-966.

[18] Reid, P.; Kantoff, P.; Oh, W. Antiandrogens in prostate cancer. Invest. New Drug, **1999**, 17, 271-284

[19] Wolf, H.; Madson, P.O. Treatment of benign prostatic hypertrophywith progestational agents: A preliminary report. *J. Urol*., **1968**, 99, 980-985.

[20] Mearini, L.; Massimo, P. Transrectal high-intensity focused ultrasound for the treatment of prostate cancer: Past, present and future. *Indian J. Urol*., **2010**, 26, 4-11.

[21] Griesinger, G.; Felberbaum, R.; Diedrich, K. GnRH-antagonists in reproductive medicine. *Arch. Gynecol. Ob*stet., **2005**, 273, 71-78.

[22] Scott, W.W.; Wade, J.C. Medical treatment of benign nodular prostatic hyperplasia with cyproterone acetate. J. Urol., **1969**, 101, 81-85.

[23] Ai, N.; De Lisle, R.K.; Yu, S.J.; Welsh, W.J. Computational model for predicting the binding afinity of ligands for the wild type androgen receptor and a mutated variant associated with human prostate cancer. *Chem. Res. Toxicol*., **2003**, 16, 1652-1660

[24] Ito, K.; Fukabori, Y.; Shibata, Y.; Suzuki K.; Mieda, M.; Gotanda, K. Effects of new steroidal aromatase inhibitor, TZA-2237 and/or chlormadinone acetate on hormone-induced and spontaneous canine benign prostatic hyperplasia. *Eur. J. Endocrinol*., **2000**, 143, 543-54.

[25] Handratta, V.D.; Vasaitis, T.S.; Njar, V.C.; Gediya, L.K.; Kataria, R.; Chopra, P. Novel C-17-heteroaryl steroidal CYP17 inhibitors/ antiandrogens: Synthesis, in vitro biological activity, pharmacokinetics and antitumor activity in the LAPC4 human prostate cancer xenograft model. *J. Med. Chem*., **2005**, 48, 2972-2984

[26] Dhingra, N.; Bhagwat, D. Benign prostatic hyperplasia: An overview of existing treatment. *Ind. J. Pharmacol*., **2011**, 43(1), 612

[27] Donovan, J.L.; Peters, T.J.; Neal, D.E.; Brookes, S.T.; Gujral, S.; Chacko, K.N. A randomized trial comparing transurethral resection of the prostate, laser therapy and conservative treatment of men with symptoms associated with benign prostatic enlargement. J. Urol., **2000**, 164, 65-70.

[28] Kumar, V.L; Wahane, V.D. Current status of 5α-reductase inhibitors in the treatment of benign hyperplasia of prostate. Indian J. Med. Sci., **2008**, 62, 167-175.

[29] Ramon, J.; Lynch, T.H.; Eardley, I.; Ekman, P.; Frick, J.; Jungwirth, A. Transurethral needle ablation of the prostate for the treatment of benign prostatic hyperplasia: A collaborative multicentre study. Br. J. Urol., **1997**, 80, 128-134

[30] Dyrstad, S.W.; Shah, P.; Rao, K. Chemotherapy for prostate cancer. Curr. Pharm. Res, **2006**, 12, 819-837.

[31] Siiteri, P. K.; Wilson, J. D. Dihydrotestosterone in prostatic hypertrophy. I. The formation and content of dihydrotestosterone in the hypertrophic prostate of man. *J. Clin. Invest.* **1970,** *49*, 1737-1745.

[32] Blohm, T. R.; Laughlin, M. E.; Benson, H. D.; Johnston, J. O.; Wright, C. L.;Schatzman, G. L.; Weintraub, P. M. Pharmacological Induction of 5 Alpha-Reductase Deficiency in the Rat: Separation of Testosterone-Mediated and 5 Alpha-Dihydrotestosterone-Mediated Effects. *Endocrinol*. **1986**, *119* (3), 959-966.

[33] Reid, P.; Kantoff, P.; Oh, W. Antiandrogens in Prostate Cancer. *Invest. New Drugs*. **1999,** *17* (3), 271-284

[34] Wolf, H.; Madsen, P. O. Treatment of Benign Prostatic Hypertrophy with Progestational Agents: A Preliminary Report. *J. Urol*. **1968**, *99* (6), 780-785

[35] Griesinger G, Felberbaum R, Diedrich K. GnRH-antag onists in reproductive medicine. *Arch Gynecol Obstet,* 2005,273(2):71-78

[36] Peters, C. A.; Walsh, P. C. The Effect of Nafarelin Acetate, a Luteinizing-Hormone Releasing Hormone Agonist, on Benign Prostatic Hyperplasia. *N.Engl. J. Med*. **1987**, *317* (10), 599-604.

[37] Scott, W. W.; Wade, J. C. Medical Treatment of Benign Nodular Prostatic Hyperplasia with Cyproterone Acetate. *J. Urol*. **1969,** *101* (1), 81-85

[38] Caine M, Perlberg S, Gordon R (1975) The treatment of benign prostatic hypertrophy with flutamide: a placebo controlled study. *J Urol* 114:564-568

[39] Ai, N.; DeLisle, R. K.; Yu, S. J.; Welsh, W. J. Computational Models for Predicting the Binding Affinities of Ligands for the Wild-Type Androgen Receptor and a Mutated Variant Associated with Human Prostate Cancer.*Chem. Res. Toxicol*. **2003**, *16* (12), 1652-1660.

[40] Ohtsu, H.; Xiao, Z.; Ishida, J.; Nagai, M.; Wang, H. K.; Itokawa, H.; Su, C. Y.; Shih, C.; Chiang, T.; Chang, E.; Lee, Y.; Tsai, M. Y.; Chang, C.; Lee, K. H. *J. Med. Chem.* **2002**, *45*, 5037.

[41] Bratoeff, E. A.; Herrera, H.; Ramirez, E.; Solorzano, K.; Murillo, E.; Quiroz, A.; Cabeza, M. Antiandrogenic effect of 16-substituted, non-substituted and D-homopregnane derivatives. *Chem. Pharm. Bull. (Tokyo)* **2000**, *48*, 1249-1255.

[42] Ito, K.; Fukabori, Y.; Shibata, Y.; Suzuki, K.; Mieda, M.; Gotanda, K.; Honma, S.; Yamanaka, H. Effects of a new steroidal aromatase inhibitor, TZA-2237, and/or chlormadinone acetate on hormone-induced and spontaneous canine benign prostatic hyperplasia. *Eur. J. Endocrinol.* **2000**, *143*, 543.

[43] Schweikert, H. U.; Tunn, U. W. Effects of the aromatase inhibitor testolactone on human benign prostatic hyperplasia.*Steroids* **1987**, *50*, 191-200.

[44] Henderson, D.; Habenicht, U. F.; Nishino, Y.; Kerb, U.; el Etreby, M. F. *J. Steroid Biochem.* **1986**, *25*, 867.

[45] Guess, H. A.; Heyse, J. F.; Gormley, G. J. The Effect of Finasteride on Prostate-Specific Antigen in Men with Benign Prostatic Hyperplasia*. Prostate.* **1993**, 22 (1), 31-37

[46] John, I. J.; Oncol, J. H. 5-Alpha reductase inhibitors and the treatment of benign prostatic hyperplasia. *Drugs of Today* **1993**, *29*, 335-346.

[47] Bruchovsky, N.; Wilson, JD. The Intranuclear Binding of Testosterone and 5-alpha-androstan-17-beta-ol-3-one by Rat Prostate. *J Biol Chem.* **1968**, *25,* 5953-5960

[48] Andriole, G.; Bruchovsky, N.; Chung, L. W.; Matsumoto, A. M.; Rittmaster, R.; Roehrborn, C.; Russell, D.; Tindall, D. Dihydrotestosterone and the prostate: the scientific rationale for 5alpha-reductase inhibitors in the treatment of benign prostatic hyperplasia. *J. Urol.* **2004**, *172*, 1399-1403.

[49] Kurup, A.; Garg, R.; Hansch, C. Comparative QSAR analysis of 5α-reductase inhibitors.*Chem. Rev.* **2000**, *100*, 909-911

[50] Faragalla, J.; Bremner, J.; Brown, D.; Griffith, R.; Heaton, A. Comparative pharmacophore development for inhibitors of human and rat 5-alphareductase. *J. Mol. Graph. Model.* **2003**, *22*, 83-92

[51] Trachtenberg, J.; Hicks, L. L.; Walsh, P. C. Androgen- and estrogen-receptor content in spontaneous and experimentally induced canine prostatic

hyperplasia *J. Clin. Invest.* **1980**, *65*, 1051-1059

[52] Liao, S. Cellular receptors and mechanisms of action of steroid hormones *Int. Rev. Cytol.* **1975**, *41*, 87-172

[53] Wilson, E. M.; French, F. S. Binding properties of androgen receptors.*J.Biol.Chem.* **1976**, *251*, 5620-5629.

[54] Quemener, E.; Amet, Y.; di Stefano, S.; Fournier, G.; Floch, H. H.; Abalain, J. H. Purification of testosterone 5 alpha-reductase from human prostate by a four-step chromatographic procedure*Steroids* **1994**, *59*, 712-718.

[55] Kelce, W. R.; Lubis, A. M.; Braun, W. F.; Youngquist, R. S.; Ganjam, V. K. Influence of rete testis fluid deprivation on the kinetic parameters of goat epididymal 5 alpha-reductase. *Steroids* **1990**, *55*, 27-31

[56] Imperato-McGinley, J.; Peterson, R. E.; Gautier, T.; Sturla, E. **Male pseudohermaphroditism secondary to 5a-reductase deficiency - a model for the role of androgens in both the development of the male phenotype and the evolution of a male gender identity.** *J. Steroid Biochem.* **1979**, *11*, 637-645.

[57] Griffin, J. E.; Wilson, J. D. The syndromes of androgen resistance.*N. Engl. J Med.* **1980**, *302*, 198-209.

[58] Imperato-McGinley, J.; Guervo, L.; Gautier, T. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE: Steroid 5α-reductase deficiency in man: An inherited form of male pseudohermaphroditism. *Sciences* **1994**, *186*, 1213-1215.

[59] Peterson, R. E.; Imperato-McGinley, J.; Gautier, T.; Sturla, E. Peterson RE, Imperato-McGinley J, Gautier T, Sturla E. Male pseudohermaphroditism due to steroid 5-alpha-reductase deficiency. *Am. J. Med.* **1977**, *62*, 170-191.

[60] Anderson, K. M.; Liao, S. Selective retention of dihydrotestosterone by prostatic nuclei. *Nature* **1968,** *219*, 277-279.

[61] Voigt, W.; Fernandez, E. P.; Hsia, S. L. Transformation of testosterone into 17 beta-hydroxy-5 alpha-androstan-3-one by microsomal preparations of human skin *J. Biol.Chem.* **1970**, *245*, 5594-5599.

[62] Monslave, A.; Blaguies, J. A. Partial characterization of epididymal 5α reductase in the rat. S*teroids* **1977**, *30*, 41-51.

[63] Andersson, S.; Berman, D. M.; Jenkins, E. P.; Russell, D. W. Deletion of steroid 5 alpha-reductase 2 gene in male pseudohermaphroditism *Nature* **1991**, *354*, 159-161

[64] Labrie, F.; Sugimoto, Y.; Luu-The, V.; Simard, J.; Lachance, Y.; Bachvarov, D.; Leblanc, G.; Durocher, F.; Paquet, N. Structure of human type II 5 alpha-reductase gene. *Endocrinology* **1992**, *131*, 1571-1574.

[65] Harris, G.; Azzolina, B.; Baginsky, W.; Cimis, G.; Rasmusson, G. H.; Tolman, R. L.; Raetz, C. R.; Ellsworth, K. Identification and selective inhibition of an isozyme of steroid 5a-reductase in human scalp. *Proc. Natl. Acad. Sci. U S A* **1992**, *89*, 10787-10791

[66] Normington, K.; Russell, D. W. Tissue distribution and kinetic characteristics of rat steroid 5 alpha-reductase isozymes. Evidence for distinct physiological functions. *J. Biol. Chem.* **1992**, *267*, 19548-19554

[67] Li, J.; Ding, Z.; Wang, Z.; Lu, J. F.; Maity, S. N.; Navone, N. M., Kim, J. Androgen Regulation of 5α-Reductase Isoenzymes in Prostate Cancer: Implications for Prostate Cancer

Prevention. PLoS One, **2011**, 6 (12), e28840.

[68] Uemura, M.; Tamura, K.; Chung, S.; Honma, S.; Okuyama, A.; Nakamura, Y.Novel 5α-Steroid Reductase (SRD5A3, Type-3) is Overexpressed in Hormone-Refractory Prostate Cancer. *Cancer Sci*. **2008**, 99, 81-86.

[69] Paba, S.; Frau, R.; C, Godar, S.; Devoto, P.; Marrosu, F.; Bortolato, M. Steroid 5α-reductase as a novel therapeutic target for schizophrenia and other neuropsychiatric disorders. *Curr. Pharm. Des*. **2011**, 17 (2), 151-167

[70] Lao, K.; Sun, J.; Wang, C.; Lyu, W.; Zhou, B.; Zhao, R.; Xiang, H. Design,Synthesis and Biological Evaluation of Novel Androst-3, 5-diene-3-carboxylic Acid Derivatives as Inhibitors of 5α-Reductase Type 1 and 2. *Steroids.* **2017**,124, 29-34

[71] Henderson, D.; Habenicht, U.F.; Nishino, Y.; Kerb, U.; El Etreby, M. F.Aromatase Inhibitors and Benign Prostatic Hyperplasia. J. Steroid Biochem.**1986**, 25 (5), 867-876.

[72] Holt, D. A.; Levy, M. A.; Matcalf, B. W. *Advances in Medicinal Chemistry*; Maryanoff, B. E., Maryanoff, C. A. Eds.; JA Press Inc: Greenwich, Connecticut, **1993**, p 1.

[73] 179 Abell, A. D.; Henderson, B. R. Steroidal and non-steroidal inhibitors of steroid 5α-reductase. *Curr.Med.Chem* **1995**, *2*, 583-597

[74] Brian, W.; Metcalf, K. J.; Joseph, P. B. Synthesis of 3-keto-4-diazo-5-α-dihydrosteroids as potential irreversible inhibitors of steroid 5-α-reductase. *Tetra.Lett.* **1980**, *21*, 15-18

[75] Foley, C. L.; Bott, S. R.; Shergill, I. S.; Kirby, R. S. An update on the use of 5alpha-reductase inhibitors. *Drugs of Today* 2004, *40(3)*, 213-223.

[76] Frye, S. V. Inhibitors of 5-alpha reductase . *Curr.Pharm.Design* **1996**, *2*, 59-84

[77] Bull, H. G.; Garcia –Calvo, M.; Andersson, S.; Baginsky, W. F.; Chan, H. K.; Ellsworth, D. E.; Milles, R. R.; Stearns, R. A. Mechanism-Based Inhibition of Human Steroid 5α-Reductase by Finasteride: Enzyme-Catalyzed Formation of NADP–Dihydrofinasteride, a Potent Bisubstrate Analog Inhibitor. *J.Amer.Chem.Soc.* **1996**, *118*, 2359-2365

[78] Guarna, A.; Marriace, A.; Danza, G.; Seirio, M. *"Sex Hormones and Antihormones in Endocrine Dependent Pathology Basic and Clinical Aspects"*; Motta, M., Seirio, M. Eds.; Elsevier Sciences: Amsterdam, **1994**.

[79] Liang, T.; Heiss, C. E.; Ostrove, S.; Rasmusson, G. H.; Cheung, A. Binding of a 4-Methyl-4-Aza-Steroid to 5α-Reductase of Rat Liver and Prostate Microsomes. *Endocrinology* **1983**, *112*, 1460-1468

[80] Erb, J. M.; Heaslip, J. I.; Brandt, M. Potent inhibition of human steroid 5alpha-reductase (EC 1.3.1.30) by 3-androstene-3-carboxylic acids. *Bioorg. Med.Chem.* **1989**, *17*, 372-376

[81] Alauddin, M.; Martin-Smith, M. Biological Activity in Steroids Possessing Nitrogen Atoms. *J. Pharm. Pharmacol*. **1962**, 14 (1), 469-495.

[82] Singh, H.; Jindal, D. P.; Yadav, M. R., Kumar, M. Heterosteroids and Drug Research. *Prog. Med. Chem*. **1991**, 28, 233-300

[83] Martínez, M. D.; Edelsztein, V. C.; Durán, F. J.; Di Chenna, P. H., Burton, G. Synthesis of 6-Azaprogesterone and 19-Hydroxy-6-Azasteroids. *Steroids*. **2013**, 78 (1), 34-37.

[84] Tian G, Mook RA, Moss ML, Frye SV. Mechanism of

time-dependent inhibition of 5 alpha-reductase by delta 1-4-azasteroids: Toward perfection of rates of time-dependent inhibition by using ligand-binding energies. *Biochemistry* **1995**;34:13453-3459.

[85] Harris GS, Kozarich JW. Steroid 5α-reductase inhibitors in androgen-dependent disorders. *Curr Opin Chem Biol* **1997**;1:254-259.

[86] Kumar VL, Wahane VD. Current status of 5α-reductase inhibitors in the treatment of benign hyperplasia of prostate. *Indian J Med Sci* **2008**;62:167-**1**75.

[87] Rittmaster RS, Lemay A, Zwicker H, Capizzi TP, Winch S, Moore E, *et al.* Effect of finasteride, a 5 alpha-reductase inhibitor, on serum gonadotropins in normal men. *J Clin Endocrinol Metab* **1992**;75:484-488.

[88] Marihart S, Harik M, Djavan B. Dutasteride: a review of current data on a novel dual inhibitor of 5-alpha reductase. *Rev Urol* **2005**;7:203-210.

[89] Miller J, Tarter TH. *Update on the use of dutasteride in the management of benign prostatic hypertrophy.* Clin Interv Aging **2007**;2:99-104.

[90] Roehrborn CG. The clinical benefits of dutasteride treatment for LUTS and BPH. *Rev Urol* **2004** ;6: S22-30.

[91] Schmidt, L. J.; Tindall, D. J. Steroid 5 α-reductase inhibitors targeting BPH and prostate cancer. *J. Steroid Biochem. Mol. Biol*. **2011,** 125, 32-38.

[92] Ludwig, P.; Holzhütter, H. G.; Colosimo, A.; Silvestrini, M. C.; Schewe, T.; Rapoport, S. M. A kinetic model for lipoxygenases based on experimental data with the lipoxygenase of reticulocytes. *Eur. J. Biochem*. **1987**, 168, 325-337.

[93] Salvador, J. A.; Pinto, R. M.; Silvestre, S. M. Steroidal 5α-reductase and 17αhydroxylase/17, 20-lyase (CYP17) inhibitors useful in the treatment of prostatic diseases. *J. Steroid Biochem. Mol. Biol*. **2013**, 137, 199-222.

[94] Tanguay S, Awde M, Brock G, Casey R, Kozak J, Lee JJ, et al. Diagnosis and management of benign prostatic hyperplasia in primary care. *Can Urol Assoc J* **2009**;3:S92-S100.

[95] Curtis NJ. BPH: Costs and treatment outcomes. *Am J Manag Care* **2006**;12:S141-8

[96] *Bullock TL, Andriole GL. Emerging drug therapies for benign prostatic hyperplasia. Expert* Opin Emerg Drugs **200**6;11:111-23

[97] Miller, J.; Tarter, T.H. Combination therapy with dutasteride and tamsulosin for the treatment of symptomatic enlarged prostate**.** *Clin. Interv. Aging***, 2009**, 4, 251-258.