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Review Article

Present and future pharmacotherapy for benign prostatic hyperplasia

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CONTENTS

Abstract

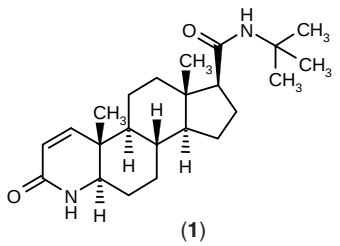
Around 50% of men 51-60 years of age have pathological benign prostatic hyperplasia (BPH). Pharmacotherapy for BPH includes the 5α-reductase inhibitor finasteride, and α_1-adrenoceptor antagonists. Finasteride reduces prostate volume and symptom scores, while increasing peak urinary flow rates. The main problem with finasteride treatment is that it increases the incidence of ejaculation disorders. All of the α_1-adrenoceptor antagonists have been shown to reduce symptom scores and increase peak urinary flow rates in BPH. The nonselective α_1-adrenoceptor antagonists (prazosin, terazosin and doxazosin) were developed as antihypertensives, and hypotensive-related side effects are the main problem with these agents in BPH. These side effects can be diminished by reducing peak concentrations of the drugs, as with once-daily alfuzosin, or by using the uroselective antagonist tamsulosin. Phytopharmaceuticals are commonly used in the treatment of BPH, such as saw palmetto berry which has been shown to improve the symptoms and peak urinary flow rate. Androgen receptor antagonists are not used in BPH because of their adverse effects. Newer drugs under development for the treatment of BPH include α_1-adrenoceptor antagonists that show more selectivity for α_{1A}-adrenoceptors than tamsulosin, combined 5α-reductase/α_1-adrenoceptor inhibitors and combined type 1/type 2 5α-reductase inhibitors. New targets for the drug treatment of BPH include endothelin, growth factors, estrogens and the phosphodiesterase isoenzymes.

Introduction

Benign prostatatic hyperplasia (BPH) comprises both static and dynamic components that contribute to the symptoms. The static component refers to the proliferation process that involves predominantly the stromal elements of the prostate. This growth may compress the urethra and obstruct urinary flow from the bladder. The dynamic component reflects the smooth muscle tone of the bladder neck and prostate smooth muscle. Initially, the clinical manifestations of BPH include obstructive and irritative lower urinary tract symptoms (LUTS). Thus, the treatment goals in most men are to relieve these bothersome symptoms that reduce the quality of life. BPH can also be progressive, with a risk of urinary retention, bladder infection, bladder calculi and renal failure.

The normal prostate reaches about 20 g in men between the age of 21 and 30 years and this weight remains essentially the same with increasing age unless BPH develops. The prevalence of pathological BPH is only 8% at the fourth decade; however, 50% of the male population has pathological BPH (33 g or more) by the time they are 51-60 years old. Since the incidence of BPH is age-related, the clinical and the economic impact of his disease will increase with increasing life span. The growth of BPH is probably initiated before the patient is 30 years old. The early phases of BPH growth (31-50 years of age) is rapid and then becomes slower with age (1). More than 50% of patients diagnosed with BPH will experience progression of these symptoms within 3 years (2). In the U.S., the estimated risk of a 50-year old man undergoing therapeutic intervention in his lifetime for BPH is about 40%.

Treatment options for BPH range from watchful waiting, with or without pharmacotherapy, for those patients with mild to moderate symptoms preferring to delay any active therapy. This is followed by the minimal invasive treatments, which include transurethral needle ablation (TUNA) of the prostate and transurethral microwave therapy. Finally, surgical interventions such as transurethral resection of the prostate (TURP) and open enucleation of the prostate are reserved for those who have moderate to severe symptoms and/or complications of BPH. Eventually, almost 20% of BPH patients undergo



(**1**)

prostatic surgery to effectively relieve symptoms. During watchful waiting a variety of drugs can be used to improve the symptoms and urinary flow rate, and these are discussed in this review.

5α-Reductase inhibition with finasteride

5α-Reductase catalyzes the conversion of testosterone to dihydrotestosterone (DHT), the principal prostatic androgen. Finasteride (**1**) selectively inhibits 5alpha-reductase type 2, the dominant isoenzyme in genital tissues such as the prostate. The first major clinical trial of finasteride in BPH was performed over 12 months in 895 men with an enlarged prostate gland on digital rectal examination and a maximum urinary flow rate of < 15 ml/sec (3). Symptoms were evaluated on the Boyarski score (4), a questionnaire on a 0-4 scale about urinary hesitancy, terminal dribbling, impairment in size and force of the urinary stream, interruption of urination, incomplete emptying, urgency, dysuria, clothes wetting and straining or pushing to start urinary flow. Finasteride (5 mg once daily) decreased serum DHT from 45 to 10 ng/dl and also decreased serum prostate-specific antigen (PSA) levels. Finasteride reduced symptoms scores by 2.7 (1.0, placebo) and increased the maximum urinary flow rate by 1.6 ml/sec (0.2 ml/sec, placebo). The prostate volume was reduced from 68.6 to 47.5 cm^3 by finasteride. Adverse effects observed with finasteride included decreased libido in 4.7% (1.3%, placebo), ejaculation disorder in 4.4% (1.7%, placebo) and impotence in 3.4% (1.7%, placebo) of the men (3). The reduction in prostate volume with finasteride represented a reduction in the inner gland epithelium with little effect on the stroma or lumina (5). Examination of prostates removed at prostatectomy showed that finasteride caused prostate involution through a combination of atrophy and cell death (6).

Canadian and Scandinavian studies (7) have shown that finasteride remains effective at 2 years. In the double-blind study of 613 Canadian men with moderate BPH, finasteride decreased symptom scores by 2.7 (0.7, placebo) and increased peak urinary flow rate by 1.4 ml/sec (0.3 ml/sec, placebo). The prostate volume was decreased from 44 cm^3 by 21% (8.8% increase, placebo). The incidence of adverse events related to sexual dysfunction was greater in the finasteride than placebo group (ejaculation disorder 7.7% *vs.* 1.7% and impotence 15.8% *vs.* 6.3%) (8). An open-label extension study of the first major trial with finasteride in BPH (3) showed that finasteride remained effective over 5 years. The nadir reduction in prostate volume of 25% was achieved after 2 years, but a 23% reduction was still evident after 5 years (9).

Pooled data from 4222 men with moderate symptomatic BPH showed that finasteride treatment for up to 2 years reduced the frequency of acute urinary retention by more than 50% and reduced surgical intervention by more than one-third compared to placebo (10). Similar findings, but for over 4 years, were reported from a trial of 3040 men with moderate to severe urinary symptoms and enlarged prostate glands treated with finasteride or placebo. During this period, fewer men in the treatment group underwent surgery (5%) than in the placebo group (10%) and fewer developed acute urinary retention (3% *vs.* 7% for placebo) (11).

Meta-analysis has shown that finasteride is more effective in men with large prostates. This analysis included some unpublished trials. The International Prostate Symptom Score (IPSS) (12) and the American Urological Association (AUA) symptom score should be identical since the IPSS was developed and validated as the AUA. This index includes 7 questions (covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying and urgency) scored 0 (absent) to 5 (severe) (13). However, to do the meta-analysis, consideration had to be given to some trials having slight modifications of the IPSS/AUA and consequently a Quasi-IPSS index was used. The analysis showed that for men with prostates under 40 cm^3, finasteride had no significant effect on symptoms or peak urinary flow rate. Finasteride did improve symptom scores and the peak urinary flow rates in men with larger prostates (14). The finding that men with enlarged prostates benefit most from finasteride treatment was subsequently confirmed in the PROWESS study (15).

Several small studies have shown that finasteride is effective in the treatment of recurrent hematuria secondary to BPH. Bleeding subsided with 2 weeks of finasteride treatment in 12 patients, and finasteride remained effective at 6 months (16). In another study, a hematuria grading system was devised and finasteride improved hematuria in 14 of 16 patients, some of whom had had prior prostatectomy (17). Long-term treatment (up to 4 years) with finasteride (n=50) showed decreased recurrence of hematuria and the need for surgery as compared to placebo (n=30) (18). The mechanism of this beneficial effect in hematuria may involve decreasing microvessel density. Finasteride treatment is associated with a decrease in microvessel density in the suburethral portion but not in the nodular hyperplasia of prostates from patients with clinical BPH and gross hematuria (19).

As the free-to-total serum PSA ratio is used to differentiate benign from malignant processes in the prostate, concern has been expressed that finasteride may upset this detection. In 20 men treated for a minimum of 9 months with finasteride, both the free and total PSA levels were decreased leaving the ratio unchanged (20).

However, when only the serum PSA levels are being measured, it is necessary to double the PSA levels in finasteride-treated patients to allow appropriate interpretation of PSA values that do not mask the detection of prostate cancer (21). This method has been proven in a trial of 3040 men with PSA levels of < 10 ng/ml who were randomized to finasteride or placebo for up to 4 years. Prostate cancer was diagnosed in 4.7% of men on finasteride and 5.1% on placebo, with an elevated PSA having prompted diagnosis in 35% of cases on finasteride and 34% on placebo (22).

Leuprolide is a stronger antiandrogen that finasteride. Leuprolide induces marked atrophy of prostate carcinoma cells making the pathologic diagnosis of cancer difficult. Needle biopsy specimens were reviewed to determine whether a similar problem arose after finasteride treatment, and this was not the case. Thus, no histologic differences were present in either the benign or cancer group between cases treated with finasteride and placebo (23).

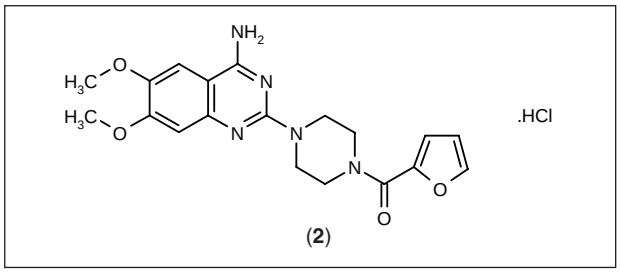
Androgens are important for normal bone cell activity and bone mass in men, stimulating proliferation and differentiation of osteoblasts and inhibiting bone resorption. Although 5α-reductase is expressed in human osteoblasts, the specific role of DHT in the maintenance of bone mass is clear. The long-term treatment (up to 4 years) of BPH with finasteride had no effect on bone mineral density as assessed by dual energy x-ray absorptiometry of the lumbar spine (24).

α_1-Adrenoceptor antagonists

Noradrenaline acts at α_1-adrenoceptors in the neck and sphincters of the urinary bladder to promote contraction and urinary retention. Noradrenaline also acts at α_1-adrenoceptors to contract the smooth muscle in the prostate capsule and prostate urethra. By opposing these actions, α_1-adrenoceptor antagonists are beneficial in BPH.

Other mechanisms may also contribute to the beneficial effects of α_1-adrenoceptor antagonists in BPH. For instance, biopsy and prostatectomy specimens from untreated and α_1-adrenoceptor antagonists (terazosin or doxazosin)-treated BPH patients suggest that these agents may induce apoptosis in both the epithelial and stromal cells of the prostate with little effect on cell proliferation. The apoptosis was associated with a decrease in smooth muscle α-actin expression and stromal regression (25). Another study did not note stromal regression, but reported that α_1-adrenoceptor antagonists decreased the expression of myosin heavy chain, a functional marker for the smooth muscle phenotype (26).

α_1-Adrenoceptor antagonists were developed to treat hypertension, where they lower blood pressure by antagonizing noradrenaline α_1-adrenoceptor-mediated vasoconstriction. There are 3 subtypes of α_1-adrenoceptor: α_{1A}, α_{1B} and α_{1D}. The α_{1B} subtype is predominant in blood vessels whereas the α_{1A} subtype is predominant in the prostate. Prazosin (**2**), the prototype α_1-adrenoceptor antagonist and the structurally similar terazosin and doxazosin, do not distinguish between these α_1-adrenoceptor subtypes. Prazosin has to be given twice a day which is not ideal for BPH, where a long-acting sustained effect is required. Terazosin and doxazosin are longer acting with elimination half-lives of 12 and 20 h and duration of actions of 18 and 36 h, respectively.



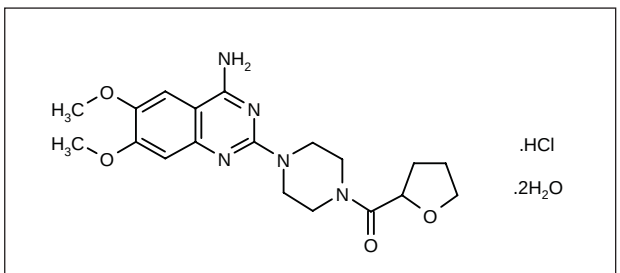
(**2**)

One of the potential problems with nonselective α_1-adrenoceptor antagonists is that by antagonizing vascular α_{1B}-adrenoceptors they may induce orthostatic hypotension which often manifests itself as dizziness and/or headache. Alternatively, α_{1B}-adrenoceptor antagonism/blood pressure lowering may be beneficial in patients suffering from both hypertension and BPH provided there is appropriate modification of other antihypertensive medication.

Terazosin

Terazosin (**3**) 10 mg daily is effective in the treatment of BPH. Compared to placebo after 16 weeks in 285 men with symptomatic BPH, terazosin decreased the Boyarsky symptom score and increased peak and mean urinary flow rates (27). These beneficial effects of terazosin were still evident 42 months after the initiation of therapy. The most common adverse events resulting in premature termination with terazosin were dizziness (6.7%), asthenia (3.8%) and somnolence (2.0%) (28). In another 24-week study, 17 of 81 terazosin-treated patients reported hypotension-related adverse events leading to 4 withdrawals from the study (29).

The beneficial effects of terazosin in BPH were further confirmed in a community-based population of 2084 men with moderate to severe BPH under usual care



(**3**)

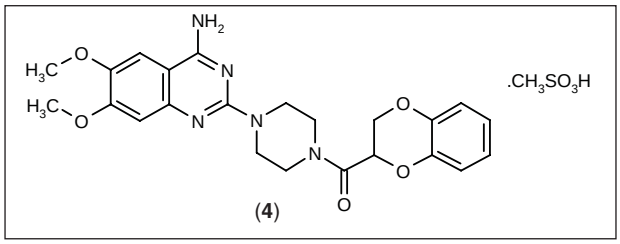
conditions. Terazosin improved the AUA symptom score by –7.6 (–3.7, placebo) and the AUA bother score by –6.3 (–3.1, placebo). Terazosin increased the peak urinary flow rate by 2.2 ml/sec (0.7 ml/sec, placebo) (30). Similar findings on symptom scores and peak urinary flow rates were reported from meta-analysis of these and other trials of terazosin in BPH (31). Terazosin decreased systolic and diastolic blood pressure (SBP and DBP) by 5.5 mmHg (0.9 mmHg, placebo) and 3.9 mmHg (1.3 mmHg, placebo), respectively (30).

Treatment of men with BPH with terazosin for 1 year did not affect serum PSA concentrations (32). Thus, terazosin does not complicate the monitoring of serum PSA levels to detect prostate carcinoma.

As finasteride and α_1-adrenoceptor antagonists have different mechanisms of action, it would be predicted that they could have an additive effect. However, terazosin and finasteride do not seem to have pronounced additive effects. Terazosin (10 mg daily) was more effective than finasteride (5 mg daily) in BPH, and the combination of terazosin and finasteride was no more effective than terazosin alone. The 1229 men with symptomatic BPH enrolled in this study had a mean symptom score of at least 8 on the AUA symptom index. Subjects also had a peak urinary flow rate of no more than 15 ml/sec and no less than 4 ml/sec. At 1 year, placebo, finasteride, terazosin and the combination of terazosin and finasteride had reduced the symptom scores by 2.6, 3.2, 6.1 and 6.2, and increased the peak urinary flow rates by 1.4, 1.6, 2.7 and 3.2 ml/min, respectively. Finasteride, but not terazosin, decreased the prostatic volume by 6.1 cm^3 (33). The main adverse effects observed with terazosin as compared to placebo were dizziness (26% *vs*. 7%), asthenia (13% *vs*. 7%) and postural hypotension (7% *vs*. 1%) (34).

In the study where finasteride was initially shown to be effective in BPH (3), the prostate glands were larger at baseline than the comparative study of finasteride and terazosin. Meta-analysis has also shown that finasteride was more effective in men with large prostates (14). In the comparative study, men with prostates 40.1-50 cm^3 had no added benefit with finasteride, and it was only men with very large prostates that had a modest benefit. Thus, in the subset of men with prostates of > 50 cm^3, placebo, finasteride, terazosin and the combination decreased AUA symptom score by 2.5, 3.6, 6.0 and 7.0, and increased the peak urinary flow rate by 0.6, 2.7, 3.6 and 4.7 ml/sec, respectively (35).

Targeted transurethral microwave thermotherapy is a minimally invasive alternative to pharmacotherapy requiring a single 1-h outpatient session. Terazosin (up to 10 mg daily) has been compared to microwave thermotherapy in 103 patients who had previously not taken an α_1-adrenoceptor antagonist or had prostate surgery, and the microwave thermotherapy was shown to be more effective than terazosin at 6 and 18 months. Thus, at 6 months the IPSS was lowered from about 19 to 6.8 and 11.0, and the peak urine flow rate was increased from about 8 to 13.9 and 11.6 ml/sec in the thermotherapy and terazosin groups, respectively. By 18 months, terazosin therapy had failed in 21 patients (13 for ineffectiveness; 8 for side effects) and thermotherapy had failed in 3 patients. The most common adverse events in the first 6 months with terazosin were dizziness (7 cases), asthenia (4 cases) and headache (3 cases) while those with thermotherapy were urinary tract infection (3 cases) and loss of ejaculation (1 case) (36).



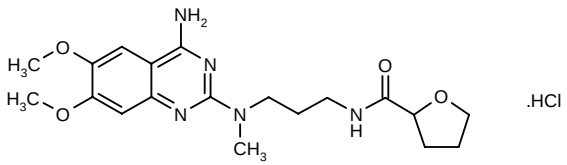
(**4**)

Doxazosin

Blood pressure was monitored in a trial of doxazosin (**4**) 8 mg daily in 100 normotensive patients with BPH. Doxazosin improved symptoms and increased peak urinary flow rates by 2.9 ml/sec (0.7 ml/sec, placebo), while decreasing mean blood pressure by about 5 mmHg. The most common adverse effects with doxazosin were dizziness (24% *vs*. 2% in placebo) and headache (12% *vs*. 2% in placebo) (37). Doxazosin (4-12 mg) had similar effects on the symptoms and peak urinary flow rates in hypertensive patients with BPH, but a greater effect on blood pressure. Thus, doxazosin reduced standing DBP/SBP by 11.6-17.4/9.8-12.7 mmHg compared to 3.4/4.3 mmHg for placebo (38).

Long-term follow-up in 272 normotensive and 178 mildly to moderately hypertensive men showed that doxazosin increased the peak urinary flow rate by 1.9 ml/sec and decreased symptoms. Doxazosin decreased SBP/DBP by 8/11 and 4/2 mmHg in hypertensive and normotensive patients, respectively. The most common adverse effects were dizziness, headache and fatigue, with dizziness being the most common reason for withdrawal from the study (39). The recent Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that when used in the treatment of hypertension, doxazosin seemed to increase the likelihood of the patients developing heart failure (40). It is not known whether this is a class action of the α_1-adrenoceptor antagonists or whether the increased tendency to heart failure in hypertension is a specific effect of doxazosin. Therefore, presently the use of doxazosin in hypertension or concurrent hypertension and BPH should not be recommended.

A recent survey of 53,824 men with BPH has highlighted that treatment with nonselective α_1-adrenoceptor antagonists (prazosin, terazosin and doxazosin) is associated with increases in the risk of a cluster of clinical events (hypotension, syncope, dizziness, fractures)



(**5**)

consistent with vascular α-adrenoceptor antagonism. These events are increased by prior initiation of other antihypertensive medication (41). As α_1-adrenoceptor antagonists showing selectivity for α_{1A}-adrenoceptors are now available for use in the treatment of BPH, the use of the nonselective agents with the propensity to cause orthostatic hypotension is in decline and may stop shortly.

Alfuzosin

Despite affinity studies on human-cloned α_1-adrenoceptor subtypes showing that alfuzosin (**5**) is a nonselective α_1-adrenoceptor antagonist, some functional and experimental animal models indicate that it may be uroselective (42). Alfuzosin has a relatively short half-life (3-5 h), but has been formulated into a sustained-release preparation for twice-daily use (SR alfuzosin) and subsequently a once-daily preparation (OD alfuzosin) for use in BPH. The apparent *in vivo* uroselectivity of alfuzosin may be due to OD alfuzosin producing lower peak levels and a lesser likelihood of vascular α_{1B}-adrenoceptor-mediated side effects.

Alfuzosin (2.5 mg every 8 h, 7.5 mg/day) was one of the first α_1-adrenoceptor antagonists to be tested in BPH, and was shown to improve symptoms with little effect on peak urinary flow rate. Alfuzosin has no effect on the size of the prostate and does not cause impotence. Alfuzosin did decrease standing SBP by 3.9 mmHg, and this was associated with an increased incidence of dizziness and headache as compared to placebo (7.2% *vs*. 5.2% and 6.4% *vs*. 4.9%, respectively) (43).

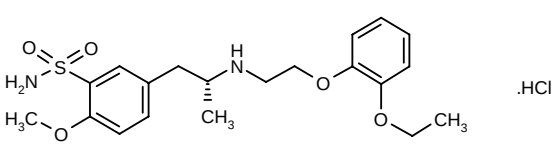
Alfuzosin has been used extensively in BPH in Europe, Asia and Latin America but is not available in the U.S. A large French prospective study (5849 patients) showed that alfuzosin (2.5 mg t.i.d.) reduced symptom severity, improved quality of life and perceived sexuality in BPH over a 12-month period (44). A short-term study has shown that SR alfuzosin (5 mg twice daily) improves urinary symptoms, increases peak urinary flow rate and reduces residual urine volume in BPH. SR alfuzosin only caused a small decrease (about 5 mmHg) in supine blood pressure in normotensives and hypertensives (45). The most frequent adverse effect with alfuzosin was dizziness, which occurred in 5.5% of patients as compared to 2.1% in the placebo group (42).

OD alfuzosin (10 or 15 mg) has been assessed in 536 patients with BPH over 3 months in a double-blind trial, and both doses had similar beneficial effects. OD alfuzosin 10 mg decreased the IPSS by 3.6 (1.6, placebo) and increased the peak urinary flow rate by 1.1 ml/sec (0 ml/sec, placebo). The most common adverse effects were dizziness and headache, which occurred in 7.4% and 5.1% of men taking OD alfuzosin as compared to 2.9% and 2.3% of placebo-treated men, respectively. OD alfuzosin had no effect on supine SBP or DBP. Orthostatic hypotension was defined as a decrease in SBP of 20 mmHg or more when standing up at any visit after randomization. The orthostatic hypotension rates were identical (3.4%) in the OD alfuzosin and placebo groups. OD alfuzosin did not cause ejaculation disorder (46).

Tamsulosin

Tamsulosin (**6**) shows selectivity for α_{1A}- (and α_{1D}-) over α_{1B}-adrenoceptors (47), which means that it may be effective in BPH without reducing blood pressure. Tamsulosin has a half-life of 5-10 h and only has to be used once a day. In a 12-week trial of 313 patients with BPH, tamsulosin (0.4 mg daily) increased peak urinary flow rate by 1.4 ml/sec (0.4 ml/sec, placebo) and decreased the total Boyarsky symptom score. More adverse effects were observed with tamsulosin (34%) than placebo (24%) but this did not reach statistical significance. The incidence of cardiovascular-related adverse events (postural hypotension, syncope and tachycardia/palpitation) were similarly low in the tamsulosin (5%) and placebo (7%) groups (48).

Tamsulosin (0.4 and 0.8 mg daily) has also been shown to be effective long term in BPH (418 patients) without inducing orthostatic hypotension. Over 53 weeks, tamsulosin reduced the AUA symptom index by 3.1. Tamsulosin also increased the maximum urinary flow rate by 1.7 ml/sec. Tamsulosin did decrease blood pressure in both hypertensives and normotensives but these effects were small and not significant. Abnormal ejaculation occurred in 26% of the tamsulosin 0.8 mg group compared with 10% and 0% in the tamsulosin 0.4 mg and placebo groups, respectively (49). An extension of this study plus other trials with open-label 0.4 mg tamsulosin have confirmed that tamsulosin is effective long term (up to 4 years) (50, 51). The main reason for withdrawal over the 4 years was insufficient efficacy in 27% of the patients. At the end of the 4 years, tamsulosin had reduced standing SBP/DBP by 1.7/3.8 mmHg (51).



(**6**)

In a comparison of tamsulosin (0.4 mg once daily) with alfuzosin (2.5 mg t.i.d.) in 256 patients with BPH, it was shown that these drugs have similar effects on peak urinary flow rate and Boyarsky symptom score. Whereas tamsulosin had no effect on blood pressure, alfuzosin reduced both standing and supine blood pressure (52). A comparison of tamsulosin (0.2 mg) with terazosin (increasing 1-5 mg) revealed similar findings. Thus, although these drugs had equivalent effects on peak urinary flow and symptoms, terazosin only decreased blood pressure and was more likely to cause dizziness (53).

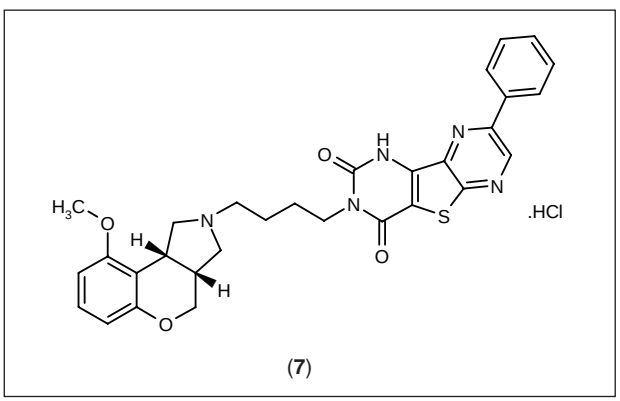
Targeted transurethral microwave thermotherapy is probably superior to terazosin in BPH (36). As hypotensive-associated side effects are less frequently associated with tamsulosin than terazosin, it would be of interest to compare microwave thermotherapy with tamsulosin to determine whether thermotherapy is also superior to tamsulosin.

New uroselective agents

Increasing the uroselectivity of alpha$_1$-adrenoceptor antagonists may allow an increase in dose/benefit in BPH without detrimental effects on the cardiovascular system, and a number of uroselective agents have been synthesized. Tamsulosin has a α_{1B}-/α_{1B}-receptor subtype selectivity of 15 for the cloned human adrenoceptors. Fiduxosin (**7**) has a higher affinity for the cloned human α_{1A}- (0.16 nM) than the α_{1B}-adrenoceptor (25 nM) (54) and a prostatic intraurethral pressure *versus* mean arterial pressure ratio of 7.5 in dogs (55), which suggested that it may be useful in the treatment of BPH. However, Abbott Laboratories have discontinued their development of fiduxosin.

Some compounds being developed by R.W. Johnson Pharmaceuticals for BPH show much greater uroselectivity than that observed with tamsulosin. At human cloned α_1-adrenoceptors, RWJ-69736 (**8**) and RWJ-38063 (**9**) have α_{1B}-/α_{1A}-receptor subtype selectivities of 340 and 953, respectively (56).

The calcium channel blocker niguldipine is a potent antagonist at α_{1A}- but not other α-adrenoceptors. The niguldipine molecule has been modified by Merck



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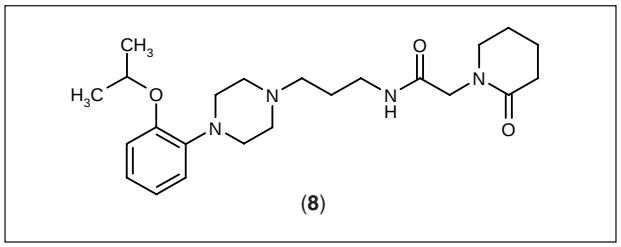

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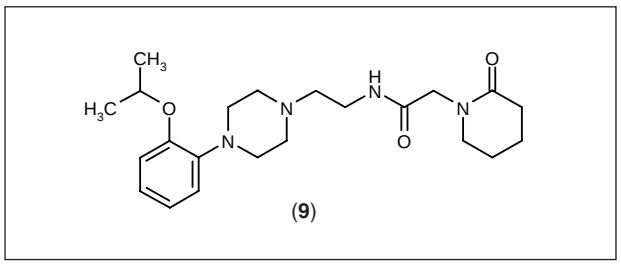

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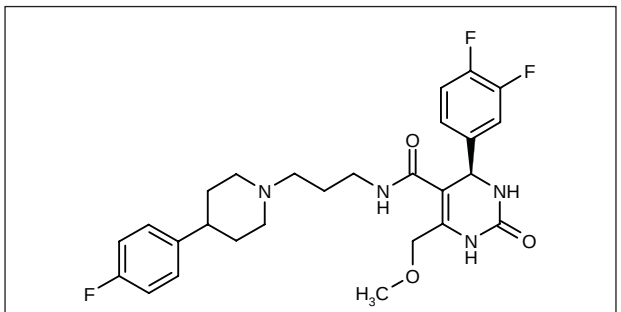
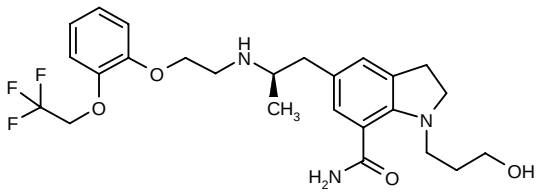


(**10**)

Research Laboratories to maintain the selective α_{1A}-adrenoceptor antagonism while reducing the calcium channel blocking activity. Many of the compounds synthesized were found to be more potent than terazosin in both a rat model of prostate tone and a dog model of intraurethral pressure without affecting blood pressure. One of the compounds tested, (4*R*)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid 3-[4-(4-fluorophenyl)piperidin-1-yl]propylamide (**10**), was selected for further development in the treatment of BPH, as it has a better pharmacokinetic profile than the other agents developed (57).

Kissei Pharmaceuticals are developing KMD-3213, (−)-(*R*)-1-(3-hydroxypropyl)-5-[2-[2-[2-(2,2,2-trifluroethoxy)phenoxy]ethylamino]propyl]indoline-7-carboxamide (**11**), as a uroselective α_{1A}-adrenoceptor antagonist. KMD-3213 has more than a 200-fold higher affinity for human prostate α_{1A}- than aorta α_{1B}-adrenoceptors (58). The greater uroselectivity of KMD-3213 than tamsulosin has been demonstrated by studying the effects on prostatic urethral pressure and blood pressure in male decerebrate dogs (59). Byk Gulden's B8805-033, (±)-1,3,5-trimethyl-6-[3-[4-(2,3-dihydro-2-hydroxymethyl-1,4-benzodioxin-5-yl)piperazin-1-yl]propylamino]-2,4(1*H*,3*H*)-pyrimidinedione (**12**) is another drug with over a 150-fold selectivity for α_{1A}- over α_{1B}- or α_{1D}-adrenoceptors, and



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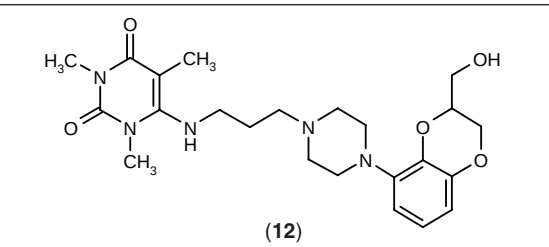
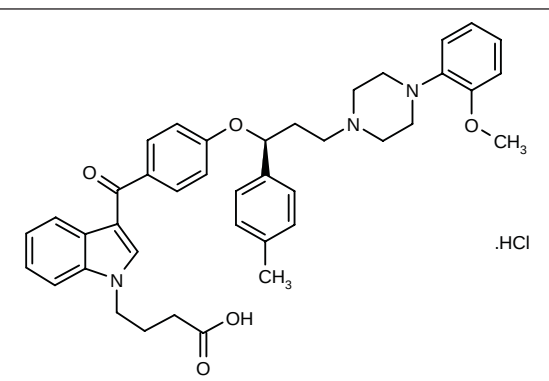


(**12**)

urethral/vascular selectivity of 52 in anesthetized dogs. However, B8805-033 also has actions at other receptors including potent agonistic activity at 5-HT_{1A}-receptors (60) which may preclude its further development for the treatment of BPH.

Combined 5α-reductase/α_1-adrenoceptor inhibitors

Finasteride and α_1-adrenoceptor antagonists are used together in the treatment of BPH despite the lack of clear-cut evidence that the combination has a greater effect than the α_1-adrenoceptor antagonist does alone, other than in the presence of a very large prostate. As finasteride and α_1-adrenoceptor antagonists have different mechanisms of action, it would be predicted that they could have an additive effect, and it is possible that a drug that combines these mechanisms may also be useful. Z-350, (*S*)-4-[3-(4-1-{4-methyl-phenyl)-3-{4-(2-methoxyphenyl)piperazine-1-yl]propoxy}benzoyl)indole-1-yl]butyric acid hydrochloride (**13**), is a more potent inhibitor of the phenylephrine α_1-adrenoceptor-mediated responses of the rabbit prostate and urethra than the aorta. Z-350 also inhibits 5α-reductase and is being developed for the treatment of BPH (61).



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Phytopharmaceuticals

Drugs derived from plants have a long tradition in the treatment of BPH in Europe and are now being used more commonly in the U.S. At present, one-third of men in the U.S. who choose nonsurgical therapy for BPH use herbal preparations alone or in combination with prescription medicines (62). This use is controversial, as no clear mechanisms of action have been established for many of these agents. Many of the phytopharmaceuticals have not been evaluated in double-blind clinical studies, and thus their effect may be a "placebo" effect as a considerable placebo effect is noted in double-blind studies of treatment for BPH. Reviews of saw palmetto berry (63), cernilton (64) and *Pygeum Africanum* (65) have all concluded that analysis of the effectiveness of these preparations is limited by the short duration of the trials, the limited number of enrollees, gaps in reported outcomes and the unknown quality of the preparations utilized. Nevertheless, it seems likely that these agents do improve symptoms and peak urinary flow rate. Long-term trials of the effects of these phytopharmaceuticals in BPH are still needed.

Saw palmetto berry

The most widely used phytopharmaceutical for BPH is the saw palmetto berry, and in 1998 sales in the U.S. exceeded $20 million. The berry contains beta-sitosterol which is chemically related to cholesterol. Extracts of saw palmetto inhibit the binding of DHT to its receptors (66). *Strogen forte* (a standardized extract of the saw palmetto berry plant, *Sabalis serrulata*) inhibits human prostatic 5α-reductase and testicular $^{\Delta}$5-3β-hydroxysteroid dehydrogenase (67). Treatment of BPH with saw palmetto herbal blend had no effect on prostate volume or PSA, but slightly decreased the prostate epithelium (68). This decrease in prostate epithelium was associated with a lowering of prostate DHT, as determined by human prostate needle biopsy, although the effect was not as great as that observed with finasteride treatment (69).

Therapeutically relevant doses of Permixon (a standardized lipid-sterolic extract from *Serenoa repens*, another name for saw palmetto berry) inhibited 5α-reductase without altering PSA in a culture model of BPH (70). Clinical studies in humans have shown that Permixon decreases DHT content in the prostate of patients with BPH (71) but not the PSA (66).

There have been many uncontrolled trials of saw palmetto berry which gave similar positive results. For instance, in a study of 38 patients treated with *Strogen forte* for 12 months, peak urinary flow rate was shown to

increase by 4.1 ml/sec, urinary residue to decrease by 47 ml and the average volume of the prostate to decrease by 11%. Symptoms abated in almost 75% of the cases and there were no adverse effects (72). However, without a control, it is not possible to determine whether this was a placebo effect.

A meta-analysis of the published trials of Permixon brand of *Serenoa repens* was not affected by trying to bring together potentially nonequivalent agents from several manufactures. The analysis included 11 randomized and 2 open-label trials with a duration ranging from 21-180 days, and showed that Permixon increased peak urinary flow rate by 2.2 ml/sec (0.5 ml/sec, placebo) and decreased nocturnal urinations (73). A Cochrane review of *Serenoa repens* included 2939 men from 18 randomized trials, lasting 4-48 weeks, and concluded that *Serenoa repens* does improve symptoms and urinary flow measures (74).

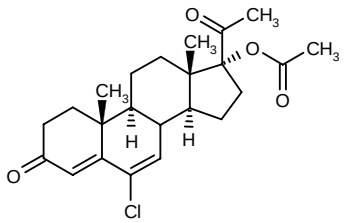
In an uncontrolled trial, Permixon was compared to finasteride in a double-blind manner in 1098 men with BPH and shown to be equivalent after 6 months. Both Permixon (320 mg) and finasteride (5 mg) decreased the IPSS and increased the peak urinary flow rate by about 2.5 ml/sec. Finasteride, but not Permixon, decreased serum PSA levels. Permixon had a smaller effect on prostate volume (reduction from 43.3 to 41.5 cm^3) than finasteride (from 44.0 to 36.7 cm^3). Permixon was generally better tolerated than finasteride and caused less impotence (1.5%) than finasteride (2.8%) (75).

β-Sitosterol

Among the contents of Harzol (also known as β-sitosterol) are phytosterols, mainly β-sitosterol with smaller amounts of campesterol and stigmasterol, and their glucosides (*e.g.*, β-sitosterol-β-D-glucoside). The effects of this preparation of β-sitosterol has been tested in a placebo-controlled, double-blind clinical trial of 200 patients with BPH over 6 months and shown to be beneficial. β-Sitosterol improved the symptoms of BPH assessed by both the Boyarsky system (–6.7 *vs.* –2.1 in placebo) and the IPSS. β-Sitosterol increased the peak urine flow rate by 5.2 ml/sec (1.1 ml/sec, placebo) and decreased residual urinary volume. β-Sitosterol caused a small decrease in the size of the prostate gland of 3.1 cm^3 (0.3 cm^3, placebo). There were no severe adverse effects with β-sitosterol (76). β-Sitosterol-β-D-glucoside alone was not effective in the treatment of BPH (77).

Cernilton

Cernilton is a pollen extract derived from several different plants in Sweden. Although cernitin T-60 (a preparation of cernilton) at 1 mg/ml inhibited the growth of a cell line derived from the human prostate, it did not inhibit 5α-reductase or androgen binding sites (78). Thus, the mechanism of action of cernilton remains unknown. Cernilton seems to be well tolerated and modestly improves urologic symptoms (64), without affecting peak urinary flow rate (79).



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Pygeum africanum

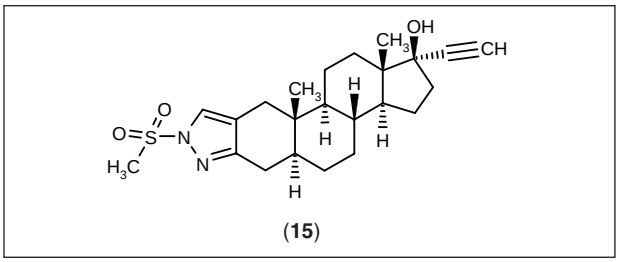
Pygeum africanum (Tadenan) is an extract from the bark of the African plum tree that contains sterols, terpenoids and plant alcohols. The mechanism of action of *P. africanum* is being investigated. In a rabbit model of experimental partial bladder outlet obstruction, Tadenan reduced the obstruction probably by effects on the myosin heavy chain. In the obstruction, there was a decrease in chain isoform SM-B which had fast shortening, and an increase in the SM-A isoform which had slow force generation and prolonged relaxation. This effect was reversed by treatment with Tadenan (80). Clinical studies show that *P. africanum* probably does cause a modest improvement in urinary flow and symptoms (65).

Androgen receptor antagonists

None of the androgen receptor antagonists have been shown to have a favorable profile in BPH as they have little benefit while commonly causing adverse effects. Chlormadinone acetate (**14**) has been used in Japan to treat BPH, although there are no large double-blind, randomized trials to support this. Chlormadinone inhibits DHT receptor binding to cause regression of the prostate epithelium but not the stroma (81).

Zanoterone (**15**) is a steroidol competitive antagonist at androgen receptors. Zanotorene (100-800 mg) was compared to placebo in 463 patients with BPH over 6 months. Zanoterone did not improve the AUA symptom score and only at 200 mg did it improve peak urinary flow rate by 1.7 ml/sec (0.5 ml/sec, placebo). Doses lower than 800 mg did not change prostate size, whereas zanoterone at 800 mg reduced the prostate size from 42.2 to 37.7 cm^3. Zanoterone increased the incidence of breast pain (56% *vs.* 1% in placebo) and gynecomastia (22% *vs.* 1% in placebo, 1%) (82).

Flutamide (**16**) is a potent nonsteriodal antiandrogen that inhibits the binding of testosterone and DHT to



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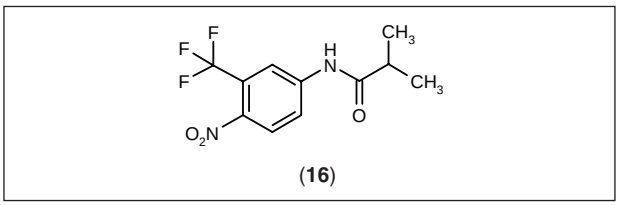

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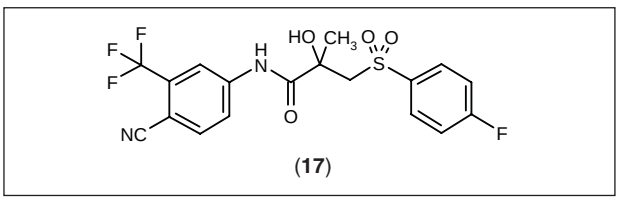


(**17**)

androgen receptors. Flutamide is not useful in the treatment of BPH because it causes limited benefit and many adverse effects. In a major study of flutamide, 367 patients were divided into a placebo group and 4 dosing regimens of flutamide and monitored for 24 weeks. Flutamide reduced the prostate volume and increased the peak urinary flow rate at 4 weeks. However, these effects did not reach statistical significance due to an increasing number of dropouts for adverse effects. The most common adverse events were nipple and breast tenderness (42-52%), diarrhea (29-34%) and gynecomastia (14-19%). Flutamide also did not improve urinary symptoms (83).

In BPH, bicalutamide (**17**), a nonsteroidal antiandrogen, acts at central androgen receptors to increase the secretion of luteinizing hormone (LH) and this causes an increased production and metabolism of testosterone (84). These are unwanted effects in BPH, and thus bicalutamide should not be used.

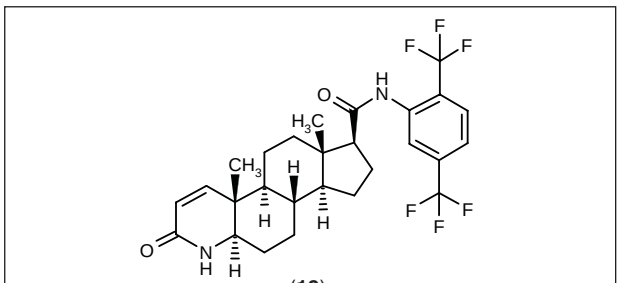
New Targets

Combined type 1/type 2 5α-reductase inhibitors

Inhibition of the prostatic type 2 5α-reductase with finasteride reduces levels of DHT by up to 80% and prostatic size by 20-30%. The rest of the DHT is probably delivered in the serum and derived from the activity of the type 1 5α-reductase in the liver and may play a role in maintaining prostatic enlargement in BPH. Drugs that inhibit both type 1 and type 2 5α-reductase are being developed for the treatment of BPH and include dutasteride (**18**) from GlaxoSmithKline, Pharmacia's PNU-157706 (**19**), FR-146687 (**20**) from Fujisawa and Lilly's izonsteride (**21**) (85).

Endothelin

Endothelins are the only agents, other than alpha-adrenoceptor agonists, that contract the prostate stroma. Endothelin precursors and the endothelin-converting enzyme (ECE) are expressed in the human prostate



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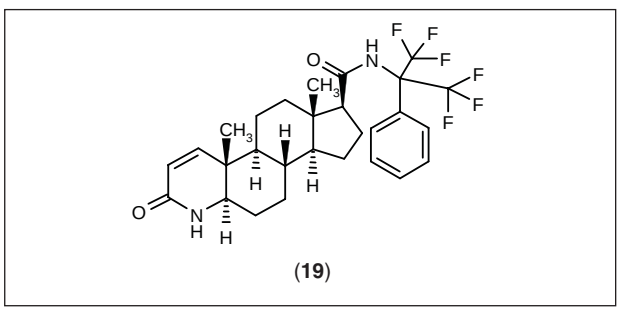

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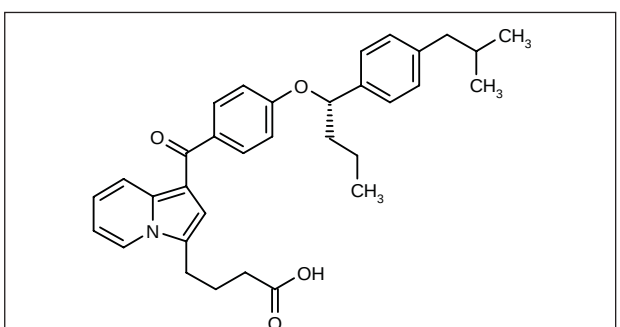

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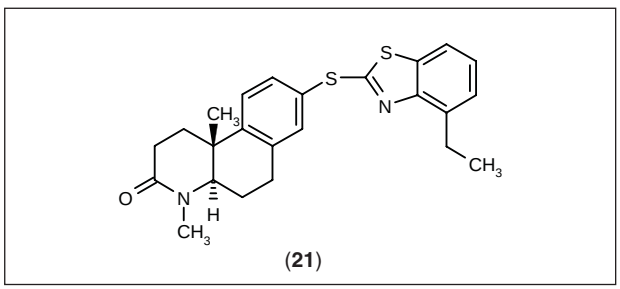

(**21**)

gland. Endothelin stimulates predominantly endothelin ET_A receptors, but also ET_B receptors, to contract the stroma, and these contractions are increased with the amounts of smooth muscle in BPH (86). Thus, endothelin receptor antagonists should be tested in BPH.

Growth factors

The growth-promoting effects of androgens in the prostate are mediated by a number of locally produced growth factors. These include epidermal growth factor (EGF) (87), which is inhibited by both finasteride and flutamide (88). Basic fibroblast growth factor (bFGF) has a mitogenic effect on prostate stroma. Finasteride reduces the levels of bFGF in the prostates of BPH patients (89). Other drugs that inhibit the effects of EGF and/or bFGF may have a role in the treatment of BPH.

Luteinizing hormone-releasing hormone

Cetrorelix is an antagonist of LH-releasing hormone that has been tested in 13 patients with moderate to severe BPH. Cetrorelix (5 mg s.c. twice daily for 2 days followed by 1 mg/day s.c. for 2 months) decreased testosterone levels to castrate levels on day 2 and by about 70% on the maintenance dose. Cetrorelix decreased the IPSS and increased peak urinary flow by 2.86 ml/sec, and these benefits were evident in long-term follow-up (up to 18 months). Cetrorelix caused a small decrease in sexual satisfaction during treatment, but an apparent increase after treatment ceased (90). As this study was not placebo-controlled, the benefits may have been due to a placebo effect.

Estrogens

Estrogen levels increase relative to androgens in aging men and may have a role in prostate growth. Inhibiting aromatase with atamestane reduces the levels of estrogens. A double-blind, placebo-controlled randomized trial in 292 patients showed atamestane to be ineffective in BPH. Atamestane reduced serum concentration of estrogens and did have some beneficial effects in BPH, but these were not greater than the placebo effects (91). By inhibiting aromatase, atamestane also increased androgen levels, and this detrimental effect in BPH may have masked any benefit.

Mepartricin is a polyene drug that can adsorb both estrogens and androgens. However, after oral administration mepartricin is not absorbed to any great extent and only the levels of estrogens are reduced. This is because the estrogens, but not the androgens, undergo enterohepatic circulation and removal by mepartricin. In a double-blind, placebo-controlled trial of 196 men with newly diagnosed BPH, mepartricin was shown to be superior to placebo over 6 months. Mepartricin reduced the IPSS (6.3 *vs*. 4.2 in placebo) and increased the maximum urinary flow rate (2.7 *vs*. 1.2 ml/sec in placebo). Mepartricin had no effect on prostate volume, PSA or sexual function (92).

Estrogens have beneficial effects on the cardiovascular system (93). Thus, although removal of estrogens may have beneficial effects in BPH, this may be associated with detrimental effects on the cardiovascular system. Until this is clarified, removal of estrogens with mepartricin should not be recommended in BPH.

Nitric oxide

Nitric oxide stimulates guanylate cyclase to increase cGMP levels and relax prostatic smooth muscle (94). Inducible nitric oxide synthase is not present in normal prostates but is induced in patients with BPH (95). Nitric oxide donors therefore may be beneficial in the treatment of BPH.

Phosphodiesterase isoenzymes

In addition to cGMP, prostatic smooth muscle relaxation is mediated by the elevation of cAMP (96). Inhibition of PDE isoenzymes elevates cAMP and cGMP. Many of the PDE isoenzymes are present in the prostate, and the hydrolytic activities of PDE4 and PDE5 are present in the cytosolic fraction of human prostatic tissue, whereas in the particulate fraction only the hydrolytic activity of PDE4 is detected. Inhibitors of PDE4 and PDE5 reversed the adrenergic tension in prostatic strip preparations (97). This suggests that inhibitors of PDE4 (*e.g.*, rolipram) and PDE5 (sildenafil, zaprinast) may have a role in the treatment of BPH.

Conclusions

At the present time, selective α_{1A}-adrenoceptor antagonists are probably the drugs of choice in BPH. Finasteride is an alternative or an addition, especially in the presence of large prostates. More uroselective α_{1A}-adrenoceptor antagonists are being developed for the treatment of BPH, as are a number of new approaches to pharmacotherapy. Some of the phytopharmaceuticals are probably effective in BPH, but most still require thorough testing. In the future, minimal invasive treatments such as transurethral microwave therapy may become more common with a decrease in pharmacotherapy for BPH.

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