

Mini-reviews

In the first of these mini-reviews the selection of therapy for the maintenance of sexual function in patients with BPH is outlined, along with an explanation of how altered regulation of neurotransmitters, especially noradrenaline, may underlie the syndrome of LUTS and sexual dysfunction.

Other mini-reviews outline the current status of robotic surgery to treat renal and adrenal disorders, and its future applications, and the potential use of the nitric oxide/cGMP pathway as a potential target to treat BOO associated with benign prostatic enlargement.

Finally, the capacity to be creative in academic departments is extolled as a core property of academicians, and its surfacing described as having the potential to revitalize individuals and departments.

Selecting therapy for maintaining sexual function in patients with benign prostatic hyperplasia

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INTRODUCTION

In patients with BPH, LUTS can diminish quality of life (QoL) by interfering with sexual function [1–3], which has been shown to be an important component of QoL among men even in their later years [4,5]. As QoL becomes more of a consideration in managing BPH, the effects of BPH treatment on sexual function need to be included in patient management decisions.

EPIDEMIOLOGY OF LUTS, BPH AND SEXUAL DYSFUNCTION

In a cohort of 80 774 Dutch men aged ≥ 45 years [6], the incidence rate of LUTS was 5 per 1000 man-years and increased with age, while the overall prevalence rate was 10.3%. It was reported that more than half of men aged >60 years have BPH, with 15–30% of such men experiencing LUTS [7].

The prevalence of sexual dysfunction, including erectile dysfunction (ED) and ejaculatory disorders (EjDs), also increases with age [8]. ED has a reported global prevalence of 18.9–69.2% [9]. In a community-based, longitudinal study of 3924

Dutch men, of whom 9–20% were determined to have BPH, ED prevalence rates were 3% in men aged 50–54 years and 26% in men aged 70–78 years, and EjD prevalence was 3–35% [10,11]. A multinational study involving both community and clinic cohorts showed ED prevalence rates of 53% and 60%, respectively, and EjD prevalence rates of 47% and 62%, respectively, among patients with LUTS [12]. A study in 1274 European men with LUTS showed prevalence rates for ED of 62% and EjDs of 63%, with both being highly bothersome to patients, even in advanced age [12].

PATHOPHYSIOLOGY OF BPH, LUTS AND SEXUAL DYSFUNCTION

BPH AND LUTS

The development of BPH requires the elaboration of testosterone by the testes. Men castrated before puberty do not develop BPH, and BPH is rare in men castrated in adulthood. Within the prostate, testosterone is converted to 5α -dihydrotestosterone (DHT) by 5α -reductase. DHT is important both for the development of the prostate and for its enlargement later in life.

The prostate has a large complement of α -adrenoceptors, particularly in the prostatic capsule, with varying concentrations in the bladder neck region and maximum concentrations in the trigone. The two classes

of adrenoceptors, α -1 and α -2, are also selectively distributed: α -1s are more abundant in the lower urinary tract and in the blood vessels. (The α -1 and α -2 also have differing effects on male sexual function, as discussed below). Three subtypes of α 1-adrenoceptors, 1A, 1B and 1D, are also selectively distributed in the prostate, penis and urinary tract, and these distributions vary with age.

The preponderance of adrenoceptors in the smooth muscle of the prostate suggests that stimulating the receptors could cause an increase in smooth muscle tone in the prostate, thereby increasing pressure on the urethra and resulting in BPO or acute urinary retention (Fig. 1) [13]. In fact, α -blockers have been shown to relax prostatic smooth muscle, with improvements in both irritative and obstructive symptoms.

SEXUAL DYSFUNCTION (ED AND EJD)

Penile erection is a complex neurovascular event involving the sympathetic, parasympathetic and somatic nervous systems, which mediate psychogenic and reflexogenic erections via the spinal cord. This process involves a balance of pro-erectile and anti-erectile neurotransmitters, e.g. noradrenaline, serotonin, dopamine and γ -amino butyric acid.

The normal process of ejaculation proceeds initially with stimulation by the sympathetic nervous system, which results in contraction of the prostate, vas deferens, epididymis and seminal vesicles, and ends with the flow of seminal fluid into the urethra. EJD may occur in the presence of any pathological disorder that involves the lower urinary tract structures in the ejaculation pathway, including the prostate. In addition, neurological and psychological factors may also be implicated in the development of EJD [14].

LUTS, BPH AND SEXUAL DYSFUNCTION

A link between LUTS/BPH and sexual function [15] is emerging despite the perception that BPH *per se* does not adversely affect sexual function. Sexual dysfunction can profoundly affect older men [16], as many still engage in sexual activity [3]; in one survey, 42% of men aged >50 years considered sex 'important' or

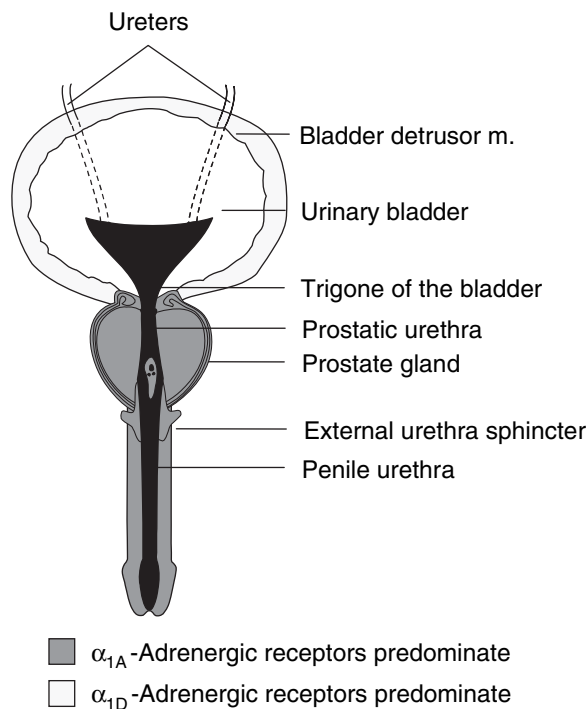


FIG. 1.
The anatomical distribution of α 1-adrenoceptor subtypes.
Adapted with permission from Schwinn [13].

'very important' [2]. Both voiding and storage symptoms have been associated with sexual dysfunction [17].

Other age-related changes that may influence the relationship between LUTS/BPH and sexual dysfunction include declines in circulating androgen levels and the effects of some medications likely to be used in elderly patients. The bothersome effect of obstructive and irritative symptoms, and negative expectations related to sexual performance, can impair sexual performance and QoL among patients with LUTS/BPH [18].

Sexual dysfunction and incontinence often occur in conjunction with LUTS [19], and this raises the possibility of a shared mechanism involving similar noradrenergic and/or other neurotransmitter pathways. BPH can be marked by increases in the concentrations and distribution patterns of α 1 receptor subtypes in the prostate, and these same receptor subtypes have been located within penile tissue, where they play an anti-erectile role. It is possible that alterations in these receptor populations may occur in the penis and contribute to the development of sexual dysfunction. Autonomic modulation of α 1-receptors and their subtypes at sites outside the genitourinary tract, including the human spinal cord and in both sympathetic and

parasympathetic tracts, may also be involved in LUTS as well as in sexual function and dysfunction [20].

MEASURES TO EVALUATE SYMPTOMS AND SEXUAL FUNCTION IN PATIENTS WITH LUTS AND BPH

Several well-validated symptom scoring scales have been developed for evaluating LUTS/BPH, and there are generic or disease-specific QoL instruments. With the recognition that treatments for BPH may affect sexual function, several instruments have been used to evaluate sexual function among patients with LUTS/BPH, including the International Index of Erectile Function, the Brief Sexual Function Inventory, the BPH-Health-related Quality of Life scale, the ICSsex questionnaire and the Danish Prostatic Symptom Score questionnaire.

Although evaluations of sexual dysfunction have traditionally focused on ED, sexual functioning encompasses many domains, including satisfaction with intercourse, ejaculation, sexual desire and overall satisfaction. Clinical experience with sexual function scales shows a strong relationship between LUTS and sexual difficulties [14,21]; in addition, sexual satisfaction progressively

decreases as the severity of LUTS advances from mild to severe [22–25]. Even when age-adjusted, patients who score higher on the IPSS have poorer sexual function, as defined by the Brief Sexual Function Inventory [23] or other sexual function scales [24]. When patients and their partners are asked about the history of urinary symptoms and sexual dysfunction, they generally recall both problems as starting concurrently [25]. Studies using these measurement instruments show that men with ED are twice as likely to have LUTS as are men without ED [3].

Not all men will be bothered to the same degree by the same symptoms. Both the prevalence and the bothersomeness of sexual disorders have been shown to be strongly associated with the severity of LUTS, even when age and comorbidities are taken into account [1]. This was the finding from the Multinational Survey of the Aging Male [1], which evaluated >12 000 men aged 50–80 years, in six European countries and the USA. In this survey, 83% of men reported frequent sexual activity, although the frequency decreased with age and was inversely associated with age and the severity of LUTS. Of the patients evaluated, 49% reported ED, 48% had EjD, and 7% had pain during sex. Both ED and EjD were reported as bothersome by most men who experienced them. Problems in each domain of sexual function were strongly associated with the severity of LUTS, independent of age and other comorbidities. Overall, LUTS were present in 90% of the men, but only 11% were being treated medically.

These data raise two significant issues that affect clinical practice: (i) the possible underestimation of the effects of LUTS on patients and therefore of a corresponding need for therapy; and (ii) the need for more thorough assessment of patients with LUTS, including evaluation of sexual function, via the use of validated scales that assess all sexual domains.

BPH THERAPIES: IMPACT ON SEXUAL FUNCTION

While the nonsexual side-effects of medical treatments for BPH, especially the vasodilatation-related symptoms of dizziness, asthenia and postural hypotension are well-documented [26–29], the effects of BPH

treatments on sexual function are less so. The following represents a summary of clinical data.

WATCHFUL WAITING AND SURGERY

Watchful waiting is often used in patients with mild symptoms or symptoms that are not particularly bothersome. For the many patients who eventually require treatment, TURP is the most common surgical procedure. Although highly effective, it is associated with significant morbidity and sexual dysfunction (EjD in 25–55% of cases; ED in 13%) [30–32]. Open prostatectomy, used especially in men with large prostates (>60 g), also has a high success rate but is associated with frequent complications, including deleterious effects on sexual function. Prospective studies evaluating the impact of minimally invasive surgery on sexual function have been few, but have assessed outcomes over periods of 1–4 years [33–35]. There have been some reports suggesting possible pain or discomfort with ejaculation [35] but also emergence of retrograde ejaculation (18%) [33], decreases in ejaculate volume, and reduced erectile strength [34].

5 α -REDUCTASE INHIBITOR (5-ARI)

Originally medical treatment for BPH was focused on androgen blockade, either by surgical castration or with medication such as the androgen-receptor blocker flutamide. Inhibition of androgens can reduce the size of the prostate but can also cause ED and reduced libido. The focus of pharmacotherapy shifted to with the discovery that men who were deficient in 5ARI due to a homozygous mutation had feminized urogenital structures and prostates only 10% of the normal size.

Conversion of testosterone to DHT by 5 α -reductase increases the potency of androgens in target tissues, including the prostate. DHT has a role in the normal differentiation and growth of the prostate, as men with enlarged prostates have higher levels of DHT. Two 5ARIs are used in the treatment of BPH, i.e. finasteride and dutasteride.

FINASTERIDE

Treatment with finasteride, a competitive 5ARI acting on one isozyme that does not bind to the androgen receptor, effectively reduces prostate size, by 19% after 1 year [36] and by 27% after 3 years [37]. The greatest

reductions appear to occur in men with larger prostates at the initiation of therapy. Finasteride has also yielded an improvement in urinary flow rates and in symptom relief.

Finasteride is associated with significant adverse effects on sexual function in \approx 10% of subjects [30,36,38], which has led to discontinuation of patients from the drug in several studies [36,38]. In a 2-year, prospective, double-blind trial of finasteride 5 mg/day, 15.8% of finasteride-treated subjects developed ED, 10% reported decreased libido and 7.7% developed EjD.

DUTASTERIDE

Dutasteride is an inhibitor of both 5 α -reductase isozymes and has been shown to reduce the risk of acute urinary retention and the need for surgery in men with BPH [39]. Similar sexual side-effects to those with finasteride are expected with dutasteride, given that these effects are directly related to the drug's therapeutic mechanism of action [39]. In a review of safety and tolerability data from several 2-year blinded trials and safety studies of dutasteride, sexual adverse events (including decreased libido, abnormal ejaculation, gynaecomastia and impotence, which occurred more often with dutasteride than with placebo) were those most frequently reported [40].

α -BLOCKERS

With the identification of α 1-adrenoceptors as the predominant mediators of contraction of prostate smooth muscle, α -blockers have become first-line treatment for BPH. The first- and second-generation drugs include prazosin, doxazosin and terazosin. More recently, two agents claimed to be selective for one or more α 1-adrenoceptor subtypes, tamsulosin and alfuzosin, were introduced. Both of these have been claimed to show clinical uroselectivity (i.e. eliciting desired effects on obstruction and LUTS relative to adverse events) and better tolerability than the traditional α -blockers [27,41–44].

NON-SUBTYPE SELECTIVE AGENTS: TERAZOSIN AND DOXAZOSIN

Terazosin and doxazosin are non-subtype selective and were originally developed for their antihypertensive properties. Both agents are effective in relieving the symptoms of BPH, but can be associated with

TABLE 1 Clinical characteristics of 5ARIs and α 1-adrenoceptor antagonists in the treatment of BPH

Drug	Effect on prostate size	Adverse events		Titration required	Reference
		Vasodilatory	Sexual		
Finasteride	Decrease \approx 27% over 1 year	N/A	EjD, ED, decreased libido	N/A	[37]
Dutasteride	Decrease 20–25% over 1 year	N/A	EjD, ED, decreased libido	N/A	[62]
Terazosin	No effect	Yes	ED	Yes	[61]
Doxazosin	No effect	Yes	None*	Yes	[61]
Tamsulosin	No effect	No	EjD†	No	[61]
Alfuzosin	No effect	No	EjD†	No	[61]

*A long-term study on sexual function in hypertensive patients [45] suggests that ED may occur with doxazosin, although the difference with placebo was not statistically significant (11.6% vs 16.7%; $P = 0.32$); †EjD rates were 4–26% [27,48,49]; ‡EjD rates were <1% [29,50]; N/A, not applicable.

cardiovascular or vasodilatory side-effects, e.g. dizziness, asthenia and postural hypotension. In a 48-month study evaluating the long-term effects of antihypertensive agents, including doxazosin, on sexual function, rates of ED at study endpoint were 11.6% with doxazosin and 16.7% with placebo, although the difference was not statistically significant ($P = 0.32$) [45]. In addition, a 1.6% incidence of ED was reported with terazosin [46].

In a more recent prospective study, the new extended-release formulation of doxazosin was shown, using the International Index of Erectile Function, to produce a substantial improvement in sexual function in patients with BPH and comorbid ED [47].

'UROSELECTIVE' AGENTS: TAMSULOSIN AND ALFUZOSIN

Tamsulosin and alfuzosin are α -blockers that are claimed to be uroselective or act preferentially on the lower urinary tract, i.e. they are clinically and physiologically uroselective agents. Both effectively improve urinary flow rates and the symptoms of BPH without affecting blood pressure at the doses used. Although tamsulosin has shown little effect on blood pressure, findings from several clinical trials indicate that use of this drug may be associated with EjD in some patients; in these studies, EjD was reported in 4–26% of patients treated with tamsulosin [27,48,49].

Alfuzosin is used extensively in Europe as a treatment for BPH and was recently approved by the USA Food and Drug Administration. Sexual dysfunction does not appear to be

increased with alfuzosin treatment; in the 3-month ALFORTI study, no EjD was reported in any of the three treatment groups [50]. In a 12-month extension of the same study, alfuzosin once daily produced sustained improvements in symptoms and urinary flow rates [50,51]. In the placebo-controlled 3-month ALFUS study [29] treatment with alfuzosin 10 mg once daily induced a 3.6-point mean reduction in the IPSS from baseline in the absence of any deleterious effect on sexual function. Temporary EjD was reported in one patient (0.6%) in each treatment group, with the cases being considered not related to the study drug, as there was spontaneous resolution with no need to discontinue therapy.

Unlike the non-subtype selective α -blockers (e.g. prazosin, terazosin and doxazosin), tamsulosin and alfuzosin are associated with a low incidence of postural symptoms, similar to that seen with placebo [26,27,52]. Although alfuzosin shows no subtype specificity on *in vitro* tests, it does appear to be clinically uroselective [44,53–56].

Alfuzosin is associated with a much lower incidence of EjD than is tamsulosin [57]. EjD has occurred in 10–11% of subjects taking tamsulosin 0.4 mg/day and 18–26% of those taking 0.8 mg/day [48,58]. In a 1-year extension study, 30% of patients had EjD during treatment with tamsulosin, causing 2% to discontinue treatment; 6% had ED [59]. In contrast, the incidence of EjD was <1% in clinical studies of alfuzosin once-daily, and other sexual adverse events did not occur at incidences significantly greater than those reported with placebo [29,50]. These findings are supported by long-term trials with other formulations of alfuzosin [54,60]. A summary

of the clinical characteristics of α -blockers and 5ARIs is shown in Table 1 [37,61,62].

COMBINED α -BLOCKADE AND 5-ARI

In contrast to α -blockers, the 5ARIs do not act rapidly and often take 0.5–1 year to be effective. Because the 5ARIs and α -blockers have different modes and onset of action, studies have examined combinations of these agents. Studies of up to 1 year in duration failed to show that combined therapy was more effective in treating symptoms than α -blocker therapy alone [63,64]. However, a recent long-term study of combined therapy with doxazosin and finasteride showed that during an average of 4.5 years of treatment, combined therapy reduced the risk of acute urinary retention by 81%, the need for invasive therapy by 67%, and symptom progression by 66% compared with observed disease progression in the placebo group [65]. These changes were significantly better than those seen with either drug alone.

Safety data reporting the effects on sexual function are available from several trials that have evaluated the use of an α -blocker (e.g. doxazosin, terazosin, alfuzosin) combined with the 5ARI, finasteride, in the treatment of BPH [63,64,66]. In the 1-year Veterans Affairs Cooperative Study, the combination of terazosin and finasteride was associated with the highest reported rates of ED (combination, 9%; terazosin, 6%; finasteride, 9%; placebo, 5%; $P = 0.05$) and EjD (combination, 7%; terazosin, 0.3%; finasteride, 2%; placebo, 10%; $P < 0.001$). In another 1-year study, again the combined therapy was associated with the highest rates of ED (combination, 10.5%; doxazosin, 5.8%; finasteride, 4.9%; placebo,

3.3%; $P < 0.01$) and EjD (combination, 2.4%; doxazosin, 0.4%; finasteride, 2.3%; placebo, 1.5%; $P = 0.16$) [64].

The 6-month ALFIN study evaluated the sustained-release formulation of alfuzosin 5 mg twice daily with finasteride 5 mg once daily and the combination of the two in the treatment of BPH [66]. Here too, combined therapy was associated with higher rates of ED than was either of the drugs when used as monotherapy (combination, 7.4%; alfuzosin, 2.2%; finasteride, 6.7%; $P < 0.002$). No episodes of EjD occurred with alfuzosin, and lower rates of EjD were reported with combined therapy than with finasteride alone (0.9% vs. 1.5%; $P = 0.04$).

CONCLUSIONS

The effect of α -blockers on sexual function merits closer attention because recent clinical experience suggests that these agents may differentially affect certain aspects of sexual dysfunction, particularly ED. Overall, the use of α -blockers not only effectively relieves the symptoms of LUTS/BPH but also preserves, and in some cases may improve, erectile function. Although some tolerability differences may be evident among individual α -blockers, the effectiveness and safety of BPH therapy must always be assured. Given the increasing evidence of comorbid sexual dysfunction in patients with BPH, the impact (negative or positive) of therapy on erectile or ejaculatory function should be an important component of selecting the most appropriate therapy.

CONFLICT OF INTEREST

None declared.

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Abbreviations: ED, erectile dysfunction; EjD, ejaculatory disorder; QoL, quality of life; 5ARI, 5 α -reductase inhibitor; DHT, dihydrotestosterone.