Review Article

The impact and management of sexual dysfunction secondary to pharmacological therapy of benign prostatic hyperplasia

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Abstract: Benign prostatic hyperplasia (BPH) is one of the most common genitourinary complications in men over 50 years of age and typically presents with lower urinary tract symptoms (LUTS). Classes of medications include α1-adrenoceptor blockers, 5α-reductase inhibitors, and phosphodiesterase 5 inhibitors. Today, α1-adrenoceptor blockers and 5α-reductase inhibitors are often combined to give a synergistic effect. A review of the current literature identified several adverse sexual side effects, including erectile dysfunction (ED), decreased libido, orgasmic disorders, and ejaculatory disorders. We believe it is important to know the extent of these side effects, as the clinician and patient will need to decide the cost of improved voiding symptoms. The chief adverse effect is ejaculatory disorders, including the absence of ejaculation. Clinical consideration for BPH should include the elements of male sexual function, patients' age, and the characteristics and comprehensive effects of each group of drugs. Methodological bias in clinical studies, such as the subjective evaluation of the sexual side effect, makes it difficult to determine the ideal drug for treatment.

Keywords: Benign prostatic hyperplasia (BPH); sexual dysfunction; ejaculatory disorders; retrograde ejaculation; 5α-reductase inhibitors; alpha1-adrenergic blockers

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Introduction

Benign prostatic hyperplasia (BPH) is a clinical syndrome which includes prostate enlargement and lower urinary tract symptoms (LUTS). The aim of BPH treatment is alleviating urination problems, preventing prostatic disease progression, and improving the quality of life. Over the past two decades, the standard of treatment has shifted from surgery to drug therapy. A greater understanding of detrusor physiology as well as the development of effective drugs for solving the dynamic and static components of the obstruction in the prostate and bladder neck have paved the path for the ubiquity of pharmacological therapy for BPH. However, clinical studies in the 1990s reported that despite the amelioration of LUTS, adverse effects of BPH drug therapy began to surface (1). These effects were noted as sexual dysfunction, which can be divided into erectile dysfunction (ED), ejaculatory dysfunction (EjD), orgasmic disorders, as well as sexual desire disorders.

Pharmacological BPH therapy protocols advocate the use of α-blockers (ABs) and 5α-reductase inhibitors (5ARI), individually or in combination, as well as phosphodiesterase-5 (PDE5) inhibitors, individually or concomitantly with ABs.

Adverse sexual side effects can occur as a result of the drug group itself or specific drugs within the group (2). Watchful Waiting is usually utilized in patients with an AUA symptom score <10. ABs bind to α_1-adrenoceptors and act by relaxing the smooth muscles of the prostate and bladder neck to improve urine flow and facilitate urination. They do not reduce prostatic volume or curb the natural progression of BPH. Nonetheless, ABs do vary in uroselectivity and the production of adverse effects (3). They can be nonselective (e.g., doxazosin, terazosin, and alfuzosin) and selective (e.g., tamsulosin and silodosin). 5ARIs cause the inhibition of 5α-reductase enzymes and prevent the conversion of non-active forms testosterone to DHT, the androgen steroid compound mainly responsible for the initial and subsequent enlargement of the prostate gland (4). The enzyme has two isoforms: type 1 (found in the liver and skin) and 2 (found in reproductive tissues). 5ARIs are prominently available as finasteride and dutasteride, with both exhibiting similar clinical effects. 5ARIs may lead to ED, EjD, and decreased libido compared to placebo (5). The combination of AB and 5ARI is an increasingly popular mode of treatment which incorporates the combined effect of both components, including combined sexual side effects. Lastly, PDE5 inhibitors (e.g., tadalafil) are commonly used in order to treat ED as well as inhibit PDE11, which is found in the prostate and testes (6). As of yet, PDE11 inhibition with therapeutic doses of tadalafil has shown no clinical significance (7). Nonetheless, findings from studies have revealed that PDE5 is highly expressed in the lower urinary tract and supporting vasculature, and that PDE5 inhibition potentially decreases smooth muscle cell proliferation in the prostate, relaxes smooth muscle in the prostate, bladder neck, and supporting vasculature, increases blood perfusion to the lower urinary tract, and modulates bladder afferent nerve activity (8). For these reasons, in 2011, the FDA approved tadalafil to also treat the signs and symptoms of BPH as well as a combination of BPH and ED when the conditions coincide.

Management of sexual dysfunction in men treated with BPH/LUTS should be focused and symptom-dependent. A validated questionnaire of enquiry, such as the international index of erectile function or male sexual health questionnaire, should be used to assess sexual function before beginning pharmacological therapy for BPH/LUTS. The clinician then must assess co-morbidities and concomitant medications, particularly those that affect erectile capacity, as well as address any risk factors for cardiovascular disease before initiating any sort of therapy. Also before pharmacological therapy, the physician must advise the patient on lifestyle modifications to improve sexual function, such as weight loss and an appropriate exercise regimen. The physician may even consider PDE5 inhibitors if necessary, especially if the patient presents with true symptoms of ED. If the patient has EjD, he must be advised to transform his BPH/LUTS therapy to an alternative AB or 5ARI. Once the relevant sexual dysfunction is tended to, the physician must provide the apposite counseling on the safety and tolerability of pharmacological therapies for BPH/LUTS. Follow up can be done in 4–8 weeks to check sexual function, after which 6-month checkups are adequate (9).

Adverse sexual side effects of select medications

ABs

A survey conducted in 2003 found that among 1,275 prescribers, including urologists and primary care physicians, AB monotherapy was the most common treatment regimen employed for BPH (10). ABs such as tamsulosin (*Flomax*) work on the dynamic component of BPH or the increased smooth muscle tone in the bladder neck and prostate responsible for obstructing urinary flow (11). This increase in smooth muscle tone in the bladder neck and prostate is mediated by sympathetic stimulation of the α_1-adrenergic receptors in these tissues (11). Blockage of the α_1-adrenergic receptors in the prostate and bladder neck causes smooth muscle relaxation and improves urinary flow (11). Three types of α_1-adrenergic receptors are present throughout the body including α_{1A}, α_{1B}, and α_{1D} (11). The majority (70%) of the α_1-adrenergic receptors in the prostate are of the α_{1A} subtype (11).

Tamsulosin

Tamsulosin is a third generation pharmacologically uroselective antagonist of α_{1A}-adrenoceptors in the prostate with minimal affinity for the α_{1B}-adrenoceptors of cardiovascular smooth muscle, thus not establishing any risk for hypotension (11,12). The degree of tamsulosin's selectivity for the α_{1A} receptor in comparison to the α_{1B} receptor has been estimated to be 15.8:1 (13). Tamsulosin has been reported to affect libido, erectile function, and ejaculation. Priapism has rarely been reported since market approval and is expected to occur in less than 1 in 50,000 patients (11). In one study that analyzed the results of the male sexual function-4 (MSF-4) questionnaire found that of 354 men treated with tamsulosin, 40.7% considered their sexual function as deteriorated after

6 months of therapy (14).

Based on the package insert, the rates of adverse events reported for tamsulosin were derived from two 13-week trials in the United States that included a total of 1,487 men (11). A decrease in libido was reported by 1.0% of men receiving the 0.4 mg dose of tamsulosin and 2.0% of men receiving the 0.8 mg dose of tamsulosin (11). These percentages are in comparison to a 1.2% incidence of decreased libido occurring in patients receiving placebo (11). A meta-analysis of two randomized controlled trials and two open label trials including a total of 2,743 patients demonstrated that a decrease in sexual desire occurred in between 1% and 4.7% of patients (15). These incidences were in comparison to 0–0.3% of patients receiving placebo or serenoa repens (*Permixon*). Decrease in erectile function was observed in between 0.6% and 6.3% of 4,789 patients included in a meta-analysis of randomized controlled and open label trials (15). In comparison, between 0% and 1.6% of patients receiving placebo experienced decreases in erectile function (15).

The results of the MSF-4 questionnaire also revealed that ejaculation disorders were the most frequently reported side effect of tamsulosin therapy (14). Abnormal ejaculation, including ejaculation failure, ejaculation disorder, and retrograde ejaculation, was reported in approximately 8.4% of men receiving the 0.4 mg dosage of tamsulosin and 18.1% of men receiving the 0.8 mg dose of tamsulosin (11). These percentages are much higher than that of the placebo group, which was 0.2% (11). These frequencies suggest a dose-related effect of tamsulosin on ejaculatory function. In other controlled clinical trials, the proportion of patients reporting EjD ranged from 0% to 26% depending on the dose of tamsulosin used and the study duration (9,15). Two studies in conducted in healthy men have suggested that tamsulosin causes decreased ejaculate volume, sometimes to the point of anejaculation (16,17). A pooled analysis of several European phase II trials found abnormal ejaculation to be more frequent in patients younger than 65 years of age (6.3%) than in patients older than 65 years of age (2.6%) (18). However, the frequency of abnormal ejaculation in both of these groups did not reach statistical significance in comparison to the placebo group (18).

In a 2015 prospective study involving 156 BPH patients, EjD was found in 64% of patients prescribed tamsulosin, with 15% of patients void of ejaculate. The effect of the uroselective tamsulosin relaxes the tone of smooth muscles of the bladder neck, thus reducing the pressure proximally to the verumontanum, leading to retrograde ejaculation. Sometimes due to the reduced amount or complete absence of the ejaculate, the extent of sensory stimuli coming from posterior urethra responsible for orgasm is reduced (19).

Alfuzosin

Alfuzosin (*Uroxatral*) is a clinically uroselective α_1-adrenergic receptor antagonist (20). However, alfuzosin's selectivity for the α_{1A} receptive subtype in comparison to the α_{1B} receptive subtype has been estimated to be much lower than that of tamsulosin (0.31:1 versus 15.8:1, respectively) (13). Still, alfuzosin exhibits selective action in the urinary tract likely due to preferential distribution into the prostate gland versus the blood and limited ability to penetrate the blood brain barrier (21). As per the prescribing information, adverse event data was obtained from three placebo-controlled clinical trials that were conducted over a three-month time period and involved 1,608 men, 473 of whom received one alfuzosin 10 mg extended-release tablet daily while the remaining 1,135 received 15 mg daily (20). Impotence was reported to occur in between 0% and 3% of patients receiving alfuzosin and not significantly more frequently than with placebo (between 0% and 1%), based on clinical trials results (22). Decrease in erectile function based on a meta-analysis of randomized controlled and open label trials has been reported to be between 0.0% and 2.8% in patients receiving alfuzosin (15). In comparison, the patients receiving a placebo in these trials reported decreases in erectile function at rates ranging from 0–2.3% (15). A meta-analysis of randomized controlled trials including a total of 1,302 patients demonstrated incidences of decreased sexual desire in 0–0.7% of patients receiving alfuzosin and 0.7% of patients receiving the placebo (15). Priapism was reported after market approval so incidence was not reported for this adverse effect (20). The reported incidence of ejaculatory disorders with the use of alfuzosin is generally less than 1.5% based on information from clinical trials (9,15). This percentage is in comparison to 0% of patients in the placebo groups reporting such adverse effects (15). No dose-effect relationship was observed with alfuzosin and the incidence of sexual side effects (23).

Interestingly, data from a preliminary open-label study of 3,076 men with LUTS or BPH have shown that the use of alfuzosin 10 mg daily for one year has resulted in improvements from baseline in ED and ejaculatory disorders ($P<0.001$ for both conditions) (24). The mean improvements from baseline in these two conditions were greater for men with more severe LUTS and BPH at baseline than men with milder symptoms (24). Further, alfuzosin is well tolerated when used in combination with

low doses of PDE5 inhibitors for ED (22). A six-month open label study conducted in 42 men demonstrated that the side effect profile of alfuzosin in combination with tadalafil was similar to that with each agent alone (25).

The effective mechanism through which the alpha1$_A$ selective antagonists cause these symptoms of sexual dysfunction is unknown (9). However, several theories have been proposed. The first theory is that these selective alpha1$_A$ antagonists may affect the emission phase of ejaculation by blocking alpha1$_A$ selective antagonists in the organs involved in this process – the seminal vesicles and the vas deferens (9). The large ratio of tamsulosin selectivity for the α_{1A} receptor subtype over the α_{1B} receptor subtype may explain its increased association with abnormal ejaculation in comparison to other α_1-adrenergic receptor antagonists. A study in rats demonstrated that 3 and 10 μg/kg doses of tamsulosin significantly decreased the amplitude and area under the curve of seminal vesicle pressure in comparison to placebo, while 3 and 10 μg/kg doses of alfuzosin did not (26). As the seminal vesicles are a major contributor to the volume of semen, this effect may an example of some of the EjD observed with the use of tamsulosin (27). Nevertheless, the effect observed in rats may not necessarily carry over to human subjects.

The second theory is that these ABs affect the central nervous system by binding to serotonin and/or dopamine receptors and blocking signals controlling ejaculation. Unlike alfuzosin, tamsulosin crosses the blood brain barrier and may consequently cause sexual dysfunction through blockage of α_1-adrenergic receptors in the central nervous system (26). Thus, patients experience retrograde ejaculation or decreased ejaculate volume. These effects are reversible with drug discontinuation (28). Effects of alpha adrenergic antagonists on blood pressure may also cause ED (15). Tamsulosin has also shown a strong affinity for the 5-HT$_{1A}$ and D_2 receptors which are both involved in the central control of ejaculation (27). This mechanism would again explain the highly reported frequency of abnormal ejaculation with tamsulosin in comparison with other BPH medications.

It has been assumed by many researchers and healthcare providers that the EjD caused by ABs was due to retrograde ejaculation. The previously mentioned study in rats also demonstrated that tamsulosin had a significantly greater inhibitory effect on bladder neck closure and seminal vesicle contractions than alfuzosin (26). Thus, because alpha adrenergic antagonists relax the bladder neck, they may allow semen to flow into the bladder during ejaculation. However, a few studies have found evidence to contradict the idea that tamsulosin causes retrograde ejaculation. A study of 17 Korean urologists demonstrated that treatment with tamsulosin 0.2 and 0.4 mg once daily significantly decreased mean ejaculate volume (17). However, no sperm was found in mid-stream urine collected after ejaculation (17). Another study included 57 healthy volunteers treated for five days with either placebo, tamsulosin 0.8 mg once daily, or alfuzosin XL 10 mg once daily; although mean ejaculate volume decreased in 90% of patients who received tamsulosin, sperm was rarely detected in post-ejaculate urine (16). Tamsulosin also caused anejaculation in 35% of participants while anejaculation was not observed in any of the participants in the alfuzosin or placebo group.

Still, a retrospective analysis of 7,974 men with BPH found that men taking tamsulosin to treat LUTS had better scores on the *Sexual Health Inventory for Men* than those taking other ABs or 5ARIs, especially in those with more severe LUTS (29). These researchers postulated how direct effects of tamsulosin and alfuzosin may be responsible for improvements in sexual functioning. These ideas were based on data from animals and *in vitro* trials, so their relevance in humans is not definitive. In precontracted rat corpora cavernosum, alfuzosin was found to fully relax cavernosal tissue *in vitro* (29). Further, tamsulosin was second only to prostaglandin E_1 in its enhancing effect on small muscle relaxation of the corpus cavernosum of dogs, rabbits, and humans *in vitro* when it was compared to other substances such as phentolamine (29). Thus, the effects of tamsulosin and other ABs on sexual health might not always be negative.

Silodosin

Silodosin (*Rapaflo*) is an α_1-adrenergic receptor antagonist used for treating BPH. It is selective for adrenoceptors in the prostate and bladder. By causing a blockage of these receptors, there is a relaxation of smooth muscle in the bladder neck and prostate, which results in an improvement of urine flow and decreased symptoms of BPH (30). It is dosed once daily with meals, and has a dose reduction for renal impairment (CrCl <50 mL/min). In a 12-week, multicenter, double-blinded, placebo-controlled trial that included 897 patients, and the most common adverse drug reaction due to silodosin was retrograde ejaculation at 28.1%. Although there is a high incidence of retrograde ejaculation due to silodosin, there is no incidence of it causing a decrease in libido. Men using silodosin may experience a "dry orgasm" during sexual activity, due to the semen entering the bladder instead of emerging through the penis during ejaculation. Patients may become nervous if unwarned of this side effect by the physician. However, the

Table 1 Distribution of α adrenoceptors in the bladder neck and prostatic urethra

Location	α adrenoceptors	Reference
Bladder	α_{1A} adrenoceptor (33%)	(32)
	α_{1B} adrenoceptor (53%)	
	α_{1D} adrenoceptor (14%)	
Bladder	α_{1A} adrenoceptor (34%)	(33)
	α_{1B} adrenoceptor (0%)	
	α_{1D} adrenoceptor (66%)	
Bladder	Evidence of α_2 adrenoceptors*	(34)
Urethra	α_{1A} adrenoceptor (100%)	(35)
	α_{1B} adrenoceptor (0%)	
	α_{1D} adrenoceptor (0%)	
Urethra	Evidence of α_2 adrenoceptors**	(36)
Prostate	α_{1A} adrenoceptor (70%)	(37)
	α_{1B} adrenoceptor (0%)	
	α_{1D} adrenoceptor (30%)	
Prostate	Evidence of α_2 adrenoceptors*	(38)

*, denotes absence of ratio; **, denotes experimental finding in non-humans.

orgasm usually stays normal. Post-orgasm urine is cloudy due to mixing of urine with ejaculate.

The major cause of this ejaculatory disorder is considered to be due to the contraction of the seminal vesicle and ejaculatory duct at the time of ejaculation (31). Of the alpha receptor subtypes (α_{1A}, α_{1B}, and α_{1D}) (*Table 1*) that are present in the seminal vesicle and prostate, α_{1A} is considerably more prominent, accounting for 75% of the receptors. It has also been determined that α_{1A} subtype is also responsible for the contraction of the ejaculatory duct (39). In one study conducted in Japan, the ejaculatory process was observed using Doppler technology in males with and without oral silodosin. In the three males that were receiving silodosin, Doppler studies showed that the bladder neck never completely closed during ejaculation, causing the seminal fluid to flow into the bladder, instead of exiting through the urethra. In only one of these three cases did the patient have a small amount of semen exit through the urethral orifice as well as into the bladder. There was no documentation of any seminal fluid traveling into the bladder in those males not using silodosin (40).

5α-reductase inhibitors

Dutasteride

Dutasteride (*Avodart*) is a competitive 5ARI that antagonizes both isoforms of 5α-reductase (41). Dutasteride is indicated alone or in combination with the α_{1A}-adrenergic receptor antagonist tamsulosin for the treatment of men with an enlarged prostate with symptomatic BPH, for symptom improvement, reduction in risk of acute urinary retention (AUR), and reduction in risk for BPH-related surgery (e.g., transurethral resection of the prostate and prostatectomy). The oral formulation of dutasteride is a 0.5 mg capsule administered as a once daily dose, without regard to meals, with or without tamsulosin. Dutasteride is contraindicated in hypersensitivity, pregnancy, women of childbearing potential and in pediatrics, and should not be handled by most of these populations since dutasteride is absorbed through the skin and could results in fetal exposure.

Based on the package insert, common adverse reactions from clinical trials [ARIA 3001, ARIA 3002 (both United States), and ARIA 3003 (19 countries)] in 4,325 men, 2,167 receiving dutasteride, were impotence, decrease in libido, breast enlargement/tenderness, and EjD (41,42). In the combination trial with tamsulosin (CombAT trial), these adverse events occurred more frequently in the combination therapy group with than either monotherapy alone (41). Although ED was the number one cause of treatment discontinuation in all study arms, discontinuation rates were low at only 1–1.5%.

Finasteride

Finasteride (*Proscar*) is the another prominent 5ARI, although finasteride selectively inhibits 5α-reductase type 2, found predominantly in the prostate gland (43,44). Finasteride is indicated alone for the treatment of symptomatic BPH for symptom improvement, reduction in risk of AUR, and reduction in need for surgery, as well as in combination with the α_1-selective antagonist doxazosin (*Cardura*), together indicated to slow the progression of symptomatic BPH. Finasteride is available in 5 mg tablets taken once daily without regard to meals with or without doxazosin. Like dutasteride, finasteride also has the following contraindications: hypersensitivity, pregnancy, women of childbearing age, and pediatrics (43).

In clinical trials, the adverse effects reported were mainly related to sexual function and included impotence, decreased libido, decrease ejaculate volume, EjD, and breast enlargement/tenderness. However, findings of studies

may vary based on setup and criteria. A 2015 study found reduced ejaculation strength and orgasmic function but no significant decrease in sexual desire, which is usually a notorious side effect of 5ARIs (19). A 5-year prospective analysis by Kaplan *et al.* found that the incidence of ED, EjD, and reduced libido was higher with dutasteride (5.1%, 2.4%, 2.7%) compared to finasteride use (2.1%, 1.8%, 1.4%) despite their equality in effectively treating LUTS (45).

Combined therapy of ABs and 5α-reductase inhibitors

In a 2015 study, complete absence of ejaculation was experienced by 23% of patients on combined therapy, but only 15% on tamsulosin and 5% on finasteride (19). In the same study, it was found that erection improved in all three treatment groups. Patients with severe urinary symptoms often identified relief in the act of urination with improved erectile function.

Phosphodiesterase-5 inhibitors

Tadalafil

A study conducted by Hellstrom *et al.* states that tadalafil (*Cialis*) does not induce any detrimental effects on spermatogenesis or testicular function (46). Tadalafil is commonly prescribed for men with ED along with LUTS secondary to BPH (47). McVary and McKenna report a multicenter, randomized, double-blind placebo-controlled study involving 281 men reported to have LUTS secondary to BPH were randomly assigned to once daily 5 mg for 6 weeks, proceeded by an increase in dosage to 20 mg for 6 weeks (12 weeks of placebo) (47). They state that there are decreases in International Prostate Symptom Score (IPSS) in regards to a mean change from baseline to 6 weeks of −2.8 with tadalafil 5 mg compared to −1.2 with the placebo ($P<0.003$), and −3.8 at 12 weeks with tadalafil 5/20 mg compared to −1.7 with the placebo ($P<0.001$) (47). A similar study by Roehrborn *et al.* was conducted using a larger sample size of men with LUTS secondary to BPH and 2.5, 5, 10, and 20 mg of tadalafil (48). An improvement of baseline to endpoint after 12 weeks, IPSS mean change was reported to be −3.9 of 2.5 mg of tadalafil ($P<0.015$), −4.9 for 5 mg of tadalafil ($P<0.001$), −5.2 for 10 mg of tadalafil, and −5.2 for 20 mg of tadalafil ($P<0.001$), compared to −2.3 for the placebo (48). Another study showed a small but statistically significant median maximum urinary flow rate improvement for tadalafil versus placebo (49). The dosage recommended for individuals experiencing LUTS secondary to BPH is 5 mg of tadalafil (48). In fact, a 2015 clinical study observed improvement in approximately two-thirds of their patients, with over 50% reporting after 1 week of therapy and more than 70% after 4 weeks (50). No unexpected adverse events have been reported; no meaningful adverse effects have been observed in visual, auditory, or cardiovascular systems. Tadalafil is also effective in men of different ages, disease severity, prior AB exposure, and prostatic volumes (51). The noted changes in IPSS may have been induced by an increased concentration of the cGMP, resulting in a decrease of prostate muscle tension (7). The effects of nitric oxide (NO) on the smooth muscle of the bladder and the inhibition of PDE in the prostate and the prostatic urethra is documented but not well studied (52). Though the current literature lacks an explicit description of the effect of tadalafil on the prostate, bladder, penis, and LUTS (52), proposed mechanisms for how tadalafil may ameliorate BPH-associated LUTS include: upregulating NO/cyclic guanosine monophosphate activity (for decreasing smooth muscle tension in the prostatic stroma and capsule and attenuating cellular proliferation associated with prostate/bladder hypertrophy), downregulating Rho-kinase and endothelin-1 activity (for increasing smooth muscle relaxation to decrease bladder outlet obstruction and restore erection), modulating autonomic hyperactivity and afferent nerve activity, reducing inflammation, as well as increasing pelvic perfusion and reducing ischemia (to reverse pelvic organ atherosclerosis) (9,53).

Administering tadalafil concomitantly with ABs have been reported to increase hypotension or orthostatic hypotension (54). The PDE5-inhibiting mechanism of tadalafil is similar to that of ABs in regards to peripheral vasodilation. In a study by Kloner *et al.*, the additive effects of tadalafil on two commonly prescribed ABs, doxazosin and tamsulosin, were compared (55). The hypotensive effects of doxazosin were increased by 10 mmHg, while there was no significant change when tamsulosin was taken with tadalafil (55). This hypotensive effect may diminish the ability to produce or maintain an erection. Kloner *et al.* determined that tamsulosin is a safe AB when combined with tadalafil (55). When concurrently administrating other ABs with tadalafil, a great deal of precaution must be taken. An alternative management approach is combining tadalafil with finasteride; a 2015 study found the combination therapy had clinically meaningful improvement in symptoms, great treatment satisfaction, and no report of adverse side effects (56). This combination therapy is well-tolerated, regardless of the presence/absence of ED at treatment

Table 2 α_1-adrenergic antagonists, 5α-reductase inhibitors, and their associated adverse sexual side effects

Drug	Adverse sexual side effects
Tamsulosin (*Flomax*)	Decrease in libido; decrease in erectile function; adverse effects in ejaculation; priapism; deterioration in sexual function
Alfuzosin (*Uroxatral*)	Impotence; decrease in erectile function; priapism
Silodosin (*Rapaflo*)	Retrograde ejaculation; dry orgasm
Dutasteride (*Avodart*)	Impotence; decrease in libido; breast enlargement; breast tenderness; ejaculation disorders
Finasteride (*Proscar*)	Impotence; decreased libido; decrease ejaculate volume; ejaculation disorder; breast enlargement; breast tenderness

initiation (57).

Due to the fact that sexual dysfunction occurs around the same age as BPH symptoms in most men, it is difficult to definitively determine the degree to which different medications used in the treatment of BPH contribute to some symptoms of sexual dysfunction (14). Further, it appears to be difficult to predict which patients will experience sexual dysfunction as a result of the use of medications for BPH (14). Studies that attempted to identify correlation between patient characteristics such as age and prostatic volume have failed to find any associations (14). Direct comparative trials of the various agents used for the treatment of BPH would also be helpful in order to provide more definitive conclusions can be made regarding which agents pose the lowest risk of causing sexual side effects, particularly impotence and decreased libido. Incidence rates of adverse sexual side effects have found to be higher at year 1 of follow-up compared to thereafter for finasteride and the finasteride-doxazosin combination (58), suggesting that the effects early in the course of treatment may later subside. This would be an important precaution for the physician to address to the patient. Also noteworthy is that adverse side effects may be linked to comorbidities typically tied to BPH patients (58). Adverse sexual side effects of select ABs and 5ARIs have been summarized in *Table 2*.

Conclusions

Before the pharmacological therapy for BPH is initiated, it is crucial that the physician discusses potential side effects with the patient so they can comprehend the risks. In some cases, patients may prefer to continue treatment with ABs or 5ARIs regardless of experiencing the sexual side effects. Other options available would be either to decrease the dosage of medication, decrease the frequency, or terminate the treatment completely and instead opt for surgery. Based on the patient's presentation of LUTS and possible sexual dysfunction, the physician may evaluate an alternative class of BPH therapy drugs. The effect of AB on libido and erectile function is similar to that of a placebo, while having different effects on ejaculation. 5ARIs produce sexual side effects and increased risk for ED, EjD, and decreased libido compared to a placebo. Combination therapy with AB and 5ARI triples the risk for EjD incidence compared to that of AB or 5ARI used individually. The phosphodiesterase-5 inhibitor tadalafil is presently a new treatment alternative to other established drugs for LUTS, such as the aforementioned ABs or 5ARIs. However, it is not just an alternative, since sexual adverse events associated with ABs and 5ARIs are avoided; tadalafil is the only drug that can treat both ED and LUTS simultaneously. Nevertheless, objective improvement on LUTS has been met with controversy. Further studies are imperative in gauging the long-term the role of combined therapy of phosphodiesterase-5 inhibitors and ABs or 5-ARIs in the management LUTS/BPH (59).

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