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REVIEW

Pharmacological treatment of lower urinary tract symptoms in benign prostatic hyperplasia: consequences on sexual function and possible endocrine effects

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ABSTRACT

Introduction: Benign prostate hyperplasia (BPH) is one of the most prevalent diseases in aging men. It may adversely affect quality-of-life due to the presence of low urinary tract symptoms (LUTS) and its effects on sexuality.

Areas covered: The impact of α1-blockers, 5α-reductase inhibitors (5-ARI), and phosphodiesterase 5 inhibitors (PDE-5i) on erectile and ejaculatory functions in men with BPH are covered. Endocrinological aspects have also been addressed, including the management of hypogonadism, which affects many patients with BPH, and the impact of the use of 5-ARI use on bone health.

Expert opinion: The adverse-event profile of α1-blockers depends on their affinity for the α1-adrenoceptors rather than selectivity. The probability of ejaculatory dysfunction is highest with silodosin than other nonselective drugs (tamsulosin, alfuzosin, doxazosin, and terazosin). Concerning the impact of finasteride and dutasteride on sexual desire, erectile function, and ejaculation, the vast majority of the studies have shown a low prevalence of treatment-related adverse events. Due to the benefits of erection, PDE5i represents the perfect class of drugs for the treatment of LUTS-BPH in patients with erectile dysfunction. Testosterone replacement therapy could be considered in some hypogonadal patients with BPH. Finally, current evidence support the safety of 5-ARI on bone tissue.

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1. Introduction

Benign prostate hyperplasia (BPH) is one of the most prevalent disorders in aging, heavily affecting the quality-of-life, mainly due to the presence of low urinary tract symptoms (LUTS). Notably, sexual dysfunction frequently occurs in patients with LUTS-BPH. The aim of this article was to review the evidence of the main drugs used for the treatment of BPH [α1-blockers, 5α-reductase inhibitors (5-ARI)] and their impact on the sexual function. The role of phosphodiesterase 5 inhibitors (PDE-5i) on erectile and ejaculatory functions in men with BPH was also covered. Finally, associated comorbidities of endocrinological relevance, such as hypogonadism and the impact of 5-ARI on bone health in patients with LUTS-BPH are discussed.

2. Pharmacological options provided by the current guidelines

The current European Association of Urology (EAU) guidelines recommend the use of α1-adrenoceptor (α1-blocker) antagonists, 5-ARI, muscarinic receptor antagonists, and PDE5i for the treatment of LUTS in men. Particularly, α1-blockers are considered as the first-line therapy and are used in the presence of moderate-to-severe symptomatology. This class of drugs is considered an excellent choice due to the rapid onset of action, their efficacy, and the low frequency and severity of adverse events. The mechanism of action of α1-blockers is to inhibit the effect of norepinephrine released endogenously on smooth muscle cells of the prostate; thus, this reduces the tone of the prostate and the consequent urethral obstruction [1]. Controlled studies show that α1-blockers generally reduce the International Prostate Symptom Score (IPSS) by approximately 30–40% and increase Qmax by approximately 20–25% [2,3]. The most frequent adverse events are orthostatic hypotension, the appearance of IFIS (intraoperative iris floppy syndrome), and ejaculatory dysfunction [4–6].

Another therapeutic option suggested by the EAU is 5-ARI. The mechanism of action of this class of drugs is based on the blockade of the enzyme 5α-reductase, which converts testosterone (T) into dihydrotestosterone (DHT), the hormone that mediates the effects of androgens on the prostate. Two 5-ARIs are available for clinical use: finasteride and dutasteride. The former selectively inhibits 5α-reductase type 2, while the latter inhibits both 5α-reductase type 1 and 2. 5-ARIs induce apoptosis of prostate epithelial cells [7] leading to a reduction in prostate size by approximately 18–28% and decrease serum PSA levels by approximately 50% after six-twelve months of treatment [8]. 5-ARI treatment should be recommended for patients with moderate-to-severe LUTS and enlarged prostate (>40 ml). Differently from α1-blockers, 5-ARI can prevent prostate enlargement and the appearance of acute urinary retention. 5-ARI therapy should be pursued for at least 1-year due to the slow onset of its action; the effects of 5-ARI on serum

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Article highlights

- The probability of ejaculatory dysfunction is highest with silodosin than other non-selective drugs (tamsulosin, alfuzosin, doxazosin, and terazosin).
- Finasteride and dutasteride are well tolerated.
- Phosphodiesterase 5 inhibitors (PDE5i) are effective for the treatment of LUTS-BPH in patients with erectile dysfunction.
- Testosterone replacement therapy (TRT) can be considered in hypogonadal patients with non-obstructive BPH.
- 5α-reductase inhibitors (5-ARI) are not harmful to bone tissue.
- This box summarizes the key points contained in the article.

PSA concentration should be considered in connection with prostate cancer (PCa) screening. Combination therapy may be considered in patients with moderate-to-severe LUTS and at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, higher post-urination residue, lower Qmax). In fact, this involves a greater improvement of LUTS and an increase in Qmax, compared to monotherapy [9]. In selected cases where bladder storage LUTS are present, the EAU guidelines recommend the use of muscarinic receptor antagonists.

Muscarinic receptor antagonists act by blocking the muscarinic receptors present on smooth muscle cells, thereby reducing irritative LUTS (urgency, frequency, or urge incontinence). However, muscarinic receptors are also present on other cell types, such as urothelial cells of the bladder, epithelial cells of the salivary glands, and of the central/peripheral nervous system. Side effects include dry mouth (up to 16%), constipation (up to 4%), difficulty urinating (up to 2%), nasopharyngitis (up to 3%), and dizziness (up to 5%). These drugs increase the volume of the bladder at the first contraction of the detrusor and the maximum cystometric capacity and decrease the contractility index of the bladder; however, the Qmax does not change. Due to the risk of urinary retention with the use of antimuscarinic drugs, the EAU guidelines recommend avoiding their use in patients with a post-empty residual volume>150 ml [10,11]. The combined use of α-blockers and antimuscarinics exposes the patient to the adverse effects of both drugs. Therefore, the guidelines recommend their use only when the patient has moderate-to-severe LUTS and if the relief of the symptomatology has been insufficient with monotherapy with one of the two drugs.

Relaxation of the detrusor can also be achieved by activating the ß3-adrenoceptors, expressed on several bladder structures, including the smooth muscle cells of the detrusor. The only drug of this class is mirabegron 50 mg, which has shown significant efficacy in the treatment of overactive bladder symptoms, including urination frequency, urgency, and urinary urge incontinence [12]. There is no evidence from the existing literature that mirabegron improves symptoms in combination with other drugs [13].

For some years, PDE5i has been included in the EAU guidelines for the treatment of LUTS. Their exact mechanism of action on LUTS remains unclear. Likely, they increase the intracellular cyclic guanosine monophosphate, thus reducing the regular muscle tone of the detrusor, prostate, and urethra and improving blood perfusion and oxygenation in the lower urinary tract [14]. To date, only tadalafil, 5 mg once daily, has been officially approved for the treatment of male LUTS with or without ED. Studies in the literature have shown that PDE5is improve both IPSS and IIEF scores, but have no effect on Qmax [15]. Side effects include headache, pyrosis, back pain, flushing, and nasal congestion. Combining tadalafil with an α-adrenergic blocker or nitrate can cause symptomatic hypotension [16]. Figure 1 illustrates the vasodilatory effects of α-blockers, PDE5is, and combination therapies.

Effects of α-blockers and PDE5i administered alone or in combination with headache, dizziness, and hypotension. Results of the studies by Gacci and coll [15], Wang and coll [17], and Sun and coll [18] are shown.

To date, phytotherapy has often been used as optional therapy or in combination with other drugs. However, the panel of

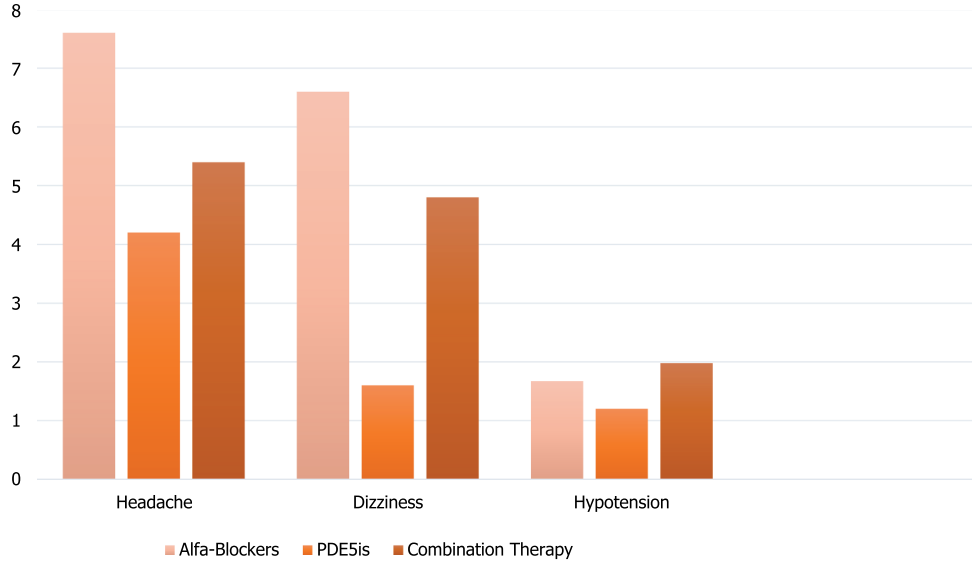

Figure 1. Adverse effects of α-blockers and phosphodiesterase 5 inhibitors (PDE5is).

guidelines does not make specific recommendations on herbal medicine for the treatment of male LUTS due to the heterogeneity of the products, the limited regulatory framework and the methodological limits of the published studies and meta-analyses [19].

3. α-Blocker administration and ejaculatory function

α-Blockers are the most widely used drugs in the treatment of symptomatic benign prostatic hyperplasia for their ability to block α1-adrenoceptors in the prostate, leading to relaxation of the prostatic smooth muscles with consequent improvement of dysuria and urinary flow [20]. Prostatic smooth muscles are not the only urological target of these drugs. A study on rat tissues has shown that α1-blockers (tamsulosin, silodosin, alfuzosin, and naftopidil) inhibit noradrenaline-induced contraction also in seminal vesicles, vas deferens, and bladder trigone [21]. This effect is responsible for ejaculatory disorders (anejaculation and decreased semen volume) that are frequent side effects of α-blocker administration [22]. Originally, bladder neck relaxation with consequent retrograde ejaculation was thought to be the mechanism by which α1-blockers are responsible for ejaculatory disorders [23]. More recently, Naguchi and colleagues, in a study on male dogs, showed that α1-blockers have a higher inhibitory effect on vas deferens than on posterior urethra [24]. It has been hypothesized that the consequent pressure difference between prostatic urethra and vas deferens may contribute to the development of ejaculatory disorders [25]. In addition, a decreased contractility of seminal vesicles contributes to semen volume reduction during α1-blocker administration. A study on healthy male volunteers showed that tamsulosin decreases not only ejaculatory volume but also fructose level and pH, indicating a dysfunction of the seminal vesicles. This effect is soon reversible after withdrawal of the treatment and, accordingly, the ejaculatory function can be restored by discontinuing these drugs for 24–36 hours [23]. In the same study, no spermatozoa were found in midstream urine after ejaculation, demonstrating that a loss of seminal emission rather than retrograde ejaculation is responsible for ejaculatory dysfunction [23]. A central action of tamsulosin on dopaminergic and serotonergic receptors has also been hypothesized [26]. The inhibitory effect on smooth muscles of genital tract is class-related and dose-dependent, and its magnitude depends on affinity for α1-adrenoceptors rather than selectivity [21]. These pharmacodynamic features are responsible for the differences in the adverse-event profiles of α1-blockers. The 2003 American Urology Association (AUA) guidelines reported a higher probability of ejaculatory dysfunction with tamsulosin than alfuzosin, doxazosin, and terazosin [27]. In the update of the same guidelines, authors state that the risk of ejaculatory disturbance associated with tamsulosin is lower in more recent studies because of the use of alternative metrics to gauge dysejaculation. However, they affirm that alfuzosin, a nonselective α1A-receptor blocker, has a more favorable profile on ejaculatory adverse effects [28]. Another recent study reported the opposite: in 80 young and middle-aged patients with benign prostatic hyperplasia, alfuzosin caused ejaculatory dysfunction more frequently than the selective α1A-adrenoceptor blocker tamsulosin [17]. This finding could confirm the low influence of receptor selectivity on the development of ejaculatory disorders. These data are in accordance with the previously mentioned study by Noguchi and colleagues in which the greater inhibitory effect on vas deferens was described for silodosin followed by naftopidil, alfuzosin, tamsulosin, and prazosin [24]. Conversely, the dose-dependent action of α1-blockers is well established. For example, it has been shown that 5 days of treatment with daily high doses of tamsulosin (0.8 mg) in healthy adult men decreased significantly the ejaculate volume in almost 90% of subjects and caused anejaculation in about 35% of them [29]. Instead, in patients with BPH, a prolonged low-dosage treatment with tamsulosin (0.2 mg daily for 12 weeks) caused ejaculatory dysfunction in about 13.4% of patients [30]. Among α1-blockers, doxazosin showed a minimal negative impact on ejaculatory function compared to placebo [31]. Conversely, the highest rate of ejaculatory dysfunction has been reported with silodosin, a compound with high affinity and selectivity for α1A-receptors [32]. A cohort study on 137 sexually active patients with BPH revealed that anejaculation and hypoposia are present in 48% and 23% of patients treated with silodosin [26]. In the same study, ejaculatory dysfunctions were associated with decreased or absent orgasmic feeling in 17% of cases. In our experience (data not published) the impact of ejaculatory dysfunction with silodosin is significantly higher. Patients with both ejaculatory and orgasmic dysfunction were the younger ones [26]. The alteration of orgasmic function may be due to the decrease in the number of bulbocavernosus/pelvic floor muscle contractions that, together with the passage of semen through the urethra, contribute to the subjective pleasure of orgasm [33]. By contrast, a systematic review and a meta-analysis suggested that doxazosin and terazosin are associated with a risk of ejaculatory dysfunction similar to placebo; treatment with alfuzosin is associated with a low risk, while tamsulosin and silodosin have the worst risk profile (OR 8:58 and 32.5, respectively) [34,35]. The combination therapy with α1-blockers and 5-ARIs seems to have a more detrimental effect on ejaculatory function than monotherapy [31]. A recent meta-analysis of five studies including 4348 patients confirmed that combination therapy with tamsulosin plus dutasteride has a higher incidence of ejaculation disorders compared to monotherapy with tamsulosin [36]. Lately, the inhibitory effect of α-blockers on ejaculatory function has been investigated in the management of premature ejaculation (PE) resistant to first-line therapy. A preliminary study showed that these drugs could increase intravaginal ejaculatory latency time (IELT) up to threefold and are particularly effective in the treatment of acquired PE [37–39].

4. Impact of 5α-reductase inhibitors on sexual function

5-ARIs, mainly including finasteride and dutasteride, represent a class of drugs which competitively inhibit 5-alpha reductase isoenzymes (5-ARs). In humans, three types of 5-ARs have been described so far: type-1 is temporarily expressed in newborn skin and scalp and is permanently detectable in skin after

puberty onset; type-2 localizes predominately in fetal genital skin and male accessory glands including prostate [40]; type-3 is expressed both into androgen-dependent tissues (e.g. smooth muscle and prostate) and in brain, heart, and other peripheral tissues [41].

In vitro experiments have shown a higher inhibitory activity of dutasteride on type 3 than type 2 5-ARs. By contrast, these isoenzymes are similarly sensitive to finasteride [41]. Several mechanisms have to be considered when the impact of 5-ARIs on sexual function is considered. First of all, dihydrotestosterone (DHT) more effectively than T enhances nitric oxide (NO) availability in the endothelium [42]. Thus, 5-ARIs can indirectly reduce the peripheral amount of NO concentration and, consequently, have a negative impact on erection. The reduction in DHT explains the reduced volume of ejaculate experienced by treated patients and, in addition, these drugs are able to prevent the conversion of progesterone and deoxycorticosterone into neurosteroids, the latter playing a role in regulating mood, anxiety, sleep, and sexual function [43,44]. Finally, finasteride can exert a central effect by crossing the blood-brain barrier and reducing the hormonal impregnation of the central nervous system [45,46]. Epidemiological studies report an association between LUTS and ED, which share common pathogenic factors such as sex steroid ratio imbalance and chronic inflammation [47]. Furthermore, approximately 20% of patients with benign prostate hyperplasia (BPH) display low T levels, which contributes to the pathogenesis of ED [48–50]. Several randomized double-blind, placebo-controlled clinical trials have been conducted to evaluate the effect of 5ARIs on sexual function (mainly sexual desire, erectile function, and ejaculation) in patients with BPH. As shown in Table 1, the vast majority of these studies have shown a low prevalence of treatment-related adverse events. Both finasteride and dutasteride are almost well tolerated. Furthermore, resolution of sexual disorders, if any, has been described in 50% and 41% of patients treated with finasteride or dutasteride, respectively, after treatment discontinuation [51]. This is in line with the findings of studies performed in patients with baldness who

Table 1. Effects of treatment with 5α-reductase inhibitors on sexual function in patients with benign prostate hyperplasia.

Authors	Study design	Study duration	Sample size	Drug, daily dosage	Hypoactive sexual desire	Erectile dysfunction	Ejaculatory disorders
Roehrborn et al., 2002 [59]	Single-blind, placebo-controlled	24 months	2951	Dutasteride, 0.5 mg	0.6% vs. 0.3%	1.7% vs. 1.2%	0.5% vs. 0.1%
Clark et al., 2004 [114]	Randomized, placebo-controlled	24 weeks	399	Dutasteride, 0.5 mg[a] Finasteride, 5 mg	11% vs. 2% 13% vs. 2%	5% vs. 3% 11% vs. 3%	NR
Debruyne et al., 2004 [56]	Randomized, double-blind, placebo-controlled	2 years	4324	Dutasteride, 0.5 mg	0.6% vs. 0.5%	1.7% vs. 1.2%	0.5 vs. 0.1%
Amory et al., 2007[c] [115]	Randomized, double-blinded, placebo-controlled	1 year	33 34	Dutasteride, 0.5 mg Finasteride, 5 mg	6.1% vs. 6.3% 8.8% vs. 6.3%		
Andriole et al., 2010[b] [60]	Multicenter, randomized, double-blind, placebo-controlled	4 years	8231	Dutasteride, 0.5 mg	3.3% vs. 1.6%	9% vs. 5.7%	NR
Na et al., 2012 [61]	Randomized, double-blind, parallel-group, placebo-controlled	12 months	253	Dutasteride, 0.5 mg	0% vs. 1%	2% vs. = %	NR
Gormley et al., 1992 [62]	Double-blind, placebo-controlled	12 months	298	Finasteride, 1 mg	4.7% vs. 1.3%	3.4% vs. 1.7%	4.4% vs. 1.7%
			297	Finasteride, 5 mg	6% vs. 1.3%	5% vs. 1.7%	4.4% vs. 1.7%
Byrnes et al., 1995 [63]	Double-blind, placebo-controlled	1 year	2342	Finasteride, 5 mg	2.9% vs. 1%	5.6% vs. 2.2%	2.1% vs. 0.5%
Nickel et al., 1996 [64]	Double-blind, parallel-group, placebo-controlled, multicentre, prospective randomized	2 years	613	Finasteride, 5 mg	10% vs. 6.3%	15.8% vs. 6.3%	7.7% vs. 1.7%
Tenover et al., 1997 [65]	Randomized, double-blind	12 months	2112	Finasteride, 5 mg	5.4% vs. 3.3%	8.1% vs. 3.8%	4% vs. 0.9%
Marberger et al., 1998 [66]	Multicenter, double-blind, randomized, placebo-controlled	2 years	3168	Finasteride, 5 mg	4% vs. 2.8%	6.6% vs. 4.7%	2.1% vs. 0.6%
McConnell et al., 1998 [67]	Double-blind, randomized, placebo-controlled	4 years	3040	Finasteride, 5 mg	2.6% vs. 2.6%	5.1% vs. 5.1%	0.2% vs. 0.1%
Lowe et al., 2003 [68]	Randomized, placebo-controlled	6 years	1105	Finasteride, 5 mg	3.8% vs. 2.3%	4.8% vs. 1.8%	3.1% vs. 1.1%
McConnell et al., 2003 [10]	Double-blind, placebo-controlled	4.5 years	1505	Finasteride, 5 mg	2.4% vs. 1.4%	4.5% vs. 3.3%	1.8% vs. 0.8%
Thompson et al., 2003[b] [69]	Randomized, placebo-controlled	7 years	18,882	Finasteride, 5 mg	65.4% vs. 59.6%	67.4% vs. 61.5%	67.4% vs. 61.5%
Proscar, 2004 [70]	Placebo-controlled study	1 year	NA	Finasteride, 5 mg	6.4% vs. 3.4%	8.1 vs. 3.7%	0.8% vs. 0.1%
Corona et al., 2012 [71]	Retrospective study	–	3837	Dutasteride, 0.5 mg or Finasteride, 5 mg	51.1% vs. 32.3%	74.5% vs. 66.0%	19.1% vs. 17.8%

aIn this study, data on Dutasteride 0.01, 0.05, 0.5, or 2.5 mg daily are also available.
bStudies performed on patients at risk for prostate cancer.
cDutasteride group reported impotence, hypoposia and decreased libido, Finasteride group reported impotence and mood swings, Placebo group reported decreased libido, gynecomastia, mental status change. **Abbreviations**: NA, not available; NR, not reported.

generally are prescribed finasteride at the dose of 1 mg daily [52–54]. In contrast, a meta-analysis on 23 studies carried out in patients with LUTS-BPH found a twofold higher risk of ejaculatory disorders in patients treated with finasteride (OR 2.70; $p < 0.0001$) or dutasteride (OR 2.81; $p = 0.0002$) compared with placebo [34]. However, much of the evidence is not based on validated structured questionnaires (e.g. IIEF-5), but on patients' self-report, which seriously compromises the reliability of the results. Some authors have found a greater prevalence of adverse events at the beginning of treatment and a subsequent decline of their frequency over the time [55,56]. Therefore, a nocebo effect in the pathogenesis of these disorders cannot be totally excluded. Accordingly, results from a study in patients with BPH and a good sexual performance at baseline who received finasteride at the daily dose of 5 mg for 12 months showed that patients who received information about the possible sexual treatment-related adverse events showed a significantly higher frequency of sexual symptoms, i.e. hypoactive sexual desire (23.6% vs. 7.7%, $p = 0.04$), ED (30.9% vs. 9.6%, $p = 0.02$) and a trend toward a higher frequency of ejaculate dysfunction (16.3% vs. 5.7%, $p = 0.06$) [57]. The effects of the simultaneous administration of finasteride and α-blockers (combination therapy) on sexual function have also been studied. A four-year prospective multicentre, randomized, placebo-controlled, double-blind study on 2783 patients with BPH evaluated the impact of 5-ARIs on sexual function using the Brief Male Sexual Function Inventory (BMSFI). Treatment with finasteride, alone or in combination, was found to worsen sexual function more than doxazosin alone (the latter having a minimal impact) [31]. Similarly, a systematic review with meta-analysis of five randomized controlled trials (overall including 6131 patients) concluded that the combination therapy is associated with a greater risk of ED but not of sexual desire alterations compared to monotherapy with 5-ARIs [58].

5. Benefits of PDE5i daily administration on sexual function

Four types of oral phosphodiesterase 5 (PDE5i) inhibitors have been developed for erectile dysfunction: sildenafil, tadalafil, avanafil, and vardenafil. For all PDE5is, men must take medications on demand prior to sexual activity [72,73]. Contrary to sildenafil, avanafil, and vardenafil, tadalafil is rapidly absorbed after oral administration and has a longer half-life (17.5 h). Steady-state plasma concentrations are reached after 5 days of administration once a day [74,75]. Therefore, its daily use has been proposed for the treatment of ED, at the dose of 2.5 and 5 mg, providing a therapeutic option of efficacy and continuous duration compared to the necessary dosage. ED/LUTS secondary to benign prostatic hyperplasia (BPH) can have a profound impact on the quality of life [76] and often occur in older males [77]. It is estimated that 70% of males with LUTS/BPH have simultaneous ED [78]. The association between ED and LUTS has previously been demonstrated in various large-scale community-based studies [79]. PDE5i have always been used for the treatment of ED, increasing the signaling of nitric oxide in the genitourinary tract tissues, which causes calcium-dependent vascular smooth muscle relaxation and increased blood flow. Recently it has been suggested that the same mechanism of action may be involved in the amelioration of BPH symptoms [80,81]. Currently, daily tadalafil is the only FDA approved PDE5i for the treatment of BPH. Patients suffering from LUTS/BPH and ED can derive maximum benefit from this treatment, although the real limit of this class of drugs is the high cost.

The first-line treatment of medical management of LUTS secondary to BPH is α-1 blocker and 5-ARI. However, especially in young patients, the side effect on sexual function is of concern for both the patient and the doctor, who tends to reduce the use of 5-ARI whenever possible. Therefore, tamsulosin can be useful and safe for the treatment of LUTS secondary to BPH with or without ED. The daily dosage of tadalafil, with the same efficacy, can provide a spontaneous approach to sexual intercourse and better sexual satisfaction [82]. Additionally, daily administration may also have positive psychological and emotional impacts giving the patient more spontaneity, with add-on effects on cytostructural cavernous erectile tissue and metabolic parameters [83]. In fact, Mostafa and colleagues [84] reported on better cavernous architecture with significant morphometric increases in the percentage area of smooth muscles and elastic tissue and a significant decrease in fibrous tissue once tadalafil was chronically administered. The potential further advantage of using PDE5i in patients with ED and BPH is that with a single pill they are treated both bladder outlet obstruction and LUTS, therefore potentially improve compliance with medical care reducing the number of medications patients need to take. Therefore, PDE5-i can be perfect drugs for the treatment of LUTS secondary to benign prostatic hyperplasia associated or not associated with ED and also in young patients.

6. Management of hypogonadism in patients with BPH

The prevalence of hypogonadism in patient with BPH is significant. Data from Medical Therapy of Prostatic Symptoms (MTOPS) Study have shown that, overall, one out of four patients with LUTS and BPH has low T levels. In these patients, the prevalence of hypogonadism increases proportionally with body mass index (BMI) [85]. Untreated low T levels in aging male may be responsible for the impairment of many organic functions such as sexual, metabolic (increased visceral fat, insulin-resistance, risk for diabetes), neurocognitive, and cardiovascular function, bone homeostasis (low bone mineral density and consequent increased risk of fracture), sleep-wake rhythm and fitness [86]. Furthermore, the reduction of total T/17ß-estradiol (T/E_2) ratio in patients with hypogonadism, especially in those with high BMI, may be an adjunctive risk factor for the progression of BPH and LUTS. Indeed, the binding of estrogens with ER-α receptors, located in prostate stromal cells, is associated with prostate hyperplasia and inflammation [87]. On the other hand, the therapy for BPH itself may worsen hypogonadism, i.e. 5-ARIs use that has a negative impact on metabolic function (fat accumulation in the liver, increased glucose synthesis, and insulin resistance) [88]. Furthermore, the increased function of liver enzymes

contributes to the decrease of circulating T levels, worsening ED, and quality-of-life of the patients [89].

For a long time, BPH and LUTS have been considered a relative contraindication to T replacement therapy (TRT). However, more recent studies have confuted the theory that hexogen androgens worsen prostate hypertrophy [86]. The saturation model has been proposed to explain the influence that T exerts on the prostate. It states that prostate androgen receptors are sensitive to T up to a saturation point, corresponding to about 250 ng/dL [90,91]. Therefore, although TRT is able to increase PSA levels in hypogonadal patients, further increases in T levels would not result in an additional rise in cellular proliferation and PSA production [91]. Thanks to this new concept, in recent years, efficacy and safety of TRT have been tested in patients with BPH, either alone or in combination with 5-ARIs and α1-blockers. A meta-analysis of 14 trials involving 2029 participants, aimed to establish if TRT may exacerbate LUTS in patients with late-onset hypogonadism (LOH), revealed no difference in the IPSS score between patients receiving TRT versus placebo [92]. A systematic review of 35 trials on hypogonadal men with BPH or LUTS receiving TRT showed that, in most of cases, no significant prostate growth or worsening of symptoms was described. On the contrary, some studies showed an improvement of LUTS, especially in patients with metabolic syndrome. However, two-thirds of the reviewed studies did not include patients with severe-range lower urinary tract symptoms [93]. More recently, data from the Registry of Hypogonadism in Men (RHYME) confirmed that TRT is not a risk factor for LUTS/BPH progression. Patients receiving TRT showed no differences in PSA levels, total IPSS, or IPSS obstructive sub-scale scores compared to untreated men, while they showed lower IPSS irritative sub-scale scores [94].

A recent study compared the efficacy of combination therapy consisting of silodosin plus Androgel 1% (T) versus monotherapy with silodosin alone in patients with BPH. After 6 months, the combination therapy caused a slight increase in prostate volume (from 55.1 to 61.3 cm^3), but improved sexual function, ameliorated urine flow rate and decreased PSA levels, residual urine volume, waist circumference, and body mass index than silodosin alone [95]. Another similar study showed that patients with LOH achieve a substantial improvement in the quality-of-life receiving TRT, compared with a control group treated with only α-blockers [96].

As far as the combination therapy with T and 5-ARIs, a meta-analysis of five studies involving a total of 250 patients, comparing the effects of T plus a 5-ARIsversusT plus placebo, showed that the combined therapy does not lead to prostate growth [97]. A review examining the literature on TRT in patients taking 5-ARIs concluded that this combination appears to be safe and efficacious [98]. The scientific evidence available to date is in favor of the use of TRT in patients with mild-moderate BPH and hypogonadism [86]. However, studies are lacking in the severe forms of BPH/LUTS that remain a relative contraindication to T administration. In these patients, alternative treatment may be considered.

In patients with moderately low total T concentrations and high BMI, the imbalance of T/E_2 ratio may be responsible for a worsening of LUTS. Aromatase inhibitors are drugs that block the conversion of androgens into estrogens. These compounds have been shown to be able to reduce estradiol concentrations and weaken the negative feedback exerted by estrogens on the hypothalamic–pituitary–gonadal axis, thus increasing LH secretion, T levels, and T/E_2 ratio [99]. Furthermore, in veterinary medicine, the aromatase inhibitor anastrozole is a safe and effective alternative medical treatment for dogs with BPH [100]. Clinical evidence recently suggested a safe role for aromatase inhibitors in the management of male infertility [101]. A randomized placebo-controlled trial firstly assessed the long-term effects of aromatase inhibitors on the prostate volume, administering transdermal T gel (5 g), oral anastrozole (1 mg), or placebo daily for 12 months. The results showed that prostate volume significantly increased by 4.5 ml only in the T group and not in the anastrozole one, despite T serum levels where comparable in all groups, thus suggesting that the trophic effect of T on prostate is mediated by the aromatization into estrogens [102]. This evidence suggests that anastrozole may be used as a possible treatment of BPH since no detrimental effect on the prostate tissue has been observed after a 12-month-long administration [102]. However, additional studies are needed to confirm these findings. Human chorionic gonadotropin (hCG) is a glycoprotein that exerts an LH-like effect, leading to an increase in T concentration. It is used in the treatment of central hypogonadism when the administration of T is contraindicated (e.g. in men seeking fertility) [99]. hCG receptors are present in prostate cells where they seem to exert a growth modulating action [103]. Only one study evaluated the effect of hCG on LUTS. Authors found that the treatment with low-dose hCG achieved an improvement in AUA scores and sexual function in patients with moderate-to-severe BPH symptoms, with no changes in PSA or prostate volume [104].

Nowadays, new drugs are being studied for the treatment of BPH and hypogonadism. Selective androgen receptor modulators (SARMs), similarly to selective estrogen receptor modulators, are compounds that exert varying degrees of both agonist and antagonist effects on the androgen receptor in different tissues [105,106]. Several new SARMs (S-40,542, S-1, S-4) have been tested in a rat model of BPH where they have shown to be as effective as 5-ARIs in decreasing prostate volume with less adverse effects linked to the induced state of hypogonadism [106]. Further studies are needed, but the results would look promising.

7. Impact of 5α-reductase inhibitors on bone health

Patients with osteoporosis show a reduced DHT concentration compared to those with normal bone mineral density (BMD) [107,108]. Type 1 5-AR is expressed in osteoblasts [109–111] and its activity has been found to be inhibited by in vitro estrogen incubation [112]. On these premises, the role of 5-ARIs on bone metabolism has been investigated. A population-based nested case–control study found a 1.52-fold higher risk to diagnose osteoporosis in patients with BPH treated with finasteride compared to those who did not receive any treatment [113]. These findings suggest that finasteride may be involved in the pathogenesis of osteoporosis. Dutasteride has a greater potency compared to finasteride since it is capable of reducing DHT

concentration by 90–95% vs. 70–75% of finasteride [108,114,115]. This led to compare the effects of dutasteride and finasteride on bone health. A recent population-based retrospective cohort study on 31,615 patients found a lower incidence of osteoporosis in patients treated with dutasteride than in those treated with finasteride [2.2 vs. 2.6 per 100-person year; hazard ratio (HR) 0.82; 95% confidence interval (CI) 0.72 to 0.93] [116]. However, the statistical significance disappeared following adjustment for potential confounders. Hence, overall, no difference was found between the two drugs, thus suggesting that dutasteride does not affect bone metabolism greater than finasteride [116]. Similarly, some studies have questioned the true role that DHT and 5-ARIs have on bone metabolism. Accordingly, T replacement therapy, alone or in combination with finasteride, has been shown to increase BMD in older hypogonadal patients, possibly suggesting that DHT is not essential for the effect of T on BMD [117]. Likewise, a rodent spinal cord injury model, the administration of T plus finasteride prevented chronic cancellous bone deficits [118]. A population-based case–control study on 7076 patients aimed at assessing the impact of 5-ARIs on hip fracture risk did not find any association [119]. Finally, a nationwide cohort study of all Swedish patients who used 5-ARIs found an unaltered risk of fractures and falls during the period of prescription [120]. In conclusion, no definite study has proven the role of 5-ARI on the etiology of osteoporosis or bone fracture risk. Thus, 5-ARIs show a safe profile in the majority of the studies.

8. Expert opinion

First-line therapy for BPH/LUTS syndrome is represented by α1-adrenoreceptor blockers. The adverse-event profile of these drugs depends on the affinity rather than selectivity for the α1A-adrenoceptor. Hence, the probability of ejaculatory dysfunctions is highest with silodosin than with other drugs with lower affinity for this receptor subtype (tamsulosin, alfuzosin, doxazosin, and terazosin). However, classifying these patients by age (older vs. younger) and sexual activity (present or not), the use of PDE5is should be considered even if this is more expensive especially when BPH/LUTS coexists with ED. Indeed, due to the benefits of erection, PDE5i represents the most advantageous class of drugs for the treatment of LUTS-BPH in patients with ED. Interestingly, remarkable effects of daily PDE5is on body composition and endothelial function other than sexual improvements are reported [121] and suggest a pleiotropic beneficial effect of these drugs. LUTS-BPH often associates with metabolic syndrome, although the exact mechanism has not been clarified yet. Molecular studies address to insulin a role in prostatic hyperplasia and inflammation [122]. Also, insulin-resistance is a predictive factor of LUTS development, likely due to the close association between the hyperactivity of the autonomous nervous system (which involves the α-adrenergic pathway) and hyperinsulinemia [123]. Data coming out from the Third National Health and Nutrition Examination Survey (NHANES III), involving 2,372 patients, also reveal the association between hypertension and LUTS-BPH [124]. BMI has been demonstrated as a predictor of LUTS development, as confirmed by an analysis of 21,694 patients [125]. In addition, the second Nord-Trondelag Health Study, involving 21,694 patients, showed a higher risk for LUTS in patients with diabetes mellitus than in non-diabetic men [125], being the risk of BPH even fourfold higher in diabetic patients with high LDL cholesterol serum levels [126]. Taken together, these data strongly highlight the close association between LUTS-BPH with metabolic abnormalities and cardiovascular risk factors which has been ascribed by some authors to the male equivalent of polycystic ovarian syndrome (PCOS) occurring in these men [127–129]. In this view, the role of PDE-5i on metabolism and endothelial dysfunction deserves to be promoted and further addressed by focused studies.

According to guidelines, 5-ARI treatment (alone or in combination with α1-blockers) should be considered in older patients with prostate volume greater than 50 mL where a significant reduction of prostate volume is expected after long-term use. Concerning the impact of finasteride and dutasteride on sexual desire, erectile function, and ejaculation, the vast majority of the studies have shown a low prevalence of treatment-related adverse events, being both almost well tolerated. However, they should be used cautiously because of their possible metabolic and reproductive adverse events, i.e. hypogonadism, that may be reverted by appropriate hormonal-specific treatments. Finally, few reported have been reported so far on the effects of these drugs on bone metabolism, the majority of these supporting the safety of 5-ARI on the bone tissue. This issue deserves to be further investigated in order to better assess the 5-ARI-related adverse events.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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