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Review

Sexual Dysfunction and Lower Urinary Tract Symptoms (LUTS) Associated with Benign Prostatic Hyperplasia (BPH)

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Abstract

Sexuality is an essential aspect of a couple's relationship and has a significant impact on life satisfaction. Benign prostatic hyperplasia (BPH) is a condition that commonly affects older men and is often associated with lower urinary tract symptoms (LUTS) and sexual dysfunction. Men with moderate-to-severe LUTS are at increased risk for sexual dysfunction, including moderate-to-severe erectile dysfunction (ED), ejaculatory dysfunction (EjD), and hypoactive desire (HD). The results of several recent large-scale studies have shown a consistent and strong relationship between LUTS and both ED and EjD. It appears that the pathophysiological mechanisms of LUTS and the related prostatic enlargement of BPH as well as certain treatments for this condition may have an impact on both the erection and ejaculation components of the sexual response. Validated questionnaires that assess sexual function provide clinicians with valuable information to help guide treatment selection decisions. Effective medical therapies for LUTS associated with BPH include α_1-adrenergic receptor antagonists (i.e., alfuzosin, doxazosin, tamsulosin, and terazosin) and 5α-reductase inhibitors (i.e., finasteride and dutasteride). The side effects of these medications, including sexual dysfunction, are important distinguishing features. The successful management of patients with LUTS associated with BPH should include assessments of sexual function and monitoring of medication-related sexual side effects. For men with LUTS and sexual dysfunction, an appropriate integrated management approach, based on each patient's symptoms and outcome objectives, is warranted.

Keywords: Benign prostatic hyperplasia; Lower urinary tract symptoms; Sexual dysfunction; Impotence; Erectile dysfunction; Ejaculatory dysfunction; Medical therapy

1. Introduction

Until recently, it was widely assumed that symptoms of male sexual dysfunction, including erectile dysfunction (ED; persistent inability to achieve and maintain an erection sufficient for satisfactory sexual performance [1]), ejaculatory dysfunction (EjD; any disturbance in the male ejaculatory reflex, including loss of ejaculation, ejaculation with a decreased amount of semen, premature ejaculation, delayed ejaculation, and retrograde ejaculation [2]), and hypoactive desire (HD; loss of desire or decreased desire) were a natural consequence of the aging process. As a result, many older men did not seek help for their sexual problems and healthcare providers frequently failed to ask their patients about their sexual concerns. Recent studies have shown that a decrease in sexual function and sexual activity is not an inevitable consequence of aging. Furthermore, effective and well-tolerated treatments (e.g., phosphodiesterase type 5 inhibitors for the treatment of ED) are available for managing many of these conditions.

Various studies have assessed the prevalence of different types of male sexual dysfunction, often using

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varying definitions for the condition being assessed. The results of a large-scale, population-based study of men aged 40 to 70 years, the Massachusetts Male Aging Study (MMAS), demonstrated that ED had a high prevalence (52%), with nearly 35% of the men reporting moderate-to-severe ED [3]. The prevalence of complete ED was age-dependent, increasing from 5% for men aged 40 years to 15% for those aged 70 years. However, ED was also significantly associated with various age-independent predictor variables [3]. Based on MMAS data, it has been estimated that the worldwide prevalence of ED will be 322 million men in 2025 [4]. Other study results indicated that older individuals retain significant interest in sexuality and that a large proportion of older men and women remain sexually active [5,6]. Furthermore, sexuality is a factor that correlates with individuals' perception of their well-being and quality of life [7]. With the development of new measures for assessing sexual function and new medications for the treatment of ED, regular discussions between healthcare providers and patients on sexual problems can lead to effective management strategies and improvements in patient quality of life.

Lower urinary tract symptoms (LUTS; urinary frequency, urgency, decreased urine flow rates, nocturia) are common problems in aging individuals. Benign prostatic hyperplasia (BPH) is the primary cause of LUTS in men aged 50 years and older. The presence of histological BPH at autopsy is approximately 8% in men aged 31 to 40 years, 50% in those aged 51 to 60 years, 70% in those aged 61 to 70 years, and 90% in those aged 81 to 90 years [8]. Unfortunately, the MMAS did not evaluate LUTS as a possible predictor variable for ED. Thus, although both male sexual dysfunction and LUTS were known to be age-dependent, the exact relationship between these 2 conditions remained unclear. However, more recent large-scale epidemiological studies with different population samples and various measurement approaches have demonstrated consistent and compelling evidence of a relationship between LUTS and sexual dysfunction in aging men that is independent of the effects of age or other comorbidities. These studies, including the Multinational Survey of the Aging Male (MSAM-7) [6], and new pathophysiological insights have provided valuable information on the relationship between LUTS and sexual dysfunction in aging men. Moreover, these advances have resulted in new approaches to the evaluation of these disorders and the selection of treatment options. The present review article provides an overview of current knowledge on the relationship between male sexual dysfunction and LUTS, with a particular focus on LUTS associated with BPH, as well as medical treatment options for symptomatic BPH and their effects on sexual function.

2. Relationship between LUTS/BPH and male sexual dysfunction

2.1. Epidemiological evidence

2.1.1. General population studies

Data from the National Health and Social Life Survey (NHSLS), a population-based representative sample of US adults aged 18 to 59 years, demonstrated a high prevalence of sexual dysfunction in men (31%) and women (43%) [9]. Increasing age in men was associated with significantly higher prevalence rates of ED and HD. The results of the NHSLS also indicated that LUTS was a significant predictor for ED [9]. A study of 2476 Spanish men aged 25 to 70 years indicated that the prevalence of ED was 12% to 19%, with the rate dependent on the self-administered questionnaire used to assess sexual function [10]. Age-adjusted risk factors for ED included LUTS, rheumatic disease, circulatory disease, lung disease, diabetes, and hypertension. A population-based multinational (4 countries) study, the UrEpik study, investigated the relationship between LUTS and sexual dysfunction in 4800 men aged 40 to 79 years [11]. The overall prevalence of ED was 21%, which was significantly associated with increasing age ($p < 0.001$). After adjusting for age and country, men with diabetes, hypertension, or LUTS had a greater risk of ED. Age- and country-adjusted risk of HD was also strongly associated with LUTS, even after adjusting for ED [11].

Some subsequent large-scale studies examining the relationship between LUTS and sexual dysfunction controlled not only for the effect of age but also for various medical comorbidities and lifestyle factors (Table 1). In the Cologne Male Survey of approximately 5000 German men aged 30 to 80 years, the overall prevalence of ED was 19%, with a significant association between ED and LUTS, hypertension, diabetes, and pelvic surgery [5]. In fact, the prevalence of LUTS was 72% in men with ED versus 38% in those without ED. An additional analysis of the Cologne Male Survey data used multifactorial methods to show that, in addition to age, diabetes, hypertension, and pelvic surgery, LUTS is an independent risk factor for ED [12].

The results of a community-based study of 1688 men in the Netherlands showed that the prevalence of severe ED increased from 3% in men aged 50 to 54

Table 1
Prevalence of sexual dysfunction and significant comorbidities in various large-scale, population-based, epidemiology studies

Study	Country	Sample	Prevalence	Significant comorbidities
Martin-Morales et al. [10]	Spain	2476 men aged 25 to 70 y	ED: 12%–19% (assessment dependent)	ED: LUTS, diabetes, lung disease, CVD, allergy, rheumatic disease, heart disease, hypertension
Boyle et al. [11]	UK, Netherlands, France, Korea	4800 men aged 40 to 79 y	ED: 21% HD: 28%	ED: LUTS, diabetes, hypertension HD: ED, LUTS
Braun et al. [5]; Braun et al. [12]	Germany	8000 men aged 30 to 80 y	ED: 19%	ED: LUTS*, hypertension, diabetes
Blanker et al. [13,14]	Netherlands	1688 men aged 50 to 78 y	Severe ED: 3% (50–54 y); 26% (70–78 y) Severe EjD: 3% (50–54 y); 35% (70–78 y)	Severe ED: LUTS*, obesity*, CVD*, COPD* Severe EjD: ED*, LUTS*
Nicolosi et al. [15]	Brazil, Italy, Japan, Malaysia	2412 men aged 40 to 70 y (n = 1335 healthy men with no CVD, prostate disease, diabetes, ulcer, or depression diagnosis)	ED (moderate-complete): 16% in healthy men (32% in diseased men)	ED: moderate-severe LUTS* (healthy men)
Rosen et al. [6]	US, UK, France, Germany, Netherlands, Italy, Spain	12,815 men aged 50 to 80 y	ED: 49% (US 55%, Europe 45%) EjD: 45% Pain during ejaculation: 7% (LUTS: 90%)	ED: LUTS* EjD: LUTS* Pain during ejaculation: LUTS*
Hansen [16]	Denmark	3442 men aged 40 to 65 y	ED: 29% (LUTS: 39%)	ED: LUTS*

BPH: benign prostatic hyperplasia; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; ED: erectile dysfunction; EjD: ejaculatory dysfunction; HD: hypoactive desire; LUTS: lower urinary tract symptoms.
* Independent risk factor based on multiple logistic regression analysis.

years to 26% in those aged 70 to 78 years and severe EjD (defined as ejaculation with decreased amount of semen or loss of ejaculation) increased from 3% to 35% [13]. Age, LUTS, obesity, cardiovascular disease, chronic obstructive pulmonary disease, and smoking were significant risk factors for ED. Significant risk factors for EjD included age, ED, LUTS, and previous transurethral resection of the prostate (TURP) [13]. The results of multiple logistic regression analyses of data from this community-based study demonstrated that LUTS was an independent risk factor for severe ED and severe EjD [14]. This study, which was the first large-scale, community-based survey of EjD in older men, also included transrectal ultrasonography of the prostate and uroflowometry for most of the men. In bivariate logistic regression analysis, prostate enlargement was a significant correlate for severe ED, but this association was not significant in multiple logistic regression models [13].

The Cross National Study on the Epidemiology of ED and its Correlates assessed the prevalence of ED in relatively healthy men in 4 countries (Brazil, Italy, Japan, and Malaysia) [15]. Of 2513 men aged 40 to 70 years who were interviewed between October 1997 and June 1998, 1335 men answered a question on ED (How would you describe yourself: always, usually, sometimes, or never able to get and keep an erection good enough for sexual intercourse?) and reported no previous diagnosis of cardiovascular disease, prostate disease or surgery, diabetes, ulcer, or depression and that they were not taking hormones. The prevalence of moderate or complete ED in these healthy men was 16%, which was markedly lower than the 32% prevalence rate in the 1077 men who reported 1 or more concomitant conditions. In the healthy men, multivariate logistic regression analysis indicated that moderate (odds ratio 2.2, 95% CI: 1.2 to 3.9) and severe (odds ratio 4.9, 95% CI: 1.4 to 16.7) LUTS were the most significant predictors for ED.

In the most comprehensive study conducted to date on the association of age, LUTS, concomitant comorbidities, and male sexual dysfunction (both ED and EjD), the MSAM-7 analyzed survey results from 12,815 men aged 50 to 80 years in the United States and 6 European countries [6]. Overall, the results of this study strongly confirmed the relationship between LUTS and sexual dysfunction in men, independent of the effects of age, other comorbidities, and lifestyle

factors. In the MSAM-7, the overall prevalence of LUTS of any severity was 90%, with the prevalence of moderate-to-severe LUTS significantly related to age ($p < 0.0001$) [6]. Interestingly, only 19% of the men with LUTS sought medical assistance and only 10% were treated. The overall prevalence of ED (difficulty achieving an erection) in the MSAM-7 was 49%, with 10% reporting complete absence of erections [6]. The prevalence of self-reported ED was somewhat higher in US men (55%) than in European men (45%). The prevalence of ED was age-dependent, with rates of 31%, 55%, and 76% in men aged 50 to 59 years, 60 to 69 years, and 70 to 80 years, respectively.

Importantly, the overall prevalence of EjD (defined as ejaculation with decreased amount of semen or loss of ejaculation) in men able to achieve erections was 46%, with 5% of the men reporting complete absence of ejaculation [6]. The rates of self-reported EjD were comparable in US men and European men. As was observed with ED, the prevalence of EjD was age-dependent, with rates of 29%, 55%, and 74% in men aged 50 to 59 years, 60 to 69 years, and 70 to 80 years, respectively. Sexual activity, which was reported as a mean of 5.9 times each month for the total sample of men, deceased significantly with increasing age and the severity of LUTS. Both ED and EjD were also significantly associated with the severity of LUTS ($p < 0.001$). The bothersomeness of EjD, although not age related, increased significantly with increased LUTS severity. Pain and/or discomfort with ejaculation were reported by 7% of the men, with the prevalence significantly associated with age ($p < 0.001$) and the severity of LUTS ($p < 0.04$). Logistic regression analysis, which controlled for age, medical comorbidities, tobacco use, and alcohol consumption, demonstrated that age and the severity of LUTS were independent risk factors for ED and EjD. Furthermore, age and LUTS were stronger risk factors for ED and EjD than was diabetes, hypertension, heart disease, or hyperlipidemia [6].

Another recent population-based study, which was conducted in Denmark, investigated the relationship between LUTS and sexual dysfunction in men and women aged 40 to 65 years [16]. In men, the prevalence of LUTS was 39% and the prevalence of ED was 29%. In multivariate logistic regression analyses, LUTS was an independent predictor of ED.

2.1.2. Clinic-based LUTS/BPH population studies

In the last several years, many clinic-based studies have investigated the prevalence of sexual dysfunction in men with LUTS associated with BPH (Table 2). The prevalence rates of ED and EjD in these studies ranged from 41% to 71% and from 38% to 70%, respectively, whereas the prevalence of HD was 32% to 66% and of pain with ejaculation was 17% to 23% [17–23]. Two of these studies were multinational studies. In a urology clinic-based sample of 1271 men aged 45 years and older from 12 countries, the prevalence rates of ED, EjD (defined as ejaculation with a decreased amount of semen or loss of ejaculation), and pain/discomfort during ejaculation were 60%, 62%, and 17%, respectively [18]. After adjusting for age, a significant positive association was found between ED and LUTS, between EjD and LUTS, and between pain/discomfort during ejaculation and LUTS in this clinic sample of men. Data on the prevalence of sexual dysfunction according to country suggested international differences in self-reported ED, EjD, and pain/discomfort during ejaculation [18]. In the second multinational study of 927 men aged 36 to 92 years with LUTS associated with BPH from 5 European countries, the prevalence rates of ED (62%) and EjD (defined as ejaculation with a decreased amount of semen or loss of ejaculation; 63%) were comparable, whereas pain/discomfort during ejaculation was less prevalent (23%) [23]. ED was significantly associated with age, LUTS, body mass index >25 kg/m^2, and hypertension treated with calcium channel blockers; age and LUTS were the main predictors of ED. EjD was significantly associated with age and LUTS, whereas LUTS was the only significant predictor for pain/discomfort during ejaculation [23]. Analysis of baseline data from the randomized, placebo-controlled, Medical Therapy of Prostatic Symptoms (MTOPS) trial also indicate a significant relationship between LUTS and erectile function, ejaculation, overall sexual satisfaction, and sexual desire after controlling for age, hypertension, lipid disorders, and diabetes [24].

2.1.3. Summary

Epidemiological evidence provides a clear and clinically meaningful association between LUTS and various types of sexual dysfunction in aging men worldwide. The results of a recent longitudinal population-based study of 428 Brazilian men without ED at baseline indicate that the adjusted relative risk of developing ED is 3.67 (95% confidence interval, 1.17 to 11.48) for those with self-reported BPH after a mean follow-up of 2 years [25]. Although this finding might suggest that LUTS causes ED, the possible role of other unidentified factors needs to be considered. Thus, the underlying mechanisms responsible for the association between LUTS and male sexual dysfunction remain to be determined. It has been suggested that this association may be psychosocial and/or pathophy-

Table 2
Prevalence of and risk factors for sexual dysfunction in men with LUTS/BPH

Study	Country	Sample	Prevalence	Significant risk factors
Namasivayam et al. [17]	UK	140 men aged 43 to 89 y with LUTS/BPH	ED: 46% EjD: 38% HD: 66%	ED: age EjD: age HD: age
Frankel et al. [18]	12 countries	1271 men aged >55 y with LUTS/BPH	ED: 60% EjD: 62% Pain during ejaculation: 17%	ED: age, LUTS EjD: age, LUTS Pain during ejaculation: LUTS
Baniel et al. [19]	Israel	131 men aged 55 to 74 y with LUTS/BPH	ED: 67%	ED: severe LUTS
Tubaro et al. [20]	Italy	877 men with LUTS/BPH	ED: 58% EjD: 56% Pain during ejaculation: 20%	ED: LUTS EjD: LUTS Pain during ejaculation: LUTS
Leliefeld et al. [21]	Netherlands	670 men aged ≥50 y with untreated LUTS/BPH	ED: 41% HD: 32%	ED: LUTS*, urologic comorbidity*, bladder stone* HD: LUTS*
Brookes et al. [22]	UK	340 men aged 48 to 90 y with LUTS/BPH	ED: 71% EjD: 70% Pain during ejaculation: 18%	ED: age, LUTS EjD: age Pain during ejaculation: age
Vallancien et al. [23]	France, Denmark, Netherlands, Switzerland, UK	927 men aged 36 to 92 y with LUTS/BPH	ED: 62% EjD: 63% Pain during ejaculation: 23%	ED: age*, LUTS*, BMI >25 kg/m^{2}*, hypertension treated with CCB* EjD: age*, LUTS*, BPH surgery* Pain during ejaculation: LUTS*

BMI: body mass index; BPH: benign prostatic hyperplasia; CCB: calcium channel blocker; ED: erectile dysfunction; EjD: ejaculatory dysfunction; HD: hypoactive desire; LUTS: lower urinary tract symptoms.
* Independent risk factor based on multiple logistic regression analysis.

siological in nature [26]. A pathophysiological mechanism is suggested by an animal model of partial bladder outlet obstruction that resulted in ultrastructural changes in the corpus cavernosum [27]. Until further research definitively elucidates the reasons for the association between LUTS and male sexual dysfunction, our knowledge of the pathophysiology of LUTS and sexual dysfunction, particularly ED and EjD, has suggested some common components that may be involved.

2.2. Pathophysiological mechanisms

Why are LUTS in aging men, with or without prostatic enlargement, associated with ED, EjD, pain/discomfort during ejaculation, and HD? Is there a single underlying mechanism to account for these effects or are several mechanisms, some perhaps indirect, involved? If there is indeed an association between LUTS and male sexual dysfunction, an understanding of the specific underlying mechanisms might have an important impact on the diagnosis and treatment of these disorders. Current research in this area is actively studying this relationship in aging men. The results of these studies will increase our understanding of the effects of LUTS/BPH treatments on male sexual function.

2.2.1. LUTS/BPH

The prostate gland contains both epithelial and stromal components; excessive growth in either or both components can contribute to the development of BPH. Increased smooth muscle tone in the prostate capsule and the bladder neck can also contribute to the LUTS associated with BPH. Although the pathophysiology of LUTS associated with BPH was historically attributed to prostate gland enlargement and bladder outlet obstruction, the weak correlation between LUTS and prostate size [28,29] has resulted in a greater focus on the role of increased smooth muscle tone in the prostate and bladder and highlighted the need to investigate other possible underlying mechanisms. Increased smooth muscle tone in the prostate in BPH is related to the stimulation of α_1-adrenergic receptors [30]. Other receptors that have been identified in human prostate tissue and that may play a role in LUTS associated with BPH include dopaminergic, muscarinic, serotoninergic (5-HT$_{2A}$), and histaminergic (H_1)

receptors [31]. Nitric oxide (NO), which is present in the human prostate [32] and modulates prostatic smooth muscle tone [33], may also have a role in the pathophysiology of LUTS associated with BPH.

2.2.2. ED

The physiology of penile erection and the pathophysiology of ED have been previously reviewed [34–36]. In brief, the tone of the corpus cavernosal smooth muscle and the penile vasculature, which regulates penile erection and detumescence, is under the control of various central and peripheral mechanisms and involves multiple neurotransmitter systems [34]. Central neurotransmitters that appear to regulate penile erection/detumescence include acetylcholine, NO, dopamine, oxytocin, noradrenaline, and serotonin [37]. In the penis, noradrenaline and endothelins are putative promotors of penile detumescence (contraction), whereas NO promotes penile erection (relaxation). Penile erection involves acetylcholine-mediated relaxation of the corpus cavernosal smooth muscle, with neurogenic NO considered the main factor responsible for rapid relaxation and endothelial NO thought to play a role in the maintenance of the relaxed state [35,38]. NO binds to soluble guanosine cyclase and stimulates the formation of cyclic guanosine monophosphate (cGMP), which signals phosphodiesterases, protein kinases, and ion channels, resulting in smooth muscle relaxation and penile erection [35]. ED can result from alterations or defects in one or more of the steps involved in the normal erectile process. Vascular disease, neurological disease, surgery, radiation therapy, injury, and treatment with certain medications are common causes of ED.

2.2.3. EjD

The physiological mechanisms of ejaculatory function and the pathophysiological mechanisms of EjD are not fully elucidated. Emission (i.e., deposition of seminal fluid and sperm from the distal epididymis, vas deferens, seminal vesicles, and prostate gland into the prostatic urethra) and ejaculation (i.e., expulsion of seminal contents through the urethral meatus) are controlled by the sympathetic/parasympathetic and somatic nervous systems. Both emission and ejaculation involve contractile processes [39]. Central serotoninergic neurotransmission also plays a role in ejaculation [40]. Interestingly, the stimulation of different serotonin (5-HT) receptor subtypes can result in an increase or decrease in the ejaculatory latency time [41]. In the rat, postsynaptic 5-HT_{1A} and 5-HT_{2C} receptors appear to play a role in ejaculatory behavior [40]. Based on the results of animal studies, Waldinger and colleagues suggested that hyposensitivity of 5-HT_{2C} receptors and/or hypersensitivity of 5-HT_{1A} receptors may be responsible for premature ejaculation in humans [41].

2.2.4. Possible common components

2.2.4.1. α_1-Adrenergic receptors. An imbalance in the autonomic control of smooth muscle contraction and relaxation may play an important role in both LUTS and sexual dysfunction. α_1-Adrenergic receptors are known to play an important role in mediating the tone of smooth muscle cells in various tissues. Various α_1-adrenergic receptor subtypes have been identified in the lower urinary tract, including α_{1A}- and α_{1D}-receptors in prostatic stromal cells [42,43], α_{1B}-receptors in epithelial cells, α_{1A}- and α_{1B}-receptors in vascular smooth muscle [44], α_{1A}- and α_{1D}-receptors in the urethra and bladder, and α_{1D}-receptors in the detrusor muscle [45]. It has been suggested that α_1-adrenergic receptors are upregulated in patients with LUTS associated with BPH, resulting in increased smooth muscle tone in the prostatic capsule and bladder neck [46]. This is supported by the fact that α_1-adrenergic receptor antagonists, which relax the smooth muscle of the prostate and bladder, are effective first-line medications for the treatment of LUTS associated with BPH.

Penile detumescence and erection are dependent on the balance between contraction and relaxation of the corpus cavernosum smooth muscle [34]. In ED, the balance favors contraction (detumescence) rather than relaxation (erection). Noradrenaline is involved in the contraction of penile tissues via activation of α_1-adrenergic receptors in the penile vasculature and corpus cavernosum smooth muscle, with androgens possibly regulating the responsiveness of these receptors [47]. With α_{1D}- and α_{1A}-adrenergic receptors identified as the receptor subtypes in the human vas deferens and prostate gland, activation of α_1-adrenergic receptors is a possible mechanism for both emission and ejaculation. Any impairment in the activation of the α_1-adrenergic receptors of the seminal tract may theoretically result in EjD.

The contraction and growth of vascular smooth muscle cells is also mediated by α_1-adrenergic receptors. In certain human arteries, α_1-receptor expression increases and the relative proportion of α_1-adrenergic receptor subtypes is modulated by aging [44]. In mammary arteries from healthy individuals aged <55 years, α_{1A}-adrenergic receptors were identified as the main subtype, whereas the α_{1B}-adrenergic receptor subtype predominated in individuals aged ≥ 65 years. Tissue-specific regulation of α_1-adrenergic receptor subtypes may also occur in various disease states, especially

those that are age-dependent. Interestingly, the mean efficacy of phenylephrine-induced contractions of vascular smooth muscle strips, mediated by activation of α_1-adrenergic receptors, was significantly greater for those isolated from the corpus cavernosum of older ($\geq$60 years) men with ED than for those isolated from younger (<60 years) men with ED, without an alteration in phenylephrine affinity [48]. Kinetic studies indicated that the maximal rate constant for the onset of these contractions was significantly greater in the older versus the younger men with ED [49].

Adrenergic-mediated contraction of smooth muscle may also be regulated by Rho and Rho-associated kinase [50], which has been found in human prostatic smooth muscle cells [51] and the vas deferens of the mouse [52]. The results of other studies have suggested a possible role for the Rho/Rho kinase pathway in the mechanism of penile smooth muscle contraction [53,54]. Thus, alterations in α_1-adrenergic receptor-mediated smooth muscle tone and its regulators may be a common component involved in LUTS associated with BPH, ED, and EjD.

2.2.4.2. Endothelial dysfunction. Another mechanism that may link the pathophysiology of LUTS and male sexual dysfunction is endothelial dysfunction, which refers to impaired endothelium-dependent vasodilation (i.e., relaxation) resulting from the decreased bioactivity of NO [55]. Endothelial dysfunction has been associated with aging, cardiovascular disease, diabetes, hypertension, and hypercholesterolemia. Possible mechanisms responsible for endothelial dysfunction include accelerated breakdown of NO by reactive oxygen species, alterations in antioxidant defense systems, and alterations in the activity or expression of the endothelial NO synthase (eNOS) enzyme [55,56]. In aging men, decreasing levels of testosterone and reductions in the conversion of testosterone to estradiol by the aromatase enzyme may contribute to the deficits in eNOS-derived NO [57]. In an animal model of age-related ED, endothelial dysfunction of the corpus carvernosum was associated with up-regulation of eNOS and alterations in intracellular calcium flux [58]. Endothelial dysfunction has been suggested as the common component linking ED and cardiovascular disease [59]. Furthermore, in prostatic tissue from men with BPH, nitrergic innervation was demonstrated to be decreased compared with that in normal prostate tissue [60], which suggests a possible role for NO in the pathophysiology of BPH. Studies in animals also suggest that NO plays a role in preventing bladder contractions that result in bladder hyperactivity, as observed in LUTS [61–63]. Thus, alterations in vascular endothelium function may be responsible for various age-related conditions, including LUTS associated with BPH and male sexual dysfunction.

2.2.4.3. Sex hormones. The development and growth of the normal prostate gland is known to be dependent on an intact sex hormone-signaling axis. Dihydrotestosterone (DHT), which is more potent than testosterone and demonstrates a higher affinity for androgen receptors, is predominantly produced peripherally from testosterone via the enzyme 5α-reductase. Androgen receptors, which are present in both the stroma and epithelium of the prostate as well as in most blood vessel endothelial cells, smooth muscle cells, and fibrocytes [64], may play a role in the interaction between the stroma and the epithelium of the prostate.

Age-related changes in circulating hormone levels and an imbalance in the testosterone/estrogen ratio may play a role in the pathophysiology of BPH and sexual dysfunction. Longitudinal data from the MMAS indicated that serum levels of total testosterone, dehydroepiandrosterone (DHEA), DHEA-sulfate, cortisol, and estrone declined, whereas levels of DHT, sex hormone binding globulin, luteinizing hormone, follicle-stimulating hormone, and prolactin increased in men who were aged 40 to 70 years at baseline and followed for 7 to 10 years [3]. It was suggested that higher levels of DHT with aging may be an adaptation to compensate for decreased testosterone levels. With sex hormones primarily produced from precursors in peripheral tissues in humans, each target tissue has the ability to modulate hormone metabolism and signaling processes through the regulation of tissue enzyme activities [64,65] and hormone receptor subtypes [66]. Additional studies are needed to assess whether alterations in sex hormone levels and their receptors play a role in the pathophysiology of BPH and sexual dysfunction.

2.2.5. Summary

Based on the possible common pathophysiological mechanisms of LUTS/BPH and sexual dysfunction (Table 3) as well as other common comorbidities observed in aging men with these conditions, further multidisciplinary studies seem warranted [67]. The

Table 3
Possible common components linking LUTS/BPH, ED, and EjD

Possible links	LUTS/BPH	ED	EjD
↑ α_1-adrenergic activity	✓	✓	✓
Alteration in α_1-adrenergic receptor subtypes	✓	✓	✓
↓ NO bioactivity (endothelial dysfunction)	✓	✓	?
Testosterone/estrogen imbalance	✓	✓	✓
5-HT	?	✓	✓

results of future studies may also provide valuable information on the most effective treatment options for the concurrent management of these common age-related conditions. If LUTS/BPH and male sexual dysfunction share a common pathophysiological mechanism, the optimal therapeutic strategy would be to treat with a single agent that improves both LUTS and sexual dysfunction. For example, preliminary data have suggested that treatment with sildenafil improves LUTS in men with ED, possibly as the result of smooth muscle relaxation in the lower urinary tract [68]. An alternative management strategy for LUTS and sexual dysfunction would be combination therapy with agents that improve LUTS or sexual dysfunction without adversely affecting the other condition. The following section focuses on various current treatment options for LUTS associated with BPH and their related effects on sexual function.

3. Therapy for LUTS associated with BPH

The main goals of therapy in men with LUTS associated with BPH are to alleviate the bothersomeness of LUTS and to improve patient quality of life. Because of the significant association between LUTS/BPH and domains of sexual dysfunction in men, an assessment of sexual function is recommended in the evaluation of all men with LUTS associated with BPH, and the effects of BPH treatments on sexual function should be carefully considered by both the patient and the clinician.

3.1. Efficacy data

Although TURP remains the benchmark therapy for LUTS associated with BPH [69], oral agents are now the standard first-line therapy for men with bothersome and moderate-to-severe LUTS. The α_1-adrenergic receptor blockers alfuzosin, doxazosin, tamsulosin, and terazosin are the most commonly prescribed oral therapies for LUTS associated with BPH. At therapeutic doses, these 4 α_1-adrenergic receptor blockers have demonstrated similar effectiveness in relieving LUTS in men with BPH [70]. 5α-Reductase inhibitors (i.e., finasteride and dutasteride) are an appropriate treatment option for patients with LUTS and evidence of marked prostatic enlargement. Based on evidence-based outcomes data, 5α-reductase inhibitors were not as effective as α_1-adrenergic receptor blockers in alleviating the symptoms of BPH [70].

3.2. Effects on sexual function

3.2.1. TURP

Surgical interventions for LUTS/BPH, such as TURP, have been reported to cause ED and EjD (particularly retrograde ejaculation). The estimated incidence of ED was 10% in 15 trials (versus 2% for sham control) and the estimated incidence of EjD was 65% in 19 trials (versus 2% for sham control) that had TURP as the control arm [70]. However, the Veterans Affairs Cooperative Group Study on TURP demonstrated that the incidence of ED in men with moderate LUTS/BPH who underwent TURP was lower than that for those in the watchful waiting group [71]. A recent randomized, controlled trial evaluated ED (stiffness of erection) and EjD (decreased amount of semen with ejaculation, loss of ejaculation, and pain/discomfort during ejaculation) at baseline and 6 to 12 months after TURP, non-contact laser therapy, or watchful waiting in 340 men aged 48 to 90 years with LUTS/BPH [22]. A significant decrease from baseline in the percentage of men with ED and a significant reduction in the percentage of men with pain during ejaculation were demonstrated after TURP (Fig. 1). Men who underwent TURP were significantly more likely to have an improvement in erectile function than those who had watchful waiting. Furthermore, men who had TURP were significantly less likely to have pain during ejaculation than those who had laser therapy or watchful waiting. The percentage of men with EjD was significantly increased from baseline after TURP, laser therapy, and watchful waiting (Fig. 1). The results of this study indicate that TURP has a more beneficial effect on certain aspects of sexual function (i.e., erectile function and pain during ejaculation) than does laser therapy [22].

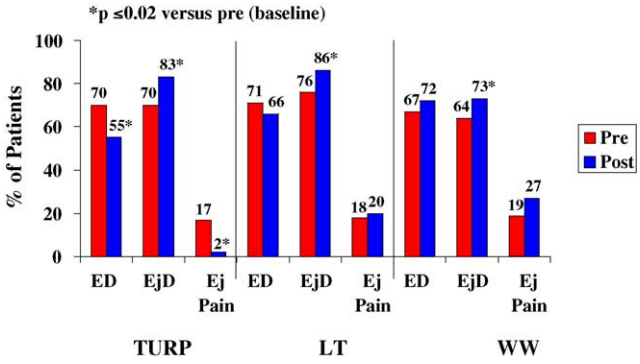

Fig. 1. Erectile dysfunction (ED), ejaculatory dysfunction (EjD), and pain during ejaculation (Ej Pain) before and after treatment with transurethral resection of the prostate (TURP), non-contact laser therapy (LT), or watchful waiting (WW) in men with LUTS/BPH (Data from [22]).

3.2.2. Alfuzosin

Alfuzosin is a clinically uroselective α_1-adrenergic receptor antagonist that is distributed preferentially in the prostate versus vascular tissue [72]. Immediate-release (2.5 mg 3 times daily) and sustained-release

Table 4
Incidence of sexual side effects in various phase III studies of medical therapies for LUTS/BPH

Drug	No. of studies (treatment duration)	ED	EjD	HD
Alfuzosin 10 mg	3 (12 weeks) [74]	1.5%	<1%	<1%
Placebo		0.6%	<1%	<1%
Tamsulosin	2 (13 weeks) [88]			
0.4 mg		<2%	8.4%	1.0%
0.8 mg		<2%	18.1%	2.0%
Placebo		<2%	0.2%	1.2%
Finasteride 5 mg	1 (1 year) [93]	8.1%	0.8% ↓ volume: 3.7%	6.4%
Placebo		3.7%	0.1% ↓ volume: 0.8%	3.4%
Dutasteride 0.5 mg	3 (2 years) [95]	7.3%	2.2%	4.2%
Placebo		4.0%	0.8%	2.1%
Doxazosin 4–8 mg	1 (1 year) [93]	14.4%	4.5%	7.0%
Finasteride 5 mg		18.5%	7.2%	10.0%
Combination		22.6%	14.1%	11.6%
Placebo		12.2%	2.3%	5.7%

(5 mg 2 times daily) formulations of alfuzosin have been widely used for more than 15 years in Europe for the treatment of LUTS associated with BPH. The once-daily (OD) formulation of alfuzosin 10 mg, which is bioequivalent to the other alfuzosin formulations [73], was launched in Europe in 2000 and in the United States in 2003.

Treatment with alfuzosin 10 mg OD in men with LUTS associated with BPH is well tolerated, as demonstrated in 3 double-blind, placebo-controlled, clinical trials [74]. The incidence of sexual side effects was low and similar in the alfuzosin 10 mg OD group (ED, 1.5%; loss of ejaculation, 0.6%) and the placebo group (ED, 0.6%; loss of ejaculation, 0%; Table 4). The low incidence of sexual side effects, which was maintained during long-term (up to 12 months) treatment with alfuzosin 10 mg OD [75], confirms the results demonstrated with the 2 other alfuzosin formulations [76,77]. In addition, there is no dose-related effect with alfuzosin with respect to the incidence of sexual side effects [78]. Moreover, recent data from an open-label study have suggested that treatment with alfuzosin 10 mg OD for 1 year significantly improves ED, EjD (defined as ejaculation with decreased amount of semen or loss of ejaculation), and pain/discomfort during ejaculation in men with LUTS associated with BPH [79]. Additional studies are needed to further evaluate these improvements in sexual function during alfuzosin treatment in men with LUTS associated with BPH.

3.2.3. *Doxazosin and terazosin*

Doxazosin and terazosin were indicated for the treatment of hypertension before being approved for the treatment of LUTS associated with BPH. Both medications do not demonstrate uroselectivity and have equal affinity for the 3 subtypes of α_1-adrenergic receptors. As a result, the incidence of vasodilatory side effects (i.e., dizziness, asthenia) with these medications is significantly higher than that with placebo [70]. During treatment with doxazosin, the rates of ED and EjD are generally comparable to those observed with placebo treatment (Table 4). Of note, in 2 randomized, double-blind, placebo-controlled studies in men with BPH, treatment for 13 weeks with doxazosin, which was titrated to 8 mg OD, resulted in significant improvements from baseline in sexual function for those patients with sexual dysfunction at baseline [80]. Furthermore, in an observational study of men with BPH, treatment with doxazosin for 1 month resulted in a significant improvement in sexual function compared with that at baseline, especially for those with moderate-to-severe ED at baseline [81].

3.2.4. *Tamsulosin*

Tamsulosin is a uroselective α1-adrenergic receptor antagonist that has been reported to demonstrate greater in vitro selectivity for α_{1A}- and α_{1D}-receptor subtypes than for α_{1B}-receptors [82,83]. The safety profile of tamsulosin has been evaluated in several randomized, double-blind, placebo-controlled trials [84–87]. In 2 US phase III trials, a significantly higher incidence of EjD was demonstrated in men receiving tamsulosin 0.4 mg OD (8%) or 0.8 mg OD (18%) than in those receiving placebo (0.2%; Table 4) [88]. The effects of tamsulosin on sexual function were dose related. In 2 European trials, the incidence of EjD was

4.5% in men receiving tamsulosin 0.4mg OD compared with 1% for those receiving placebo ($p = 0.45$) [85]. In a long-term (>1 year), open-label, phase III, extension study of treatment with tamsulosin 0.4 mg OD, 30% of patients experienced EjD and 6% reported ED [89].

Pharmacologic selectivity for the α_{1A}-adrenergic receptor subtype in the bladder neck and seminal vesicles may play a role in the EjD observed during tamsulosin treatment. A study in rats investigating the effects of tamsulosin and alfuzosin on bladder neck closure and seminal vesicle contractions induced by electrical stimulation indicated that tamsulosin had a significantly greater inhibitory effect than did alfuzosin at the same dose [90]. Another possible explanation for tamsulosin-induced EjD may be the medication's ability to cross the blood-brain barrier and block α_1-adrenergic receptor subtypes within the central nervous system [91]. More recently, it has also been suggested that tamsulosin binding to 5-HT_{1A}-receptors and/or dopamine receptors may play a role in the EjD observed during tamsulosin treatment [92]. Additional studies are needed to evaluate whether central non-adrenergic mechanisms are involved in tamsulosin-induced EjD.

3.2.5. 5α-Reductase inhibitors

Because DHT is the androgen primarily responsible for prostate growth and enlargement, inhibition of the enzyme 5α-reductase enzyme, which catalyzes the formation of DHT from testosterone, represents another approach to treating LUTS associated with BPH. Of the 2 isozymes of 5α-reductase, type 1 is expressed in most tissues, whereas type 2 is the dominant isozyme in reproductive tissues, including the prostate. Two 5α-reductase inhibitors are currently used in the treatment of symptomatic BPH in men with enlarged prostates, finasteride and dutasteride.

Treatment with finasteride, a selective inhibitor of 5α-reductase type 2, is generally well tolerated, but side effects related to sexual function occur significantly more frequently in men treated for 1 year with finasteride 5 mg OD than in those receiving placebo (Table 4) [93]. In patients treated with finasteride 5 mg OD or placebo in the PROSPECT Study, a 2-year double-blind, placebo-controlled prospective randomized trial, 16% of patients who received finasteride experienced ED compared with 6% of patients who received placebo ($p \leq 0.01$) [94]. Moreover, the incidence of EjD was 8% for finasteride-treated patients versus 2% for placebo-treated patients. Dutasteride, a newer 5α-reductase inhibitor that blocks both the type 1 and type 2 isozymes, provides a greater suppression of DHT production than finasteride. Patients treated with dutasteride 0.5 mg OD in 3 randomized, double-blind, clinical trials experienced significantly higher incidence rates of ED (7% versus 4% for placebo group), EjD (2% versus 1% for placebo group), and HD (4% versus 2% for placebo group) than those treated with placebo (Table 4) [95]. In patients treated with a combination of finasteride 5 mg OD and doxazosin 4 mg or 8 mg for 1 year, the incidence of sexual side effects was approximately the sum of the rates for each medication alone [93]. The effects of 5α-reductase inhibitors on sexual function may be related to inhibition of androgen-stimulated NOS expression [96].

3.2.6. Summary

Of the 2 uroselective α_1-adrenergic receptor blockers used in the treatment of LUTS associated with BPH, alfuzosin 10 mg OD appears to demonstrate a more favorable safety profile with respect to sexual side effects than does tamsulosin 0.4 mg OD or 0.8 mg OD. Treatment with finasteride or dutasteride can also negatively affect sexual function in men with BPH who are already at increased risk for sexual dysfunction. Thus, sexual function should be assessed and discussed when selecting a therapy for men with LUTS associated with BPH and when evaluating the outcomes of a selected therapy.

4. Instruments for assessing male sexual function

Patient self-assessment questionnaires are extremely useful in assessing sexual function in a clinical setting. Validated questionnaires used in the assessment of male sexual function include the International Index of Erectile Function (IIEF; 15 items; 5 domains of male sexual function: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction [97], the Brief Sexual Function Inventory (11 items that focus on sexual drive, erection, ejaculation, perceptions of problems in each of these areas, and overall satisfaction [98], and the International Continence Society Sex Questionnaire (4 items assessing erectile function, ejaculatory function, pain/discomfort during ejaculation, and the extent that urinary symptoms spoil the patient's sex life) [99]. The Danish Prostate Symptom Score Sex questionnaire has also been used to assess erection, ejaculation, and pain/discomfort during ejaculation and the bothersomeness of each of these items [100].

Since its development and validation in conjunction with the clinical trial program of sildenafil [97], the

IIEF has become the gold standard for the assessment of treatment outcomes in clinical trials of ED in heterosexual men and can also be used to provide a quantitative index of ED severity [101]. A new instrument for evaluating erection quality (Erection Quality Scale; 15 items assessing the ability to achieve an erection, duration of erection, hardness of erection, sensitivity of erection, and general feelings), which was designed to be applicable to men of any sexual orientation, may become a useful adjunct to the IIEF in assessments of erectile function [102]. Although the IIEF includes domains for sexual desire, orgasmic function, and sexual satisfaction, the main focus of this instrument is erectile function. As a result, the IIEF should not be used for assessments of ejaculation or orgasm.

To address the need for an instrument to assess specific aspects of ejaculation in older men, a new self-administered questionnaire, the 25-item Male Sexual Health Questionnaire (MSHQ), was recently developed and validated [103]. The MSHQ, which has domains for erection (3 items), ejaculation (7 items), and sexual satisfaction (6 items), provides a more in-depth assessment of ejaculatory function and sexual satisfaction than the IIEF and other instruments. The ejaculation domain of the MSHQ assesses loss of ejaculation, delayed ejaculation, the force of the ejaculation, the amount of semen ejaculated, pleasure associated with ejaculation, and pain/discomfort during ejaculation. In validation studies, the 3 domains of the MSHQ demonstrate a high degree of internal consistency, rest-retest reliability, and construct validity as well as the ability to differentiate between men with LUTS and sexual dysfunction and healthy men [103]. Of the 3 domains of the MSHQ, the ejaculation domain has the most significant correlation with LUTS severity. Linguistic validation studies of the MSHQ are currently ongoing. The MSHQ is also being used to assess sexual function in a national survey of US men, a US observational BPH Registry that is collecting data on patient outcomes and the relationship between LUTS/BPH and sexual dysfunction, and various placebo-controlled clinical trials of the effects of treatment with alfuzosin 10 mg OD on sexual function in men with LUTS/BPH. The results of these studies will provide valuable new information on EjD in the general population of men and in those with LUTS/BPH.

5. Conclusions and future directions

Research during the past decade has firmly established that ED and EjD are highly prevalent conditions in aging men, particularly those with LUTS associated with BPH. Furthermore, the results of recent large-scale studies have demonstrated that LUTS associated with BPH is an independent risk factor for male sexual dysfunction. Interestingly, LUTS is also an independent predictor of sexual dysfunction in women [16]. Although the underlying mechanisms responsible for the relationship between LUTS and male sexual dysfunction are not fully elucidated, possible common links include the activation of α_1-adrenergic receptors, endothelial dysfunction, and alterations in sex hormone concentrations and receptor subtypes.

With our knowledge of the relationship between LUTS and sexual dysfunction has come new insights into the evaluation and management of patients with these conditions. It is now recommended that men presenting with LUTS should be evaluated for sexual dysfunction and those presenting with sexual dysfunction should be evaluated for LUTS. Furthermore, as it is now recognized that certain oral therapies for LUTS/BPH can adversely affect sexual function in patients who are already at increased risk for sexual dysfunction, healthcare providers should discuss sexual function with their patients both before and during treatment. The development and validation of sexual function questionnaires that allow more detailed assessments of the different aspects of male sexual function, including erection, ejaculation, and sexual satisfaction, has facilitated this process. Additional basic research and clinical studies are needed to gain a better understanding of the mechanisms by which currently available oral therapies for LUTS/BPH exert their effects on LUTS and sexual function. Furthermore, studies evaluating combined treatments (e.g., medical, surgical, and psychological) for LUTS, sexual dysfunction, and other concomitant age-associated conditions are needed to provide new insights on optimal management strategies for these prevalent symptoms in aging men.

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