



## Review article

# Impacts of medical treatments for lower urinary tract symptoms suggestive to benign prostatic hyperplasia on male sexual functions<sup>☆</sup>

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## ABSTRACT

Although alpha blockers with or without 5-alpha reductase inhibitors (5-ARIs) have become the standard of treatment for men with moderate to severe lower urinary tract symptoms suggestive to benign prostatic hyperplasia (LUTS/BPH), their negative adverse effects on male sexual functions have become another major issue, which may have a direct impact on patients' quality of life and overall satisfaction. Erectile dysfunction, ejaculation disorders, reduced libido, or anorgasmia have been noted among patients receiving these standards of treatments and these adverse events may be irreversible even after discontinuation of medications. Physicians should inform and discuss with their patients about these potential side effects before prescribing these medications for their LUTS/BPH treatment. Tadalafil is the first phosphodiesterase type 5 inhibitor which has the indications for LUTS/BPH and erectile dysfunction and its efficacy is comparable to alpha-blockers with regards to the reduction of LUTS and improvement of quality of life. Moreover, early clinical studies have showed that the combination use tadalafil with alpha blockers or 5-ARIs may have an additional benefit on symptom relief and maximum urinary flow rate ( $Q_{max}$ ) improvement. As expected, the improvement on erectile function is significant, especially among patients taking 5-ARIs regularly. Although there are promising data from the combination use of tadalafil with 5-ARIs or tadalafil with alpha-blockers, more large-scale clinical studies are still needed to confirm their long term safety and efficacy profiles.

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## 1. Introduction

Lower urinary tract symptoms suggestive to benign prostatic hyperplasia (LUTS/BPH) is common among men aged over 60 years. Uncontrolled LUTS/BPH may have a direct impact not only on quality of life (QoL) but also on sexual functions. Erectile dysfunction (ED) and ejaculation disorder (EjD) are two common male sexual disorders among men with LUTS/BPH in daily urology practice. Although age has been noted as an independent factor for the development of ED and BPH, more epidemiological evidence shows that sexual dysfunction is significantly more prevalent in patients with LUTS/BPH than in men without LUTS/BPH, even after

correcting for age and comorbidity. Therefore LUTS/BPH is also an independent factor for developing sexual dysfunction.<sup>1–5</sup> Furthermore the uses of medical or surgical treatments for LUTS/BPH management have initiated another impact on male sexual functions. This review will focus on the impacts of medical treatments for LUTS/BPH on male sexual functions. Newer therapeutic modalities with their impacts on sexual dysfunction side effects will be discussed in this review article.

## 2. LUTS/BPH

LUTS includes a broad range of symptoms and is highly prevalent among both men and women. Originally, LUTS are defined by the International Continence Society (ICS) as all urinary symptoms occurring during the phases of storage (increased daytime frequency, nocturia, urgency, and/or urinary incontinence), voiding (terminal dribble, hesitancy, intermittency, straining, and/or splitting/spraying/slow stream), and postmicturition (incomplete emptying or

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postmicturition dribble).<sup>6</sup> In a large cross-sectional, multi-national study, which is the first epidemiologic study using standard terminology defined by ICS, showed that the prevalence of storage LUTS (men, 51.3%; women, 59.2%) was greater than that for voiding (men, 25.7%; women, 19.5%) and postmicturition (men, 16.9%; women, 14.2%) symptoms. The most common storage symptom in this multinational study was nocturia (48.6% men; 54.5% women) followed by urgency (10.8% men; 12.8% women). Terminal dribble (14.2% men; 9.9% women) was the most common voiding symptom, and incomplete emptying (13.5% men; 12.3% women) was the most frequently reported postmicturition symptom.<sup>7</sup>

### 3. The impacts of LUTS/BPH on male sexual functions

Libido, erection, ejaculation, and orgasm are four major components in male sexual functions. Although ED is one of the most common male sexual disorders, EjD, loss of libido or hypoactive sexual desire, and orgasm dysfunction are also common among men with LUTS/BPH. Although age is an independent factor for ED, the development of these male sexual dysfunctions may be multifactorial. The prevalence and severity of sexual dysfunctions had been found to be closely related to the severity of LUTS, even after controlling for confounding variables such as age or comorbidities.<sup>5</sup> Most population- or community-based epidemiological studies have confirmed that LUTS alone might have a direct impact on sexual dysfunction and sexual life satisfaction. Braun et al<sup>2</sup> found that the prevalence of LUTS in men suffering from ED was about 72.2% ( $n = 621$ ) versus 37.7% ( $n = 1367$ ) in men with normal erections. The occurrence of LUTS can be considered as an age-independent risk factor for the development of ED with an odds ratio (OR) of 2.11 ( $p < 0.001$ ).<sup>2</sup> Rosen et al<sup>5</sup> conducted the first multinational survey involving 12,825 men aged 50–80 years to confirm that sexual disorders and their impact on quality of life were strongly related to both age and severity of LUTS/BPH. The severity of ED is also correlated to the severity LUTS in the same age group. This relationship between ED and LUTS/BPH is independent of comorbidities including diabetes, hypertension, cardiac disease, and hypercholesterolemia.<sup>5</sup> One cross-sectional study for LUTS prevalence using ICS terminology criteria also revealed that men with multiple LUTS had more severe ED and more frequent EjD and premature ejaculation. Moreover, the findings of multiple LUTS were associated with worse sexual functions, which were independent of age, race, education, and body mass index.<sup>8</sup>

In another cross-sectional, multi-national study enrolling 5999 sexually active men with LUTS, reduced force of ejaculation (77.9%) and reduced semen amount (74.4%) were two common ejaculatory dysfunctions.<sup>9</sup> The severity of LUTS was the strongest predictor for the development of EjD. Men receiving previous BPH-related surgery and men treated with a 5 $\alpha$ -reductase inhibitor plus an  $\alpha$ 1-blocker or tamsulosin had the highest rates of dry ejaculation (67.4%, 57.2%, and 52.3%, respectively) compared with controls (31.6%,  $p < 0.001$ ).<sup>10</sup> Painful ejaculation is another one of the most common sexual dysfunctions among men with LUTS/BPH. In a real-life, prospective study, 688 out of 3700 (18.6%) sexually active men with LUTS/BPH were bothered by prostatitis-like symptoms or discomfort on ejaculation. Men with LUTS/BPH associated with prostatitis-like symptoms or discomfort on ejaculation had higher prevalence of ED (72% vs. 57%), and reduced ejaculation (75% vs. 56%), compared with LUTS/BPH men without prostatitis-like symptoms.<sup>11</sup> Therefore LUTS/BPH should be considered as an independent risk factor for the development of sexual dysfunctions based on an epidemiological survey. The exact linkage between LUTS/BPH and sexual dysfunctions is unclear, but aging with increased sympathetic tone, pelvis arteriosclerosis, increased smooth muscle Rho-kinase activity, and reduced nitric oxide–cyclic

guanosine monophosphate signal pathway had been suggested as common pathogenesis to LUTS/BPH and ED.<sup>12</sup> Recently aging, diabetes mellitus, and endothelial nitric oxide synthase 894T allele carrier gene polymorphism were the three independently common risk factors for both ED and BPH/LUTS in the Taiwanese population.<sup>13</sup>

### 4. The impact of LUTS/BPH medical treatments on male sexual function

The goal of medical treatments for men with LUTS/BPH is to relieve the bothersome symptoms and to prevent the development of complications. Since sexual dysfunction has a direct negative effect on the patient's QoL, any treatment of LUTS/BPH should aim not only to alleviate urinary symptoms, but also to maintain or improve sexual function. The mainstay choices of medical treatments for LUTS/BPH consist of alpha-blockers, 5-alpha reductase inhibitors (5-ARIs), or a combination of both for men with moderate to severe symptoms or larger prostates. Alpha-blockers (alpha adrenergic antagonists) are smooth muscle relaxants and can relieve the dynamic component in prostate stroma. Although alpha-blockers may also play an important role in relaxation of smooth muscles within corpus cavernosum, its impact on erectile function is still controversial. Intracavernosal injection of phentolamine, a nonselective alpha-blocker for smooth muscles relaxation, has been used as one of the pro-erectile agents for ED treatment before the era of phosphodiesterase type 5 inhibitors (PDE5Is). But the pro-erectile potential of these alpha-blockers should be balanced by their blood pressure lowering potential.<sup>14</sup> Furthermore 5-ARIs inhibit the transformation of dihydrotestosterone from testosterone, which is the active hormone for prostate growth and enlargement. EjD and ED are two common side effects among patients receiving 5-ARIs with or without alpha-blockers.<sup>15–19</sup> Reduced libido, orgasm disorder, or gynecomastia have also been noted among patients receiving 5-ARIs, which may be irreversible and lasted even after stopping medication. Therefore the Food and Drug Administration requested a 5-ARIs label revision in 2012 to state that libido disorders, ejaculation disorders, and orgasm disorders may continue after discontinuation of these drugs.<sup>20,21</sup>

### 5. Alpha-blockers

Five alpha-blockers including three pharmacologically non-uroselective  $\alpha$ 1 antagonists (alfuzosin, doxazosin, terazosin) and two highly uroselective  $\alpha$ 1A antagonists (tamsulosin and silodosin) are commonly used for the treatment of LUTS/BPH in Taiwan. The structures among these five agents may be different but their effectiveness on LUTS/BPH therapy is similar. However, their impacts on sexual function may be different. The influences on libido or sexual desire ranged from 0.6% to 2% and no documented orgasm disorder had been described in their package inserts. Moreover, the incidence of ED is also mild with <2% described in the package inserts (Table 1). Only limited clinical studies showed that the use of alpha-blockers may actually improve erectile function in men with LUTS/BPH.<sup>22,23</sup> However, all package inserts from the five drugs mentioned case report of priapism (Table 1). Ejaculation disorders might also become one of the major adverse events when prescribing highly uroselective  $\alpha$ 1A antagonists including tamsulosin and silodosin.<sup>15–19</sup> About 8.4–18.1% of patients receiving 0.4–0.8 mg tamsulosin and 28% of patients receiving 8 mg silodosin developed abnormal ejaculations such as reduced semen amount or dry ejaculation possibly due to highly uroselective  $\alpha$ 1A receptors inhibition on vas and seminal vesicles.<sup>14,18,19</sup> Physicians should inform patients about these potential sexual side events when prescribing these alpha-blockers for their LUTS/BPH treatment.

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