Ejaculatory dysfunction in the treatment of lower urinary tract symptoms

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Abstract: The link between lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) and sexual dysfunction is well established. Sexual dysfunction can encompass both ejaculatory dysfunction (EjD) and erectile dysfunction (ED). Ejaculatory dysfunction can consist of premature ejaculation, delayed ejaculation, retrograde ejaculation, anejaculation, decreased force of ejaculation and pain upon ejaculation. The impact of different medical and surgical therapies on ejaculatory function will be reviewed. We reviewed the various categories of LUTS treatment including the canonical epidemiology and pathophysiology as well as the surgical and medical treatments for LUTS/BPH. We note that most surgeries and several medical treatments have a certain but ill-defined negative impact on ejaculatory function. Several MISTs and selected medical therapies appear to have little impact on EjD. Both EjD and BPH are very common disorders in men under the care of an urologist. It is well documented that there is a clinical association between these two entities. Unfortunately many of the medical treatments and almost all surgical treatment impact the ejaculatory function of the patient. The surgical treatment of BPH often leads to retrograde ejaculation while medical treatment leads to anejaculation.

Keywords: Ejaculatory dysfunction (EjD); lower urinary tract symptoms (LUTS); benign prostatic hyperplasia (BPH); sexual dysfunction

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Introduction

The link between lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) and sexual dysfunction is well established. Sexual dysfunction can encompass both ejaculatory dysfunction (EjD) and erectile dysfunction (ED). Ejaculatory dysfunction can consist of premature ejaculation, delayed ejaculation, retrograde ejaculation, anejaculation, decreased force of ejaculation and pain upon ejaculation. The Multinational Study on the Aging Male (MSAM-7) has firmly established an epidemiological relationship between worsening LUTS and both ED/EjD (1).

Treatment for LUTS includes observation, medical management, and surgical therapy. Either medical management or surgical therapy is recommended for those with moderate to severe LUTS both to improve quality of life and reduce the risk of disease progression. Unfortunately both options increase the risk of EjD. The risk of EjD with medical management depends upon which agent is used. Alpha blockers frequently lead to anejaculation. The addition of a 5-α reductase inhibitors (5ARI) further increases the risk of EjD. The incidence of EjD following surgical therapy is highly dependent upon which intervention is chosen. The current gold standard, transurethral resection of the prostate (TURP), causes EjD
in 65% of patients and most urologist appropriately counsel patients accordingly (2). Less invasive therapies may spare ejaculatory function but at the cost of reduced efficacy in relieving LUTS. This review will survey the relationship between LUTS/BPH and EjD. The impact of different medical and surgical therapies on ejaculatory function will be reviewed.

Prevalence of LUTS/EjD in the general population

Multiple large scale studies have established the epidemiologic relationship between LUTS and EjD. The MSAM-7, a large scale multinational study involving six European countries and the USA, demonstrated that the prevalence of overall EjD was greater than 90% with 5% of respondents reporting the complete absence of ejaculation. In this study it appears that moderate-to severe EjD symptoms increase with age with ejaculatory complaints in 30.1%, 54.9%, and 74.3% of men 50–59, 60–69, 70–80 respectively (1). A recent analysis by Wein et al. suggested that both EjD and premature ejaculation are increased in patients with multiple LUTS (3). Multiple studies with diverse geographic locations have firmly established the link between LUTS and EjD (Table 1).

Pathophysiology of ejaculatory function

Few studies have investigated the pathophysiology linking BPH to EjD. Most research efforts have been clinical studies exploring the relationship between the medical and surgical treatment of BPH with EjD. Currently the basic understanding of the pathophysiology is limited. Ejaculation is a complex process, composed of two main phases, emission (ejaculate is deposited into the prostatic urethra from testes and accessory sex glands) and expulsion (sperm is forcefully expelled from the urethral meatus). The reflex involves an interplay of somatic, sympathetic, and parasympathetic pathways (9).

Pathways related to endothelial dysfunction have been implicated as being involved in both the development of LUTS as well EjD. The pathophysiologic mechanisms discussed in the literature include: reduced signaling in the...
Nitric oxide/cGMP pathway, increased RhoA-Rho-kinase (ROCK) signaling, autonomic hyperactivity, and pelvic atherosclerosis with associated pelvic ischemia (10,11). Nitric oxide synthase (NOS) containing neurons have been identified in the smooth muscle, urothelium, blood vessels, and bladder. Their highest concentration is at the region around the bladder neck and bladder outlet (12). NOS activity is necessary for the production of nitric oxide and therefore formation of cGMP, which mediates smooth muscle relaxation by decreasing intracellular levels of calcium. RhoA-Rho-kinase (ROCK), a mediator of \( \alpha \)-adrenergic and endothelin-1 (ET-1) triggered smooth muscle contraction, is another important player in maintaining proper smooth muscle tone in the LUT. An up-regulated RhoA/ROCK pathway could impair smooth muscle relaxation, and be involved in LUTS and EjD. Since normal ejaculatory function, particularly the emission phase, relies on the proper balance between sympathetic and parasympathetic nervous activity (13), any condition which disturbs the balance should be investigated for its role in EjD. Autonomic hyperactivity (AH), a component of metabolic syndrome, is a dysregulation between the sympathetic and parasympathetic tone. AH has been implicated as having a role in the development of LUTS as well as causing subjective dysfunctional voiding (14). Pelvic atherosclerosis reduces NO signaling, up regulates RhoA-ROCK contractile signaling, and is a component of metabolic syndrome and autonomic hyperactivity. Therefore, atherosclerosis of the lower urinary tract, particularly the prostate, penis and bladder, is regarded as the mechanism responsible for tying together all the theories previously described (15).

EjD, defined as any disturbance in ejaculation, entails a wide array of disorders, each with a potentially different mechanism related to LUTS. Retrograde ejaculation is the result of a problem during the expulsion phase of ejaculation. Emission of semen into the prostatic urethra remains intact. However, during expulsion, semen is sent into the urinary bladder, rather than being sent antegrade into the penile urethra. The retrograde flow of ejaculate into the bladder is permitted by a pathologically open internal vesical sphincter, or bladder neck (16). Endothelial dysfunction that leads to irregular NOS signaling and smooth muscle relaxation at the bladder neck/outlet could play a major role in the development of retrograde ejaculation and LUTS. Anejaculation, the complete loss of ejaculation, and decreased volume of ejaculate could be caused by decreased force of LUT smooth muscle contraction. Decreased secretions from the prostate gland, seminal vesicle, testis, or epididymis also play a role in anejaculation. One understood cause of painful ejaculation is aberrant sensation and inflammation from the prostate, which is also a known cause of LUTS. As will be explored subsequently many of the medical treatments for BPH are a cause of anejaculation.

**Effect of BPH treatments on ejaculatory function**

**Surgery**

**TURP**

It is well established that TURP causes ejaculatory dysfunction although it remains the gold standard for the treatment of BPH. The AUA BPH guideline panel estimates the incidence of of EjD with TURP at 65% (2). Consistent with this a review of 30 RCTs involving TURP showed the rate of EjD at 66.1% (8). It is must be appreciated however that pre-operative ejaculatory dysfunction is common in men undergoing TURP being estimated around 30–35%. In this CLasP study, which randomized men to either watchful waiting, TURP, On Nd: YAG resection, the rates of EjD were 43%, 62%, and 65% respectively. It is interesting to note that the rates of ejaculatory pain were decreased post-operatively in men undergoing TURP or Nd:YAG resection (17). A trial comparing monopolar versus bipolar TURP did not show a difference in the rate of ejaculatory dysfunction although the study was likely not sufficiently powered to detect a difference (18). The volume of resection does not appear to impact the incidence of EjD (19).

**HOLEP**

Holmium laser emits a 2,140 nm wavelength, preferentially absorbed by water which can be used to enucleate and/or resect prostatic adenoma. A RCT by Kunz et al. with 200 men comparing HOLEP with TURP showed very similar rates of EjD at 74.0% and 70.3% respectively (20). A smaller study by Wilson et al. with 61 patients with prostates larger than 40 grams showed similar rates of EjD in the small number of men sexually active 75.0% for HOLEP versus 61.5% for TURP (21). A recent pilot study explored a technique of sparing tissue within 1 cm of the verumontanum. Twenty-six patients underwent conventional HOLEP and 26 underwent an ejaculatory sparing HOLEP. The ejaculatory sparing technique did not dramatically reduce the rate of EjD. Of patients who underwent conventional HOLEP none had any ejaculatory dysfunction.
function while only 15% in the ejaculatory sparing technique avoided EjD (22). Clearly these modifications of standard procedures will require additional study before any endorsement can be made.

**Photovaporization**

PVP vaporization uses a light wavelength between 53 and 1,064 nm which is preferentially absorbed by hemoglobin over water leading to rapid vaporization of prostatic tissue (2). The GOLIATH study, a multicenter randomized trial, compared the Greenlight XPS to TURP. Greenlight XPS was noninferior to TURP for IPSS improvement, Qmax, and complications. The study reported EjD as an adverse event with similar rates of 67.1% and 65.1% for Greenlight PVP and TURP respectively (23).

**Transurethral microwave therapy (TUMT)/transurethral needle ablation (TUNA)**

TUMT and TUNA results in lower rates of EjD than TURP. The studies examining the difference are reporting EjD as an adverse event and it is not assessed by validated questionnaires. TUMT used both radiating heat energy and conductive cooling to induce damage of the lateral lobes while sparing the urethra. Francisca et al. conducted a randomized trial in 147 patients comparing TUMT to TURP. At 3 months 74% of those who underwent TUMT had preserved antegrade ejaculation with 27% in the TURP group (24). Likewise another randomized study comparing TUMT and TURP showed a similar difference in rates of antegrade ejaculation (77.8% vs 36.9%). In the latter study, consistent with the bulk of the literature, TUMT did not match TURP for objective improvement in LUTS (25).

**Urolift**

The prostatic urethral lift, Urolift, is a tissue sparing approach which involves the use of implants placed under cystoscopic guidance to retract the obstructing lateral lobes of the prostate. Data thus far indicate that the Urolift demonstrates a modest improvement in ejaculatory function with this treatment. The implant consists of a nitinol capsule tab, an adjustable polyeyletheleterphthalate filament, and a stainless steel urethral piece which epithelializes. Prospectively collected data from the L.I.F.T. study using the MSQH-EjD questionnaire showed improvement in EjD in patients undergoing Urolift and reduced bother at one year of follow up (26). A recent review of this data it appears that at the 3-year mark the confidence interval (CI) crosses 0 suggesting that improvement in EjD may be transient (27).

**Convective water vapor energy ablation**

The recently introduced Rezum System (NxThera, Inc., Maple Grove, MN) uses convective water vapor energy (WAVE™) as a thermal therapy to the transition zone of the prostate. This wet thermal energy in the form of water vapor that is dispersed into the prostatic adenoma which subsequently undergoes cell death and necrosis. No thermal effect occurs outside of the prostate. The initial trial by McVary et al. showed greater improvements in IPSS, Qmax, and peak flow rate in those who underwent thermal therapy as opposed to a sham procedure. No de novo erectile dysfunction was reported in the treatment group. Anejaculation, reported as an adverse event occurs in 2.9% of those who had thermal therapy and 0% in the sham group (28). In this RCT the IIEF and MSHQ-EjD-function score were not different from control at 3 months or from baseline at 1 year. The ejaculatory bother score improved 31% over baseline (P=0.0011). Also, 32% of subjects achieved minimal clinically important differences (MCID) in EF scores at 3 months, and 27% at 1 year including those with moderate to severe erectile dysfunction (ED). IPSS and Qmax were significantly superior to controls at 3 months and throughout 1 year (P<0.0001) (29).

**Medical therapies**

**Alpha-blockers**

Alpha adrenoreceptor antagonists are a mainstay in the treatment of LUTS associated with BPH. α1-adrenoceptors are stimulated physiologically by catecholamines. Catecholamines act on α1-adrenoreceptors on vascular smooth muscle to increase vascular tone and raise blood pressure. Additionally, these agents act on the smooth muscle in the prostate and bladder neck. Nonselective agents (terazosin, doxazosin) are associated with significant postural hypotension. Alfuzosin is also a nonselective agent although it does have lower rates of hypotension compared to terazosin and doxazosin. Tamsulosin and silodosin are α1a receptor antagonist associated with lower rates of postural hypotension but higher rates of ejaculatory dysfunction secondary to the predominance of α1a receptors in the vas deferens and seminal vesicles (30).

Many studies label the ejaculatory dysfunction associated with alpha blockers as retrograde ejaculation. Although this term is used in many of the large studies on the treatment of LUTS in BPH patients it actually represents anejaculation.
Animal studies using knockout mice for the α1A adrenoreceptor have shown decreased rates of pregnancy and decreased contraction of the vas deferens in response to norepinephrine (31). In a study of 15 healthy male volunteers in a double-blind crossover trial all participants reported the complete absence of ejaculation. Post masturbation urinalysis did not demonstrate notable levels of sperm in any of the patients consistent with anejaculation rather than retrograde ejaculation (32). A double blind trial comparing tamsulosin, alfuzosin and placebo by Hellstrom et al. showed similar levels of semen in post-ejaculatory urinalysis, thus supporting the hypothesis that alpha blockers induce anejaculation not retrograde ejaculation (33).

**Alfuzosin**

Alfuzosin is a nonselective α adrenoreceptor antagonist with equal affinity for α1A-, α1B-, and α1D subtypes but rarely causes hypotension (34). It does not enter the central nervous system. It is administered as a 10 mg daily dose and does not require titration. Three large double blind, placebo control trials demonstrated the safety and efficacy of alfuzosin for treating LUTS in BPH patients. The incidence of impaired ejaculation was 0.6% versus 0% of those taking placebo (35). An open label extension of one of the double blind trials showed that the incidence of ejaculatory dysfunction did not increase with one year of follow up (36). In fact a one year observation study of men treated with alfuzosin for LUTS reported improvements in the quality of ejaculate and reduced pain/discomfort associated with ejaculation (37). A randomized, double-blind, placebo-controlled, 3-way crossover design, with healthy male volunteers by Hellstrom et al. also showed that tamsulosin negatively impacts semen parameters (33).

**Doxazosin/terazosin**

These alpha adrenoreceptor antagonists were used in the treatment of hypertension before being used for the treatment of LUTS/BPH. Both these agents show equal affinity for α1A-, α1B-, and α1D receptor subtypes; therefore, these agents are associated with higher rates of asthenia and dizziness than placebo. Consistent with its nonselective features multiple trials have demonstrated that these agents have no higher rate of ejaculatory dysfunction compared with placebo (38,39).

**Silodosin**

Silodosin is a selective α1A adrenoreceptor antagonist approved for the treatment of BPH. It has the highest selectivity for the α1A versus α1B (162:1 ration) receptor of the commercially used alpha blockers (40). A large phase III trial in Europe demonstrated equal efficacy with tamsulosin for LUTS associated with BPH (41). During the 12 weeks of follow up with this study those taking silodosin had a higher rate of ejaculatory dysfunction than those taking tamsulosin (14.2% vs. 2.1%). An observational study of 30 men with moderate to severe LUTS who took silodosin 8 mg/daily reported a 90% prevalence of impaired ejaculation during the 4 weeks of follow up. Additional TRUS imaging of the seminal vesicles demonstrated a mean doubling of their volume after four weeks of therapy (8.1±6.4 vs. 16.4±8.2 cc) (42). There are conflicting studies whether orgasmic function is impaired in patients taking silodosin. A study out of Japan examined the effect of 4 mg daily silodosin on 15 healthy volunteers. One hundred percent reported anejaculation. All participants reported having an orgasm with although 80% reported that this was either somewhat uncomfortable or unsatisfying (43).

**Tamsulosin**

Tamsulosin is a selective α1-adrenoreceptor antagonist used in the treatment of BPH which has affinity for α1A over α1B. Tamsulosin also acts on dopaminergic and serotonergic receptors in the CNS (44). α1A adrenoreceptors are distributed in the epididymis, vas deferens, seminal vesicles, prostate, and bladder neck, all of which are involved in the emission phase of ejaculation. The seminal vesicles contribute approximately 80% of the ejaculate volume therefore blockade of α1A adrenoreceptors leads to anejaculation. Data from the AUA BPH Guideline panel shows a median incidence of EjD of 10% in those treated with tamsulosin (45). The duration of therapy does appear to impact the incidence of EjD. One open label study extension study with tamsulosin (follow up duration 77–104 weeks) the incidence of abnormal ejaculation was 30%.

Animal studies have shown that the effects of tamsulosin and alfuzosin on the bladder neck and seminal vesicles are similar (46). This raises the likelihood that the pronounced effects of tamsulosin on ejaculation are at least in part due to effects on the CNS. This is consistent with studies showing intravenous administration of tamsulosin impaired impaired contraction of the bulbospongious muscle while alfuzosin did not (47).

**5-alpha-reductase inhibitors**

Inhibition of the enzyme 5-alpha reductase, which catalyzes the conversion of testosterone to dihydrotestosterone is another medical therapy used for the treatment of BPH/
LUTS. The type 1 isoenzyme is expressed in most tissues while the type 2 isoenzymes is primarily within the male reproductive tract. Finasteride selectively inhibits the type 2 isoenzyme. Dutasteride inhibits both the type 1 and type 2 isoenzymes. Those taking finasteride have a 4% adverse event rate of EjD compared to 1% in those taking placebo (30). A multicenter double blind RCT comparing dutasteride to placebo demonstrated a 2.2% and 0.8% incidence of EjD as an adverse event (48). The prevalence of EjD appears to decrease after one year of treatment. The mechanism of this adverse effect is not completely understood. Fwu et al. analyzed prospectively collected data on EjD from the EjD using the BMSFI questionnaire. This study found a small but statistically significant increase in EjD in men taking finasteride with 18% reporting worsening of ejaculatory function versus 12% in those taking placebo at four years of follow-up (49).

In 2011 the FDA took an interest in adverse events (AEs) related to 5ARI exposure and began collecting information on all 5ARIs using the adverse event reporting system (FAERS) (50). Meanwhile, the National Institutes of Health sent out a Global Public Health Advisory recognizing a cluster of symptoms that are associated with finasteride: Post-Finasteride Syndrome (PFS). A small percentage of men on finasteride 1 mg complained of erectile dysfunction, change of libido or semen quality compared to placebo (3.8% vs 2.1%) (51). Some studies with questionable methodology noted the 1mg dose for male pattern baldness (MPB) was associated with persistent symptoms (52,53). Although there was no conclusive evidence regarding AEs seen with finasteride 5 mg (versus 1 mg finasteride), the FDA mandated a label change on all finasteride products advising a risk of libido loss, erectile dysfunction, ejaculatory disorders, gynecomastia, and other adverse sexual experiences. Shortly thereafter, the company that makes dutasteride voluntarily changed their product label, presumably with the thought that the AEs surrounding finasteride would apply to all 5ARIs. In a recent review of the FDA database, dutasteride was not implicated for PFS. The reported persistent nature of AE associated with finasteride or whether or not PFS is real or imagined cannot be assessed from the FAERS database. PFS requires further research utilizing a matched control group that shares baseline characteristics of those reporting PFS.

**Combination therapy (5 ARI with alpha blocker)**
The sexual side effects associated with combined therapy consisting of an alpha blocker and a 5ARI are qualitatively them same but with a higher incidence in those on combination compared to monotherapy. The MTOPS study compared finasteride/doxazosin monotherapy, monotherapy with finasteride, monotherapy with doxazosin, to placebo. The rates of EjD were 14.1% for combination therapy, 7.2% for finasteride monotherapy, 4.5% for doxazosin monotherapy, and 2.3% for placebo (54). The COMBAT trial was a large multicenter RCT comparing tamsulosin monotherapy, dutasteride monotherapy, and tamsulosin/dutasteride combination therapy. There was no placebo arm. This study also demonstrated a higher rate of EjD with combination therapy than monotherapy (55).

**PDE5I and anti-muscarinics**
PDE5I are first line treatment for use in erectile dysfunction. These agents have been increasingly utilized for the treatment of LUTS/BPH. By increasing cellular levels of cGMP these medications have been shown to increase LUT oxygenation, induce smooth muscle relaxation in the prostate and bladder neck, decrease prostatic stromal proliferation, and reduce afferent nerve activity from the LUT (56). These agents have been shown to reduce prostatic inflammation, particularly in men with the metabolic syndrome (57,58). When used to treatment men with BPH, PDE5Is have shown improved IPSS scores, improved QOL scores with minimal effect on maximum urinary flow rate (59,60). While PDE5Is have been used for premature ejaculation, particularly in conjunction with SSRIs, at the current time there is no data measuring their impact upon ejaculatory function in patients with BPH (61).

Antimuscarinics are used in the treatment of both male and female OAB symptoms. There are five muscarinic receptor types (M1, M2, M3, M4 and M5). M2 and M3 are the primary receptors in the male LUT (62). Animal studies suggests that the M3 receptor is active in both the vas deferens and seminal vesicles (63,64). At this time there is no data clarifying the impact that anticholinergic medications may have on ejaculatory function.

**Phytotherapy**
Phytotherapeutic agents are frequently taken for the treatment of LUTS/BPH. They are derived from the roots, seed, bark, and fruits of plants (Table 2). They are generally well tolerated. Overall there is little data addressing the impact of phytotherapeutic agents for EjD. In a randomized trial comparing Serenova Repens with Tamsulosin the rate of EjD was higher with Tamsulosin (4.2% vs 0.6%) (65).
Conclusions

Both EjD and BPH are very common disorders in men under the care of an urologist. It is well documented that there is a clinical association between these two entities. Unfortunately many of the medical treatments and almost all surgical treatment impact the ejaculatory function of the patient. The surgical treatment of BPH often leads to retrograde ejaculation while medical treatment leads to anejaculation. Selective $\alpha$-blockers, tamsulosin and silodosin are more likely to be associated with EjD although they tend to be better tolerated. Alfuzosin, doxazosin, and terazosin rarely cause EjD. The most effective surgical therapies for BPH (TURP, HoLEP, Photovaporization) tend to cause highest rates of EjD despite overall QOL scores being higher postoperatively. Patients should be thoroughly counseled regarding the ejaculatory impact any BPH therapy may have.

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Footnote

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