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Management of Overactive Bladder After Treatment of Bladder Outlet Obstruction

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Abstract

Purpose of Review To discuss the epidemiology and pathophysiology of overactive bladder (OAB) after bladder outlet surgery (BOS), review the prognostic factors associated with persistent OAB, and present evaluation and management strategies.

Recent Findings A randomized trial of preoperative urodynamics in male lower urinary tract symptoms is underway; however, high-level evidence for management of persistent OAB after BOS is lacking.

Summary Identification of prognostic factors for persistent OAB symptoms is important for counseling patients before BOS; however, the data guiding such counseling are limited. In general, patients who are older, have lower bladder capacity, and higher amplitude and earlier detrusor overactivity are more likely to have persistent symptoms. After BOS, men may be less likely than women to respond favorably to advanced therapies for OAB than women and should be appropriately counseled.

Keywords Overactive bladder · Bladder outlet obstruction · Storage symptom · TURP · Pelvic organ prolapse

Introduction

Accurate assessment of which patients will experience resolution of detrusor overactivity (DO) and associated symptoms after a bladder outlet procedure has important clinical implications. In men, lower urinary tract symptoms (LUTS) frequently result in large part from prostatic enlargement with resultant bladder outlet obstruction (BOO). In women, anatomic obstruction is most commonly secondary to high-grade anterior and apical compartment pelvic organ prolapse (POP). Both men and women may also experience iatrogenic or traumatic obstruction from stricture or anti-incontinence procedures. Regardless of etiology, prior to proceeding with potentially morbid procedures to correct outlet obstruction, patients understandably wish to know whether their most bothersome storage symptoms (e.g., urgency, frequency, and nocturia) are likely to resolve. Clinicians know that while most patients will do well after addressing presumed BOO, some will fail to experience improvement in storage symptoms and a subset may even worsen, a dreaded outcome for patients and clinicians alike.

Because relief of BOO is the primary goal of intervention, and objective measures of "success" (e.g., flow rates, post-void residual) are fairly simple to measure, more is known regarding the efficacy of pharmacologic and evolving surgical options for BOO in improving obstruction and voiding LUTS. In contrast, knowledge regarding the likelihood of non-resolution or worsening of storage symptoms—and management of these symptoms—is relatively more limited despite persistent storage dysfunction being fairly common. Specifically, DO and its associated symptoms, such as urgency, frequency, and nocturia, may be present in 20 to 40% of patients despite absence of residual BOO [1••]. This subset of patients is the focus of this manuscript, which will describe the pathophysiology of overactive bladder (OAB) related to BOO in men and women, review clinical predictors and frequency of persistent storage symptoms after treatment of BOO, and present strategies for their evaluation and management.

This article is part of the Topical Collection on *Overactive Bladder*

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Epidemiology

BOO can result from a number of pathologic states or diseases, but the most common culprit in men is benign prostatic enlargement (BPE). BPE generally correlates with benign prostatic hyperplasia (BPH), a histologic diagnosis often used clinically to refer to male LUTS thought to be related to BPE. The prevalence of BPH rises with age, affecting roughly 70% of American men 60–69 years of age and increasing to nearly 80% of those aged 70 years or older [2]. In women, high-grade POP is a common cause of BOO, impacting approximately 70% with this condition for which over 300,000 surgeries are performed in the USA annually [3, 4].

OAB is a syndrome defined by the International Continence Society (ICS) as "urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence (OAB-wet) or without (OAB-dry), in the absence of urinary tract infection or other detectable disease." [5]. OAB impacts 12–14% of men and women > 40 years of age and 50–80% of men with BOO [6]. Urge urinary incontinence (UUI) disparately impacts women, with a reported prevalence of 2–29% across studies; however, as many as 9% of men report UUI [7, 8]. Despite differences in the rate of associated incontinence, bother from urgency, frequency, and nocturia are common to both sexes and incontinence common even among men with OAB. Specifically, the presence of all four storage symptoms, i.e., urgency, frequency, nocturia, and UUI, has been reported in 51.3% of men and 59.2% of women with OAB [7]. Although voiding symptoms of slow flow, split stream, intermittency, hesitancy, and straining are more commonly found in men (25.7%), these symptoms impact 19.5% of women as well [8].

When voiding and storage symptoms coexist, as is often the case, the storage symptoms tend to be associated with the greatest degree of bother. In a study looking at 632 men with BOO from BPH, the investigators found that while the most prevalent symptoms were voiding predominantly, men were most bothered by their storage complaints reporting maximal detriment to quality of life coming from episodes of incontinence, nocturia, and frequency [9]. Unfortunately, persistence of OAB symptoms can be expected in over 20% of men after BOS, and only 50% of men undergoing transurethral resection of the prostate (TURP) and 20–30% of men undergoing simple prostatectomy can expect resolution of their preoperative DO on urodynamics following intervention [1••]. Rates of persistent OAB after POP surgery have been reported to be as high as 33–39%, and de novo OAB may be observed in 6% after surgical correction [10•, 11].

Pathophysiology of OAB and BOO

OAB apart from BOO is a clinical syndrome based on symptoms. Its pathophysiology is multifactorial across all levels of neural and muscular control, with several hypotheses regarding the etiology of OAB. The urothelium-based hypothesis attributes aberrations in homeostatic bladder function to the level of the urothelium. In response to local mechanical, osmotic, inflammatory, and chemical stimuli, the urothelium triggers afferent nerve signaling in excess of normal levels, leading to alterations in sensitivity, expression of cell membrane receptors, and release of chemical mediators that act on adjacent afferent neurons [12]. This increased afferent activity then augments the "normal" afferent stimulation produced by bladder fullness, resulting in premature activation of the micturition reflex.

The myogenic hypothesis proposes that detrusor overactivity contractions result from both an increased predisposition to abnormal smooth muscle contraction and increased signal propagation to the rest of the bladder [13, 14]. In the context of this hypothesis, a frequently proposed mechanism for the relationship between OAB and BOO is that chronic obstruction results in muscle hypertrophy and secondary histological changes that predispose to abnormal afferent and efferent activity [15]. These changes on a neuromuscular level may result in altered compliance secondary to composition changes in collagen, elastin, and smooth muscle within the wall of the bladder and the development of asynchronous or uncoordinated contractile efforts from areas of localized micromotions adjacent to quiescent areas [16]. This discordant motor function predisposes the bladder to unstable contractions or detrusor overactivity that circumvents the normal micturition reflex and overrides the guarding reflex. Furthermore, Barbosa and colleagues have found the histological alterations to normal composition of the detrusor muscle lead to a direct decrease in calcium-activated potassium channels, ultimately destabilizing the contractile function on a receptor level and predisposing to overactivity [17].

An additional factor that appears to contribute to the development of OAB in the setting of BOO is alteration in neuronal signaling both independent from and as a direct consequence of myogenic dysfunction and urothelial changes. With prolonged obstruction, the integration of information underpinning coordinated motor behavior of the lower urinary tract and voiding reflex becomes faulty and leads to increased afferent activity. To this end, histology from men with BOO from BPH after TURP showed increased M2 and M3 receptors, with concentrations highest among those with persistent overactivity following surgical intervention [17]. Ultimately, peripheral afferent changes lead to detrusor muscle cells with altered innervation, causing upregulation of surface membrane receptors with altered membrane potential, which increases the likelihood of spontaneous contraction in that cell.

Ischemia may also contribute to OAB in the setting of chronic BOO via oxidative stress pathways. Hypoxia results in damage to epithelial cells, smooth muscle cells, microvasculature, and nerve fibers which leads to alteration in expression of apoptotic markers, resulting in patchy denervation, periodic ischemia, and neuronal death [15, 18]. Andersson et al. proposed that detrusor hypertrophy in BOO causes cyclic ischemia/hypoxia, with generation of free radicals and disruption of calcium homeostasis, resulting in specific damage to neuronal membranes, the sarcoplasmic reticulum, and mitochondria, with resultant OAB [19].

The pathophysiology of OAB, whether resulting from or independent of BOO, suggests that many changes will not be completely reversible after treatment of outlet obstruction, thereby resulting in persistent symptoms.

Clinical Characteristics Associated with Persistent and Concomitant Symptoms of OAB

Aging

Older age is directly linked with increased prevalence of both BOO and OAB; however, OAB is often present even in the absence of BOO. Holm and Horn reported that histologic changes in detrusor nerve density and fibrosis seen in BOO are not distinguishable from those of aging, suggesting that OAB symptoms and BOO are at least in part unrelated events occurring with an incidence increasing with age [20]. To this end, urodynamics demonstrate DO in more than 50% of men older than 70 years who do not have obstruction [21•]. Knutson and associates reported that among 162 patients with BOO, 55% had pure BOO and 45% concomitant BOO and OAB [22]. Those with BOO and OAB tended to be older (> 75 years of age) and were more obstructed.

By consequence, persistence of OAB symptoms after treatment of BOO appears to be associated with age. A study inclusive of 26 men with preoperative DO who underwent TURP found that those with persistent DO on 12-month post-operative urodynamic testing were significantly older (68.9 vs. 63.4 years, $p = 0.043$) [1••]. Similarly, age was independently associated with persistent storage symptoms at 6 months (OR 1.05, $p < 0.05$) in 116 men who underwent TURP [23••].

De Nunzio et al. compared post-operative symptoms at 1 and 5 years in men who had undergone TURP with those in a control group who continued pharmacologic treatment and "watchful waiting." While they noted a 54% reduction in DO in the intervention arm, there was an increase in DO from 45 to 55% with no significant change in the degree of obstruction based on uroflowmetry and urodynamic studies in the watchful waiting group. This further suggests that aging alone impacts the increasing prevalence of DO in this population [24].

Aging also appears to be an important prognostic factor for OAB symptom persistence in women undergoing repair of POP. A study inclusive of 80 women undergoing transvaginal mesh repair of anterior and/or apical prolapse repair with preoperative OAB symptoms identified persistence or worsening of OAB symptoms in 31% of women over age 60 years vs. just 12% in those under age 60 ($p = 0.042$) [25]. Johnson et al. similarly found age to be an independent risk factor for persistent OAB symptoms after prolapse repair [10•]; however, this association is not consistent across the literature [26, 27].

Prostate Size

Antunes et al. found that prostate volume was greater in men with persistent DO after TURP (61.5 g vs. 48.4 g); however, the 13.1-g difference did not reach statistical significance ($p = 0.098$) [1••]. Others have not found their data to support this relationship between volume and persistent DO [15, 23••].

Kim et al. sought to identify factors related to improvement in storage symptoms on International Prostate Symptom Score (IPSS) in patients after TURP; they specifically examined the impact of prostate shape on preoperative TRUS. In a group of 160 patients, 67 (41.8%) were separated into a preoperative "irritative" group and 93 (58.2%) to the "non-irritative" group. They found that in patients with pre- and post-TURP storage symptoms, hyperplasia limited to the transition zone without retrourethral enlargement showed a statistically significant decrease in IPSS post-operatively compared with patients with retrourethral enlarged prostates [28].

Post-void Residual and Acute Urinary Retention

Hur et al. found that only 71/139 men (51.1%) had improved urgency a minimum of 3 months after holmium laser enucleation of the prostate (HoLEP) [29]. Persistent urgency was associated with absent history of acute urinary retention (AUR) (persistent urgency in 9% with history of AUR vs. 25% without, $p = 0.010$) and lower preoperative post-void residual (PVR) (69 mL vs. 111 mL, $p = 0.035$) [29]. In contrast, Wada et al. found that vascular resistive indices, a signal of ischemia and associated with persistent storage symptoms in their study, were significantly higher in men with preoperative PVR > 60 mL, perhaps indicative of adverse pathophysiologic changes that may be associated with increased residual urine [30].

Baseline Lower Urinary Tract Symptoms

In general, worse baseline storage LUTS have been found to be associated with increased likelihood of post-operative OAB, whether indicated by baseline symptom scores or more adverse urodynamic storage parameters. Choi et al. found that persistent storage symptoms 6 months after TURP were significantly associated with severity of baseline storage symptoms [23••]. However, other studies have suggested that those with worse storage symptoms may have the most to gain from an outlet procedure [31].

Severity of Pelvic Organ Prolapse

Several studies have assessed the effect of surgical POP correction on OAB symptoms as well as their relationship with various urodynamic parameters. Interestingly, isolated correction of posterior compartment prolapse may also result in improvement in OAB symptoms, suggesting that the relationship between POP and OAB is not simply related to obstruction from anterior and apical descent [32].

Johnson et al. found that 61% of women with preoperative OAB symptoms undergoing POP repair of any compartment experienced resolution of symptoms post-operatively [10•]. Speaking to the complex relationship between POP and OAB, in this cohort, neither stage of POP nor concomitant sling was significantly associated with resolution of OAB symptoms.

Miranne and colleagues investigated how overactive bladder symptoms changed after correction of symptomatic apical or anterior compartment POP. The investigators analyzed 183 women undergoing POP surgery and excluded those who did not have OAB symptoms preoperatively. They found that post-operative rates of both urinary frequency and urge urinary incontinence did not differ based on severity of POP [33]. In their cohort, 5–10% of patients had their urge urinary incontinence worsen and 10–15% of patients had persistent UUI [33]. Taken together, these data suggest that while most women experience an improvement in their OAB symptoms after correction of POP, the relationship of prolapse severity to symptom response remains equivocal.

Urodynamic Parameters Associated with Persistent and Concomitant Symptoms of OAB

The AUA and EUA do not mandate urodynamic studies prior to intervention for presumed outlet obstruction but acknowledge their potential to aid clinicians in counseling and clinical decision-making. The Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM) is an ongoing randomized control trial in the UK evaluating the utility of urodynamics (UDS) in men with LUTS considering outlet surgery [34]. A total of 820 men will be randomized to urodynamic evaluation and non-invasive evaluation (i.e., flow rate, symptom score, and bladder diary) vs. non-invasive evaluation alone. The primary outcome measure will be symptom score improvement. Secondary outcome measures include the proportion of men proceeding to outlet surgery, cost-effectiveness, maximum flow rates, adverse events, and directed questionnaires. While the role for urodynamics is not yet well established in this space, several studies have shed light on the ability of urodynamic parameters to predict storage symptom response to BOO surgery.

Maximum Urinary Flow

Jiang and colleagues found that men with BOO with persistent or residual OAB symptoms after initial medical management were more likely to have total prostate volume > 40 mL with a maximum urinary flow (Qmax) < 12 mL/s [35]. While an enlarged prostate may not indicate the presence of BOO, the mean prostate volume of patients with BOO was significantly greater than that of patients without BOO. These parameters are in contrast to those exclusively with OAB symptoms and no BOO who had prostate volume < 40 mL and Qmax> 12 mL/s.

Detrusor Overactivity

Jiang et al. found that 62.4% of patients with persistent storage symptoms after initial medical treatment pursuing surgery still had BOO, whereas the remaining 37.6% had DO only [35]. These findings suggest the importance of strict counseling with patients seeking surgical treatment of BPH with DO regarding the uncertainty of symptom resolution with intervention.

Zhao and colleagues performed a retrospective study on 128 patients with urodynamically demonstrated BOO and preoperative storage symptoms who underwent TURP. They found statistically significant improvement in mean OAB symptom scores after TURP in all men but found that the presence of terminal DO on preoperative urodynamic studies was associated with a significantly higher incidence of persistent OAB symptom scores compared with patients with phasic and no DO [36••]. Not only the presence but also the severity of DO appears to influence likelihood of resolution. Antunes et al. found that men with persistent DO at 12 months were more likely to have preoperative DO amplitude > 40 cmH_2O (71% vs. 22%, $p = 0.04$) [1••].

DO may be an important predictor of symptom resolution after POP repair as well. Tomoe conducted a prospective study of 100 women undergoing POP surgery for grade 2 or greater anterior compartment POP. Urodynamic evaluation was performed both before and after surgery. Fifty-three percent of the cohort had OAB, of whom 52.8% had DO on preoperative urodynamics [11]. Interestingly, 80% (20/25) of patients in whom DO improved or disappeared with gauze reduction of POP experienced resolution of DO post-operatively vs. 66% overall, suggesting this may be a clinically meaningful predictive parameter.

Maximum Cystometric Capacity

Decreased maximum cystometric capacity (MCC) (< 200–250 mL) has been associated with persistent storage symptoms [23••] and greater likelihood of persistent DO following TURP [1••]. Decreased MCC may be an even more meaningful predictor of persistent OAB symptoms in older patients, as men older than 75 years with diminished bladder capacity have been shown to be more likely to be dissatisfied after intervention, much of which may be attributed to 83% having persistent OAB symptoms 1 year post-operatively [21•].

Other Factors Associated with Persistent Symptoms of OAB

Ischemia

One of the most important mechanisms associated with bladder damage may be a decrease in lower urinary tract perfusion. Mitterberg et al. investigated the proposed ischemia model underlying mechanism of detrusor overactivity in BPH patients using color Doppler ultrasonography (CDUS) to calculate the resistive index (RI), related to both blood flow and pressure, and used it as an indicator of vascular resistance to small vessels. They correlated the vascular outcomes with clinical and urodynamic findings and found patients with BPH and UDS evidence of obstruction had significantly lower perfusion of the bladder with a significantly higher resistive index prior to surgery [18]. After intervention with TURP, a statistically significant difference was observed in bladder perfusion in those with persistent OAB vs. those without, corresponding to increased vascular resistance, decreased blood flow, and hypoxia [18]. Saito and colleagues found increased bladder perfusion following HoLEP to be the only independent predictor of a decrease in storage symptoms, suggesting that in many patients relief of BOO may improve blood flow in the bladder mucosa and reverse adverse pathophysiologic changes that may have exacerbated storage symptoms [37].

Assessment and Management of Persistent Symptoms of OAB

Initial Assessment and Advanced Evaluation(s)

When patients are present for evaluation of persistent OAB symptoms after outlet surgery, management is guided principally by a thorough history, physical exam, and diagnostic testing. History may reveal improvement in voiding symptoms with persistent or worsened storage symptoms. Nocturia persisting after BOO is addressed and may require directed therapy towards comorbid conditions such as sleep apnea or nocturnal polyuria secondary to decreased renal concentrating ability. Timing from BOO surgery is important. Improvement in urinary incontinence may take up to 12–24 months, although it will persist in many [38]. The physical exam should include a full genitourinary and pelvic exam to look for anatomic factors associated with OAB symptoms such as recurrent or residual POP in women and meatal stenosis in men. If the surgery was performed at an outside institution, every effort should be made to obtain a copy of the original operative report to assess for any intraoperative deviations from the planned procedure or complications.

Although the indications for preoperative cystoscopic evaluation and urodynamic testing are not clear in the previously unoperated patient, these studies should be strongly considered in those with persistent symptoms despite surgery. Cystoscopy may reveal urethral stricture, bladder neck contracture, or persistent obstructing prostate tissue. Urodynamics may reveal detrusor underactivity, overactivity, residual outlet obstruction, or even stress urinary incontinence. We generally prefer to perform video urodynamics in these patients, as we find there is significant diagnostic benefit in visualizing the bladder neck and sphincter during voiding to evaluate for anatomic obstruction. This may be especially true in patients with detrusor underactivity in whom definitive cystometric outlet obstruction will not be found.

Medical and Behavioral Therapy

There is relatively limited data on management specific to persistent *or* de novo storage lower urinary tract symptoms after surgery. Persistent anatomic obstruction may be managed with a repeat outlet procedure whereas severe detrusor underactivity in the absence of apparent obstruction may be best managed with intermittent catheterization. In the absence of either of these findings, much of the treatment of persistent OAB symptoms after an outlet procedure should follow OAB guidelines.

For the urologist charged with managing and treating these patients with persistent storage symptoms after outlet surgery, there is a bevy of options available. First-line therapy includes lifestyle modifications, i.e., caffeine and bladder irritant avoidance and pelvic floor physical therapy. Antimuscarinic therapy has been demonstrated to improve storage symptoms of men and women with OAB [39–41]. Similarly, beta 3 agonists have also been shown to improve storage symptoms, both as monotherapy and in combination with either alpha blockers or anticholinergics [42, 43]. Although not as commonly employed due to side effects, combination anticholinergic therapy can improve urinary frequency, urgency, and UUI, as well as improve bladder capacity and detrusor compliance in appropriately selected men with BPH [44, 45]. In men with possible residual obstruction unwilling to undergo repeat surgery, alpha blocker and anticholinergic therapy may be appropriate, as the combination has been shown to improve overall symptom scores as well as storage-specific metrics in men with mixed lower urinary tract symptoms [46].

Botulinum Toxin

Should medical monotherapy or combination therapy not prove effective in alleviating persistent storage symptoms, there are several surgical options available. Intradetrusor botulinum toxin injections have been shown to significantly improve quality of life in patients with overactive bladder refractory to medical therapy [47], reduce UUI, frequency, urgency, and nocturia, and increase voided volumes [48]. In general, men may not expect to experience as dramatic a response to intradetrusor botulinum toxin injection as compared with women [49, 50]; however, in the absence of residual outlet obstruction, the difference in efficacy may narrow. Habashy et al. evaluated outcomes in 43 men undergoing onabotulinumtoxinA injection for medication-refractory non-neurogenic OAB, 11 of whom had undergone radical prostatectomy and 9 TURP [51]. Those who had undergone prior prostate surgery experienced a mean decrease in pad use from 2.8 to 1.6 ($p = 0.01$) and reported a Patient Global Impression of Improvement (PGI-I) score of 2.6 ± 0.5 (i.e., between much better and a little better). However, breakdown by procedure type found that most of the reported gains were due to improvements in the radical prostatectomy group, as the 9 post-TURP patients experienced no significant mean reduction in pad usage and had a mean post-treatment PGI-I score of 3.3 ± 0.8 (i.e., a little better to no change).

Neuromodulation

Neuromodulation, including tibial nerve stimulation [52] and sacral nerve stimulation, remains a viable alternative in treating refractory OAB with success rates as high as 70–80% [53, 54]. Those with DO may not be expected to respond as well to tibial nerve stimulation, but men and women may be able to expect similar results [55]. However, men with storage symptoms before or after an outlet procedure tend not to fare as well as women with sacral nerve stimulation. In a review of 128 cases of sacral nerve stimulation at their institution, Stensland and colleagues found that male sex, diagnosis of BPH, and lower volume at first urge on urodynamics (specifically < 100 mL) were all associated with unsuccessful sacral nerve stimulation trial [56]. Similarly, only 12/17 (71%) men vs. 101/110 (92%) women went onto second-stage sacral nerve stimulation in a contemporary cohort of patients ($p = 0.01$) [57].

Beyond the trial period, women who have had prior prolapse surgery may not be as likely to experience sustained benefit despite similar outcomes at 3 months [58]. Nevertheless, in general, both men and women initially responding to neuromodulation can expect to experience sustained benefit at 3 years across multiple storage symptoms [59].

Conclusions

While surgery for BOO helps many patients with bothersome lower urinary tract symptoms, there remains a significant proportion of patients who experience persistent OAB symptoms after outlet surgery. The etiology is multifactorial, and there are a number of pathophysiologic factors that play a role in the development of OAB that may not be reversible upon treatment of BOO. In general, worse baseline symptoms and urodynamic parameters (e.g., DO onset and amplitude and cystometric capacity) are associated with greater likelihood of persistent storage symptoms. Pharmacologic therapy and procedural OAB management can be efficacious, with greater anticipated benefit in women. Overall, both men and women with prior outlet procedures or surgery for prolapse may be less likely to benefit. Future research should focus on optimal patient selection for BOO surgery and management strategies for those with persistent symptoms.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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- •• Of major importance

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