Overactive Bladder and Men: Indications for Anticholinergics

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Similar to bladder outlet obstruction (BOO), overactive bladder (OAB) symptoms are very common and increase in prevalence as men age. Whether or not OAB symptoms are thought to be secondary to BOO, the goal of treatment of symptoms should result in an improved quality of life and ultimately prevent clinical deterioration. A common dilemma when treating men with obstruction and OAB is the risk of acute urinary retention or morbidities related to increasing postvoid residuals. In this article, the relationship of OAB to BOO is examined and the role of urodynamics and data on the use of anticholinergics in men with OAB and obstruction are reviewed. An algorithm for managing men with OAB also is proposed. In men with OAB without evidence of obstruction (including OAB after treatment for BOO), first-line medical therapy with anticholinergics is indicated. However, in men with OAB and concomitant BOO, nomogram has been developed to assist in the management of patients at risk for urinary retention. Men with significant obstruction should be appropriately treated to decrease bladder outlet resistance before adding anticholinergics for the treatment of OAB.

Introduction

Overactive bladder (OAB) describes a symptom syndrome suggestive of lower urinary tract dysfunction, specifically defined as "urgency, with or without urge incontinence, usually with frequency and nocturia… if there is no proven infection or other obvious pathology" [1••]. OAB symptoms are very common among aging men. In a population-based symptom-prevalence survey across six European countries that included more than 7000 men older than 40 years of age, more than 16% suffered from OAB symptoms. Considering only the men older than 60 years of age, this percentage increases from almost 20% to more than 42% in men older than 75 years [2•]. Furthermore, more than 79% of these patients had experienced OAB symptoms for longer than 1 year, demonstrating the chronic nature of the condition. Similarly, a survey of 5000 US residents by the National Overactive Bladder Evaluation program found that the overall prevalence of OAB in men was 16% and increased with age [3].

The chronicity of lower urinary tract symptoms (LUTS) in men develops from the nature of the contributing causes, including benign prostatic hyperplasia (BPH), primary bladder neck dysfunction, and abnormal voiding dynamics from neurologic defects. Each of these entities can result in problems with emptying, filling/storage, or both, resulting in combinations of irritative and obstructive voiding symptoms. When these symptoms are present to a moderate or severe degree, they may herald urinary retention and untreated LUTS may place male patients at risk for potential clinical deterioration [4]. As LUTS worsen in severity, they portend poorer overall quality of life and general health status compared with the unaffected general population [5].

Because of the negative impact of worsening LUTS on the quality of life and health status of aging men, treatment is clearly indicated. Optimal therapy depends on the treatment of bladder outlet or storage problems to achieve symptom relief and a reduction in BOO. Treatment of BOO is hardly controversial; however, the use of anticholinergics in men for OAB is an evolving therapeutic concept. This article examines the role of anticholinergics in the treatment of men with OAB.

The Relationship of Bladder Outlet Obstruction and Overactive Bladder

There is no doubt that detrusor overactivity (DO), which is the presumed mechanism of OAB, and BOO coexist. In the study by Kaplan *et al.* [6•] of more than 2800 consecutive men older than the age of 50 years who were evaluated for LUTS, 62% had urodynamic evidence of BOO. Of these, 66% had concomitant DO. This is consistent with several studies reporting that, in patients with BPH, concomitant DO is present in 40% to 60% [7••,8•–10•].

Although many OAB symptoms in aging men often are ascribed to BOO secondary to BPH, these symptoms likely result from abnormalities in detrusor function because no correlation between irritative symptom score and prostate histopathology has been demonstrated [11]. As men age, the incidences of BOO and OAB increase [2•]. However,

the quandary in the relationship between BOO and OAB lies in whether they are inter-related or develop independently with age. Each statement is partially true and there is evidence to support both.

Abdel-Aziz and Lemack [12] review some of the pathophysiologic explanations for BOO-induced bladder instability. Animal models and human studies have revealed that obstruction-induced changes include neuronal hypertrophy secondary to increased nerve growth factor [13], selective axonal degeneration [14], cholinergic receptor up-regulation [15], and microstructural changes (protrusion junctions and ultraclose abutments) that facilitate stronger and faster micturition contractions and capacitate involuntary activation of detrusor muscle cells [16]. These findings suggest that BOO may induce changes in bladder innervation and contractile properties that subsequently cause DO [12].

On the other hand, the independent development of OAB symptoms, in the absence of BOO, often is accompanied by changes in the detrusor itself. In the aging bladders of men and women, investigators have demonstrated the loss of detrusor volume, decreased neuronal density, and increased intramuscular fibrosis [16–18]. Because these findings also are seen in obstructed bladders, a similar pathophysiologic explanation may link these outwardly distinct etiologies to the common symptom complex of OAB [4].

The Role of Urodynamics in Evaluating Overactive Bladder in Men

Before discussing urodynamic studies, some terminology must be clarified. When reviewing past studies, the reference to detrusor instability (DI) was changed to DO to reflect changes in the International Continence Society's recommendations of terminology. DO may be qualified, when possible, by cause as "neurogenic" when there is a known neurologic condition (replaces detrusor hyperreflexia) and "idiopathic" when there is no defined cause (replaces detrusor instability) [1••].

To determine the role of urodynamics in treating and following OAB, we should first analyze the relationship between OAB symptoms and urodynamic measurements. Although the urodynamic finding of increased DO is thought to result in OAB symptoms [12,19•], the link between OAB symptoms and urodynamic findings has been difficult to establish. Symptom scores (*eg*, those assessed with the International Prostate Symptom Score) are not reliable predictors of urodynamic findings [8•,9•,20].

However, two independent studies suggest a relationship between the OAB symptoms of urge and urge incontinence with DO. In the first study, of 160 men with LUTS, 68% had BOO and 46% had concomitant DO; the symptom of urge incontinence correlated with the presence of DO on urodynamic evaluation [9•]. In a separate study of 459 men in Egypt, the presence of DO correlated with the perception of the urge symptom and quality of life on the International Prostate Symptom Score [20]. Otherwise, the relationship of other OAB symptoms such as frequency and nocturia to the presence of DO is weak, at best. The next question concerns who should have urodynamics.

Which Men Should Have Urodynamic Evaluation for Overactive Bladder?

Urodynamics are most useful in the following three groups of men with LUTS: men with suspected neurologic deficit (*eg*, Parkinson's disease, diabetes, cerebrovascular accident, or spinal cord injury), young men without an obvious cause of their symptoms, and men with suspected BOO secondary to BPH refractory to medical therapy before surgical intervention.

In men with a neurologic deficit resulting in neurogenic DO, urodynamic evaluation is essential for defining abnormalities in storage and emptying functions. Findings on urodynamics can run the gamut of urodynamic diagnoses depending on the level of the neurologic deficit. Even a single diagnosis such as diabetes can result in an array of urodynamic findings ranging from neurogenic DO to detrusor areflexia [21•]. Because OAB symptoms can result from a variety of causes, effective treatment depends on identification and characterization of the underlying pathophysiology.

In young men with OAB, anatomic abnormalities (*eg*, stricture) and infections must be excluded. If symptoms persist, urodynamic evaluation is key. Urodynamics can identify patients with discreet etiologies of their symptoms, such as bladder neck dysfunction [22]. In the authors' experience, men referred for refractory prostatitis often have primary bladder neck dysfunction as the cause of their LUTS [23–25].

Lower urinary tract symptoms in aging men generally are attributed to BPH and BOO. This is not surprising given the finding that 50% of men over the age of 50 years have BPH. Increased age is associated with the urodynamic finding of increased DO, which is thought to result in OAB symptoms [12,19•]. However, the evaluation and management of patients with OAB hinges on identifying the presence and degree of BOO, whether it be caused by BPH, primary bladder neck dysfunction, or any other cause.

By identifying and treating unequivocal obstruction, more than 50% of patients with pretreatment DO will have resolution of DO with concomitant symptomatic improvement of BOO [26,27•]. On the other hand, patients with demonstrable DO with equivocal obstruction on urodynamics are unlikely to benefit from treatments for BOO, including transurethral resection of the prostate (TURP). In 62 patients observed with urodynamics before and after TURP, symptomatic and overall outcomes were significantly worse in patients who did not have an obstruction, but had DO. Persistent DO postoperatively was noted more frequently in patients without clear obstruction (60%) than in those who had an obstruction (27%) [26].

Table 1. Effect of tolterodine on urodynamic parameters in men with bladder outlet obstruction

	Placebo, *n* = 72		Tolterodine alone, *n* = 149		Tamsulosin and tolterodine, *n* = 25*		Tamsulosin alone, *n* = 25*	
Urodynamic parameter	**Baseline**	**Week 12**	**Baseline**	**Week 12**	**Baseline**	**Week 12**	**Baseline**	**Week 12**
Q_{max}, mL/sec	8	8.5	8.8	8.5	10.5	11.8	10.3	11.5
$PdetQ_{max}$, cm H_2O	60	60	68	60	69.5	61.3	70	64.8
PVR, mL	27	27	22	47	27	22.8	27.2	19
VFC, mL	209	178	163	217	193	294	197	228
MCC, mL	293	285	260	320	499	536	481	482

*Tolterodine is administered orally in doses of 2 mg twice daily and tamsulosin is administered in 0.4-mg doses four times daily.
MMC—maximum cystometric capacity; $PdetQ_{max}$—detrusor pressure at maximum flow; PVR—postvoid residual; Q_{max}—maximum flow; VFC—volume at first unstable contraction.
Adapted from Abrams *et al.* [30] and Athanasopoulos *et al.* [31••].

A study by Nitti *et al.* [28•] further supports the findings mentioned previously. By reviewing the urodynamics of 50 consecutive men with voiding dysfunction after TURP, they noted that more than 50% had DO and only 16% were obstructed by the Abrams-Griffiths nomogram parameters. When considering those men with complaints of urinary incontinence only, 15 of 20 men (75%) had DO [28•]. It is this population of men with DO and without clear obstruction on urodynamics that is most likely to benefit from medical treatment with anticholinergics.

The Effects of Anticholinergics in Men with Detrusor Activity and Bladder Outlet Obstruction

Bladder contractions are primarily under the control of the parasympathetic nervous system through muscarinic cholinergic pathways. Consequently, drugs with antimuscarinic properties have become the first-line therapy for OAB symptoms. Multiple randomized, controlled trials have consistently demonstrated a significant improvement in symptoms compared with placebo [29].

Although anticholinergics improve symptoms of increased frequency and urgency, the fears of worsening obstructive symptoms or causing acute urinary retention often keep practitioners from prescribing anticholinergics to men who may have concomitant BOO. Only two randomized, controlled studies have addressed this concern directly. The first is a multicenter, multinational, double-blind study by Abrams *et al.* [30] who examined the safety concerns involved in treating men with BOO and symptomatic DO with tolterodine. A total of 221 men with OAB and urodynamically verified BOO were randomized to 2 mg of tolterodine twice daily (n = 149) or placebo (n = 72). They were followed for 3 months with urodynamics and for adverse events. Concurrent treatment with 5α-reductase inhibitors or α-blockers was not allowed. Patients were excluded if they had a postvoid residual (PVR) urine volume of more than 40% of the maximum cystometric capacity and if they underwent past prostate or bladder surgery. Most of the patients had moderate or severe BOO and were evenly distributed between tolterodine and placebo groups. There were no differences between tolterodine and placebo in acute urinary retention (one patient in each group) or in withdrawal from the study because of adverse events (6.0% tolterodine and 6.9% placebo). Up to 24% of the patients who were administered tolterodine complained of dry mouth, but this did not result in treatment discontinuation. Changes from baseline in maximum flow rate and detrusor pressure at maximum flow rate for tolterodine recipients were statistically equivalent to placebo (Table 1). Median increase in PVR was significantly higher in the tolterodine group (+25 mL) compared with placebo (0 mL); however, this increase is not felt to be clinically significant because of the absence of higher urinary system adverse events. Additionally, tolterodine significantly increased the volume at first contraction and the maximum cystometric capacity compared with placebo.

There are two obvious limitations to this study. First, the results were not analyzed by the degree of obstruction; it is unclear if differences in urodynamic parameters were greater in the more obstructed patients. Second, patients with significant PVR were excluded from this study probably because patients with larger residuals are more likely to experience urinary retention if treated with anticholinergics. This study is the first to specifically examine the incidence of urinary retention in men with DO and BOO who are treated with anticholinergics.

A second randomized, controlled trial investigating the combination of tolterodine and tamsulosin (an α-blocker) in men with BOO and concomitant DO is by Athanasopoulos *et al.* [31••]. A total of 50 consecutive Greek men with urodynamically established BOO (mild or moderate according to Schafer's nomogram) and concomitant DO were included. Exclusion criteria included known neurologic deficit, a history of bladder/prostate surgery or cancer, and any medical therapy for BPH 3 months before enrollment. All of the men were placed on 0.4 mg of tamsulosin daily and 25 (50%) of these men were randomly chosen to also take 2 mg of tolterodine twice daily. Qual-

ity-of-life scores and urodynamic assessments were performed before and 3 months into the treatment. Two patients in the tolterodine group withdrew from the study because of dry mouth symptoms and one patient in each group withdrew because of orthostatic hypotension attributed to tamsulosin. Only the patients receiving combination therapy (tamsulosin and tolterodine) had statistically significant improvements on QOL scores. Some of the urodynamic parameters for the combination treatment group are summarized in Table 1. The combination treatment group demonstrated a significant reduction in maximum detrusor pressure during micturition and unstable contractions. Both groups experienced a statistically significant increase in flow rate and volume at first unstable contraction. There was a trend toward a reduction in PVR in each group; however, the change was not statistically significant. The only significant differences between the groups at the end of the study revealed that combination therapy resulted in a significantly larger bladder capacity, lower maximum unstable contraction pressure, and higher volume at first unstable contraction. None of the patients experienced acute urinary retention in 3 months.

The applicability of this study is limited by the lack of a placebo-controlled arm. Additionally, the 3-month duration may not have been long enough to detect an episode of urinary retention in a study of only 50 men. These preliminary data suggest that combination therapy of an anticholinergic with an α-blocker is safe and effective at improving the quality of life in patients with DO and mild to moderate BOO.

There are no published randomized, controlled trials describing the effects of other anticholinergic drugs or extended-release formulations of these drugs. However, the extended-release formulations of tolterodine and oxybutynin likely are to have equal or better drug efficacy while still decreasing tolerability concerns and side effects such as dry mouth [32]. Prospective studies of extended-release formulations in men with DO and BOO would be ideal and informative.

Indications for Anticholinergics

The following question remains: What are the indications for anticholinergics in men? From the available data discussed previously, it is clear that anticholinergics are effective at reducing symptoms of OAB whether or not there is concomitant BOO. Nevertheless, the risk of increasing PVR and causing urinary retention remains tangible, albeit small.

Algorithm to Evaluate and Treat Overactive Bladder in Men

Overactive bladder with normal flow rate and low postvoid residual

An algorithm has been proposed for the evaluation and treatment of men with OAB based on the authors' clinical experience (Fig. 1). These are clinical recommendations based on our experience and should not be interpreted as fixed rules of management. In men with OAB symptoms, which are judged by a validated scale (*eg*, International Prostate Symptom Score), a flow rate was performed and a PVR was assessed. "Low" and "high" PVR should be based on institutional standards. The authors consider a high PVR volume to be ≥ 40% of the functional bladder capacity. If the patient has normal flow and a low PVR, it is safe to consider a trial of anticholinergics. The extended-release formulation of tolterodine (4 mg daily) or oxybutynin (10 mg daily) is recommended. After administering anticholinergics, reassess the patient after 2 to 4 weeks of treatment by assessing symptom scores, flow rate, and PVR.

Overactive bladder with low flow rate and low postvoid residual

In men with a low flow rate (< 12 mL/sec) and a low PVR, it is acceptable to consider an empiric trial of anticholinergics; however, the patient should be re-evaluated within 2 weeks to rule out worsening symptoms or increasing PVR. Ideally, men in this group should be evaluated with urodynamics. If there is no evidence of obstruction, as defined by the Abrams-Griffith nomogram, a trial of anticholinergics is indicated. If there is equivocal obstruction, we recommend using our nomogram (Fig. 2; see discussion in the next section) to assess the risk of acute urinary retention. If the risk of urinary retention is less than 20%, it is sensible to try anticholinergics with or without combination therapy with an α-blocker.

If the risk of retention is ≥ 20%, but < 50%, it is prudent to begin medical therapy for BOO. Treatment with an α-blocker has been shown to reduce the detrusor pressure at maximum flow rate by an estimated 4 to 10 cm of water [32,33]. On our nomogram, a 10-cm reduction in detrusor pressure at maximum flow could reduce the probability of retention anywhere from 5% to 15% depending on the detrusor contraction duration (DCD). After 2 to 4 weeks of medical treatment, the patient should be re-evaluated with a flow rate and PVR and treated along the appropriate arm of the algorithm.

If our nomogram indicates a high risk (> 50%) of urinary retention, patients should be offered surgical treatment for their BOO and be reassessed for symptoms, flow rate, and PVR postoperatively. Depending on their postoperative symptoms, they should be re-evaluated through this algorithm. This will help determine whether they would benefit from adding anticholinergic therapy for persistent symptoms.

Overactive bladder with low flow rate and high postvoid residual

In men with OAB and a flow rate < 12 mL/sec and a high PVR or a history of urinary retention, urodynamics are indicated. A trial of anticholinergics is not recommended without excluding or treating BOO in this group. If urodynamic evaluation confirms obstruction, patients with BOO

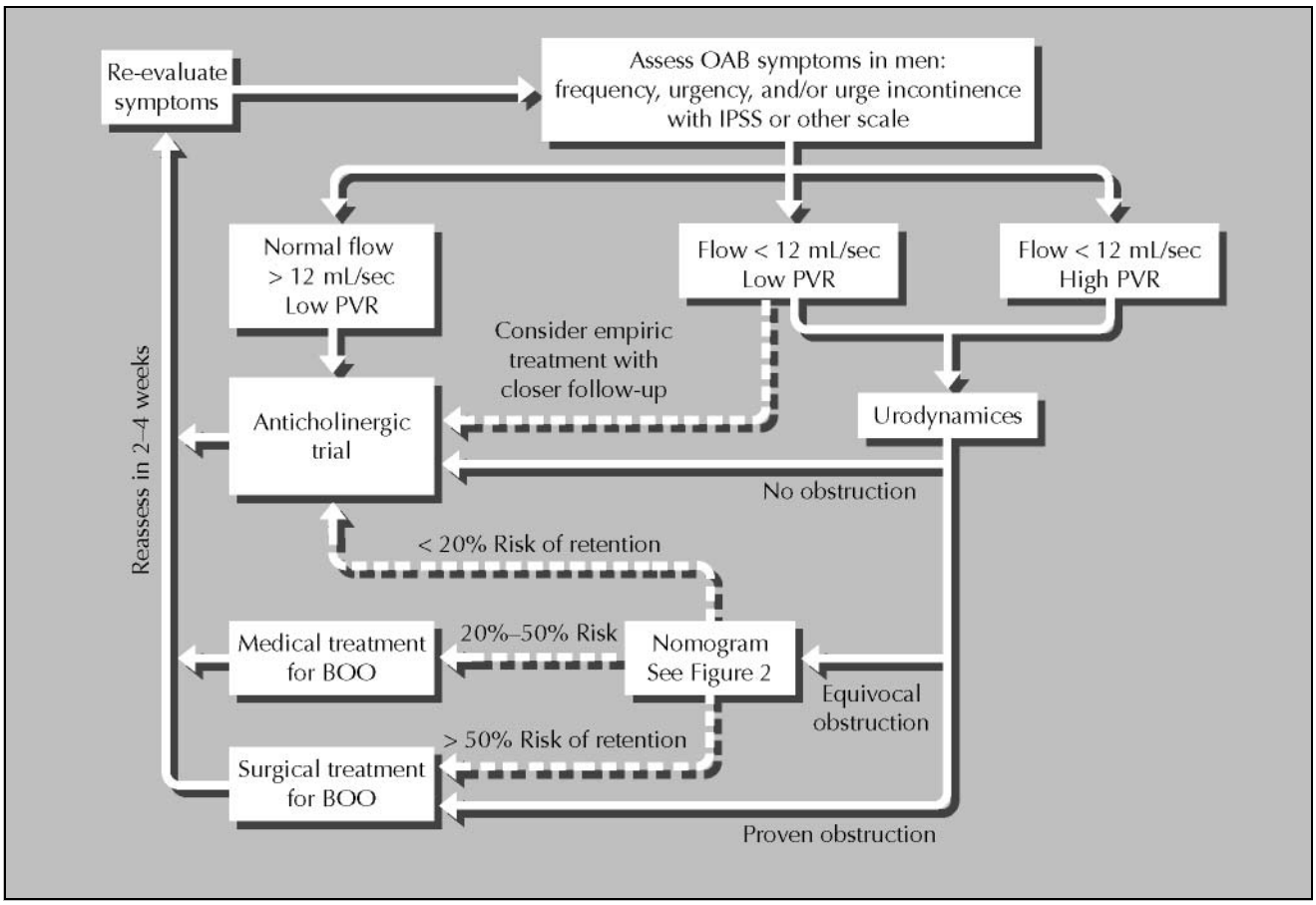

Figure 1. Algorithm for the evaluation and treatment of men with overactive bladder and without genitourinary malignancy, infection, or neurologic deficit. BOO—bladder outlet obstruction; IPSS—International Prostate Symptom Score; OAB—overactive bladder; PVR—postvoid residual.

should undergo appropriate surgical therapy for their BOO. If there is equivocal obstruction, the nomogram presented in Figure 2 is recommended to determine the risk of urinary retention. If the risk of urinary retention is ≥ 50%, patients would most likely benefit from surgical treatment of their BOO. If the risk is ≥ 20%, but < 50%, medical therapy for BOO may be offered to the patient if he or she is not interested in surgical therapy. If the risk of retention is < 20%, medical therapy with an anticholinergic or an α-blocker should be considered and the symptoms should be re-evaluated in 2 to 4 weeks.

Nomogram to Predict Urinary Retention Based on Urodynamic Parameters

In those men with equivocal obstruction on the Abrams-Griffith nomogram, the risk of urinary retention remains unclear. With equivocal obstruction (*ie,* moderate BOO), it is unknown whether the symptomatic benefits derived from anticholinergics outweigh the risks of urinary retention. The authors propose the use of a nomogram to help clarify this issue (Fig. 2).

To create this nomogram, the authors examined the association of urodynamic parameters with urinary retention. We retrospectively analyzed 944 consecutive men evaluated for LUTS during a 2-year period, comparing men with no history of urinary retention with men with a history of retention. Urodynamically obstructed patients in acute retention or those who had a history of urinary retention had higher detrusor pressures at maximum flow rates and longer DCD compared with patients with symptoms of obstruction, but without a history of retention. Using these findings, we created a nomogram to assess the risk of retention in patients with BOO. We found that patients with BOO and a detrusor pressure at maximum flow rate of 80 cm of H_2O or higher and a DCD of 100 seconds or more have a 50% risk of going into urinary retention [35]. The last four colums in the nomogram table indicate those with > 50% chance of having urinary retention.

The use of these urodynamic parameters of DCD and detrusor pressure at maximum flow rate may help develop more effective treatment algorithms. They also may help counsel patients regarding different forms of therapy for their symptoms. The authors propose that men with a > 50% chance of urinary retention be treated with more aggressive surgical therapy to relieve BOO before using anticholinergics.

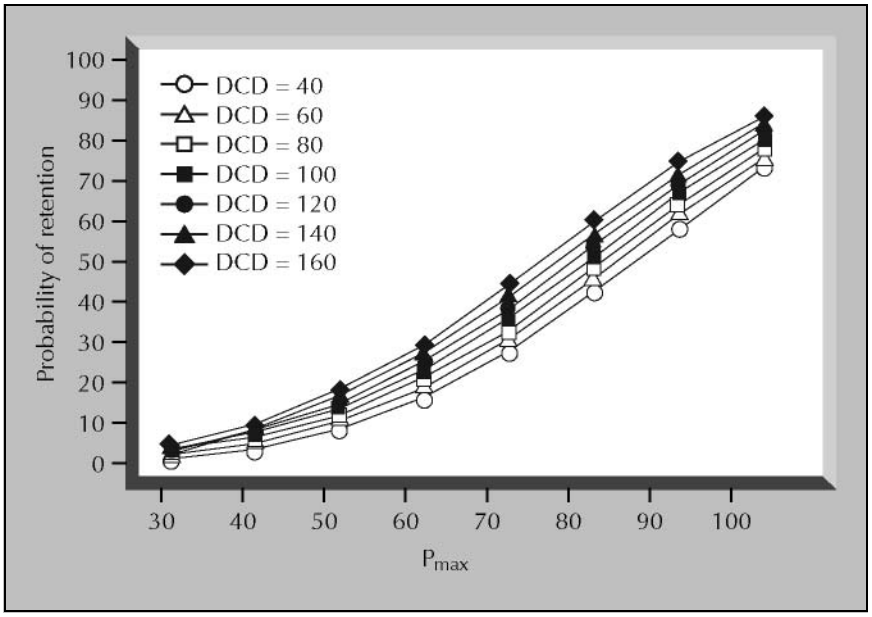

Figure 2. Nomogram for estimating the probability of retention using urodynamic parameters. DCD—detrusor contraction duration in seconds; P_{max}—detrusor pressure at maximum flow rate. *(Adapted from* Te *et al.* [35].)

Conclusions

As men age, the prevalence of OAB and BOO secondary to BPH increases. Whether or not OAB symptoms are thought to be secondary to BOO, the treatment goal remains improving quality of life and preventing clinical deterioration. A common dilemma when treating men with obstruction and OAB is the risk of acute urinary retention or morbidities related to increasing PVR. This article examined the relationship between OAB and BOO, reviewed the role of urodynamics, and reviewed data on the use of anticholinergics in men with obstruction and BOO. An algorithm for managing men with OAB also was proposed. In men with OAB without evidence of obstruction (including OAB after treatment for BOO), first-line medical therapy with anticholinergics is indicated. However, for men with OAB and concomitant BOO, the authors propose the use of our nomogram to assist in the management of men at risk for urinary retention. Men with significant obstruction should be treated appropriately to decrease bladder outlet resistance before adding anticholinergics for the treatment of OAB.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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This is a population-based survey of more than 16,000 men and women older than 40 years of age designed to estimate the prevalence of OAB symptoms. Approximately 16% of the patients complained of OAB symptoms, with only minor differences between men and women. Advancing age corresponded to the increased likelihood of reporting symptoms.

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6.• Kaplan SA, Bowers DL, Te AE, *et al.*: **Differential diagnosis of prostatism: a 12-year retrospective analysis of symptoms, urodynamics, and satisfaction with therapy.** *J Urol* 1996, **155:**1305–1308.

This is a retrospective analysis of 2845 consecutive men with LUTS who underwent urodynamic evaluation in a 12-year period. Of these patients, 523 (62%) had verifiable evidence of BOO of whom 345 (66%) had concomitant DO. Of the entire group, 843 (77%) had evidence of DO, which was the sole diagnosis in 199 (24%). Surgical treatment was associated with a higher level of satisfaction than was medical therapy, regardless of the urodynamic presence of BOO.

7.•• Eckhardt MD, van Venrooij GE, Boon TA: **Interactions between prostate volume, filling cystometric estimated parameters, and data from pressure-flow studies in 565 men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia.** *Neurourol Urodyn* 2001, **20:**579–590.

A group of 565 men with LUTS suggestive of BPH were assessed with urodynamics; only 53% were confirmed to have obstruction and 46% had DO. Increased grades of obstruction were associated with increasing likelihood of DO. Although this study did not find a correlation between age and BOO, patients with DO were older than those without.

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This study is from the same investigators and patient population described in the previous reference. Symptoms on the IPSS were not found to correlate with objective measurements on urodynamic evaluation. Of the 259 (46%) men with DO, scores of frequency, urgency, and nocturia were significantly higher compared with men with a stable bladder. However, the difference in symptom index was not significant.

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This is a study of 160 consecutive neurologically intact men with LUTS who underwent urodynamic evaluation. Of the 68% of men with demonstrable BOO, 46% had concomitant DO. Evidence for DO was identified in 75% of men with a chief complaint of urge incontinence. Other than the expected correlation of urge incontinence with DO, no other symptom was found to correlate well with any specific urodynamic finding.

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One hundred and sixty-two consecutive men underwent urodynamic evaluation for LUTS; 55% had BOO alone and 45% had concomitant BOO and DO. Men with DO were more likely to be older, have BOO, and have higher prostate-specific antigen levels. Symptom scores, maximum flow rate, and PVR did not differ between groups.

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A group of 170 men older than 50 years of age with LUTS were observed with urodynamics to determine which clinical and urodynamic parameters influence bladder compliance (BC) in elderly men. They found that BC decreases with advanced age, BOO, higher voiding pressures, and DO in men with LUTS. A multivariate analysis identified DO, bladder capacity, and maximum detrusor pressure as independent predictors for a low BC.

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This is a review of 182 consecutive patients with diabetes who underwent videourodynamic evaluation. They found that 55% had DO, 23% had impaired detrusor contractility, 11% had indeterminate findings, 10% had detrusor areflexia, and 1% had no abnormalities. BOO occurred in 57% of the men. These data suggest that the "classical" diabetic cystopathy is not the most common urodynamic finding in patients with diabetes and voiding dysfunction; in fact, these patients may present with variable pathophysiologic findings.

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