
Overactive bladder

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Overactive bladder (OAB) is a common condition (prevalence 14%-18% of Canadians) and has a significant negative impact on quality of life. OAB may be idiopathic or may occur with other common conditions such as bladder outlet obstruction, neurological disease, or stress incontinence. Primary care physicians may safely diagnose this condition by history and physical exam with a minimum of widely available lab tests. Management with behavioral therapies and pharmacotherapy is generally quite successful and warranted. Multiple anticholinergic medications are available and have been

shown to be effective. Subtle differences in structure and mechanism of these agents may yield improved therapeutic benefit or tolerability and thus it is reasonable to try more than one drug to achieve the optimal results. For patients that fail behavioral and initial pharmacotherapy or when other complicating conditions are identified, referral to a specialist is indicated; however, the majority of patients with OAB do not require cystoscopy or urodynamics. Successful treatments for OAB do exist and it is worth screening for these disabling complaints at the primary care level.

Key Words: urinary incontinence, overactive bladder

Definition

Overactive bladder (OAB) is a condition characterized by urgency with or without urge incontinence, generally in the presence of frequency and nocturia.¹ The hallmark symptom of urgency is defined as the sudden compelling desire to pass urine which is difficult to defer. Normal frequency in a 24-hour period is eight micturitions and nocturia up to once per night is considered normal. OAB is often subcategorized as OAB wet or OAB dry depending upon whether there is accompanying urge incontinence.

Demographics

The prevalence of OAB in Canada was estimated at 14%-18%^{2,3} based on two large scale phone surveys of thousands of men and women. A similar prevalence of

OAB of 16% for men and 16.9% for women was found in The National Overactive Bladder Evaluation (NOBLE) study of more than 5000 adult men and women in the United States.⁴ OAB occurred with a similar frequency in women and men⁴ but OAB wet was more common in women⁴ and rates increased with aging.^{2,4}

Impact on quality of life and costs

OAB with urge incontinence has been associated with a significant impairment quality of life. Using the generic quality of life measure (SF-36), people with urge incontinence suffered impairment compared to age and gender matched controls in the domains of physical function, social functioning, physical and emotional role functioning, and vitality.⁵

In a survey of the total impact of urinary incontinence, Jackson⁶ found psychological concerns amongst individuals suffering from the incontinence along with family and caregivers. Individuals with urinary incontinence expressed embarrassment, anger, social restriction and isolation, and loss of self esteem. The

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desire to be sexually intimate was often impaired. Family and caregivers reported guilt, frustration, and concerns over social burden and job absenteeism. Physically, urinary incontinence was associated with skin rashes and breakdown, urinary tract infections, sleep disturbances, depression, and falls.⁷ In women over 65 with OAB, Brown et al found higher rates of falls and resultant fractures leading to a high rate of morbidity and mortality.⁸

The economic costs of OAB and urinary incontinence are immense for both individuals and the health care system. Individual costs are associated with pads, laundry, and medications. Health care systems bare costs for diagnosis, supplies, and often long term care. One of the most common reasons for institutionalizing of an elderly patient to a long term care facility is the added burden of managing urge incontinence in the home. One study estimated the 1995 societal cost of incontinence for individuals over 65 years of age at \$26.3 billion dollars.⁹

Despite the large potential impact OAB has on patients, they are often reluctant to discuss their concerns with primary care physicians or seek help. Reasons for underreporting of OAB were found to be: embarrassment, false impression that it is a natural part of aging, lack of information regarding management options, low expectations of benefit from reporting, and the fear that it is an indication of failing health.¹⁰

Etiology and differential diagnosis of OAB

OAB may occur as an isolated condition (idiopathic) or may be found in association with a known neurological condition (multiple sclerosis, stroke, Parkinson's Disease, spinal cord injury, etc), bladder outlet obstruction (prostatic enlargement, pelvic floor dysfunction), or other bladder irritants (urinary tract infection, carcinoma in situ or bladder cancer, etc).

OAB results from neuromuscular control problems of the bladder. Spontaneous, involuntary contractions of the detrusor muscle during bladder filling may be observed on urodynamic testing. These abnormal, overactive contractions of the bladder are associated with urgency and urge incontinence. Coordinated, control of micturition involves a complex number of nerve pathways from higher cortical centers, the pontine micturition center, spinal cord nerves, peripheral nerves, and local receptors at the bladder level. Abnormalities at any of these levels may lead to OAB.

Investigations for OAB

For most patients complaining of OAB, basic office based evaluation by primary care physicians is sufficient

to safely rule out other complicating conditions and initiate first line therapy.¹¹ History should focus on other coexistent lower urinary tract symptoms, medical conditions such as diabetes mellitus or neurological disease, medications (diuretics), and contributors such as chronic constipation, peripheral edema, and excessive fluid or caffeine intake. Physical exam should rule out a distended bladder, check for an enlarged prostate in men or vaginal prolapse, masses, or atrophy in women, and screen for neurological deficits. A urinalysis to rule out hematuria or signs of infection, serum creatinine, PSA in age appropriate men, and fasting blood sugar may be all that are required in a healthy patient with simple OAB. An ultrasound post void residual measurement via an outpatient diagnostic center or bladder scanner would be appropriate for patients with coexistent conditions that may lead to poor bladder emptying such as benign prostatic hypertrophy, diabetes mellitus, neurological disease, and the frail elderly. Controversy exists regarding what represents a clinically significant elevation of post void residual, but a conservative measure would be considering any volume greater than 50 cc as potentially significant.¹² A frequency volume chart (patients record the time and volume of each void for a 24 hour period) may be useful to identify polyuria or isolated nocturnal polyuria as a cause of nocturia. A fluid intake diary may also identify excessive fluid intake including caffeinated beverages. Specialist investigations including cystoscopy and urodynamics are not required for evaluation and successful management of the majority of patients with OAB. The purpose of cystoscopy is to rule out other causes of urgency and frequency or factors that may exacerbate OAB such as bladder cancer, chronic inflammation, bladder stones, etc. A multichannel urodynamic study is performed by a nurse or clinician and requires the passage of small catheters into the bladder and rectum for measurement of pressures. Water, contrast, or gas is infused into the bladder and the presence of abnormal overactive bladder contractions along with their magnitude and associated leakage can be demonstrated. Testing can also be done for other types of incontinence such as stress incontinence, problems with bladder compliance, and at the conclusion of the study the presence of bladder outlet obstruction may be identified during voiding. Urodynamics will not change the management of most patients with OAB, but they may be indicated for patients with neurological bladder dysfunction (high bladder pressures may be associated with renal function deterioration), mixed incontinence, or possible bladder outlet obstruction.

Management of OAB

Patients with OAB associated with other conditions (as discussed previously) may improve with treatments targeting these coexistent pathologies. For example, relieving bladder outlet obstruction with transurethral resection of the prostate or release of an obstructing bladder neck sling may lessen OAB symptoms. Similarly, patients who have symptoms of OAB caused by diuretics prescribed for hypertension may benefit from switching to an alternate antihypertensive.

While the mainstay of therapy for OAB is generally anticholinergic medications, one cannot overstate the importance of first line or simultaneous behavioral therapy interventions. Behavioral therapy incorporates pelvic floor strengthening (Kegel exercises with or without adjuncts such as biofeedback, electrical stimulation, or weighted vaginal cones), timed voiding, urge suppression, and fluid management. Prompted or timed voiding may avoid the bladder reaching volumes that trigger urgency and practice delaying the initiation of voiding by utilizing the guarding reflex may help. Fluid intake should be encouraged evenly throughout the day and caffeinated beverages should be limited.

The importance of behavioral therapy for treating OAB was nicely demonstrated in a recent Health Education Trial.¹³ During this 16 week trial patients were randomized to tolterodine alone or tolterodine with a 5 minute health education intervention. The group receiving the counseling reported significantly increased use of non-drug OAB therapies, better medication compliance, and higher levels of improvement of OAB symptoms.

The mainstay of pharmacotherapy for OAB is the anticholinergic (antimuscarinic) group of medications.

TABLE 1. Antimuscarinic selectivity of currently available agents

Nonselective for M3 receptors	Selective for M3 receptors	Combined
Atropine		
Propantheline	Darifenacin (M3)	Oxybutynin
Tolterodine	Solifenacin (M3 > M2)	
Trospium		

Recent years have shown an expansion of the number of agents available to be prescribed in this grouping and a brief overview of the specific receptors responsible for activity and side effects is important to aid in selection of an appropriate medication for an individual patient. The detrusor has both M2 and M3 receptors. It is felt that the M3 receptors may be the most important to block with pharmacological agents. M3 receptors are also found on the salivary glands and the smooth muscle of the gastrointestinal tract. Inadvertent blockade of the receptors on these other organs is responsible for undesired side effects including dry mouth and constipation. M5 receptors are found on the heart and effects on these receptors could lead to arrhythmias. Central nervous system side effects are also possible with anticholinergic agents that cross the blood brain barrier or interfere with M1 receptors found in the brain. Table 1 characterizes currently available anticholinergic agents based on their selectivity or additional mechanisms of action and Table 2 summarizes the currently available formulations of these agents. All agents with the

TABLE 2. Currently available formulations of antimuscarinic agents to treat OAB

Oxybutynin IR	Generic oxy	5 mg	Daily to QID
Oxybutynin ER	Ditropan XL	5 mg or 10 mg	Once daily 30 mg maximum
Oxybutynin ER	Uromax	10 mg or 15 mg	Once daily
Oxybutynin TDS	Oxytrol	3.9 mg	Twice weekly
Tolterodine IR	Detrol	1 mg or 2 mg	BID
Tolterodine ER	Detrol LA	2 mg or 4 mg	Once daily
Darifenacin	Enablex	7.5 mg or 15 mg	Once daily
Solifenacin	Vesicare	5 mg or 10 mg	Once daily
Trospium	Trosec	20 mg	BID (empty stomach)
Trospium	*Sanctura XR	60 mg	Once daily

*Available in the USA not Canada at this time

exception of trospium, have hepatic metabolism. Thus, in a patient with hepatic insufficiency or taking multiple medications which are metabolized via the liver, there may be a theoretical advantage to the use of trospium. Contraindications to the use of anticholinergic medications are: untreated narrow angle glaucoma (the majority of patients with glaucoma may safely take anticholinergics but this should be cleared by their ophthalmologist before commencing) and urinary or intestinal obstruction.

The choice of a particular anticholinergic agent should balance patient variables (age, compliance, hepatic or renal impairment, other medications, etc) with drug variables (dosing frequency, side effects, hepatic or renal metabolism, propensity to worsen cognition, etc). For patients without private drug insurance or covered on provincial drug formularies, the practical considerations of coverage and cost are often the overriding consideration when selecting an initial agent. While studies suggest that all available agents are effective at reducing symptoms of OAB compared to placebo, it is clear from clinical practice that some patients do better (efficacy and tolerability) with one agent versus another. Thus, it is often worthwhile to encourage patients to try two or three different anticholinergic agents to find the medication with the best balance of side effects and benefit.

Special considerations

Two common clinical conditions may coexist with OAB and warrant mention: prostatic enlargement in men and postmenopausal genital atrophy in women.

Lower urinary tract symptoms in men with prostatic enlargement/bladder outlet obstruction include both voiding symptoms (slow stream, hesitancy, intermittency, double voiding, post void dribble) and storage symptoms (frequency, nocturia, urgency, and urge incontinence). In men with predominately storage symptoms, there is obvious overlap with OAB. While these lower urinary tract symptoms may be due to prostatic pathology, it is also reasonable to believe that primary detrusor activity could be contributing. Thus, in men with storage symptoms who have not responded to classic benign prostatic hypertrophy pharmacotherapies with alpha blockers or 5 alpha reductase inhibitors, there is an increasing role for the addition of anticholinergic agents. The potential concern of worsening post void residual urines volumes or triggering urinary retention, appears to be very small.^{14,15}

Postmenopausal women are a common demographic to suffer from OAB and a finding of vaginal atrophic

changes occurs frequently in this group. There is data to suggest that women who have symptomatic vaginal atrophy (dryness, burning, etc) and coexistent OAB symptoms may benefit from local vaginal estrogen supplementation.¹⁶ However, there is no data to suggest that full systemic hormone replacement therapy (HRT) is indicated and large trials of HRT have found higher levels of OAB symptoms in women taking HRT for prolonged periods suggesting an adverse association.¹⁷

Other managements for OAB refractory to behavioral and pharmacotherapy

Despite the number of new pharmacotherapies for OAB, there remains a group of patients that do not achieve a satisfactory level of control of their frequency or urge incontinence. Other options for management of such patients include off label intravesical injection of botulinum toxin A, sacral or peripheral neuromodulation, or major reconstructive surgery such as a bladder augmentation (ileal enterocystoplasty) or urinary diversion.

While botulinum toxin A is not currently approved for the management of refractory OAB in Canada or the United States, there is increasing evidence that injection of this agent into multiple sites of the bladder under cystoscopic guidance can result in significant improvement of both subjective and objective measures in both idiopathic¹⁸ and neurogenic¹⁹ OAB and off-label use of this agent is increasing. Botulinum toxin A inhibits the release of acetylcholine into the synaptic cleft of the motor nerve and as such can be a potent muscle relaxant of both smooth and skeletal muscle. One of the limitations to the use of botulinum toxin A is the chance of inducing urinary retention. Some elderly patients with refractory OAB may not be able or willing to consider a treatment that could potentially require them to perform clean intermittent catheterization.

Sacral neuromodulation (Interstim) and peripheral neuromodulation (Stoller Afferent Nerve Stimulator) have both been shown to reduce the symptoms of OAB and urge incontinence.^{20,21} Unfortunately, the cost of these devices and the supportive programs for operation, have led to very limited access in Canada.

OAB summary

OAB is a common medical condition that is not confined to the elderly. It is associated with significant impairment of quality of life and may contribute to other serious health concerns such as falls and fractures.

Patients may fail to bring up concerns of OAB with their primary care physician for many reasons including embarrassment, so it is paramount that physicians screen for bothersome symptoms. Most patients with OAB require only simple, office-based evaluation. Primary care physicians should feel comfortable initiating behavioral and pharmacotherapies for OAB. Patients who fail to respond to these managements or have other concerns such as hematuria or high post void residual (> 50 cc) identified, should be referred for specialist evaluation.

Take-home messages

Indications for specialist referral

- Microscopic or gross hematuria
- Elevated post void residual (> 50 cc)
- History of neurological disease (multiple sclerosis, Parkinson's disease, stroke, spinal cord injury, etc)
- History of recurrent urinary tract infections
- Pelvic pain
- Previous genitourinary trauma or surgery
- Abnormal prostate exam or elevated PSA
- Not responding to behavioral therapy and a trial of an anticholinergic medication

Disclosure

Dr. Lesley Carr has received compensation for lecturing and/or participating in advisory boards for Astellas, Pfizer, Janssen-Ortho, Purdue Pharma, Triton, Medtronic, and Allergan. □

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DISCUSSION

Question (Dr. Rosenberg):

At which point should the patient be referred for cystoscopy and/or urodynamics studies?

Answer (Dr. Carr):

A patient should be referred for further investigations, possibly including cystoscopy, when evaluations by the PCP pick up other co-existent problems such as hematuria or pyuria, recurrent urinary tract infections, elevated post void residual (> 50 cc), or pain possibly referable to the urinary tract. In addition, patients with potentially contributing conditions such as bladder outlet obstruction (BPH, pelvic floor dysfunction), stress urinary incontinence, or neurological disease (multiple sclerosis, stroke, spinal cord injury, Parkinson's disease, etc) may benefit from multichannel urodynamic evaluation

Question (Dr. Greenberg):

Please comment on the impact of alcohol and caffeine on patients with OAB.

Answer (Dr. Carr):

Behavioral therapies such as diet modification may yield significant reduction in OAB symptoms. For example, attempts should be made to minimize caffeine and alcohol intake. These agents may aggravate OAB by bladder irritant effect or diuretic challenge.

Question (Dr. Laroche):

Please discuss your pharmaceutical approach when treating a patient on an active medication for cognitive impairment (Aricept, Exelon, Reminyl, Ebixa...)

Answer (Dr. Carr):

Patients with Alzheimer's disease and other neurocognitive degenerative diseases frequently suffer from OAB. Behavioral therapies such as prompted voiding may be very important in this group as perception of warning time and mobility may be significant impediments to the control of urge incontinence. Caution should be used in prescribing anticholinergic agents due to potential CNS side effects especially if the patient is already taking active treatment with agents for cognitive impairment such as Aricept. Anticholinergic agents such as trospium or darifenacin may be potentially safer choices, but my recommendation is to discuss the use of any anticholinergic drug in this population with their neurologist or geriatrician prior to commencing use.