Overactive bladder

Jack Barkin, MD
Humber River Regional Hospital, University of Toronto, Toronto, Ontario, Canada

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Overactive bladder (OAB) is common and has a negative impact on a patient's quality of life. It is important for physicians to know how to identify and manage patients with this condition. Usually only basic clinical evaluations and a good patient history are necessary to diagnose OAB. Effective and safe oral therapy is available and can be initiated by primary care physicians.

Key Words: overactive bladder, oral therapy

Background

Overactive bladder (OAB) can be defined as urgency with or without urge incontinence, generally accompanied by frequency and nocturia.[1] Urgency, which is usually the main presenting symptom, is defined as a sudden, compelling desire to pass urine, which is difficult to defer. Frequency is generally defined as more than eight micturitions in a 24 hour period, and nocturia is generally defined as more than one micturition per night.[2] OAB may be classified as "wet" (if it occurs with urge incontinence) or "dry" (without urge incontinence).

The incidence and prevalence of OAB with or without urge incontinence increases with increasing age. While the prevalence of OAB is similar in men and women, men are less likely to have accompanying urge incontinence. A large national United States telephone survey that was part of the National Overactive Bladder Evaluation (NOBLE) program found that in the general population, 16.9% of women had OAB -- 9.3% with urge incontinence and 7.6% without urge incontinence. The survey found that 16% of men had OAB -- 2.4% with urge incontinence and 13.6% without urge incontinence.[3] In Canada, it has been estimated that OAB affects 12% to18% of the population, and, of these individuals, one-third have wet OAB and two-thirds have dry OAB.[4]

The symptoms of OAB are similar to those of lower urinary tract symptoms (LUTS), so to make the diagnosis of pure OAB, physicians must rule out other causes of the symptoms such as benign prostatic hyperplasia (BPH) (in men), urethral stricture, bladder stone, atrophic vaginitis or vaginal prolapse (in women), a neuropathic process, interstitial cystitis, painful bladder syndrome, diabetes (or other causes of polyuria), genitourinary malignancy, and urinary tract infection.

Address correspondence to Dr. Jack Barkin, Chief of Staff, Humber River Regional Hospital, 960 Lawrence Avenue West, Suite 404, Toronto, Ontario M6A 3B5 Canada

Discussion

Impact of untreated OAB

Untreated OAB can have a profound negative impact on patients' psychological well-being, quality of life,[5,6] and physical health (due to increased risk of falling and, with wet OAB, increased risk of vaginal and groin infections).[2,7] Brown and colleagues reported that women with OAB had an increased risk of falling, fracturing a hip, and losing independence.[8] Hu and colleagues estimated that in 2000, the annual economic impact in using drugs, diapers and treating the sequelae of OAB n the United States was $12.0 billion dollars.[9] In 2009, Irwin and colleagues[10] reported on the estimated total costs associated with OAB treatment in six western countries, including Canada. They estimated that direct costs for OAB treatment per patient per year ranged from € 11,329 in Canada to € 34,717 in Italy (about $15,473, and $47,418, respectively, in March 2011 Canadian dollars). In Canada, annual OAB-related nursing home costs and absenteeism were estimated to be € 338 million and € 65 million, respectively (about $462 million and $88.8 million, respectively, in March 2011 Canadian dollars).

Despite the negative impact of OAB symptoms on quality of life, patients often do not mention these symptoms to their physicians. They may feel the symptoms are a normal part of aging, or they may be too embarrassed to speak about them.

Diagnosing OAB

In general, the initial patient work up for OAB can be done by primary care physicians. Rarely should patients be initially referred to the specialists for additional invasive testing such urodynamics or cystoscopy.

When obtaining the patient's history, the physician should look for the presence of LUTS (including difficulties in voiding) or medical conditions related to OAB (such as diabetes mellitus, congestive heart failure, neurological disease, or constipation), and find out about medication use (including diuretics and antidepressants) and dietary habits (such as excessive fluid or caffeine intake). A simple questionnaire can be used to help to make the diagnosis, Figure 1.

The physical examination should look for distended bladder, vaginal prolapse or atrophy, enlarged prostate (determined by a digital rectal examination [DRE], signs of neurological diseases, phimosis, or meatal stenosis.

In patients with incontinence, it is important to try to differentiate between the three main types: urgency incontinence, stress incontinence, or mixed incontinence. A proper diagnosis is essential, because stress incontinence is primarily treated with surgery whereas urgency incontinence is managed medically.

A urinalysis (including RBCs, WBCs, nitrites, and glucose) is done to rule out hematuria or signs of a urinary tract infection (UTI). Appropriate blood tests include blood glucose and creatinine. An ultrasound postvoid residual (PVR) measurement is appropriate for patients with coexistent conditions – diabetes mellitus, neurologic conditions, a large prostate, or frailness in the elderly – that could lead to poor bladder emptying.

Patients with OAB who may require further work up or referral for cystoscopy include those with hematuria, pain, recurrent UTIs, or risk factors for bladder cancer (older age, male, smoker, family history of bladder cancer), or those who are not responding to therapy.

Urinate:	Do you urinate > 8 times in a 24-hour period?	Yes/No
Rush:	Have you ever rushed to the bathroom for fear of not making it on time?	Yes/No
Garments:	Have you ever used pads or diapers to protect your garments from leakage?	Yes/No
Embarrassment:	Do you ever feel embarrassed by your symptoms?	Yes/No
Night:	Do you often wake up more than twice a night to urinate?	Yes/No
Control:	Do you ever feel the sensation that you will loose control of your bladder?	Yes/No
Your fluid consumption:	Do you limit your fluid consumption?	Yes/No

* Interpretation of the answers: A "yes" reply to one or more of the above questions may indicate the presence of overactive bladder.

Figure 1. "URGENCY" questionnaire to screen for overactive bladder.*

A simple algorithm, which was designed by a consensus panel and approved by the Canadian Urological Association, can be used to help diagnose and manage most patients with typical OAB and to diminish the risk of missing other significant pathologies that may mimic the signs and symptoms of this condition.[11]

Managing OAB

Behavioral therapy

After a patient has been diagnosed with OAB, and other contributing factors have been identified and treated, treatment for OAB should begin with behavioral therapy. Behavioral therapies include physiotherapy (instructions about Kegel pelvic-floor strengthening exercises and biofeedback) and strategies for scheduled voiding, bladder retraining (to adopt longer intervals between voiding), and fluid management (including limiting consumption of caffeine).

Antimuscarinic agents

Medical management of OAB focuses on relaxing the bladder. If the bladder is relaxed, it is less sensitive to filling and to bladder irritants, which improves the storage phase in the bladder function cycle. As a result, the bladder can hold a larger volume of urine, which leads to less frequency, less urgency, fewer episodes of urgency with incontinence, and increased bladder latency time (the time from the first urge to void until the bladder must be emptied).

The mainstays of pharmacotherapy for OAB are the antimuscarinics (anticholinergics), which, by acting on muscarinic receptors in the bladder, reduce the amplitude of normal and involuntary bladder contractions. They also improve the functional capacity of the bladder by increasing the bladder's storage volume at the first involuntary contraction.[2]

In the bladder, M3 muscarinic receptors play a role in stimulating detrusor muscular contraction. M3 receptors are also found in the salivary gland and the gut, however. Drugs that block M3 muscarinic receptors in the bladder can also cause dry mouth and constipation. M1 muscarinic receptors are found in the brain, so drugs that block M1 muscarinic receptors in the bladder could cause a side effect of confusion, if the drug crossed the blood-brain barrier. M5 muscarinic receptors are found in cardiac muscle, so a drug that blocks M5 muscarinic receptors could result in a prolonged QT interval, which could lead to an arrhythmia. Drugs that are more selective for certain muscarinic receptors are expected to have the fewer side effects and secondary effects.

Side effects of antimuscarinics may include pupillary dilatation, paralysis of lens accommodation, tachycardia, changes in mental status, decreased sweating, dry mouth and respiratory tract, and inhibition of gastrointestinal (GI) motility.

In addition to blocking muscarinic (cholinergic) receptors, in higher doses, all long-acting antimuscarinics may result in ganglionic blockade in some patients. Side effects of ganglionic blockade may include orthostatic hypotension, impotence, and muscle weakness.

Antimuscarinic agents are contraindicated in patients who have narrow-angle glaucoma (untreated), obstructive or atonic disease of the GI and urinary tract, or myasthenia gravis.

In Canada, many antimuscarinic agents are available for the medical management of OAB, see Table 1. Different ones are listed in different provincial formularies. Drug manufacturers have focused on developing long-acting, once daily dosage forms of these drugs, since patients are more likely to be compliant with this dosing schedule. In most cases, generic, immediate-release (IR) oxybutynin is the comparator drug during clinical trials. Patients showed improved compliance, improved efficacy (decreased frequency, urgency, and episodes of incontinence) and fewer side effects with the newer agents compared with placebo or generic oxybutynin.

The most worrisome side effect from antimuscarinics prescribed for OAB, which is seen mainly in elderly patients, is confusion or change in cognition. If the drug crosses the blood brain barrier, that side effect can be prominent. Various authors have reported potential CNS impairment in elderly patients who are treated with antimuscarinics for OAB.[12-15] Antimuscarinics may cause memory deficits (that patients may be unaware of), sleep disruption, confusion, or hallucinations. The extent of CNS deficits depends on age-related decreases drug elimination and changes in the blood-brain barrier integrity or in muscarinic receptors. The side effects also depend on the drug's ability to cross the blood-brain barrier or block M1 receptors in the brain.

In one trial looking at potential CNS impairment with drugs for OAB, patients receiving oxybutynin extended release (ER) had memory impairment and significantly lower memory scores compared to patients receiving placebo or darifenacin.[16]

In a similar trial that compared solifenacin versus placebo or immediate release (IR) oxybutynin, the authors found no evidence of cognitive impairment with solifenacin 10 mg versus placebo overall and at Tmax (6 hrs post-dose). Significant worsening of cognitive function -- information processing, learning,

TABLE 1. **Antimuscarinic agents for overactive bladder available in Canada**

Generic Name	Brand Name	Dosage
First-line agents		
oxybutynin IR	–	2.5 mg to 5 mg four times daily
flavoxate*	–	100 mg-200 mg three times daily
Second-line agents		
tolterodine IR	Detrol	1 mg or 2 mg twice daily
tolterodine ER	Detrol LA	2 mg or 4 mg once daily
oxybutynin ER	Ditropan XL	15 mg to 30 mg once daily
oxybutynin TDS	Oxytrol	36 mg patch twice weekly
oxybutynin ER	Uromax	10 mg or 15 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 twice daily, on an empty stomach

ER = extended release; IR = immediate release; LA = long-acting; TDS = transdermal; XL = extended release
*flavoxate is considered to be an "antispasmotic" bladder drug and a very weak anti-cholinergic

memory, and self-ratings of alertness -- were seen for oxybutynin 10 mg versus placebo at Tmax (2 hrs post-dose).[17]

A study by Anderson and colleagues showed that compared to oxybutynin, long-acting tolterodine (tolterodine LA) had no negative impact on memory.[18]

Elderly patients are both more likely to have OAB and to be very susceptible to the side effects of antimuscarinics. Therefore, if an elderly patient is prescribed an antimuscarinic drug for OAB, the patient must be followed carefully and seen soon after initiation of therapy, to ensure that he or she does not sustain side effects that are "missed" or wrongly attributed to the aging process or other morbidities.

Antimuscarinic drugs have different side effects, depending on their specificities for different muscarinic receptors. When choosing an antimuscarinic drug to prescribe for OAB, the physician should adopt the "ASTEP" approach, which stands for "availability, safety, tolerability, efficacy and preference." The initial drug is usually generic IR oxybutynin. This is the required initial drug for OAB that must be offered in provinces where non-generic, newer, long-acting antimuscarinics are listed as limited use [LU] drugs. If IR oxybutynin is ineffective or if the side effects are too bothersome, only then is the physician authorized to prescribe one of the newer, once-daily anti-muscarinics. If that drug is ineffective or the side effects are too great, the dose may be increased, or the patient may be switched to another drug.

Nonmuscarinic agents

Nonmuscarinic drugs may be used alone or in combination with an antimuscarinic drug, to treat OAB. Desmopressin acetate, which is a synthetic form of the anti-diuretic hormone vasopressin, is a nonmuscarinic drug that may be used to treat OAB. Desmopressin acetate is sometimes prescribed for nocturnal enuresis (bedwetting) in elderly people. Some elderly people have a decreased secretion of antidiuretic hormone (ADH), which decreases their ability to concentrate urine and can lead to high urine volumes and nocturia. Desmopressin acetate may reverse this process, but the patient's serum sodium levels must be carefully monitored since the drug can cause hyponatremia. The drug is available as a "melt" (60 mcg or 120 mcg), a tablet (0.1 mg or 0.2 mg), or nasal spray. In 2008, Health Canada issued a warning that the desmopressin acetate nasal spray is contraindicated in primary nocturnal enuresis, due to risk of hyponatremia. It is now listed as "to be used with caution," particularly in elderly patients who appear to be more predisposed to developing hyponatremia.[19]

The tricyclic antidepressants imipramine (Tofranil) and amitriptyline (Elavil) are other nonmuscarinic drugs that may be used to treat OAB. Tricyclic antidepressants have a central sedating effect, relax the bladder walls, and, through stimulation of alpha-adrenergic receptors, cause tightening of the sphincter, which may be helpful in some patients. This combination of effects may treat the symptoms

of OAB and prevent urgency incontinence. However, some patients who take a tricyclic antidepressant feel very tired.

The most common cause of symptoms of frequency, nocturia, and urgency in men over age 50 is bladder outlet obstruction (BOO) secondary to BPH. Even with combination therapy for BOO (an alpha blocker and a 5-alpha reductase inhibitor), some men still have frequency and urgency. These persistent symptoms are believed to be the result of up-regulation of nerve fibers in the detrusor muscle, which results in OAB. Some studies have reported that men with BOO secondary to BPH after full treatment for BPH, who still have non-relenting frequency and urgency symptoms can be treated with drugs for OAB and expect greatly improved outcomes.[20,21] Other studies are looking at the use of low-dose, daily PDE-5 inhibitors to treat frequency and nocturia in men with BOO that is secondary to BPH and who are not responding to standard medications for the prostate. Preliminary results suggest that these drugs diminish frequency and urgency but do not increase urine flow rates.[22]

Invasive therapies for refractory OAB

Patients with severe OAB who do not respond to behavioral therapy or cannot tolerate or do not respond to conventional polypharmacologic agents used to treat OAB may be offered other highly specialized, expensive therapies. These therapies include botulinum toxin A (BOTOX) injections (which are not approved for treatment refractory OAB), neuromodulator (nerve stimulator) implants, and augmentation cystoplasty. These are third-line, last resort approaches that are only recommended and accepted in the most refractory, devastating cases.

Conclusion

In most cases, patients with OAB can be initially managed at the primary care level. However, certain patients may later be referred to a urologist or other specialist for follow up. These include patients who fail to respond to behavioral and pharmacological therapy, or have certain coexisting conditions (hematuria, pyuria, recurring UTIs, or BPH), or have PVR urine volumes greater than 100 mL, or have associated confounding neurological conditions.

The prevalence of OAB increases significantly with increasing age. It can have a dramatic effect on a patient's quality of life, and at the same time it has a significant impact on healthcare costs. If a physician performs a careful patient history and a complete physical examination, with minimal laboratory tests, in most cases, the diagnosis of OAB can be made easily. With behavioral modification and compliance with effective medical therapy most patients will enjoy a very satisfactory improvement in their OAB symptoms.

Researchers are still searching for the most effective drug with the fewest or least bothersome or insignificant side effects. This ideal drug would encourage patients to comply with taking this drug for the rest of their lives in order to provide the maximum benefit and response in treating this chronic condition. □

Disclosure

Dr. Jack Barkin is an active urologist and Chief of Staff at the Humber River Regional Hospital in Toronto. He sits on the medical advisory board for Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Frosst, Paladin, Pfizer, sanofi-aventis and Solvay. He has done the clinical research on Androgel, Avodart, Casodex, Cialis, Detrol, Flomax, Hytrin, Levitra, Xatral, Proscar and Viagra. He has spoken all over the world for all of the companies outlined.

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