Overactive bladder symptoms in women: current concepts in patient management

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The symptoms of overactive bladder (OAB) -- urinary urgency, frequency, and urge incontinence -- can cause significant lifestyle limitations. Social isolation, depression, employment difficulties, and relationship stress are common findings in patients with this condition. This article focuses on women with OAB who are seen in primary care. Occasionally, OAB (or detrusor overactivity) may be the result of neurological disease, metabolic disease, or urinary tract abnormalities. Primary care practitioners can play a key role in identifying affected individuals by including a focused question in every annual patient physical assessment. Investigation and treatment can then be initiated, beginning with behavioral modification strategies (such as modifying fluid intake) and adding antimuscarinic pharmacotherapy or possibly local estrogen therapy where needed. Only patients with certain concurrent diseases or those who are refractory to conventional management will require referral to a specialist.

Key Words: overactive bladder, urinary incontinence, antimuscarinic agents, detrusor overactivity

Introduction

Loss of control of excretory functions is a social stigma in all cultures. Although it is difficult to determine the exact incidence of overactive bladder (OAB) syndrome, due to under reporting by individuals with the condition, researchers estimate that OAB affects 14%-18% of adults to some degree.[1] As with many conditions, incidence increases with age. The prevalence of OAB is the same in men and women, although women begin to have OAB symptoms at a younger age. Given the growing population of individuals aged 55 years and older, OAB has the potential to become a major burden on healthcare resources in the future. Fortunately, modern behavioral modification strategies and pharmacologic treatments can significantly modify or even eliminate bothersome symptoms of OAB. This article focuses on women with OAB who are seen in primary care.

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Precipitating factors of OAB

Although the International Continence Society has developed a formal definition of OAB,[2] in practical terms, all patients who report that they are bothered by voiding urgency or frequency (to any degree) should undergo clinical investigations and, if needed, they should receive treatment for OAB. Patients' reluctance to self report abnormalities of voiding function makes it even more important to investigate

further when patients do report these symptoms. Because of patient hesitancy to discuss voiding control problems with anyone, even their family doctor, primary care practitioners are encouraged to routinely include a screening question about voiding control in every patient assessment, regardless of the patient's presenting symptoms.

Factors that can contribute to OAB are summarized in Table 1. Although OAB can be seen in women who have no identifiable contributing factors, careful screening-- even before other necessary investigations are done-- will often uncover contributing behaviors that can be modified.

Many women still believe that drinking at least eight glasses of water a day is essential to maintain good health. In the absence of medical conditions that dictate otherwise, individuals should be advised to drink only when they are thirsty, and then to drink only enough caffeine free fluids to quench their thirst.

Another persistent myth centers on the potential harm from not responding to the first urge to void. Well-meaning but misinformed caregivers in early childhood may be the root of this false assumption, which can lead to unnecessary frequency and limited or absent voiding delay techniques in adulthood. Obesity is a risk factor in most forms of incontinence, and it requires aggressive management.

Pelvic floor evaluation is an essential component of investigating female voiding dysfunction or urinary incontinence. Estrogen deprivation atrophy of the vaginal skin can be considered a proxy for atrophy in the trigone and urethra, since they share a common embryologic origin. Following menopause, the peri-urethral venous plexus diminishes in size, with loss of the so-called "hydraulic sphincter." With local estrogen treatment, this "hydraulic sphincter" again becomes a significant contributor to continence.

Comorbidities

Inability to choose the time and place of bladder emptying-- with or without involuntary urine loss

TABLE 1. **Screening patients for overactive bladder**

Precipitating causes of OAB	Caffeine intake Detrusor hyperactivity with impaired contractility Diabetes – autonomic neuropathy Excessive fluid intake Obesity Outlet obstruction Pelvic organ prolapse Poor voiding habits Urogenital atrophy
Underlying diseases or causes of OAB	Bladder tumor Cardiovascular disease Lower urinary tract infection Metabolic disease – diabetes Neurological disease Outlet obstruction Pharmacologic contributors Spinal cord compression syndromes
Causes and symptoms of OAB in older patients	**DIAPPERS:** **D**ementia **I**nfection **A**trophy **P**harmaceuticals **P**sychological factors **E**xcessive urine production **R**estricted mobility **S**tool impaction

OAB = overactive bladder

on the way to the bathroom-- places significant limits on a normal lifestyle. In addition, urinary urgency, frequency, and nocturia may be causally related to other conditions that threaten health and well-being.

Particularly in an elderly population, nocturnal urgency can lead to incidents where patients trip and fall on the way to the bathroom, which can cause long-bone fractures and significant morbidity.[3] Apart from the suffering of the individual involved, these incidents require surgical and medical management, often with prolonged rehabilitation, which add extra costs to an already overburdened healthcare system. Effective management of OAB can, in some measure, prevent these negative outcomes.

Chronic use of pads and other protective undergarments can result in irritation and excoriation of the vulvar skin. In severe cases, prolonged contact with urine soaked pads can lead to skin breakdown.

Nocturnal frequency of any cause can result in significant sleep disruption. Interruption of sleep by a frequent need to void can interfere with an adequate duration of rapid eye movement (REM) or restorative sleep, resulting in daytime somnolence and irritability.

Women with OAB often limit their social interactions for fear of an embarrassing accident. Travel, even for example, staying overnight at a friend's home, is a frequent casualty of this condition. Not surprisingly, social isolation and clinical depression are seen more frequently in women with all types of urinary incontinence.[4,5] Relationship stress, including avoidance of sexual contact, only adds to the psychological stress associated with deficiencies of bladder control.

Stress in the workplace -- particularly for women in high visibility, group employment situations such as factory work -- can be extreme. When "bio breaks" are rigidly defined by the employer and sanctions are exercised against employees who leave the assembly line at other-than-defined intervals, some women choose to leave their employment rather than subject themselves to repeated criticism and embarrassment.

Investigating OAB

Urge is the defining feature of OAB. This may be present without involuntary urine loss on the way to the bathroom (dry OAB) or with urge incontinence (wet OAB). The perception of urge in OAB patients is difficult to describe, but is different from the gradually increasing awareness of the need to void as the bladder fills, in patients with normal voiding function. If a patient responds affirmatively to a screening question about bladder control, it is worthwhile to direct further questions to the intensity of the urge component.

In most cases of OAB, a focused patient history and a physical examination that emphasizes the anatomic and functional aspects of the lower urinary tract and other pelvic organs are all that is needed to arrive at a correct diagnosis. Questions about the quantity (volume) and quality (for example, caffeine content) of daily fluid intake are often revealing, and they can provide an opportunity to instruct the patient about appropriate fluid management. Patients may have misconceptions about normal voiding, perhaps mistakenly believing that voiding should only occur twice a day. Asking patients to fill in a three day voiding diary can be helpful.

The physical examination of the patient should focus on identifying features likely to initiate or exacerbate urinary incontinence, including obesity, pelvic organ prolapse, and vaginal skin atrophy, Table 1.

Advanced degrees of pelvic organ prolapse may cause mechanical outlet obstruction. Any clinical manifestations of major neurological disease such as multiple sclerosis or Parkinson's disease should be noted as potential contributors to voiding dysfunction. Identification of musculoskeletal disorders with restricted mobility may move the diagnosis away from true OAB to one where measures to enhance the proximity of toilet facilities, including a commode, would solve the problem of urine loss on the way to the bathroom.

While a significant number of patients have OAB of idiopathic origin,[6] it is important to rule out predisposing diagnoses at an early stage of investigation. Table 1 lists potential underlying disease that the physicians should always look for in patients with OAB symptoms.

The incidence of OAB increases with age. In elderly women, the acronym DIAPPERS (which stands for dementia, infection, atrophy, pharmaceuticals, psychological factors, excessive urine production, restricted mobility, and stool impaction) can be a helpful reminder of what to screen for, Table 1.[7]

Women older than 70 years are more likely to be affected by detrusor hyperactivity with impaired contractility (DHIC). If the bladder muscle (detrusor) is constantly or intermittently squeezing, it will give the patient the sensation of the need to void urgently. When the bladder tries to empty, decreased contractility leads to inefficient and incomplete emptying, resulting in increased frequency. Topical vaginal estrogen and a timed-toileting regime can be helpful whereas antimuscarinic agents are of little benefit for these patients.

Treatment

After other contributing factors have been identified and treated, multimodal intervention is the key to success in treatment of OAB. Treatment should begin with strategies to modify behavior (manage fluid intake) and diet (address obesity, restrict caffeine intake). Then pharmacotherapy (such as antimuscarinic agents) can be added where indicated and where necessary. Pharmacologic treatments appear to have a synergistic effect and should be used in combination with behavioral and dietary interventions, wherever possible.

Behavioral interventions and dietary factors

Behavioral therapies include fluid management strategies, Kegel exercises (pelvic floor rehabilitation exercises), and strategies such as timed voiding and urge suppression.

Bladder re-training can be accomplished at any stage of life, and patients should be instructed to increase their voiding interval by 30 minutes per week until a three-hour or longer interval is reliably obtained. An even simpler approach is to instruct patients to tell their bladder to "Call back in 20 minutes – I'm busy."

Patients should be given instructions about the type and amounts of fluids to drink, including advice about not drinking any diet drinks that contain caffeine, and drinking only when they are thirsty (except of course, if they have renal or bowel conditions where they need to drink more fluids).

Kegel exercises are beneficial for patients with either stress or urge incontinence. Patients need to be carefully instructed in the correct technique, as many women instinctively recruit the rectus abdominus, quadriceps, and gluteal muscles in addition to the levators. Those who have difficulty identifying and isolating the correct muscle group may benefit from a course of biofeedback and electrostimulation,[8] after which they may continue with self-initiated exercises. Fifty squeezes per day appears to be the minimum number required to produce an observable benefit, and this level of exercise intensity needs to be continued indefinitely.

Antimuscarinic agents and their side effects

Antimuscarinic pharmacotherapy, in conjunction with behavioral therapies, is the mainstay of OAB management. In Canada, the following antimuscarinic agents are available for treating patients with OAB: darifenacin (Enablex), imipramine (Tofranil), oxybutynin immediate release (generic oxybutynin), oxybutynin extended release (Ditropan XL, Uromax), oxybutynin patch (Oxytrol), solifenacin (Vesicare), tolterodine immediate release (Detrol), tolterodine extended release (Detrol LA), and trospium (Trosec).

Clinicians need to find the drug that results in the fewest side effects and has the greatest efficacy for the patient. In a patient who is refractory to treatment, a combination of different drugs may be beneficial.

All of the antimuscarinic agents act by competing with acetylcholine on the muscarinic receptors in the bladder. M2 and M3 receptors are predominant in the bladder, but all five muscarinic receptors have been identified at this site. In the bladder, close to 80% of the muscarinic receptors are M2 receptors, while close to 20% are M3 receptors, although the M3 receptors are thought to be responsible for detrusor contraction.[9] The function of M2 receptors has not been clarified.

The presence of muscarinic receptors in other organs -- including the brain, salivary glands, eyes, heart and bowel -- explain some of the common side effects from antimuscarinic agents, such as dry mouth, neurologic effects, and cardiovascular effects. Antimuscarinic drugs are commonly contraindicated in patients who have narrow angle glaucoma.

Patients often stop taking antimuscarinic agents due to unpleasant side effects such as dry mouth. However, since the maximum benefit from these drugs does not usually occur until 30 days of treatment, it is important to encourage patients to take these drugs for at least that long, and patients can be given oral moisturizing agents for dry mouth. Researchers are trying to develop a truly M3-specific agent for OAB, but so far, only darifenacin has significant M3 specificity.[1]

The incidence of side effects appears to be somewhat idiosyncratic, so a patient who is unable to tolerate one agent may do well on another agent, even one with a similar molecular structure.

Dry mouth

Dry mouth and constipation are the most common side effects from antimuscarinic agents. The VEsicare in Comparison To Oxybutynin for oveRactive bladder patients (VECTOR) study was designed to compare dry mouth in patients with OAB who were treated with solifenacin versus immediate-release oxybutynin, and trial results presented at the 2009 AUA meeting showed that patients receiving solifencin had fewer and milder episodes of dry mouth.[10] In a sub-analysis of this trial presented at another recent meeting, researchers reported better tolerability with solifencin

TABLE 2. **Properties of antimuscarinic agents that affect their ability to cross the blood brain barrier[13]**

	Tolterodine	Darifenacin	Trospium	Oxybutynin	Solifenacin
Solubility	slight	low	low	soluble	soluble
Size	475.6	507.6	427.9	357	480.6
Charge	+	+	+	neutral	unknown

than with oxybutynin, in younger patients as well as patients over age 65.[11]

Neurological effects

Muscarinic receptors are critical in cognitive function, especially memory.[12] Antimuscarinic drugs--particularly agents that are lipophilic and have relatively low molecular weight-- can have a significant harmful effect on the brain. Agents with a neutral charge are also more likely to cross the blood-brain barrier, Table 2.[13]

Increased permeability of the blood-brain barrier begins after the age of 45 years, and can be exacerbated by the presence of diseases or conditions such as diabetes, multiple sclerosis and hypoxia.

A 2006 study by Kay and colleagues[14] compared the cognitive effects in geriatric patients who received oxybutynin, darifenacin or placebo for 3 weeks. The study subjects had a mean age of 67 years and, based on pretreatment tests, had age appropriate memory. After treatment, patients who received oxybutynin had a decrease in memory consistent with aging 10 years, whereas darifenacin had no significant effects on memory compared to placebo.

A study by Anderson and colleagues showed that compared to oxybutynin, long-acting tolterodine (tolterodine LA) had no negative impact on memory.[15]

According to FDA 2009 prescribing guidelines for oxybutynin chloride tablets (Ditropan), "a variety of CNS anticholinergic effects have been reported, including hallucinations, agitation, confusion and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered. Ditropan should be used with caution in patients with preexisting dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms."[16]

TABLE 3. **Cardiovascular effects of antimuscarinic agents**

Drug	QT prolongation
Darifenacin	No
Oxybutynin	No
Solifenacin	Yes
Tolterodine	Yes
Trospium	No

Cardiovascular effects

Some OAB drugs can prolong the QT interval, leading to potentially fatal tachyarrhythmias including torsades de pointes, Table 3.

In practical terms, the use of these drugs in conventional doses in patients without major cardiac risk factors confers little additional risk. It is essential for the clinician to take a careful drug history, as many other drugs are also associated with QT prolongation, and the effect may be additive.

Local estrogen therapies

In postmenopausal women, irritative voiding symptoms and nocturia become more troublesome, and stress urinary incontinence may become more severe. These issues can be effectively addressed through the use of local vaginal estrogen preparations, which are more effective than systemic estrogen.

Various local estrogen preparations are available, including a conjugated equine estrogen cream (Premarin vaginal cream), an estradiol vaginal suppository (Vagifem), and a sustained release (depot preparation) in the form of an estradiol vaginal ring (Estring) that requires removal and reinsertion every 3 months. All are effective. Systemic absorption of estrogen is significantly lower with Vagifem and Estring than with Premarin vaginal cream.

Until fairly recently, the only option available was conjugated estrogen vaginal cream which has a systemic absorption rate of approximately 15%. Newer agents such as Estring and Vagifem contain slow-release preparations of 17-beta estradiol with a systemic absorption rate of between 2% and 3%. In

fact, these new local estrogen delivery systems can even be used in patients with breast cancer who experience vaginal dryness and dyspareunia associated with vaginal mucosal atrophy.[17]

Surgery

Obesity is a significant contributor to both stress and urge incontinence. However, surgical procedures to reconstruct the pelvic floor are more prone to fail in patients who are significantly overweight. For this reason, the author believes that anti-incontinence surgery should not normally be offered to patients who have a body mass index (BMI) that is higher than 30.

Other treatments

If the patient has idiopathic OAB and does not respond to conventional pharmacologic or behavioral interventions, new methods of treatment such as neuromodulation and intravesical injection of botulinum toxin A show promise for managing refractory cases. A discussion of these treatment modalities is beyond the scope of this paper.

Conclusion

OAB affects approximately 15% of Canadian women, often with a profoundly negative impact on their health, social, and personal well-being. Many women are reluctant to seek help either due to embarrassment or the mistaken belief that diminished bladder control is a normal part of aging, and nothing can be done.

Primary care practitioners can play a key role in identifying affected individuals by including a focused question such as "Do you ever have any trouble controlling your bladder?" in every annual patient assessment. Investigation and treatment can then be initiated, beginning with behavioral modification strategies (such as modifying fluid intake) and adding antimuscarinic pharmacotherapy where needed. Only patients with concurrent neurological disease or symptomatic pelvic organ prolapse, or patients who are refractory to conventional management will require referral to a specialist.

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