
Gender differences in overactive bladder

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EAPEN RS, RADOMSKI SB. Gender differences in overactive bladder. *Can J Urol* 2016;23(Suppl 1):2-9.

Overactive bladder (OAB) is a common condition in both women and men. Although prevalence's are similar in both genders, sex specific differences do exist in relation to individual OAB symptoms as well as degree of bother and quality of life. The added effect of prostatic enlargement in men leads to slightly different evaluation and treatment regimens in both genders. This review will examine the

gender differences in OAB related to epidemiology, OAB evaluation, investigation and treatment. This information will assist the primary care physician in assessing and initiating treatment in patients with OAB. It will further the understanding of the spectrum of treatments available for OAB and assist in determining the appropriateness and timing of referral of such patients to a urologist.

Key Words: OAB, overactive bladder, BPH, benign prostatic hyperplasia

Introduction

Overactive bladder (OAB) is a prevalent condition in both men and women. It can have a significant

impact on overall quality of life, sexual function, sleep and mental health in both genders. According to the International Continence Society (ICS) definition, OAB consists of urinary urgency with or without urge incontinence (UI), often accompanied by frequency and nocturia. The urodynamic characteristic of OAB is detrusor overactivity (DO). Many publications have studied the prevalence of OAB in developed

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countries. Multiple studies have also assessed the treatment options and impact that OAB has on quality of life.^{1,2} Although the overall prevalence of OAB is similar between the two genders, there are sex specific differences in the prevalence of various symptoms within the OAB complex.^{3,4} Anatomical and physiological differences in the lower urinary tract of males and females may help to explain these variations.⁴ Additionally, the underlying mechanisms that cause the outwardly similar symptomatology in men and women may be different. This review will focus on the prevalence data in regards to gender differences and the differences between men and women in terms of diagnosis, investigations and treatment of OAB.⁵⁻⁹

Epidemiology

EPIC study^{6,7}

This is one of the largest population based surveys that studied the prevalence of lower urinary tract symptoms (LUTS) and OAB. Conducted in five countries including Canada and the United Kingdom, the EPIC study was a cross sectional telephone survey of adults aged over 18 years. The study had over 19000 participants and showed an overall OAB prevalence of 11.8% with similar rates in men and women.

The EPIC study showed that the prevalence of LUTS suggestive of OAB was 10.8% in men and 12.8% in women. LUTS in general were more common in women than in men (66.6% versus 62.5%). Looking specifically at urinary incontinence (UI), women had a much higher rate of any UI (urge, mixed, stress and other) than men (13.1% versus 5.4%). These studies dispel the commonly held misconception that OAB symptoms affect the older population. Approximately 73% of men and 72% of women who participated in the EPIC study were less than 60 years of age. However, it appears that the prevalence of OAB symptoms does increase with age in both genders.

The EPIC study reported urinary incontinence in 13.1% of women and 5.4% of men. Stress urinary incontinence was the most common type in women and other urinary incontinence (urge, mixed) was more common in men.

The EPIC study assessed the prevalence of frequency in the study population, which largely depends on the definition used. ICS defined frequency as the perception of urinating too often during the daytime.⁷ Using this definition, the EPIC study reports that 31% of men and 25% of women who suffered from OAB symptoms had frequency. Of these, 75% of men and 60% of women urinated 8 or fewer times during the day, most of them falling within the 5-8 voids per day range. Women

were more likely than men (19% versus 12%) to report frequency of more than 8 times per day. Women were also more likely to be bothered by frequency of urination than men (66% versus 46%).

The EPIC study used the ICS definition of nocturia as one or more voids during the night. It was found that the general prevalence of nocturia is 48.6% in men and 54.5% in women. In OAB sufferers, however, the prevalence is 75% of men and 74% of women suggesting that nocturia occurs commonly in this syndrome.

The EPIC study confirmed that most patients with OAB had a combination of symptoms. Urgency with or without UI in the absence of frequency or nocturia was present in only 21% of men and 23% of women. Approximately 50% of OAB patients had a combination of two symptoms and approximately one third of patients reported a combination of three OAB symptoms.

*NOBLE study*⁸

The National Overactive Bladder Evaluation (NOBLE) program was developed to estimate the prevalence of OAB and its burden in the United States. It also assessed the influence of gender on OAB and its symptoms. The study also focused on the impact of OAB on quality of life, sleep and general mental health. The study showed an overall OAB prevalence of approximately 16% with no significant differences between the two sexes (16% in men, 16.9% in women). The general belief that OAB and urgency symptoms are more common in women than men is not supported by the NOBLE study. However, the manifestation of OAB symptom clusters, level of bother, urodynamic findings and responses to treatments may differ significantly between the two genders.

The NOBLE study discovered that specific OAB symptoms were more common in women than in men but with increasing age, especially over the age of 60 years, symptoms were predominant in men. Although the overall prevalence of OAB in men and women was similar, the incidence of OAB with and without urge incontinence showed significant gender variation. The NOBLE study demonstrated that in all age groups, OAB without UI was more common in men than in women.

The NOBLE study also found an association between OAB with UI and body mass index (BMI) in women but not men. Women with BMI > 30 were 2.2 times more likely to have OAB with UI than women with BMI < 24. Men who reported a history of prostate problems had a higher prevalence ratio of OAB with and without UI.

*EpiLUTS study*⁵

The Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) survey is a population based, cross sectional survey conducted in the United States, United Kingdom and Sweden to evaluate the prevalence and both of OAB as well as to update the results of the NOBLE survey done in 2003.

Gender specific differences could be seen in the EpiLUTS study. In men, the prevalence of OAB symptoms “sometimes” and “often” were 27.2% and 15.8% respectively, whereas in women, the prevalence of OAB symptoms “sometimes” and “often” was 43.1% and 32.6%. Women had an overall higher prevalence of symptoms such as urgency, UI or both. All these symptoms increased in prevalence with increasing age in both sexes.

*MILSOM study*⁹

Milsom et al conducted a population based prevalence study to determine the prevalence and symptoms of OAB. The surveys were carried out in France, Germany, Italy, Spain, Sweden and United Kingdom. Telephone and direct interviews were conducted in 16776 randomly selected men and women aged over 40 years. Milsom’s study found an overall prevalence of OAB symptoms of 16.6%. This study also looked at the rate at which OAB patients sought medical advice and treatment.

Women were slightly more likely than men to report OAB symptoms with the gender specific prevalence being 15.6% in men and 17.4% in women. This is interesting to note as other studies have suggested that male OAB was much more likely to have DO as an underlying cause than female OAB.¹⁰ In Milsom’s study, the overall prevalence of frequency and urgency were comparable irrespective of gender. However, UI was found to be more prevalent among women than men. The prevalence of OAB symptoms in men increases slowly until the age of 70 but then a sharp increase can be observed after 75 years of age, with a slight fall in prevalence between the ages of 70 to 75 years. In women, there is also a gradual increase seen until the age of 60, with a leveling off seen between 60-70 years of age and a gradual increase in prevalence thereafter.

Quality of life

It is interesting to take note of the thought processes and behaviors of participants with OAB symptoms as demonstrated by Milsom’s study.⁹ OAB symptoms adversely affected quality of life in 65% of participants. However, less than one third of patients who sought medical help were receiving medications. Frequency

and urgency symptoms were almost as much of a precipitant to seek help as was UI. Two thirds of participants with OAB had tried various conservative measures such as decreasing fluid intake to manage their symptoms. Women were twice as likely as men to use various coping strategies such as physiotherapy and absorbent products as non-medical management of OAB.⁹ Older patients are more likely to consult a doctor than younger patients with OAB. One of the main reasons for not seeking help or advice was the lack of awareness that effective treatment was available for such conditions.

Irwin et al’s review of the EPIC study showed, as would be expected, that the degree of bother amongst OAB sufferers increased as the number of LUTS increased.⁷

The effect of nocturia on quality of life is interesting. The significance of one episode of nocturia per night is debated as in the minds of many, this falls within the normal clinical spectrum.⁷ Studies have shown that even in healthy individuals, any episodes of nocturia can have a significantly negative impact on quality of life, sleep, work performance and general well being.⁷

Studies assessing quality of life highlight the significant negative impact that OAB has on daily activities, mental health and sexual function.^{11,12} Under-reporting, under-recognition and under-treatment can lead to long term suffering that affects multiple facets of patients’ lives.

Evaluation and investigations

When patients present with symptoms suggestive of OAB, a basic evaluation must be undertaken. A history is particularly important in eliciting the symptoms as well as the level of bother for the patient.^{13,14} Whilst important in both genders, a thorough history that covers all the relevant questions is particularly important in men who may not be forthcoming about their issues. In men, often OAB and bladder outlet obstruction can coexist and men are often more bothered by the OAB symptoms.¹⁵ The degree of bother is important in guiding treatment and management of expectations. Physical examination differs in the genders. In females, a pelvic examination is important and in males, a digital rectal examination (DRE) to examine the prostate is routinely performed as is examination of the penis. Any signs of neurological disease should be sought for in both genders. The algorithm in Figure 1, offers a practical approach in evaluating the patient with symptoms consistent with OAB.¹⁶

The diagnosis of OAB is usually clinical but sometimes an initial work up is required.¹⁷ Basic

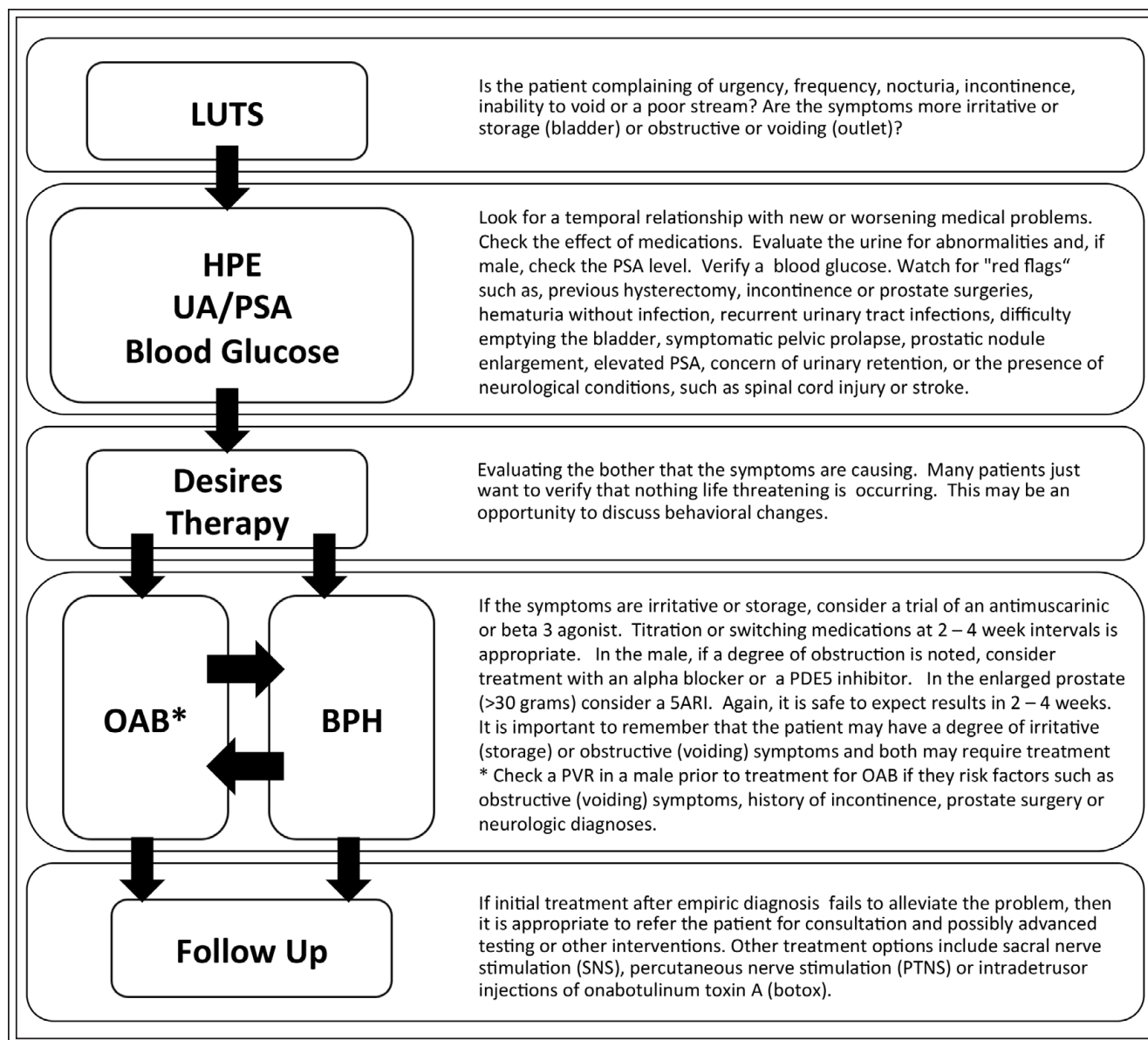


Figure 1. Algorithm that offers a practical approach in evaluating the patient with symptoms consistent with overactive bladder (OAB).¹⁶

clinical investigations are similar in both genders and should include a urinalysis, urine culture, serum creatinine, post void residual (PVR) bladder volume and a bladder diary. For the family physician, usually that is all that is needed to initiate treatment. In males however, extra measures may need to be taken to assess for bladder outlet obstruction. This may include a pelvic ultrasound to assess PVR volume and prostate size. For the urologist, a voiding flow rate study and bladder scan PVR may be performed. Furthermore, cystoscopy may be used to exclude anatomical causes for symptoms such as urethral strictures or malignancy.

Also in the realm of urologist is urodynamic testing, which can be an important tool in the diagnosis of OAB. Whilst not absolutely necessary before starting conservative treatments and medications, it can guide management in patients with mixed symptoms, unusual symptoms or in those who are failing first line medical therapy. In male patients, it can differentiate bladder outlet obstruction from OAB or if they co-exist and can help guide treatment and patient counseling. Urodynamics is particularly important in patients who have a suspicion of neurogenic DO, bladder outlet obstruction or a possible urethral diverticulum

or fistula. Urodynamics should be undertaken before any invasive treatments are pursued for OAB.

The main role of further investigations is to exclude an underlying cause for the symptoms. Imaging such as plain x-ray and urinary tract ultrasound can be used to exclude stones and bladder lesions.

Treatment

Treatment for OAB in both genders should take a graded approach with the most conservative measures attempted first. Any underlying medical conditions should be managed and optimized especially urinary tract infections, diabetes, cardiac disease and constipation. Lifestyle modifications and behavioral therapies should be embarked upon by patients early and maintained alongside various other treatments. Weight loss, exercise, smoking cessation and modification of fluid and caffeine intake can be difficult for patients to successfully implement into their lives, but these measures should be encouraged. Behavioral therapy aims to teach patients to learn bladder control and improve their symptoms. Timed voiding and bladder retraining techniques can reduce symptoms of frequency and urgency. Pelvic floor physiotherapy is also important, especially in women. Apart from very mild cases, pharmacotherapy is much more efficacious than behavioral measures in reducing symptoms and improving quality of life. The ideal approach is to combine pharmacotherapy with conservative measures to produce an optimal outcome.

A wide range of medical treatments are available at the urologists' disposal. Some gender differences are apparent in our use of medical treatments for this condition. The broad classes of drugs used to treat OAB include anticholinergic or antimuscarinic agents, desmopressin, tricyclic antidepressants, beta 3 agonists and intravesical Botox injections.¹⁷⁻²⁰ Specifically in men, the role of alpha blockers in conjunction with anticholinergics has been extensively studied.^{21,22} Male patients may also benefit from PDE5 inhibitors for LUTS.²² In resistant cases, sacral neuromodulation and posterior tibial nerve stimulation have been trialed with encouraging results.¹⁷ End stage cases may need to resort to augmentation enterocystoplasty but this has now become exceedingly rare.

Anticholinergic medications

Antimuscarinic or anticholinergic agents are usually the first line pharmacotherapy in OAB. They work by blocking the effects of neurotransmitter acetylcholine by binding to nicotinic and muscarinic receptors.²³ More selective anticholinergics have more affinity

for M2 and M3 receptors (the predominant receptors in the bladder) and therefore may have a better side effect profile. Antimuscarinics work by reducing involuntary detrusor contractions, thereby reducing symptoms of frequency and urgency. It also improves bladder capacity. Traditional and more selective anticholinergics are used in both men and women with good results.

Some unique features of some of the anticholinergics do exist. Darifenacin (Enablex) is highly specific for M3 receptors. Although its effectiveness is comparable to other OAB medications, its unique feature is its lack of effect on cognitive function.^{24,25} This is an important issue in elderly patients that commonly have OAB. One downside of this medication is its slightly higher incidence of constipation as compared to other anticholinergics.²³

Fesoterodine (Toviaz) is extensively hydrolyzed by serum esterases to 5-HMT, being the same active metabolite as tolterodine (Detrol). Unlike tolterodine, fesoterodine is not metabolized by the liver, which results in more consistent and predictable blood levels.²³ Furthermore, two well designed trials have shown that fesoterodine is effective and well tolerated in the elderly and even in the fragile elderly with no significant cognitive dysfunction.^{26,27} Fesoterodine is one of only three drugs that received a Fit for the Aged (FORTA) classification B or "beneficial" rating in the oral drug treatment of lower urinary tract symptoms in the elderly.²⁸

One particular concern in using anticholinergic medications in men is the potential risk of acute urinary retention (AUR), especially in men with co-existing OAB and bladder outlet obstruction. The safety and efficacy of anticholinergic medications used alone or in combination with alpha blockers in men with OAB has been reviewed in the literature. Abrams et al studied the safety of tolterodine for the treatment of OAB in men with bladder outlet obstruction.²¹ This study demonstrated that tolterodine was safe in men with mild to severe bladder outlet obstruction who also had urodynamically confirmed DO. It did not precipitate urinary retention or worsen preexisting LUTS with the incidence of adverse events being comparable in both treatment and placebo groups. Anticholinergic treatments appear to be safe and effective in men with predominant OAB symptoms. Combination therapy (anticholinergic drug and alpha blocker) has been found to be more effective than monotherapy in treating men with OAB.¹⁸ According to Kaplan et al, the incidence of AUR in men receiving anticholinergic medications was low (< 3%) with no significant changes in maximum flow rate or PVR

volume.¹⁸ The highest risk of AUR appeared to be in the first month of treatment but reduced significantly afterwards.

Other agents

Although not commonly used, tricyclic antidepressants (TCAs) inhibit muscarinic, alpha adrenergic and histamine H1 receptors. Studies of animal models have shown that TCAs can improve bladder volume and reduce the strength of bladder contractions.²³ The side effect profile can be vast and can include dry mouth, constipation, cardiac arrhythmias, urinary retention and drowsiness. It should be used with caution especially when considering combination therapy.

Desmopressin (Nocdurna) acetate has a limited role in the treatment of OAB. A synthetic form of the antidiuretic hormone vasopressin, it is mainly used as treatment in patients with primarily nocturia due to nocturnal polyuria and nocturnal enuresis. Studies have assessed the dosage of desmopressin and it appears that a minimum dose of 25 µg orally disintegrating desmopressin is effective in women.¹⁹ Men generally benefit from a higher dose of 50 µg.¹⁹ In both women and men, these doses significantly reduced the number of nocturnal voids along with significant increases in health related quality of life and sleep quality.²⁹ Desmopressin was well tolerated in both doses. Regardless of dose and gender, care should be taken to avoid hyponatremia and other electrolyte disturbances especially in elderly patients in whom there is a risk of worsening cardiac failure. Serum sodium levels need to be especially monitored in elderly patients.

Mirabegron (Myrbetriq) is a beta 3 agonist that is now used in both males and females with OAB. Since its mechanism of action is different, the typical side effects seen of anticholinergics are avoided with the use of mirabegron. It is generally well tolerated and the most common adverse effects are hypertension and headaches, the rates of which are very low. Nitti et al studied the urodynamic safety and efficacy of mirabegron in males with co-existing LUTS and bladder outlet obstruction.²⁰ Both 50 mg and 100 mg doses were assessed in the study population and it was found that neither dose affected flow and bladder contractility. Both doses were associated with a statistically significant reduction in urinary frequency. Furthermore, the 50 mg dose was associated with a reduction in urgency episodes.²⁰ Hence, mirabegron can be used in women with OAB and men with OAB with or without benign prostatic hyperplasia (BPH).

Hormone replacement therapy has been used in postmenopausal women with OAB. Studies

have looked at combination therapy with estrogen and an anticholinergic agent like tolterodine with mixed results.²³ The long term efficacy of hormone replacement therapy is not known.

Alpha blockers are generally used to manage voiding symptoms in men, especially those with an element of bladder outlet obstruction. OAB is a common sequelae of chronic obstruction in men and therefore it is necessary at times to manage both voiding and storage symptoms in male patients. Combination therapy with an anticholinergic as well as an alpha blocker has been assessed in clinical studies for the treatment of storage and voiding symptoms in men. The NEPTUNE I and II studies looked at the combination of solifenacin (Vesicare) and tamsulosin, where it was found that long term treatment with this combination for up to 52 weeks was tolerated well and provided clinical efficacy and quality of life benefits, compared to tamsulosin monotherapy.¹⁵ In patients who commenced treatment with low PVR volumes, the risk of AUR is rare.

Botulinum toxin is a potent neurotoxin. Derived from clostridium botulinum, Botox is given as an intradetrusor injection in patients with idiopathic and neurogenic DO. Being an invasive procedure, it is generally reserved for patients who are refractory to medical treatment. According to randomized placebo controlled studies, the adverse effects of Botox treatment include dysuria, bacteriuria and urinary retention.²³ Systemic adverse effects are very rare. Although tolerated generally well, men have a higher risk than women of urinary retention following Botox treatment. Posterior tibial nerve stimulation (PTNS) and sacral neuromodulation (SNS) may be offered as third line treatments in carefully selected patients. Usually, these are patients who have severe refractory OAB symptoms or those who cannot tolerate medical therapy.

When to refer

Both female and male patients with OAB can have treatment initiated by their family physician. However, patients should be referred to a urologist when they have refractory OAB symptoms, hematuria, recurrent urinary tract infections, large PVR volumes and complicated neurological conditions.

Summary

Multiple studies have assessed the prevalence of OAB and the impact it has on quality of life. These studies have shown that OAB is common in both women

and men. The prevalence of OAB and its symptoms increases with increasing age in both genders. Whilst the overall prevalence is similar in both genders, there are some sex-specific differences. Urinary urge incontinence is more common in women than in men. OAB has a significant impact on the quality of life, quality of sleep and mental health in both males and females. Investigations are similar in both genders with extra measures being taken in men to exclude bladder outlet obstruction. Treatments should take on a multidisciplinary approach with the implementation of lifestyle modifications and behavioral therapies alongside pharmacotherapy for the most optimal outcome. In most cases of OAB, treatment can be easily initiated by the family physician and referral to a urologist can be undertaken when symptoms are refractory to treatment or if the OAB appears to be complex.

Disclosure

Dr. Renu S. Eapen has no disclosure.

Dr. Sidney B. Radomski is on advisory boards for Astellas, Pfizer, Allergan, Merus Labs and Lilly. □

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Gender differences in overactive bladder

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