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Evaluation and Management of Overactive Bladder: Current UK Practice

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Abstract

Over Active Bladder (OAB) is a common problem affecting millions of men and women worldwide. It has far-reaching consequences on individual quality of life. No single treatment has been proven to be most effective, although many management options exist. Often a combination of options is required to successfully tackle OAB symptoms. In this review, we provide an overview of OAB, including risk factors for OAB; keys to diagnosis and therapeutic options including conservative and medical treatment, as well as management of refractory OAB; when to consider referral to a specialist; and resources for clinicians and patients. The aim of this review is to inform clinicians regarding OAB management in order to improve patient counseling and care in primary care setting.

Keywords: Overactive bladder • Haematuria •Dysuria •Dyspareunia •Pelvic organ prolapse

Introduction

Over Active Bladder (OAB) in women is a common and costly problem. It is defined by the International Continence Society (ICS)/ International Urogynecological Association (IUGA) as "a symptom syndrome of urinary urgency, usually accompanied by frequency and nocturia, with or without urge incontinence, in the absence pathological (e.g. UTI, stones, bladder tumor) or metabolic factors (e.g. diabetes)". Existing national and international guidelines on over active bladder state that OAB is generally not life-threatening, that the benefits of treatment should be weighed against potential adverse events and that not actually offering any treatment is acceptable choice [1]. Nevertheless, most patients report a high degree of bother from their OAB symptoms and desire medical intervention. The conventional first-line approach is behavioral modification, Pelvic Floor Muscle Training (PFMT), bladder retraining and biofeedback, followed by medications such as antimuscarinics or β3 agonists. Failure to manage OAB with conservative, conventional and pharmacotherapeutic measures leads to a refractory state. The options for managing refractory OAB are neuromodulation (sacral afferents/posterior tibial), intravesical injections of botulinum toxin or surgery (augmentation cystoplasty or urinary diversion). As OAB is a symptom complex, the main goal in the management should be patient satisfaction [2]. The objective of this review article is to describe the aetiology and risk factors for OAB, diagnosis and management options, and when to refer for specialized management.

Risk factors

OAB is a highly prevalent disease. Age is probably the best known risk factor for developing OAB. Prevalence increases with age, rising to 30.9% in those older than 65 years. The Lower Urinary Tract Symptoms (LUTS) that define OAB were reported by 12.8% of women and 10.8% of men. Nearly half of the women who reported symptoms of OAB also reported UI (6.3%/12.8%). Another risk factor for OAB is African American and Hispanic race [2]. A Body Mass Index (BMI) of >30 kg/m2, high caffeine intake (>400 mg/d) and smoking have also been associated with OAB. In women, postmenopausal status has also been associated with an increase in OAB symptoms. Although women with pelvic organ prolapse have a greater prevalence of OAB symptoms, there is no consistent evidence demonstrating a relationship between the compartment or stage of prolapse and the presence of OAB. Studies have shown that treatment of prolapse (whether with pessary or surgery) results in improvement of OAB symptoms. The development of OAB is a known risk after colposuspension & midurethral sling surgery for incontiance with de novo OAB occurring in between 15% and 29% of patients within 1-3 months postoperatively [3]. Finally, neurologic

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disease is also known to affect lower urinary tract function. Identifying modifiable risk factors earlier on can aid in the treatment of OAB.

Evaluation

The diagnosis of OAB is a diagnosis of exclusion of other causes, therefore requires a thorough clinical evaluation.

The history should include patients' baseline urinary function and the duration of patients' current symptoms. A key component of the history is determining whether the patients are bothered by their symptoms. Validated questionnaires can be used to quantify both bladder symptoms and amount of bother from these symptoms. Commonly used questionnaires include the ICIQ-UI SF, ICIQ OAB. These questionnaires can also be used to track improvement and to objectively assess the effectiveness of various treatment modalities. All medications should be reviewed, and co-morbidities such as sleep apnea, diabetes, and heart failure should be assessed, as all these can potentially contribute to lower urinary tract symptoms. Additional red flag symptoms, such as haematuria, dysuria, dyspareunia, pelvic organ prolapse, pelvic pain, and neurological deficits, should lead the clinician to consider an alternative diagnosis [3]. A 3 day bladder diary is useful in gaining an objective measure of daily intake in terms of the type of fluids, the amount of fluid intake, and voiding habits. A post-void residual should also be performed to evaluate bladder emptying in patients with obstructive symptoms, neurological disease, or prior surgery for incontinence, prolapse, or prostate issues [3].

A focused physical examination is also needed, with special attention paid to the abdominal and genitourinary examination and lower extremity edema evaluation. In patients with multiple sclerosis, diabetes, stroke, or spinal injury, a neurological examination of the genital region may be considered.

Laboratory testing should include a urinalysis to rule out both infection and haematuria. For more complicated or refractory patients, including patients with prior pelvic reconstructive surgery or those without symptom improvement with first- and second-line therapies, additional testing, including urodynamic evaluation, cystoscopy, and/or genitourinary tract imaging, can be used to differentiate between OAB and other aetiologies [3].

Management

Various international & national associations have developed guidelines regarding treatment of OAB Table 1.

Table 1. International and national associations recommendation for overactive bladder therapy. [a]: Date from reference 1,7,8. To meet criteria, patients must have failed first-line therapy and second-line therapy.

Level of therapy	Type of therapy	Examples of therapy
First-line therapy	Behavioral therapy	Bladder diet, bladder training, pelvic floor physical therapy, and biofeedback
Second-line therapy	Medical therapy	Anticholinergic medication and β3 agonist medication
Third-line therapy	Botulinum toxin A/ Neuromodulation [a]	Botox, SNS, and PTNS
Forth-line therpy	Surgery	Augmentation cystoplasty/urinary diversion

Conservative Options

In general, there are two categories of conservative management options:

1) Lifestyle modifications.

2) Control techniques.

Lifestyle modifications:

Lifestyle modification includes a variety of behavioral changes that can reduce and even eliminate OAB symptoms. Most of these modifications are based on expert opinion with limited scientific evidence due to lack of trials.

- Decrease fluid intake to six to eight glasses of water per day and avoid fluid intake for the 2–3 hours prior to bedtime to reduce urine production overnight.
- Reduce intake of bladder irritants such as caffeine, carbonated beverages, spicy food, artificial sweeteners, and alcohol.
- Avoid constipation.
- Smoking cessation [1].
- Optimize overall health by reducing weight improved control of hypertension, diabetes, sleep apnea, and other chronic health conditions to reduce urine production and improve bladder neurological function [1].

Control techniques

The control technique includes bladder retraining/PFMT. NICE 2019 recommendation is to offer bladder training lasting for a minimum of 6 weeks as first-line treatment. If women do not achieve satisfactory benefit from bladder training programmes, the combination of an overactive bladder medicine with bladder training should be considered if frequency is a troublesome symptom [1]. Bladder retraining involves scheduled toileting as well as urges control techniques. Supervised PFMT of at least 3 months duration has also been shown to improve urinary incontinence symptoms. Pelvic floor muscle training programmes should comprise at least 8 contractions performed 3 times per day. Electrical stimulation and/or biofeedback should be considered only for women who cannot actively contract pelvic floor muscles to aid motivation and adherence to therapy [1].

Pharmacological treatment

Oral medications are conservative non-invasive treatment options for OAB, which are considered to be second-line treatments by the AUA/NICE guidelines on OAB. Traditionally, this has been anti-muscarinic agents, though β3 agonists have recently been developed and approved for OAB. Anti-muscarinics have shown to be longstanding safe and effective treatment options for OAB with or without UI. Anti–muscarinic medications reduce bladder contractility by competitively inhibiting postganglionic acetylcholine receptors (M2, M3) (Figure 1) [4].

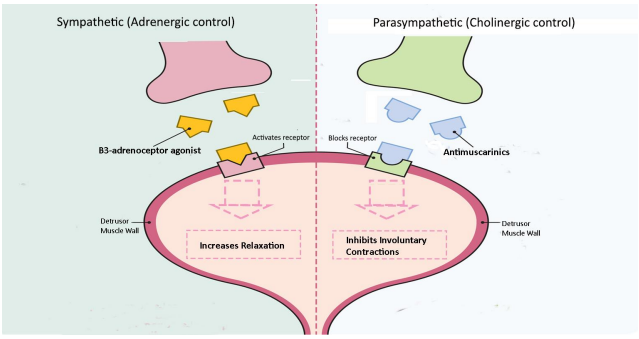

Figure 1. Anticholinergic and mirabegron mechanism of action.

Meta-analysis was performed using fixed-effects regression models and more than 27,000 women participating in randomized controlled trials suggests that improvement in symptoms with anticholinergic management of overactive bladder is modest and rarely fully resolves symptoms. Anticholinergic treatment provides symptom relief that is often not complete. Although women who struggle with overactive bladder may value some symptom relief, health care providers and their patients should understand the limitations of pharmacologic treatment and set expectations accordingly when deciding on treatment approaches. The primary difference between medications is the side effect profiles, not differences in their efficacy [5]. While effective in reducing symptoms in approximately 50 %, they are best known for their commonly associated side effects such as dry mouth, constipation, cognitive changes, blurred vision, dyspepsia, and urinary retention. The long-term effects of anticholinergic medicines for OAB on cognitive function are uncertain [1]. As a whole, anti-muscarinics can cause many bothersome side effects resulting in low patient compliance. There are several antimuscarinic agents available for the treatment of OAB worldwide: oxybutynin, tolterodine, fesoterodine, trospium, darifenacin, and solifenacin. Both the European Association of Urology (EAU) and the AUA performed an extensive review of the randomised trials evaluating these agents for OAB and found no compelling evidence for differential efficacy across medications [6,7]. Thus the choice of medication is largely determined by patient factors that include age, side effect profiles, and cost. NICE 2019 recommendation is to offer a trail of atleast 4 week with a drug of lowest acquisition cost. A women who remain on long-term medicine for overactive bladder should be reviewed in primary health care every 12 months, or every 6 months if they are aged over 75[1].

Historically, antimuscarinics have been the only oral medication option for patients with bothersome OAB. However, in 2012 the Food and Drug Administration (FDA) approved mirabegron for OAB. Mirabegron is a β3 adrenoreceptor agonist, which promotes relaxation of the detrusor muscle (Figure 1) [8]. Mirabegron is indicated as second line medical treatment by NICE Technology appraisal guidance [TA290] 2013 if anticholinergic are contraindicated, clinically ineffective and have unacceptable side effects. It can be consider as first-line use in patient aged >65 years with cognitive deficit [1]. An increased risk of hypertension has been the largest concern regarding mirabegron. Other adverse effects are uncommon, with the incidence of dry mouth and constipation less than 2%, making it a more desirable option than anti-muscarinics for many patients. Vibegron (Urovant) is a potential new drug for OAB that will avoid risk of hypertension [9].

Intravaginal estrogen's is used to treat overactive bladder symptoms in postmenopausal women with vaginal atrophy [1].

In 2018 the Food and Drug Administration (FDA) approved combination therapy with solifenacine and mirabegron for OAB. In a randomised, double-blind phase II study, combination therapy demonstrated statistically significant improvement over monotherapy with solifenacin 5 mg. The side effect profile was not increased compared with mirabegron or solifenacin monotherapy, although there may be a slightly increased risk of constipation [10].

Treatment of refractory OAB

Failure to manage OAB with conservative, conventional and pharmacotherapeutic measures leads to a refractory state. There are many inconsistencies in the definition of "refractory OAB". This could be absence of any effect, loss of efficacy, inability to remain on treatment due to side effects and contraindications to treatment [11]. Given its drastic and radical nature, surgery is usually the last resort and the debate as to whether intravesical injection therapy with botulinum toxin or neuromodulation is the best intermediate option is ongoing. If patients meet these criteria, they are eligible for third-line treatment.

The Botox® (onabotulinum toxin A) (Allergan, Inc., Irvine, CA, USA), was FDA approved in 2013 for idiopathic OAB. More recently the use of onabotulinumtoxinA (Botox®) in neurogenic and idiopathic detrusor overactivity has been approved by the Medicines and Health Products Regulatory Agency (MHRA). Botulinum toxin is injected directly into the detrusor muscle in the bladder wall. (Figures 2A and 2B)

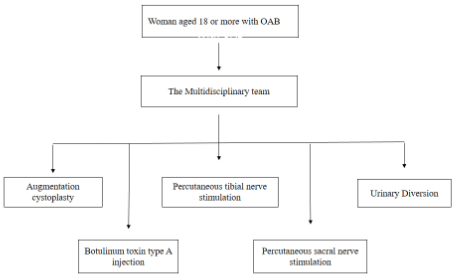

Figure 2A. NICE pathway for refractory OAB.

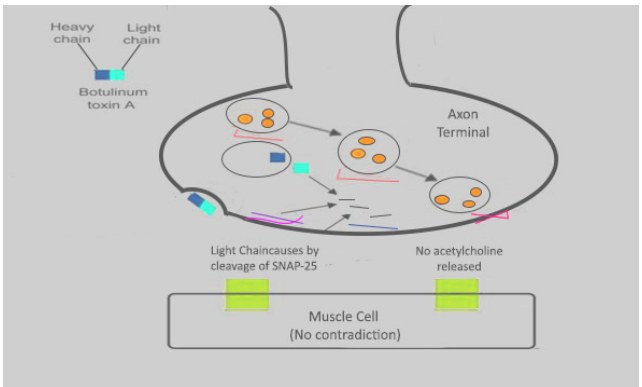

Figure 2B. Botulinum toxin type A mechanism of action.

In a systematic review and network meta-analysis study, 56 RCTs were studied and compare botulinum toxin A with other pharmacotherapies, mean differences favoured onabotulinum toxin A 100 U .The efficacy range from 36% to 89% (mean 70%).The effect last from 4 to 10 months(mean 6 months). Botulinum toxin A much more effective in neurogenic detrusor overactivity [10].

Third-line therapy also includes neuromodulation of the nerves controlling bladder function. The following two distinct types of neuromodulation therapy exist: Sacral Neuro Modulation (SNM), Peripheral Tibial Nerve Stimulation (PTNS). Sacral Neuro Modulation was FDA approved in 1997 InterStim®. NICE 2019 recommend offering SNM after discussion in local MDT if OAB patient not willing to perform CISC or if patient has not shown any response to conservative treatment and botulinum toxin A injection. Sacral neuromodulation involves stimulation of the afferent neural pathways that control bladder function via the sacral nerve plexus in order to restore normal storage and voiding function. Unlike PTNS, this form of sacral neuromodulation is accomplished with a permanent surgical implant. The first step in this treatment is a test phase. Patients must demonstrate at least a 50% improvement in baseline symptoms from the test phase before they can proceed with permanent implantation [12]. Overall, 50-88% responds to test phase. Once implanted, a generator battery lasts 5 years on average, at which time the battery would need to be exchanged surgically. The lead wire has no expiration. Reported adverse events include pain at implantation site, lead migration, infection, technical or device problems, adverse change in bowel or voiding function, and undesirable stimulation. Axonics is currently the only rechargeable SNM system on the market. It is designed to reduce the number of invasive battery replacement procedures that would be needed every 3 to 5 years with a non-rechargeable system. The Axonics system is also smaller than non-rechargeable SNM devices. This is claimed to help reduce the risk of implant site pain and make it more suitable for people with low BMI. Another advantage of this system is the potential for whole body MRI, while interstim is only approved for head MRI [13]. Contraindications to sacral neuromodulation include inadequate response to the test phase, need for frequent magnetic resonance imaging and use of diathermy. Sacral neuromodulation demonstrated a significant improvement in OAB symptoms (61%), urge incontinence episodes (71%), and urinary frequency (61%) [12]. However, EAU Guideline 2019 (ROSETTA trial) stats SNS is not more effective than Botox 200 U at 6 months [7].

PTNS was approved by the US Food and Drug Administration (FDA) in 2005 for the treatment of refractory OAB under the brand name Urgent PC® (Uroplasty, Minnetonka, MN, USA). Treatment is accomplished through stimulation from the posterior tibial nerve to the afferent nerves of the sacral plexus. Treatment extends for a period of 12 weekly 30 minutes sessions, followed by a tapering of treatment over several months. Ongoing therapy is continued as needed to maintain symptom relief. Treatment response can be seen as early as the first session, but may take up to six sessions. The recommendation is to complete all twelve sessions before reevaluating. No serious adverse events have been reported with PTNS [14].

NICE 2019 do not recommend transcutaneous sacral nerve stimulation or transcutaneous posterior tibial nerve stimulation to treat OAB in women [1].

NICE guideline 2013 recommends augmenation cystoplasty for the management of detrusor overactivity only if non-surgical management has failed and patient is willing and able to self-catheterise [1].

Similarly, urinary diversion is only offered to patients who have failed less invasive therapies and willing to accept a stoma and have been warned about the possible small risk of malignancy [1,4].

When to refer?

From the information provided in this review, clinicians should be able to provide their patients with information regarding diagnosis and treatment options for OAB. First line and second line therapy can be offered at primary level. For third line therapy, it is recommended to refer to a specialist who performs these procedures regularly. Patients are candidates for third-line therapy when they have failed conservative measures (first-line therapy), and either failed two medications (second-line therapy) or cannot tolerate medical therapy due to contraindications or side effects.

Conclusion

OAB is a complex condition, but there are promising treatment options available.

Take home message

- OAB is generally not life-threatening, that the benefits of treatment should be weighed against potential adverse events and that not actually offering any treatment is an acceptable choice.
- Myriad factors contribute to the choice of prescribing an anti-muscarinic such as: the need for a favourable molecular structure and pharmacokinetic profile, a titratable formulation with daily dosing to improve compliance and decrease side effects, and a cost effective option for varying insurance coverage and out-of-pocket costs.
- Botulinum toxin is a clinically and economically effective treatment option for refractory OAB.
- Sacral neuromodulation (SNS) has shown promising result in refrectory OAB with success rates of up to 70% .
- Surgery is only considered as a last resort if non-surgical management has failed.

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