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OVERACTIVE BLADDER (U LEE AND S ADELSTEIN, SECTION EDITORS)

The Role of Local Hormone Replacement in Overactive Bladder

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Abstract

Purpose of Review Overactive bladder (OAB) is a common and distressing condition which is known to increase with age and to have a significant effect on quality of life (QoL). Whilst OAB is a symptomatic diagnosis, many patients will require basic investigations prior to initiating the appropriate management. This paper will explore the prevalence and pathophysiology of OAB as well as diagnosis and management of the condition.

Recent Findings There is increasing evidence that local oestrogen therapy may be beneficial in the management of postmenopausal women with OAB, either when used alone or as combination therapy with an antimuscarinic drug. This paper will review the postulated mechanisms of action as well as exploring the available evidence base supporting efficacy.

Summary There is now a substantial evidence base to support the use of local vaginal oestrogen therapy in postmenopausal women with OAB either in isolation or alternatively as an adjunctive therapy when used with antimuscarinic medication. Available evidence supports an improvement in lower urinary tract symptoms as well as a significant improvement in health-related quality of life (HRQoL).

Keywords Oestrogen · Vaginal oestrogen · Overactive bladder · OAB · Detrusor overactivity · Antimuscarinics

Introduction

Overactive bladder (OAB) describes the symptom complex of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [1].

North American epidemiological studies have reported a prevalence of OAB in women of 16.9%, and the prevalence increases with age rising to 30.9% in those over the age of 65 years [2]. European studies [3] have shown the overall prevalence in women over the age of 40 years to be 16.6%. Frequency was the most commonly reported symptom (85%) whilst 54% complained of urgency and 36% urgency incontinence.

This article is part of the Topical Collection on *Overactive Bladder*

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Pathophysiology

The symptoms of OAB are due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. These involuntary contractions are termed detrusor overactivity [1] and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors [4]. However, OAB is not synonymous with detrusor overactivity as the former is a symptom-based diagnosis whilst the latter is a urodynamic diagnosis. It has been estimated that 64% of patients with OAB have urodynamically proven detrusor overactivity and that 83% of patients with detrusor overactivity have symptoms suggestive of OAB [5].

Muscarinic Receptors

Molecular cloning studies have revealed five distinct genes for muscarinic acetylcholine receptors in rats and humans, and it has been shown that five receptor sub-types (M_1-M_5) correspond to these gene products [6]. In general, it is thought that the M_3 receptor is responsible for the normal micturition contraction, although in certain disease states, such as neurogenic bladder dysfunction, the M_2 receptors may become more important in mediating detrusor contractions [7].

OAB: Clinical Presentation

Overactive bladder usually presents with a number of lower urinary tract symptoms. Those most commonly seen are urgency, daytime frequency, nocturia and urgency incontinence although women may also complain of other lower urinary tract symptoms such as stress incontinence, nocturnal enuresis and coital incontinence.

Whilst there are no specific clinical signs in women with overactive bladder, it is important to perform a pelvic examination to exclude a pelvic mass and to assess for urogenital atrophy and urogenital prolapse, particularly in postmenopausal women. Should a neurological lesion such as multiple sclerosis be suspected, then, a basic neurological examination should also be performed.

OAB: Investigation

Despite overactive bladder (OAB) being a symptomatic diagnosis, all patients are required a basic clinical assessment in order to confirm the diagnosis as well to exclude any other underlying causes for lower urinary tract dysfunction.

A midstream specimen of urine should be sent for microscopy, culture and sensitivity in all cases of incontinence to exclude a lower urinary tract infection.

In order to exclude voiding dysfunction, all patients should have a post-void residual urine volume excluded either by ultrasound or catheterisation.

All patients should complete a bladder diary evaluating fluid intake and the voiding pattern. As well as the number of voids and incontinence episodes, the mean volume voided over a 24-h period can also be calculated in addition to the diurnal and nocturnal urine volumes.

Urgency is now generally regarded as being the driving symptom of OAB and is known to play an important role in the development of daytime frequency, nocturia and urgency incontinence. Several validated urgency scoring systems (Patient Perception of Intensity of Urgency Score (PPIUS) [8], Urgency Perception Score (UPS) [9] and Indevus Urgency Severity Scale (IUSS) [10] have been developed to attempt to measure urgency severity, and these may be used in conjunction with frequency volume charts in clinical practice.

OAB: Quality of Life Assessment

Health-related quality of life (HRQoL) is assessed by the use of questionnaires and allows the quantification of morbidity and the evaluation of treatment efficacy as well as being a measure of how lives are affected and coping strategies adopted.

Generic questionnaires, such as the Short Form 36 [11], are general measures of QoL and are therefore applicable to a wide range of populations and clinical conditions whilst disease-specific questionnaires, such as the Kings Health Questionnaire (KHQ) [12], are designed to focus on lower urinary tract symptoms.

OAB: Urodynamic Investigations

Whilst the majority of women complaining of OAB symptoms may be managed on the basis of simple investigations, those women with refractory or complex symptoms may benefit from urodynamic investigations. Urodynamic investigations include uroflowmetry, filling cystometry and pressure/flow voiding studies. Patients with refractory symptoms may also benefit from further investigation using videocystourethrography or possibly ambulatory urodynamics.

OAB: Cystourethroscopy

Although cystoscopy is not helpful in diagnosing OAB, it may be used to exclude other causes for the symptoms associated with OAB. Cystourethroscopy should be considered in all women complaining of ‘red flag’ symptoms such as haematuria, painful bladder syndrome, suspected bladder tumour, bladder calculus, recurrent urinary tract infections and recurrent incontinence.

Conservative Management

All women with OAB initially benefit from advice regarding simple measures which they can take to help alleviate their symptoms. Many patients drink excessively and should be told to reduce their fluid intake to between 1 and 1.5 L per day [13] and to avoid tea, coffee and alcohol if these exacerbate their problem. In addition, there is also increasing evidence to suggest that weight loss may improve symptoms of urinary incontinence [14].

Bladder Retraining

Bladder retraining was first described by Jeffcoate and Francis [15] and both inpatient and outpatient therapy can be effective. A meta-analysis has concluded that bladder retraining is more effective than placebo and medical therapy although there is insufficient evidence to support the effectiveness of electrical stimulation and too few studies to evaluate the effect of pelvic floor exercises and biofeedback in women with urinary urge incontinence [16]. Nevertheless, the National Institute of

Clinical Excellence (NICE) (NG123, 2019) [17••] and International Consultation on Incontinence (ICI) [18••] recommend that bladder retraining should be considered first line treatment in all women with OAB.

Antimuscarinic therapy may be a useful addition to bladder retraining in the management of overactive bladder (OAB). In a Cochrane review of 23 trials including 3685 patients, symptomatic improvement was more common amongst those on antimuscarinic therapy compared with bladder retraining (RR 0.74; 95% CI, 0.61–0.91) and combination treatment was also associated with more improvement than bladder training alone (RR 0.57; 95% CI, 0.38–0.88). Similarly, there was a trend towards greater improvement with a combination of antimuscarinic therapy with bladder retraining compared with antimuscarinic therapy alone (RR 0.80; 95% CI, 0.62–1.04) although this was not statistically significant [19••]. The evidence would therefore appear to suggest that bladder retraining and drug therapy act synergistically and may be used in combination.

Medical Management

Whilst a conservative approach is justified initially, drug therapy remains integral in the management of women with OAB and there are currently a number of different antimuscarinic drugs available as well as the newer β3-agonist, mirabegron.

Antimuscarinics

Traditionally, tolerability, compliance and persistence have limited the usefulness of many of the antimuscarinic agents, although with the introduction of newer bladder-selective drugs, once daily dosing and differing routes of administration, it is possible that persistence with therapy may increase.

There are now a number of different licensed antimuscarinic drugs available, and these have all been recently reviewed by the International Consultation on Incontinence [20••] (Table 1) and all have level 1 evidence [21] and a grade A recommendation [22].

Table 1 Antimuscarinic drugs used in the treatment of overactive bladder

Antimuscarinic drugs	Level of evidence	Grade of recommendation
Darifenacin	1	A
Fesoterodine	1	A
Oxybutynin	1	A
Propiverine	1	A
Solifenacin	1	A
Tolterodine	1	A
Trospium	1	A

A systematic review and meta-analysis of 83 studies, including 30,699 patients and six different drugs (fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine and trospium), support the efficacy of antimuscarinic therapy in the management of OAB. Overall, there was a significantly higher return to continence favouring active treatment over placebo, the pooled RR across different studies and different drugs being 1.3–3.5 ($p < 0.01$). Antimuscarinic therapy was also shown to be statistically significantly more effective in reduction of incontinence episodes per day, reduction in number of micturitions per day and reduction of urgency episodes per day [23].

Anticholinergic Burden

Whilst antimuscarinic therapy remains integral in the management of women with OAB, there is increasing evidence to suggest that these drugs may act on the central nervous system and may lead to a long-term reduction in cognitive function and an increase in the risk of dementia [24].

A systematic review of 46 studies (including 60,944 participants) demonstrated a significant decline in cognitive ability with increasing anticholinergic load with an increasing trend in terms of mortality, although this was not significant [25]. These findings were supported by a 2-year longitudinal study of 13,004 participants over the age of 65 years taking anticholinergic medication. Overall use of drugs with an anticholinergic effect was associated with a significant decline in the Mini Mental State Examination (MMSE) and an increased risk in terms of 2-year mortality (OR = 1.68; 95% CI, 1.30–2.16; $p < 0.001$) [26].

Further evidence of a possible association with cognitive decline is provided by a large prospective cohort study from North America investigating the association of Total Standardised Daily Dose (TSDD) of anticholinergic medication and the onset of dementia and Alzheimer's disease. Overall, there was a 10-year dose response relationship observed for both dementia and Alzheimer's disease (test for trend $p < 0.001$) with the greatest risk being associated with the highest anticholinergic dose, adjusted hazard ratio 1.54 (95% CI, 1.21–1.96) [27•].

Consequently, whilst the use of antimuscarinic medication is not contraindicated in the elderly, it is important before treating OAB to be aware of comorbidities and particularly the risk of polypharmacy. Many medications have an anticholinergic effect, and it is important to be aware of this prior to initiating therapy in order to reduce the overall anticholinergic load; this may be assessed clinically using an anticholinergic burden scale (www.agingbraincare.org) [28••].

β-Adrenoceptors and OAB

Adrenoceptors are members of a family of seven transmembrane receptors, with two main groups: α and β, with a number of subtypes comprising each group. β1-, 2- and 3-adrenoceptors have been identified in human urothelium and detrusor muscle, with β3 being highly expressed in the urinary bladder [29, 30].

β3-Adrenoceptor agonists have been demonstrated to cause dose-dependent detrusor relaxation during the storage phase of the micturition cycle and to inhibit neurogenic detrusor overactivity during in vitro studies [31, 32].

Mirabegron is the only commercially available selective, β3-agonist for the treatment of OAB. The efficacy and tolerability of mirabegron has also been reported in a large multicentre randomised double-blind, parallel group, placebo and tolterodine-controlled phase III trial [33] demonstrating mirabegron was significantly superior to placebo in the co-primary endpoints of incontinence episodes and micturition frequency. This was also supported by a significant improvement in QoL in the mirabegron arm. The rates of dry mouth and constipation in the mirabegron groups were no different to placebo.

The long-term safety of mirabegron is supported by a 12-month randomised double-blind phase III study in 2444 patients [34] which reported low rates of dry mouth and constipation in the longer term as well as demonstrating no significant cardiovascular changes in terms of pulse rate and blood pressure.

Combination Therapy: Mirabegron and Solifenacin

The efficacy and safety of combination therapy with solifenacin and mirabegron in patients with an inadequate response to solifenacin monotherapy has been investigated in the BESIDE study [35]. This was a prospective randomised double-blind study of 2174 patients randomised to combination therapy (solifenacin 5 mg and mirabegron 50 mg) or solifenacin monotherapy (5 mg or 10 mg). Overall, the efficacy of combination therapy was superior to solifenacin 5 mg with significant improvements in incontinence episodes, and micturition frequency and combination therapy was non-inferior to solifenacin 10 mg for micturition frequency and incontinence episodes.

Role of Oestrogen in the Pathogenesis of OAB

Whilst the effect of oestrogen therapy on lower urinary tract function remains controversial, there is evidence to show that oestrogen deficiency may increase the risk of developing OAB [36].

In vitro studies suggest that oestrogen may inhibit the function of Rho-kinase in bladder smooth muscle, hence effecting smooth muscle contractility. Consequently oestrogen deprivation following the menopause may lead to the development of OAB symptoms [37], and further studies have demonstrated that ovariectomised rats showed a significant decrease in voided volume and an increase in 24-h frequency with an increase in basal- and stretch-induced acetylcholine releases. Conversely, there was a reduction in acetylcholine release from nerve fibres. This may explain why there is a decrease in detrusor contractility following the menopause with a corresponding increase in the development of OAB symptoms. Interestingly, oestrogen replacement therapy has been shown to reverse these changes [38].

More recently, the role of voltage-gated big potassium (BK) channels has also been investigated in the pathogenesis of OAB [39]. These large conductance Ca^{2+}-activated K^+ BK channels are thought to be regulators of detrusor smooth muscle, and BK channels [40] are directly activated by 17β-oestradiol to reduce detrusor smooth muscle excitability [41]. 17β-Oestradiol has also been shown to regulate Ca^{2+}-activated K^+ BK channels in detrusor smooth muscle and to reduce phasic detrusor contractions in a dose-dependent manner [42].

These studies would appear to support a role of oestrogen deficiency in the pathogenesis of OAB, and more recent work has also has suggested that oestrogen deprivation also leads to changes in urothelial thickness and a reduction in the tight junction protein Zona Occludens-2 (ZO-2) which may increase the risk of OAB. These changes are reversed with oestradiol replacement [43].

In summary, there is now a considerable body of evidence to support the role of oestrogen deficiency in the pathogenesis of OAB in postmenopausal women and further evidence to suggest a role for oestrogen replacement therapy in postmenopausal women with symptoms of OAB.

Oestrogen in the Management of Overactive Bladder

Oestrogen therapy has been used in the treatment of urinary urgency and urgency incontinence for many years although there have been few controlled trials to confirm the efficacy. A double-blind placebo-controlled crossover study using systemic oral oestriol in 34 postmenopausal women produced subjective improvement in symptoms [44], although a double-blind multicentre study of the use of oestriol in postmenopausal women complaining of urgency has failed to confirm these findings [45].

Whilst the evidence to support the use of systemic oestrogen therapy is largely lacking, there is now much greater evidence supporting the use of local oestrogen replacement therapy.

Vaginal 17β-oestradiol tablet (Vagifem) therapy has been shown to be useful in managing the symptoms of OAB and in particular improving the symptom of urgency [46]. A double-blind, randomised, placebo-controlled trial has shown the lower urinary tract symptoms of frequency, urgency and urgency and stress incontinence to be significantly improved [47]. However, some of the subjective improvement in these symptoms may simply represent local oestrogenic effects reversing urogenital atrophy rather than a direct effect on lower urinary tract function.

In a review of 10 randomised placebo-controlled trials, oestrogen was found to be superior to placebo when considering symptoms of urgency incontinence, frequency and nocturia, although vaginal oestrogen administration was found to be superior to placebo for the symptom of urgency [48].

Combination Therapy: Vaginal Oestrogen and Antimuscarinics

There is now emerging evidence regarding the synergistic use of vaginal oestrogen therapy with antimuscarinic therapy in the management of postmenopausal women with OAB.

A 12-week prospective randomised trial comparing tolterodine 2 mg bd and vaginal conjugated oestrogen cream versus tolterodine 2 mg bd alone in 80 postmenopausal women complaining of OAB [49•] showed combination therapy had a significantly greater improvement in mean daytime frequency and voided volume as compared with monotherapy. These objective observations were also supported by a significantly greater improvement in HRQoL in the combination therapy group. Whilst there was a trend to improvement in symptoms of nocturia, urgency and urgency incontinence, these findings were not significantly different between the groups.

These findings are supported by a 12-week prospective randomised trial comparing the oestradiol-releasing vaginal ring and oral oxybutynin 5 mg bd which has been reported in 59 postmenopausal women with OAB [50•]. Those women who received oxybutynin had a mean decrease of 3.0 voids per day as compared with a decrease of 4.5 voids per day in women using the oestradiol ring with a significant improvement in HRQoL in both groups.

These findings have been supported by two further small studies demonstrating the synergistic effect of topical oestrogens with antimuscarinic therapy.

A multicentre randomised, open parallel-controlled study has investigated the efficacy and safety of solifenacin with, and without, intra-vaginal promestriene in 104 postmenopausal women over 12 weeks [51]. Overall, there was no significant difference in terms of the reduction of daytime frequency or urinary urgency although there was a significantly greater improvement in the combination therapy arm in HRQoL evaluation.

These findings are supported by a smaller study investigating the use of fesoterodine with, and without, vaginal Premarin in 23 women [52•]. After 12 weeks, both groups had a significant improvement in OAB symptoms, although when the two groups were compared, there was a greater improvement in terms of symptom severity, HRQoL and sexual function in the combination therapy arm.

However, these findings in patients with OAB have not been replicated in a 12-week prospective study of 229 postmenopausal women with a urodynamic diagnosis of detrusor overactivity treated with tolterodine extended release (ER) 4 mg od with or without vaginal oestriol [53•]. Overall, there were no significant differences between the two treatment groups in terms of efficacy which was assessed subjectively.

It remains unclear why the results of these studies are contradictory. This may be due to the difference in the patient populations; one study included women with detrusor overactivity whilst the others simply recruited OAB patients. In addition, the different oestrogen preparations investigated may also have a significant effect on efficacy as conjugated oestrogens (Premarin) are absorbed systemically and therefore may have a greater effect on the lower urinary tract.

These findings would suggest that, whilst vaginal oestrogen therapy may be useful in women with a symptomatic diagnosis of overactive bladder, they are perhaps less useful in women with a urodynamic diagnosis of detrusor overactivity. This again suggests that the treatment of urogenital atrophy is important in the management of postmenopausal women with OAB.

The role of oestrogen therapy in the management of women with urinary incontinence has recently been reported in two large systematic reviews.

The most recent Cochrane review [54••] identified 34 trials involving 19,676 women of whom 9599 received oestrogen. The combined results of the six trials of systemic oestrogen resulted in worsening incontinence when compared with placebo (RR 1.32; 95% CI, 1.17–1.48). There was also a worsening of incontinence with systemic combined HRT (RR1.11; 95% CI, 1.04–1.18). Conversely, there was some evidence to suggest that local oestrogen therapy may improve incontinence (RR 0.74; 95% CI, 0.64–0.86), although interestingly, one small study showed a greater improvement after pelvic floor muscle training (PFMT) as compared with local oestrogen therapy (RR 2.30; 95% CI, 1.50–3.52).

The findings from Cochrane are also supported by a more recent systematic review investigating the role of local oestrogen therapy in pelvic floor dysfunction [55•]. In total, 532 papers were screened and 31 were suitable for review. Overall, subjective and urodynamic outcomes, vaginal maturation and vaginal pH changed in favour of vaginal oestrogen when compared with placebo and there were no differences in efficacy in terms of the mode of administration. The authors concluded that topical oestrogen therapy is effective for the

treatment of urogenital atrophy and also decreases complaints associated with OAB and urinary incontinence, although unfortunately, there is a lack of data with regard to the prevention and management of urogenital prolapse.

Conclusions

Overactive bladder is a common and distressing condition which is known to have a significant effect on HRQoL. The clinical diagnosis of OAB is often one of exclusion although urodynamic investigations are helpful in those women with refractory or unusual symptoms. The majority of women will benefit from conservative measures in the first instance although many will eventually require drug therapy. At present, antimuscarinics are the most commonly used drugs for OAB although there usage is limited by the common anticholinergic side effects of dry mouth, constipation, somnolence and blurred vision. For those with refractory symptoms, switching to an alternative class of therapy, such as mirabegron, may be useful and there is now considerable evidence to support the use of combination therapy in those women with persistent symptoms.

The available evidence would also appear to suggest that whilst systemic oestrogen does not have a role in treating OAB, vaginal oestrogen may be helpful and may also act synergistically with antimuscarinic drugs. Combination therapy should improve patient acceptability and compliance by minimising adverse effects, and in the longer term, this should improve persistence with therapy and ultimately HRQoL.

Compliance with Ethical Standards

Conflict of Interest Dudley Robinson has received fees for Consultancy work and Speaking from Astellas, Allergan, Ixaltis, Contura and Ferring. He has performed Research with Astellas, Ixaltis and Allergan. Linda Cardozo has received fees for Consultancy work and Speaking from Atlantic Therapeutics, Boston and Allergan.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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