Climacteric

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: https://www.tandfonline.com/loi/icmt20

Managing overactive bladder

D. Robinson & L. Cardozo

To cite this article: D. Robinson & L. Cardozo (2019) Managing overactive bladder, Climacteric, 22:3, 250-256, DOI: 10.1080/13697137.2018.1552254

To link to this article: https://doi.org/10.1080/13697137.2018.1552254

Published online: 29 Apr 2019.

CLIMACTERIC
2019, VOL. 22, NO. 3, 250–256
https://doi.org/10.1080/13697137.2018.1552254

Taylor & Francis
Taylor & Francis Group

REVIEW

Managing overactive bladder

D. Robinson and L. Cardozo

Department of Urogynaecology, King's College Hospital, London, UK

ABSTRACT

Overactive bladder (OAB) is a common and distressing condition which is known to increase with age and has a significant effect on quality of life. Whilst OAB is a symptomatic diagnosis, many patients will require basic investigations prior to initiating the appropriate management.

This article will review the initial clinical assessment and management of women complaining of OAB including conservative measures and drug therapy, and will also focus on the role of estrogen. In addition, the management of refractory OAB will also be discussed including more invasive strategies such as neuromodulation, Botulinum Toxin, and reconstructive surgery.

ARTICLE HISTORY
Received 12 November 2018
Accepted 17 November 2018
Published online 24 April 2019

KEYWORDS
Overactive bladder; antimuscarinics; estrogen; β3 agonists; Botulinum Toxin; neuromodulation

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% of urgency incontinence.

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 subtypes (M_1–M_5) correspond to these gene products[6]. In general, it is thought that the M_3 receptor is responsible for 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].

Overactive bladder: clinical presentation

OAB 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 stress incontinence, nocturnal enuresis, and coital incontinence.

Whilst there are no specific clinical signs in women with OAB, it is important to perform a pelvic examination to assess for urogenital atrophy and urogenital prolapse. In addition, occasionally an underlying neurological lesion such as multiple sclerosis will be discovered by performing a basic neurological examination.

Overactive bladder: investigation

Despite OAB being a symptomatic diagnosis, all patients require a basic assessment in order to confirm the diagnosis as well as to exclude any other underlying cause for lower urinary tract dysfunction.

A midstream specimen of urine should be sent for microscopy, culture, and sensitivity in all cases of incontinence in order to exclude a lower urinary tract infection. In order to exclude voiding dysfunction, all patients should have a postvoid residual urine volume excluded either by ultrasound or catheterization. In addition, all patients should complete a

CONTACT Dudley Robinson Dudley.robinson@nhs.net Department of Urogynaecology, King's College Hospital, Denmark Hill, London SE5 9RS, UK.

Table 1. Antimuscarinic drugs used in the treatment of overactive bladder.

Antimuscarinic drug	*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

bladder diary in order to evaluate fluid intake and 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 as well as 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[8], Urgency Perception Score[9], Indevus Urgency Severity Scale[10]) have been developed to attempt to measure urgency severity and these may be used in conjunction with frequency volume charts in clinical practice.

Overactive bladder: quality-of-life assessment

Health-related quality of life (HRQoL) is assessed by the use of questionnaires that allow 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 King's Health Questionnaire[12], are designed to focus on lower urinary tract symptoms.

Overactive bladder: 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 ambulatory urodynamics.

Overactive bladder: 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 hematuria, painful bladder syndrome, suspected bladder tumor, bladder calculus, recurrent urinary tract infections, and recurrent incontinence.

Conservative management

All women with OAB 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 liters 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[17] and the International Consultation on Incontinence[18] recommend that bladder retraining should be considered as first-line treatment in all women with OAB.

Antimuscarinic therapy may be a useful addition to bladder retraining in the management of OAB. In a Cochrane review of 23 trials including 3685 patients[19], symptomatic improvement was more common amongst those on antimuscarinic therapy compared to bladder retraining (relative risk [RR] 0.74; 95% confidence interval [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 toward greater improvement with a combination of antimuscarinic therapy and bladder retraining compared to 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

While 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].

A systematic review and meta-analysis of 83 studies, including 30,699 patients and six different drugs (fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, and trospium), supports the efficacy of antimuscarinic therapy in the management of OAB. Overall, there was a significantly higher return to continence favoring 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 of cognitive function and 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 0.33-point decline in the Mini Mental State Examination ($p = 0.03$) and an increased risk in terms of 2-year mortality (odds ratio 1.68; 95% CI 1.30–2.16; $p < 0.001$)[26].

The evidence therefore suggests that anticholinergic drugs should be used with caution in the elderly and further evidence is provided by a large prospective cohort study from North America investigating the association of the total standardized daily dose of anticholinergic 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 co-morbidities, 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[28].

β-Adrenoceptors and overactive bladder

Adrenoceptors are members of a family of seven transmembrane receptors, with two main groups, α and β, and a number of subtypes comprising each group. β1, β2, and β3-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

Mirabegron is the first commercially available selective β3 agonist for the treatment of OAB. The efficacy and tolerability of mirabegron have also been reported in a large multicenter, randomized, double-blind, parallel-group, placebo and tolterodine-controlled phase III trial in 1978 patients with OAB[33]. Overall, mirabegron 50 mg and 100 mg were found to be significantly superior to placebo in the co-primary endpoints of incontinence episodes and micturition frequency, although tolterodine was not shown to be significantly better than placebo and this was supported by a significant improvement in QoL in the mirabegron arm. Rates of dry mouth (2.8% and 2.6%) and constipation (1.6% and 1.4%) in the mirabegron groups were no different to placebo.

The long-term safety of mirabegron has also been investigated in a 12-month randomized, double-blind phase III study in 2444 patients with mirabegron 50 mg and 100 mg and tolterodine extended release 4 mg as an active comparator[34]. Dry mouth was reported in 2.8%, 2.3%, and 8.6% of patients, respectively, whilst mean changes in systolic blood pressure were 0.2 mmHg, 0.4 mmHg, and −0.5 mmHg, respectively.

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 have been investigated in the BESIDE study[35]. This was a prospective, randomized, double-blind study of 2174 patients randomized 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 ($p = 0.001$), and micturition frequency ($p < 0.001$) and combination therapy was non-inferior to solifenacin 10 mg for micturition frequency and incontinence episodes.

Role of estrogen in the pathogenesis of overactive bladder

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

Animal data would suggest that estrogen might inhibit the function of Rho-kinase in bladder smooth muscle, and hence effect smooth muscle contraction, whilst having no

effect on its expression. Consequently, estrogen deprivation following the menopause may lead to the development of OAB symptoms[37] and in-vitro studies have demonstrated that ovariectomized rats showed a significant decrease in voided volume and an increase in 24-h frequency with an increase in basal and stretch-induced acetylcholine release. Conversely, there was a reduction in acetylcholine release from nerve fibers. 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, estrogen replacement therapy reversed these changes[38].

More recently, the role of voltage-gated big potassium (BK) channels has also been explored in the pathogenesis of OAB[39]. These large-conductance Ca^{2+}-activated K^{+} BK channels are thought to be regulators of detrusor smooth muscle[40] and BK channels are directly activated by 17β-estradiol to reduce detrusor smooth muscle excitability[41]. 17β-Estradiol has also been shown to regulate Ca^{2+}-activated K^{+} BK channels in detrusor smooth muscle and reduces phasic detrusor contractions in a dose-dependent manner[42]. These studies would appear to support a role of estrogen deficiency in the pathogenesis of OAB, and more recent work has also suggested that estrogen deprivation 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 estradiol replacement[43].

Estrogen in the management of overactive bladder

Estrogen 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 their efficacy. A double-blind, placebo-controlled crossover study using oral estriol in 34 postmenopausal women produced subjective improvement in symptoms[44], although a double-blind, multicenter study on the use of estriol in postmenopausal women complaining of urgency failed to confirm these findings[45].

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

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

Combination therapy: vaginal estrogen and antimuscarinics

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

A 12-week prospective randomized trial comparing tolterodine 2 mg twice daily and vaginal conjugated estrogen cream versus tolterodine 2 mg twice daily alone in 80 postmenopausal women complaining of OAB[49] showed that combination therapy had a significantly greater improvement in mean daytime frequency and voided volume as compared to 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 randomized trial comparing the estradiol-releasing vaginal ring and oral oxybutynin 5 mg twice daily in 59 postmenopausal women with OAB[50]. Those women who received oxybutynin had a mean decrease of 3.0 voids per day as compared to a decrease of 4.5 voids per day in women using the estradiol 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 treatment with solifenacin[51] and fesoterodine[52] with vaginal estrogen in patients with OAB.

However, these findings in patients with OAB were 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 4 mg once daily with or without vaginal estriol[53]. Overall, there were no significant differences between the two treatment groups in terms of efficacy which was assessed subjectively.

These findings would suggest that, whilst vaginal estrogens may be useful in women with a symptomatic diagnosis of OAB, they are less useful in women with a urodynamic diagnosis of detrusor overactivity.

Managing refractory overactive bladder

Botulinum Toxin

For those patients who are able and willing to self-catheterize, intravesical Botulinum Toxin A is currently recommended as first-line therapy for refractory OAB symptoms[17]. The efficacy and safety of Botulinum Toxin A (Botox®) 100 u has been reported in a large multicenter phase III study of 557 OAB patients[54]. Overall, there was a significantly greater reduction in daily incontinence episodes with Botulinum Toxin A compared to placebo with 22.9% of patients achieving complete continence, and there was a corresponding significant improvement in HRQoL. Overall, the most commonly reported adverse effect was urinary tract infection and self-catheterization rates were 5.4%. Long-term studies

have shown that the effect generally lasts for 9–12 months and repeated injections remain efficacious over time.

Percutaneous tibial nerve stimulation

The tibial nerve is a mixed nerve containing L4–S3 fibers and originates from the same spinal cord segments as the innervation to the bladder and pelvic floor. Consequently, peripheral neural modulation may have a role in the management of urinary symptoms.

Percutaneous tibial nerve stimulation (PTNS) is achieved by the temporary insertion of a needle in the lower leg posterior to the tibia above the medial malleolus. Treatment is performed in the clinic and is weekly for the first 12 weeks and then maintenance therapy is generally monthly with each session lasting 30 min.

PTNS has been shown to be a safe and effective treatment and comparable to that of pharmacotherapy[55]. A recent systematic review and meta-analysis[56] reported a pooled subjective success rate of 61.4% (95% CI 57.5–71.8) and an objective success rate of 60.6% (95% CI 49.2–74.7). A significant drawback of PTNS in treating a chronic condition such as OAB is the need for repeated stimulations, as symptoms deteriorate by 6–12 weeks[57]. There are limited long-term data in the literature with few studies looking at ongoing treatment over 12 months. A recent study has shown PTNS therapy as a safe, durable, and valuable long-term treatment option for OAB symptom control[58].

Sacral neuromodulation

Sacral nerve stimulation (SNS) uses a surgically implanted lead and generator to stimulate the S3 sacral nerve root. The stimulation of afferent nerve fibers modulates reflex pathways involved in the filling and evacuation phase of micturition through spinal circuits mediating somato-visceral interactions within the sacral spinal cord. SNS is thought to activate or 'reset' the somatic afferent inputs that play a central role in the modulation of sensory processing and micturition reflex pathways in the spinal cord[59].

SNS incorporates a temporary test, percutaneous nerve evaluation, that allows patients and physicians to assess SNS over a trial period. If there is a 50% improvement, then the patient is offered the second stage consisting of a permanent implantable pulse generator, which is placed in the soft tissue of the patient's buttock.

SNS has been shown to be effective in more than 40 studies. Most of these studies define success as greater than 50% improvement in clinical symptoms. Whilst the reported success rates for subjects who actually received the implantation varied between 60 and 100%, an intention-to-treat analysis in a recent systematic review revealed success rates between 21 and 48% for one-stage implantation with percutaneous nerve evaluation and between 75 and 80% for two-stage implantation[60].

Long-term follow-up reported a gradual decrease of the success rate from 87% at 1 month to 62% at 5 years[61].

Reconstructive surgery

Reconstructive procedures including clam cystoplasty, substitution cystoplasty, and ileal conduit continue to have a small role for truly refractory OAB cases, although their use has decreased significantly with the introduction of neuromodulation and Botulinum Toxin.

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. For those with refractory symptoms, switching to an alternative class of therapy 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 estrogen does not have a role in treating OAB, vaginal estrogen may be helpful and may also act synergistically with antimuscarinic drugs. Those patients with refractory OAB who fail to improve with medical therapy may benefit from intravesical Botulinum Toxin or neuromodulation.

Potential conflict of interest Linda Cardozo: Atlantic Therapeutics, Boston, Dekka, Fotona. Dudley Robinson: Astellas, Allergan, Ixaltis, Ferring, Boston.

Source of funding Nil.

References

1. Haylen BT, de Ridder D, Freeman RM, *et al.* An International Urogynaecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol J* 2010;21:5–26
2. Stewart WF, Corey R, Herzog AR, *et al.* Prevalence of overactive bladder in women: results from the NOBLE program. *Int Urogynaecol J* 2001;12:S66
3. Milsom I, Abrams P, Cardozo L, *et al*. How widespread are the symptoms of overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001;87:760–6
4. Anderson KE. The overactive bladder: pharmacologic basis of drug treatment. *Urology* 1997;50:74–89
5. Hashim H, Abrams P. Is the bladder a reliable witness for predicting detrusor overactivity? *J Urol* 2006;175:191–5
6. Caulfield MP, Birdsall NJ. International union of pharmacology XVII. Classification of muscarinic acetylcholine receptors. *Pharmacol Rev* 1998;50:279
7. Braverman AS, Ruggieri MR. The M_2 receptor contributes to contraction of the denervated rat urinary bladder. *Am J Physiol* 1998;275:1654
8. Cartwright R, Panayi D, Cardozo L, Khullar V. Reliability and normal ranges for the patient's perception of intensity of urgency scale in asymptomatic women. *BJU Int* 2010;105:832–6
9. Cardozo L, Coyne KS, Versi E. Validation of the urgency perception scale. *BJU Int* 2005;95:591–6

10. Nixon A, Colman S, Sabounjian L, *et al.* A validated patient reported measure of urinary urgency severity in overactive bladder for use in clinical trials. *J Urol* 2005;174:604–7
11. Jenkinson C, Coulter A, Wright L. Short Form 36 (SF-36) health survey questionnaire. Normative data for adults of working age. *Br Med J* 1993;306:1437–40
12. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol* 1997;104:1374–9
13. Swithinbank L, Hashim H, Abrams P. The effect of fluid intake on urinary symptoms in women. *J Urol* 2005;174:187–9
14. Subak LL, Wing R, West DS, *et al.* PRIDE investigators. Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med* 2009;360:481–90
15. Jeffcoate TNA, Francis WJA. Urgency incontinence in the female. *Am J Obstet Gynecol* 1966;94:604–18
16. Berghmans LC, Hendricks HJ, de Bie RA, *et al.* Conservative treatment of urge urinary incontinence in women: a systematic review of randomised clinical trials. *Br J Urol Int* 2000;85:254–63
17. NICE Guideline 40. The Management of Urinary Incontinence in Women. Department of Health. www.nice.org.uk. 2013
18. Dumoulin C, Adewuyi T, Booth J, *et al.* Adult conservative management. In Abrams P, Cardozo L, Wagg A, Wein A. ed. *Incontinence*, 6th ed. IUCD ICS; 2017: 1443–1628
19. Prasad Rai B, Cody JD, Alhasso AA, Stewart L. Anticholinergic drugs versus non drug active therapies for overactive bladder syndrome in adults. *Cochrane Database Syst Rev* 2012;12: CD003193
20. Andersson KE, Cardozo L, Cruz F, *et al.* Pharmacological treatment of urinary incontinence. In Abrams P, Cardozo L, Wagg A, Wein A. ed. *Incontinence*. 6th ed. IUCD ICS; 2017: 805–958
21. Hadorn DC, Baker D, Hodges JS, Hicks N. Rating the quality of evidence for clinical practice guidelines. *J Clin Epidemiol* 1996;49: 749–54
22. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323:334–6
23. Chapple CR, Khullar V, Gabriel Z, *et al.* The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *Eur Urol* 2008;54:543–62
24. Araklitis G, Thiagamoorthy G, Hunter J, *et al.* Anticholinergic prescription: are healthcare professionals the real burden? *Int Urogynaecol J* 2017;28:1249–56
25. Fox C, Smith T, Maidment I, *et al.* Effect of medications with anticholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. *Age Ageing* 2014;43: 604–15
26. Fox C, Richardson K, Maidment ID, *et al.* Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc* 2011;59:1477–83
27. Gray SL, Anderson ML, Dublin S, *et al.* Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med* 2015;175:401–7
28. www.ageingbraincare.org/uploads/products/ACB_Scale_-_legal_size.pdf
29. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. *Physiol Rev* 2004;84:935–86
30. Otsuka A, Shinbo H, Matsumoto R, Kurita Y, Ozono S. Expression and functional role of beta-adrenoceptors in the human urinary bladder urothelium. *Naunyn Schmiedebergs Arch Pharmacol* 2008; 377:473–81
31. Sacco E, Bientinesi R, Tienforti D, *et al.* Discovery history and clinical development of mirabegron for the treatment of overactive bladder and urinary incontinence. *Expert Opin Drug Discov* 2014;9:433–48
32. Hicks A, McCafferty GP, Riedel E, *et al.* GW427353 (solabegron), a novel, selective beta3-adrenergic receptor agonist, evokes bladder relaxation and increases micturition reflex threshold in the dog. *J Pharmacol Exp Ther* 2007;323:202–9
33. Khullar V, Amarenco G, Angulo JC, *et al.* Efficacy and tolerability of mirabegron, a beta 3 adrenceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase III trial. *Eur Urol* 2013;63:283–95
34. Chapple CR, Kaplan SA, Mitcheson D, *et al.* Randomised double-blind, active-controlled phase III study to assess 12 month safety and efficacy of mirabegron, a beta 3 adrenoceptor agonist, in overactive bladder. *Eur Urol* 2013;63:296–305
35. Drake MJ, Chapple C, Esen AA, *et al.* BESIDE investigators. Efficacy and safety of mirabegron add-on therapy to solifenacin in incontinent overactive bladder patients with an inadequate response to initial 4-week solifenacin monotherapy: a randomised double blind multicentre phase 3B study (BESIDE). *Eur Urol* 2016; 70:136–45
36. Cheng CL, Li JR, Lin CH, de Groat WC. Positive association of female overactive bladder symptoms and oestrogen deprivation: A nationwide population based cohort survey in Taiwan. *Medicine (Baltimore)* 2016;95:e4107
37. Hong SK, Yang JH, Kim TB, Kim SW, Paick JS. Effects of ovariectomy and oestrogen replacement on the function and depression of Rho-kinase in rat bladder smooth muscle. *BJU Int* 2006;98:1114–17
38. Yoshida J, Aikawa K, Yoshimura Y, *et al.* The effects of ovariectomy and oestrogen replacement on acetylcholine release from nerve fibres and passive stretch induced acetylcholine release in female rats. *Neurourol Urodyn* 2007;26:1050–5
39. Petkov GV. Central role of the BK channel in urinary bladder smooth muscle physiology and pathophysiology. *Am J Physiol Requl Integr Comp Physiol* 2014;307:R571–584
40. Xin W, Li N, Fernandes VS, *et al.* BK Channel regulation by phosphodiesterase type 1: a novel signaling pathway controlling human detrusor smooth muscle function. *Am J Physiol Renal Physiol* 2016;310:F994–9
41. Provence A, Hristov KL, Parajuli SP, Petkov GV. Regulation of guinea pig detrusor smooth muscle excitability by 17β oestradiol: the role of the large conductance voltage and Ca^{2+} activated K^{+} channels. *PLoS One* 2015;10:e0141950
42. Hristov KL, Parajuli SP, Provence A, Rovner ES, Petkov GV. Nongenomic modulation of the larger conductance voltage and Ca^{2+} activated K^{+} channels by oestrogen: a novel regulatory mechanism in human detrusor smooth muscle. *Physiol Rep* 2017;5: e13351
43. Chen HY, Chen CJ, Chen WC, Wang SJ, Chen YH. A promising protein responsible for overactive bladder in ovariectomised mice. *Taiwan J Obstet Gynaecol* 2017;56:196–203
44. Samsioe G, Jansson I, Mellstrom D, Svanberg A. Urinary incontinence in 75 year old women. Effects of oestriol. *Acta Obstet Gynaecol Scand* 1985;93:57
45. Cardozo LD, Rekers H, Tapp A, *et al.* Oestriol in the treatment of postmenopausal urgency: a multicentre study. *Maturitas* 1993;18: 47–53
46. Benness C, Wise BG, Cutner A, Cardozo LD. Does low dose vaginal oestradiol improve frequency and urgency in postmenopausal women. *Int Urogynaecol J* 1992;3:281
47. Eriksen PS, Rasmussen H. Low dose 17β-oestradiol vaginal tablets in the treatment of atrophic vaginitis: a double-blind placebo controlled study. *Eur J Obstet Gynaecol Reprod Biol* 1992;44:137–44
48. Cardozo L, Lose G, McClish D, Versi E. Estrogen treatment for symptoms of an overactive bladder, results of a meta analysis. *Int J Urogynaecol* 2001;12:V
49. Tseng LH, Wang AC, Chang YL, *et al.* Randomized comparison of tolterodine with vaginal estrogen cream versus tolterodine alone for the treatment of postmenopausal women with overactive bladder syndrome. *Neurourol Urodyn* 2009;28:47–51
50. Nelken RS, Ozel BZ, Leegant AR, Felix JC, Mishell DR. Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder. *Menopause* 2011;18:962–6
51. Jiang F, Zhu L, Xu T, *et al.* Efficacy and safety of solifenacin succinate tablets versus solifenacin succinate tablets with local estrogen for the treatment of overactive bladder in

postmenopausal women – a multicenter, randomized, open label, controlled comparison study. *Menopause* 2016;23:451–7
52. Chughtai B, Forde JC, Buck J, *et al*. The concomitant use of fesoterodine and topical vaginal oestrogen in the management of overactive bladder and sexual dysfunction in post menopausal women. *Post Reprod Health* 2016;22:34–40
53. Serati M, Salvatore S, Uccella S, Cardozo L, Bolis P. Is there a synergistic effect of topical oestrogens when administered with antimuscarinics in the treatment of symptomatic detrusor overactivity? *Eur Urol* 2009;55:713–19
54. Nitti V, Dmochowski R, Herschorn S, *et al*., EMBARK Study Group. Onabotulinumtoxin A for the treatment of patients with overactive bladder and urinary incontinence: results of a phase III randomised placebo controlled trial. *J Urol* 2013;189:2186–93
55. Peters KM, Macdiarmid SA, Wooldridge LS, *et al*. Randomised trial of percutaneous tibial nerve stimulation versus extended release tolterodine: results from the overactive bladder innovative therapy trial. *J Urol* 2009;182:1055–61
56. Burton C, Sajja A, Latthe PM. Effectiveness of percutaneous posterior tibial nerve stimulation for overactive bladder: a systematic review and meta-analysis. *Neurourol Urodyn* 2012;31:1206–16
57. van der Pal F, van Balken MR, Heesakkers JP, Debruyne FM, Bemelmans BL. Percutaneous tibial nerve stimulation in the treatment of refractory overactive bladder syndrome: is maintenance treatment necessary? *BJU Int* 2006;97:547–50
58. Peters KM, Carrico DJ, Macdiarmid SA, *et al*. Sustained therapeutic effects of percutaneous tibial nerve stimulation: 24-month results of the STEP study. *Neurourol Urodyn* 2013;32:24–9
59. Oerlemans DJ, van Kerrebroeck PE. Sacral nerve stimulation for neuromodulation of the lower urinary tract. *Neurourol Urodyn* 2008;27:28–33
60. Monga AK, Tracey MR, Subbaroyan. A systematic review of clinical studies of electrical stimulation for treatment of lower urinary tract dysfunction. *Int Urogynecol J* 2012;23:993–1005
61. Groen J, Blok BF, Bosch JL. Sacral neuromodulation as treatment for refractory idiopathic urge urinary incontinence: 5-year results of a longitudinal study in 60 women. *J Urol* 2011;186:954–9