CLINICAL INVESTIGATION

Clinical trials and overactive bladder: lessons learned

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Overactive bladder is a prevalent, costly and bothersome condition that greatly affects quality of life. Several therapeutic interventions have been introduced over the years – some conservative and others more invasive – to address the needs of this patient population. Scientific evidence to support these interventions varies widely with respect to number of clinical trials as well as the caliber of these trials to evaluate efficacy. Comparative effectiveness of these interventions is vastly understudied, as are patient-reported outcomes and understanding of what matters most to patients. This article will review the available data and level of evidence for the therapeutic alternative used in the contemporary management of overactive bladder, highlight recent advances in research and address the ongoing challenges in evolving care for this condition.

Keywords: β-3 adrenergic receptor agonists • antimuscarinics • frequency • neuromodulation • nocturia • overactive bladder • urgency • urgency incontinence • uroselectivity

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The International Continence Society has defined overactive bladder (OAB) as urgency of urination, with or without urgency urinary incontinence (UUI), usually accompanied by frequency and nocturia [1]. OAB is a bothersome condition affecting between 8.0 and 13.9% of the population in developed nations [2,3]. Prevalence increases with age, making it a considerable public health concern given the forecasted population growth among those aged 65 and older. Although recent epidemiologic studies have suggested only a slight gender difference in OAB prevalence, UUI is disproportionately more common among women [4]. The impact of OAB on health-related quality of life is substantial and its association with comorbid conditions, institutionalization and mortality is considerable [5,6]. The contemporary treatment of OAB is aimed at improving patient quality of life by decreasing symptom severity, reducing patient bother from the condition and minimizing side effects of treatment. Variable levels of evidence are available from clinical trials to guide this management.

This article will address the evidence from clinical trials for the contemporary management of OAB including: behavioral and lifestyle modification, pelvic floor muscle therapy, biofeedback, drug therapy, neuromodulation and botulinum toxin. This article will also highlight recent significant advances in research, including new drugs and therapies brought into clinical use over the last few years, as well as promising new agents in the advanced stages of development. The ongoing challenges and unmet needs will also be discussed.

The International Consultation on Incontinence (ICI) utilized the Modified Oxford Guidelines [201], as set forth by the Agency for Health Care Policy and Research, to evaluate the level of evidence and grade of recommendation for the available treatment modalities of several urinary tract conditions. Boxes 1 & 2 define the levels of evidence and grades of recommendation, respectively, used by the ICI in their most recent assessment [7]. The specific level of evidence and grade

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Box 1. Modified Oxford Guidelines: levels of evidence
Level 1: Systematic reviews, meta-analyses, good-quality randomized controlled trials
Level 2: Randomized controlled trials, good-quality prospective cohort studies
Level 3: Case-control studies, case series
Level 4: Expert opinion
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Box 2. Modified Oxford Guidelines: grades of recommendation
Grade A: Based on level 1 evidence (highly recommended)
Grade B: Consistent level 2 or 3 evidence (recommended)
Grade C: Level 4 studies or majority evidence (optional)
Grade D: Evidence inconsistent or inconclusive (no recommendation possible)
Reproduced from [201]

of recommendation granted by the ICI, when available, is included for each of the treatments discussed below. This information is included as the authors believe this work represents the most comprehensive evaluation of the literature available for treatment of OAB. It is important to note that levels and grades can be assigned in support of or against a particular treatment, depending on the evidence available.

Conservative treatment

Clinical trials for OAB have evaluated conservative treatment options including behavioral and lifestyle modifications, timed voiding, pelvic floor muscle therapy and biofeedback. These therapies boast minimal to no side effects, but require substantial effort on the part of the patient to adhere to treatment, frequently leading to poor compliance and limited efficacy. Furthermore, the clinical trial designs to assess the efficacy of these interventions have been less than ideal, leaving little evidence-based data to support their use.

■ Behavioral modifications

Behavioral modifications for the treatment of OAB include caffeine and fluid restriction, weight loss, smoking cessation, treatment of constipation, timed voiding and bladder training. They are considered effective at improving symptoms through identification of the patient's behavior, lifestyle habits, environmental effects and activities that are contributing to or triggering their symptoms [8]. Variable, but mostly limited, levels of evidence exist for each of these recommendations and patient compliance with these measures is known to be poor. Nonetheless, clinical experience and expert opinion support the primary use of these measures for the treatment and possibly prevention of OAB [9].

Caffeine

Caffeine consumption is pervasive in 'Western' society, with >80% of US adults consuming at least 200 mg/day [10]. Aside from the volume of fluid ingested with these beverages, caffeine has been shown to have a diuretic effect and may increase OAB symptoms by increasing bladder pressure and bladder muscle excitability [11–13]. In addition, caffeine is a CNS stimulant and animal research has suggested that caffeine increase calcium release from smooth muscle, leading to excitatory contraction of smooth muscle organs like the bladder [13]. Few well-designed studies have addressed the impact of caffeine on bladder symptoms and these have produced conflicting results. Bryant *et al.* reported that decreasing caffeine consumption to a mean of 96.5 mg, compared with 238.7 mg in the control group, resulted in a significant reduction in urgency episodes (12 vs 61%) and a nonsignificant reduction in incontinence episodes (26 vs 55%) [14]. Swithinbank *et al.* found that reducing fluid intake was effective in reducing voiding frequency, urgency and incontinent episodes, but changing from caffeinated to decaffeinated beverages did not improve symptoms [15]. Caffeinated beverages are commonly carbonated and often taken with artificial sweeteners (particularly aspartame), both of which have been implicated as dietary factors that contribute to OAB symptoms [16,17]. Several small clinical trials and years of clinical experience suggest decreasing caffeine intake improves continence, and most experts in the field agree that caffeine plays a role in exacerbating OAB and incontinence [18]. The ICI rated the evidence a level 2 and the grade of recommendation a grade B for the impact of reduction in caffeine intake on improved urinary continence [18].

Fluid intake

Excessive fluid intake can certainly increase urinary frequency and exacerbate OAB symptoms [19]. Interestingly, excessive restriction of fluid may also exacerbate symptoms due to poor elimination of irritants from the bladder, decreasing the functional capacity of the bladder and increasing the risk of urinary tract infections [20]. Appropriate fluid intake should be balanced against activity level, climate and fluid content of ingested foods. For most older adults, fluid intake should be approximately six 8-oz glasses per day [21]. The type of fluids ingested can have an important impact on bladder symptoms, with the effects of caffeinated beverages, carbonations and artificial sweeteners noted above. In addition, citrus juices and fruits, highly spiced drinks and foods, and alcoholic beverages can worsen bladder symptoms [22,23]. The timing of fluid intake is also important since nocturia can often be improved by restricting oral intake 3–6 h before bed [24]. The ICI found that fluid intake played a minor role in urinary incontinence and due to its potential negative impact should only be recommended in those with excessive fluid intake (grade of recommendation: C) [18].

Obesity

Obesity, which is defined as a BMI ≥30kg/m^2, was traditionally considered a risk factor for stress urinary incontinence only, but more recently has been appreciated as a risk factor for OAB and UUI as well [16]. It is hypothesized that chronically increased intra-abdominal pressure leads to stress on the pelvic floor structures, leading to weakening of the pelvic floor muscles, nerves and blood vessels. The resultant impact on vascular perfusion and neural innervations may be the cause of OAB symptoms and incontinence [25]. Bump *et al.* showed improvement in both stress urinary incontinence and UUI following surgical weight reduction in morbidly obese women [26]. However, even moderate weight loss can improve bladder symptoms in overweight women. In fact, loss of 5–10% of body weight can decrease incontinence episodes by as much as 50–60% [27]. The ICI rated the evidence a level 1 and the grade of recommendation a grade A for the impact of moderate weight loss on reduction in urinary incontinence prevalence [18].

Smoking

Smoking, particularly nicotine, has been implicated as a risk factor for OAB and incontinence [28,29]. Potential etiologies are increased intra-abdominal pressure from chronic cough and increased nicotine induced detrusor overactivity (as shown in cats) [30]. Few clinical data assessing the impact of smoking cessation on bladder symptoms are available. The ICI rated the evidence a level 3 for the impact of smoking on severity of urinary incontinence. They recommend further studies be performed to assess prevention and resolution of urinary incontinence secondary to smoking cessation [18].

Constipation

Constipation is a common comorbid complaint among patients with OAB [31]. Several factors have been implicated, including reduced fluid intake (in attempts to control bladder symptoms), limited exercise and reduced fiber intake [32,33]. Straining to defecate and chronic constipation have been implicated as contributors to both lower urinary tract symptoms and pelvic organ prolapse [34]. While patients often report an exacerbation of bladder symptoms during times of constipation, few clinical studies exist that suggest that resolving constipation improves OAB symptoms. A small cohort study from Turkey suggests that constipation treatment with laxatives can relieve symptoms of urgency and frequency [35]. Furthermore, a recent study by Panayi *et al.* reported that rectal distention using a rectal balloon significantly decreased several urodynamic parameters, including volume at first sensation, volume at strong desire and maximum bladder capacity [36]. Presumably, bowel distention leads to increased pelvic afferent input and could be grouped with those factors leading 'increasing afferent noise', which is felt to increase spontaneous detrusor contractions and urgency [37]. The ICI rated the evidence a level 3 for the impact of chronic straining on the development of urinary incontinence. They recommend further studies be performed to assess the role of straining on the pathogenesis of urinary incontinence [18].

Timed voiding

Timed voiding or prompted voiding is a mechanism to increase bladder awareness. Timed voiding involves a voiding schedule that starts with interval voiding on a fixed schedule regardless of the desire to go [38]. The most commonly used timed-voiding programs involve voiding frequently enough in order to prevent incontinence or urgency episodes. With routine, scheduled voids, which may initially be prompted by an alarm or by a caregiver, new habits are established. The predetermined time schedule (for example every 2, 3 or 4 h) is generally based on a bladder diary that documents how often a patient voids, experiences urgency and/or has leakage. The actual interval varies from patient to patient and is influenced by bladder capacity, fluid intake, activity level, climate and access to a toilet [39]. Few clinical data assessing the impact of timed voiding on bladder symptoms are available. The ICI rated the evidence a level 3 and the grade for recommendation a grade C for the impact of timed voiding with a 2 h voiding interval on reduction in urinary incontinence in women with mild symptoms and an infrequent voiding pattern [18].

Bladder training

Bladder training through urgency control and suppression techniques is considered an effective means of decreasing the intensity of urgency and incontinence in well-motivated patients. Bladder training, sometimes referred to as bladder retraining, bladder re-education or bladder drills, may be effective as the result of rewiring of complex circuitry between the

bladder and the brain [40]. The training consists of three important components:

- Education about bladder function, dysfunction and urgency control strategies;
- A timed-voiding regimen that evolves to gradually increase the interval between voids;
- Positive feedback and reinforcement by caregivers [41,42].

Utilization of relaxation techniques including slow, deep breathing and distraction techniques (mental concentration on other tasks) are most popular during urgency suppression [43]. Additional strategies including rapid contractions of the pelvic floor, or 'quick flicks' (described below), and the use of self-motivating statements ('I can do it' or 'I am in control') are also popular [44]. A randomized controlled trial (RCT) of 123 women with mixed urinary incontinence showed a 57% reduction in incontinence episodes and a 54% reduction in quantity of urine loss after implementation of a bladder-training program [45]. The ICI rated the evidence a level 1 (based on scant evidence) and the grade for recommendation a grade A for the impact of bladder training on reduction in urinary incontinence [18].

■ Pelvic floor muscle therapy & biofeedback

Pelvic floor muscle training

The aim of pelvic floor muscle training (PFMT) in the treatment of OAB is to suppress urgency and detrusor overactivity. This type of pelvic exercise program was first described by Arnold Kegel who prescribed isometric, repeated, high-intensity contractions of the pelvic floor that became known as 'Kegels' [46]. Several variations on the originally described Kegel have been described and together these exercises are now referred to as pelvic floor exercises or PFMT. The training includes teaching patients to identify, isolate and contract the skeletal muscles surrounding the urethra, vagina and rectum [47]. PFMT consists of repetitive contractions of the pelvic floor muscles; various techniques including quick flicks or rapid, intense muscle contractions and sustained pelvic contractions can be utilized. It is generally felt that the quick flicks are more effective at suppressing urgency and detrusor overactivity while sustained contractions are more effective at improving occlusion of the sphincteric unit during increases in intra-abdominal pressure [39]. The goal of therapy is to increase the strength and control of the pelvic floor muscles such that maximal force can be generated when needed to overcome urgency and leakage. Over time, increased firmness and broadening of the muscles may be noted, indicating proper identification and improved strength of these muscles [48]. The proposed mechanism of effectiveness of this therapy for OAB is thought to be prevention of urethral sphincter relaxation in response to detrusor activity via active sphincteric contraction, thereby leading to reflexive detrusor relaxation [49]. Additional mechanisms of effectiveness for stress-related urinary incontinence include increased closure pressure of the urethra to counterbalance increases in abdominal pressure and prevention of perineal descent, thereby maintaining the urethra inside the abdominal cavity such that abdominal forces are equally transmitted on the bladder and urethra and thereby preventing the pressure differential that allows bladder pressure to overcome urethral resistance [42]. Intensive therapy is recommended for 8–12 weeks; however, continuous exercises to maintain strength are required [50].

Several studies have shown marked efficacy in reducing OAB symptoms, as well as incontinence of all types with implementation of PFMT [51]. However, outside of clinical trials, the vast majority of women do not receive proper instruction on how to perform these exercises, with as little as 10% reporting that they learned by demonstration during pelvic examination [52]. Written and verbal instructions in the absence of formal Kegal training leads to adequate muscle isolation in only 49% of patients [53]. Pragmatic efficacy, although never measured, is therefore likely to be less than that appreciated in clinical trials. The ICI rated the evidence a level 1 and the grade for recommendation a grade A for the impact of PFMT on reduction in stress, urgency and mixed urinary incontinence [18].

Biofeedback

Biofeedback incorporates instrumentation and technology to give the patient 'feedback' on their pelvic floor exercise efforts. Most systems use a combination of electrodes placed on the pelvic floor and a computer program that can assess the input to these electrodes and determine the strength of muscle contraction. The system confirms for the patient that they are isolating the correct muscle group and also allows strength assessment for comparison over time. Most biofeedback units utilize surface electromyography to graph the electrical activity of a muscle during relaxation and contraction [42]. The feedback to the patient may come in the form of sounds, lights or other images on a computer screen to allow easy interpretation of their performance. Compliance with PFMT can be improved with the addition of biofeedback. Patients receive input and can watch their muscles improve in strength as they progress through treatment.

Few studies have addressed the benefit of biofeedback over PFMT alone. One study looking at 222 women with UUI randomized to behavioral modifications plus PFMT plus four sessions of biofeedback versus behavioral modifications plus PFMT instructed by the clinician versus behavioral modifications plus PFMT from a self-administered book, showed no significant difference in reduction of frequency and incontinence episodes (63.1, 69.4 and 58.6%, respectively) [54]. The ICI rated the evidence a level 1 and the grade for recommendation a grade A for the impact biofeedback assisted PFMT versus PFMT alone on reduction in stress, urgency and mixed urinary incontinence [18].

■ Pharmacologic therapy

Pharmacologic therapies, primarily antimuscarinic agents, have been the mainstay of treatment for OAB and have been studied in numerous clinical trials [55]. These drugs produce variable efficacy, a moderate rate of side effects and rare occurrences of cure.

Years of experience have proven antimuscarinic therapy to be moderately effective in the treatment of OAB, with the initial proposed mechanism of action being decreasing bladder contractility via blockage of the muscarinic receptors on efferent nerves of the detrusor muscle [56]. When effective, these agents produce symptomatic improvement by reducing urgency and thereby reducing UUI and frequency, decreasing detrusor overactivity or involuntary contractions of the bladder muscle and increasing bladder capacity [57]. Andersson has shown, however, that at the doses used for the treatment of OAB symptoms, there is little reduction in detrusor contractility [56]. Furthermore, clinical experience has taught us that antimuscarinics reduce storage symptoms including frequency, urgency and urgency incontinence and increase bladder capacity, suggesting a mechanism of action during the storage phase [58]. With recent advances in the science of OAB through basic research, it has become clear that the functioning and malfunctioning of the urinary bladder are much more complex than previously appreciated, and that the therapeutic effects of antimuscarinic agents may not result from mitigating bladder contractility, as originally described. The effects of antimuscarinics on afferent sensory nerves have gained prominent acceptance and more likely explain the therapeutic benefit of these drugs, which is felt during the storage phase of the micturition cycle rather than the emptying phase [59–61]. The bladder urothelium has become a focus of scrupulous interest, as it is known to release afferent signaling molecules including ACh and contain muscarinic receptors [59]. Yoshida *et al.* have shown that urothelium has a basal level of ACh release of non-neuronal origin that increases with bladder distention [62]. Further work has linked urothelial ACh to activation of both muscarinic and nicotinic receptors with subsequent release of ATP [63]. ATP acts on purinergic receptors on afferent nerve terminals, possibly providing the important link between ACh and a sensory mechanism of action [64]. Given this foundation, antimuscarinic medications, which tend to produce an improvement in storage symptoms, may in fact act during bladder filling affecting sensory feedback from the urothelium, producing less urgency and greater storage capacity. Continued research in this area is currently underway as understanding the affects of these agents during bladder storage, when symptoms are present, is critical.

A recent meta-analysis on antimuscarinic agents found that these agents are more effective than placebo in improving continent days, mean voided volume, urgency episodes and micturition frequency [55]. The vast majority of agents studied provided improvement in health-related quality of life. Across large patient samples, all of the currently available antimuscarinics appear to have comparable efficacy but do show some measurable differences in tolerability [65]. Since the profiles of each drug and the dosing schedules differ, these things, along with medical comorbidities and concomitant medications, should be considered when individualizing treatment for patients.

The currently available antimuscarinic drugs lack selectivity for the bladder and as a result produce side effects on other organ systems. The most common adverse effects include dry mouth, constipation, blurred vision, pruritis, tachycardia, somnolence, impaired cognition and headache. Dry mouth and constipation are reported as the most burdensome side effects [55]. This class of drug is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, as well as uncontrolled narrow-angle glaucoma.

The major criticism with respect to the clinical trials to assess antimuscarinics is the inability of statistically significant results to translate to clinically significant outcomes. Several other criticisms exist, including primarily drug company-sponsored trials, a lack of head-to-head trials, data manipulation to emphasize statistically favorable results, failure of studies to report the poor compliance and persistence with treatment, and poor outcome measures [66].

There are several antimuscarinic agents available today, with multiple dosing regimens and several

Table 1. Available antimuscarinic agents, formulations and dosing regimens for the treatment of overactive bladder.

Drug	Available formulation	Dosing regimen
Atropine (hyoscyamine)	0.125 mg sublingual tablet	1–2 tablets every 4 h
	0.125 mg/1 ml oral drops, 0.125 mg/5 ml elixir	1–2 doses every 4 h
	0.375 mg ER capsule	1–2 tablets twice daily
Belladonna & opium	16.2/30 mg, 16.2/60 mg suppository	1- to 2-times daily
Darifenacin	7.5 or 15 mg tablet	Daily
Fesoterodine	4 or 8 mg tablet	Daily
Flavoxate	100 mg tablet	1–2 tablets 3- to 4-times daily
Oxybutynin	5 mg tablet	2- to 4-times daily
	5 mg/5 ml syrup	2- to 4-times daily
	5, 10, 15 mg ER tablet	Daily
	3.9 mg/day ER patch	Twice weekly
	100 mg/1 g transdermal gel	Daily
Propantheline	15 mg tablet	1–2 tablets, 4-times daily
Propiverine	15 mg tablet	1–4 tablets, 3-times daily
	30 mg ER capsule	Daily
Solifenacin	5 or 10 mg tablet	Daily
Tolterodine	1 or 2 mg tablet	Twice daily
	2 or 4 mg ER capsule	Daily
Trospium	20 mg tablet	Twice daily
	60 mg ER capsule	Daily

ER: Extended release.

formulations; despite this, no true market leader has evolved and several agents remain in common clinical use at present. The search for newer and better formulations and derivatives of this class of medication, as well as novel therapies, is ongoing; fueled primarily by the high prevalence of bothersome disease in our aging population, the pervasiveness of bothersome side effects with existing medications and the tremendous amounts spent by healthcare bodies on contemporary therapy.

Antimuscarinics

Several antimuscarinic treatment options exist and recently three newer alternatives (oxybutynin [OXY] gel, fesoterodine and trospium extended release [ER]) have become available for use. Specific antimuscarinic drugs are listed below with available data on efficacy and comparative efficacy with other drugs in class. Table 1 lists the available drugs, their formulations and recommended dosages. Table 2 lists the ICI levels of evidence and grades for recommendations for the various medications.

Atropine

Atropine, along with hyoscyamine and scopolamine, is an active belladonna alkaloid, derived from the toxic belladonna plant with anticholinergic properties [67]. Atropine has significant systemic side effects including ventricular fibrillation, tachycardia, dizziness, nausea, blurred vision, loss of balance, dilated pupils, photophobia, extreme confusion and dissociative hallucinations, which limit its oral use for the treatment of OAB. Its mention is more of a historic one.

Darifenacin

Darifenacin is a tertiary amine with moderate lipophilicity and is a relatively selective M3 receptor antagonist. Theoretically at least, darifenacin's advantage is its ability to relatively selectively block the M3 receptor, which – although less prevalent than the M2 receptor – appears to be more important in bladder contraction. This selectivity is expected to increase efficacy in patients with OAB while reducing the adverse events related to the blockade of other muscarinic subtypes [68]. Darifenacin has been developed as a controlled release formulation to allow daily dosing and is available at doses of 7.5 and 15 mg per day. A review of the pooled data from three Phase III, multicenter, double-blinded RCTs was performed by Chapple *et al.* in 2005 [69]. A total of 1059 patients (85% female) with urgency, UUI and frequency were treated with darifenacin 7.5 or 15 mg, or placebo daily for 12 weeks. Significant dose related improvements in number of incontinence episodes per week were seen: 8.8 fewer episodes per week with the 7.5-mg dose and 10.6 fewer episodes per week with the 15-mg dose. Improvements in micturition frequency, bladder capacity and severity of urgency were also seen. The most common side effects were dry mouth and constipation, resulting in a few discontinuations. The effects of darifenacin on cognitive function in elderly volunteers were tested in a randomized, double-blinded, three-period crossover study with 129 patients 65 years of age or older [70]. After 2 weeks of treatment, no effect on cognitive function compared with baseline was found. The authors hypothesized that this was related to its relative M3 receptor selectivity.

Fesoterodine

Fesoterodine is a newer antimuscarinic drug that is metabolized rapidly and extensively to 5-hydroxymethyl tolterodine (5-HMT), the same active metabolite of tolterodine (TOLT) [71]. 5-HMT is metabolized in the liver, but there is significant renal excretion without additional metabolism, raising the possibility that 5-HMT could also work from the luminal side of the bladder (a mechanism that has also been proposed for trospium and solifenacin) [72]. One unique feature is its variability in pharmacokinetics due to primary metabolism by ubiquitous nonspecific esterases to 5-HMT, which has a greater variety of degradation paths available than TOLT. This allows a narrower therapeutic window and the ability to offer two dosing regimens. Fesoterodine is indicated for the treatment of OAB at doses of 4 and 8 mg daily. In a multicenter, double-blinded, double-dummy RCT with TOLT ER, 1132 patients were enrolled and received treatment [71]. The trial showed that both the 4- and 8-mg doses of fesoterodine were effective in improving symptoms of OAB with the 8 mg dose having a greater effect at the expense of a higher rate of dry mouth. Only one subject from the fesoterodine 8 mg group and one subject from the TOLT ER 4 mg group withdrew from the study due to dry mouth. The dose–response relationship was confirmed in another study that pooled data from two Phase III RCTs [73]. Fesoterodine 8 mg performed better than the 4 mg dose in improving urgency and UUI as recorded by 3-day bladder diary, offering the possibility of dose titration.

Propantheline bromide

The classic oral agent for antimuscarinic effects on the lower urinary tract was propantheline bromide, a nonselective quaternary ammonium compound that is poorly absorbed after oral administration [67]. It has a short plasma half-life of less than 2 h and varying biologic availability requiring individual titration. It is initially prescribed at 15–30 mg four-times daily but larger doses are often required [74]. Despite having antimuscarinic binding potential quite similar to atropine, there is a lack of convincing data on the effectiveness for the treatment of OAB. Contradictory studies are available that show complete response in 25/26 patients [75] and no difference from placebo in 154 and 23 patients, respectively [76,77]. By today's standards, the effect of propantheline on OAB has not been well documented in RCTs; however, with its long history of use, it can be considered effective and may, in individually titrated doses, be clinically useful. This drug is no longer available in the USA.

Solifenacin

Solifenacin is a tertiary amine with modest selectivity for the M3 receptor over the M2 and marginal selectivity over the M1 receptors [78,79]. It is a once-a-day antimuscarinic that is being marketed at 5- and 10-mg doses. Cardozo *et al.* performed a multinational RCT comparing solifenacin 5 and 10 mg daily with placebo in 857 patients [80]. Both doses significantly improved

Table 2. International Consultation on Incontinence: levels of evidence and grades of recommendation for overactive bladder medications.

Drug	Level	Grade
Atropine (hyoscyamine)	3	C
Darifenacin	1	A
Fesoterodine	1	A
Flavoxate	2	D
Oxybutynin	1	A
Propantheline	2	B
Propiverine	1	A
Solifenacin	1	A
Tolterodine	1	A
Trospium	1	A
YM-178 (mirabegron)	2	B

micturition frequency, urgency, volume voided and incontinence episodes compared with placebo as determined by 3-day micturition diaries. Of patients who reported any incontinence at baseline, 50% achieved continence after treatment with solifenacin compared with 27.9% after placebo. Dry mouth was reported in 7.7% of patients taking solifenacin 5 mg, 23.1% in solifenacin 10 mg and 2.3% in the placebo arm. Only a small percentage of patients (2–4%) did not complete the study due to adverse events and this was comparable in all groups. The STAR trial was a prospective double-blinded, parallel group, 12-week study comparing solifenacin 5 and 10 mg once daily with TOLT ER 4 mg once daily [81]. After 4 weeks of treatment, patients were given the option to increase medication dosage. However, only those on solifenacin actually received the dose increase. The results showed noninferiority of solifenacin's flexible dosing regimen compared with TOLT ER for voiding frequency. Solifenacin showed increased efficacy in decreasing urgency episodes, incontinence and pad usage compared with TOLT ER. Additionally, more solifenacin patients achieved dryness, as documented by 3-day voiding diary, by the end of the study (59 vs 49%). However, these symptomatic improvements were accompanied by an increase in adverse events, with dry mouth and constipation occurring in 30 and 6.4% of the solifenacin group, respectively, versus 23 and 2.5% in the TOLT group. The discontinuation rate was comparably low in both groups.

TOLT

TOLT is a tertiary amine with a major active metabolite, 5-HMT, which significantly contributes to the

therapeutic effect of the drug [82]. Both TOLT and its metabolite have plasma half-lives of 2–3 h, but their effects on the bladder seem to be more long lasting. Whether this could be the result of urinary excretion of the drug with direct bladder mucosal effects remains unknown. TOLT is available in two formulations: an immediate release (IR) form prescribed as 2 mg twice daily and an ER form prescribed as 2 or 4 mg once daily. There appears to be advantages in both efficacy and tolerability with the ER form [83]. There also appears to be a very low incidence of cognitive side effects with TOLT, which is likely due to the low lipophilicity of the drug and its metabolite, minimizing penetration into the CNS [84]. The efficacy of TOLT has been documented by several double-blinded RCTs on patients with OAB. In the IMPACT study, the efficacy of TOLT in improving patients' most bothersome symptoms was assessed [85]. It found significant reduction in bothersome symptoms, whether it be incontinence, urgency episodes or micturition frequency. Dry mouth occurred in 10% of patients and constipation in 4%. The OPERA trial compared TOLT ER 4 mg daily to OXY ER 10 mg daily in 790 women with OAB symptoms [86]. This was a double-blinded RCT with duration of 12 weeks. Improvements in UUI episodes were similar between the two groups but cure of UUI was greater in the OXY ER group (23.0 vs 16.8%). OXY ER was also more effective in reducing micturition frequency at the price of increased rates of dry mouth. Adverse events were mild and occurred at low rates, with both groups having similar rates of discontinuation of treatment.

Trospium

Trospium is a hydrophilic, quaternary amine with limited ability to cross the blood–brain barrier. This, in theory at least, should result in minimal cognitive related dysfunction [87]. It is mainly eliminated unchanged in the urine by renal tubular secretion and, as a result, may affect the urothelial mucosal signaling system as has been shown in rats [88]. Whether this contributes to clinical efficacy in humans remains unknown at this time. In a study comparing the efficacy of trospium 20 mg twice daily with TOLT 2 mg twice daily and placebo in 232 patients with OAB or mixed urinary incontinence, Jünemann and Al-Shukri *et al.* found trospium to be significantly more effective in decreasing the frequency of micturition than either TOLT or placebo [89]. Additionally, trospium caused a greater reduction in incontinence episodes with a similar rate of dry mouth as TOLT. A long-term tolerability and efficacy study comparing trospium 20 mg twice daily and OXY 5 mg twice daily in 358 patients with OAB undergoing treatment for 52 weeks was performed [90]. Urodynamics and patient recorded voiding diaries were performed at baseline, 26 and 52 weeks. Mean maximum cystometric capacity increased in the trospium group by 92 ml at 26 weeks and by 115 ml at 52 weeks. No other significant urodynamic differences were seen between the groups. The micturition diaries indicated a reduction in micturition frequency, incontinence frequency and a reduction in urgency episodes in both treatment groups. At least one adverse event occurred in the majority of patients: 64.8% in the trospium group and 76.6% in the OXY group. The most common side effect in both groups was dry mouth. Overall, both drugs were comparable in efficacy in improving urinary symptoms, but trospium had a better benefit:risk ratio than OXY due to better tolerability. An ER formulation of trospium, 60 mg once daily, has been shown in RCTs to have similar efficacy and side-effect rates lower than those of a previously approved and efficacious twice-daily preparation [91]. Intravesical installation of trospium was studied with a single center, single-blinded RCT with 84 patients [92]. Since intravesical trospium does not seem to be absorbed, an opportunity exists for treatment with minimal systemic antimuscarinic effects [93]. Compared with placebo, intravesical trospium produced a significant increase in maximum bladder capacity and a decrease in detrusor pressure. No improvement in uninhibited bladder contractions was seen. No adverse events were reported but, an increase in residual urine was noted.

Dual musculotropic relaxants: antimuscarinic agents

Some agents have been identified that have dual mechanisms of action. They have antimuscarinic activity as well as direct musculotropic relaxant effects on the bladder smooth muscle at a site metabolically distal to the antimuscarinic receptor. It is felt that the clinical effects of these drugs are primarily explained by an antimuscarinic action.

Flavoxate

Flavoxate also has direct inhibitory action on smooth muscle along with very weak anticholinergic properties [94]. The drug has also been found to possess moderate calcium antagonistic activity, exhibit local anesthetic properties and have the ability to inhibit phosphodiesterase [95]. In rats and cats there is some evidence that flavoxate may also have central effects on the inhibition of the micturition reflex [96,97]. Clinical studies addressing the efficacy of flavoxate in the treatment of OAB have been mixed. In a double-blinded crossover study comparing flavoxate 1200 mg daily with OXY 15 mg daily in 41 women with idiopathic detrusor overactivity, both drugs had similar efficacy with flavoxate having fewer and milder side effects [98]. A very small study in the elderly population with non-neurogenic detrusor overactivity showed flavoxate had essentially no effect on cystometric capacity and incontinence [99]. Chapple *et al.* also suggest no beneficial effect of flavoxate in the treatment of idiopathic OAB [100]. In general, few side effects were reported during treatment. No recent RCTs addressing the efficacy of this drug have been performed.

OXY

OXY is a moderately potent antimuscarinic agent that has strong independent musculotropic relaxant activity and local anesthetic activity (that is likely only important during intravesical administration). The recommended adult oral dose for the IR formulation is 5 mg three- or four-times daily. An ER once-daily oral formulation, a transdermal delivery system (TDS) with twice-weekly dosing and a newer transdermal gel with once-daily dosing are available. Side effects are secondary to nonspecific muscarinic receptor binding. Initial reports documented success in depressing neurogenic detrusor overactivity [101] and subsequent reports documented success in inhibiting idiopathic detrusor overactivity as well [102]. A meta-analysis summarizing 15 RCTs (n = 476) reported a 52% mean reduction in incontinence episodes, a 33% mean reduction in micturition frequency and a mean overall improvement rate of 74%. This came at the expense of 70% of patients experiencing an adverse event [103]. The therapeutic effect of OXY IR is associated with a high incidence of side effects that are often dose limiting [104]. The ER form of OXY uses an osmotic system to release the active compound at a controlled rate over a period of 24 h. As a result, there is less absorption in the proximal portion of the gastrointestinal tract, less first-pass metabolism and fewer side effects, especially dry mouth, thus improving patient compliance [105]. Three difference doses of OXY (5, 10 and 15 mg) were compared in a RCT and a significant dose–response relationship for both UUI episodes and dry mouth was found. The greatest patient satisfaction was with the 15 mg dose [106]. Transdermal administration of OXY (OXY-TDS) alters the metabolism of the drug, further reducing the production metabolites compared with OXY ER. The 3.9-mg daily dose patch decreased both micturition frequency and incontinence episodes, while increasing mean voided volume [107]. Dry mouth rate was similar to placebo. In a study comparing OXY-TDS with OXY IR, similar reductions in incontinence episodes were found but significantly less dry mouth was seen with OXY-TDS (38 vs 94% with OXY IR) [108]. In a third study, OXY-TDS was compared with placebo and TOLT ER [109]. Both drugs had similarly significant reduced daily incontinence episodes and increased voided volume, but TOLT ER was associated with a higher rate of adverse events. The major side effect for OXY-TDS was pruritus at the application site in 14% and erythema in 8.3%. In a review by Cartwright and Cardozo on the published and presented data, they concluded that the good balance between efficacy and tolerability with OXY-TDS was offset by the rate of local skin reaction [110]. Intravesical administration of OXY is a conceptually attractive form of drug delivery, especially for patients who already perform intermittent self catheterization. A specific intravesical formulation of the drug is not available and currently the oral formulation, either liquid or crushed tablet in solution, is delivered by periodic insertion through a catheter. Several nonrandomized, unblinded and nonplacebo-controlled studies have demonstrated efficacy of this therapy in a variety of patients with neurogenic bladders showing significant improvements in cystometric capacity, volume at first involuntary bladder contraction, bladder compliance and overall continence [111,112]. In a study looking at the pharmacokinetics of intravesical OXY versus oral, it was found that plasma OXY levels following oral administration rose to 7.3 mg/ml within 2 h then precipitously dropped to <2 mg/ml at 4 h [113]. In the intravesical group, plasma levels rose gradually to a peak of 6.2 mg/ml at 3.5 h and remained between 3 and 4 mg/ml at 9 h. From these data it is unclear whether the intravesically applied drug acted locally or systemically. In a double-blinded RCT in 52 women with OAB, patients received once daily intravesical OXY (20 mg in 40 ml sterile water) or placebo for 12 days [114]. The results revealed significant differences in first desire to void (from 95 ml pretreatment to 150 ml post-treatment), cystometric capacity (205 to 310 ml), maximum pressure during filling (16 to 9 cm H_2O), daytime frequency (7.5 to 4.0 voids), and nocturia (5.1 to 1.8 nightly voids). Side effects were similar in the treated and placebo groups. For unexplained reasons, 19/23 patients in the treated group continued to have symptomatic relief after termination of the study. OXY topical gel is a new transdermal formulation that is applied once daily to the abdomen, thigh, shoulder or upper arm area [115]. For many patients, the side effects of oral administration of antimuscarinics are intolerable, producing a clear demand for an agent that bypasses first-pass metabolism in the liver. The new OXY gel serves this purpose without the local skin effects seen with the previously approved OXY patch. The 1 g application dose delivers approximately 4 mg of drug to the circulation with stable plasma concentrations. In a multicenter RCT, 789 patients (89% women) with urge predominant urinary incontinence were assigned to OXY gel or placebo once daily for 12

weeks. Mean number of UUI episodes, as recorded in 3-day voiding diary, were reduced by 3.0 episodes per day versus 2.5 in the placebo arm ($p < 0.0001$). Urinary frequency was decreased by 2.7 episodes per day and voided volume increased by 21 ml (vs 2.0 episodes; $p = 0.0017$ and 3.8 ml; $p = 0.0018$ in the placebo group, respectively). Dry mouth was reported in 6.9% of the treatment group versus 2.8% of the placebo group. Skin reaction at the application site was reported in 5.4% of the treatment group versus 1.0% in the placebo arm. It is felt that improved skin tolerability of the gel over the OXY-TDS delivery system is secondary to lack of adhesive and skin occlusion. The gel dries rapidly upon application and leaves no residue; persxon-to-person transference via skin contact is largely eliminated if clothing is worn over the application site.

Propiverine

Propiverine is a musculotropic smooth muscle relaxant with nonselective antimuscarinic activity. Calcium antagonistic properties have also been found, but the importance of this component for the drug's clinical effects has not been established [116]. In an analysis of nine RCTs using propiverine in a total of 230 patients, a 17% reduction in micturition frequency was seen. Additionally, there was a 64 ml mean increase in bladder capacity and a 77% subjective improvement rate. Side effects were found in 14% of subjects [117]. Several comparative studies have confirmed the efficacy of propiverine and suggested that the drug may be equally efficacious in increasing bladder capacity and lowering bladder pressure, with fewer side effects than OXY [118,119]. In 2006, Abrams *et al.* presented data that refuted these prior studies [120]. In a double-blinded, placebo-controlled crossover study comparing propiverine 20 mg daily, propiverine 15 mg three-times daily, OXY 5 mg three-times daily and placebo, propiverine 20 mg daily was inferior to OXY in reducing involuntary bladder contractions. Additionally, propiverine had a more pronounced effect on gastrointestinal, cardiovascular and visual function. A large Japanese study of 1584 patients, randomized patients to solifenacin 5 or 10 mg, propiverine 20 mg or placebo [121]. All active treatments showed superiority to placebo in reducing voiding frequency, increasing voided volume and improving health-related quality of life. Solifenacin 10 mg showed greater reduction in nocturia and urgency episodes, and increased volume voided compared with propiverine 20 mg. Side effects were also greater for the solifenacin 10 mg group, with more dry mouth and constipation. This drug is not available in the USA.

Clinical implications

Determining which of these antimuscarinic agents should be used as first-, second- and third-line therapy is a challenge, as few head-to-head trials resulting in comparative efficacies of these agents have been performed. Furthermore, where the three new antimuscarinic options fit among the other available drugs in the same class is unknown at this time and remains purely the clinician's preference. Whether the theoretical advantages of certain antimuscarinic agents pan out to true clinical advantages is yet to be determined, but analysis of the currently available literature suggests no clear winner in the race for the perfect OAB drug.

New drug development: β-3 adrenergic receptor agonists

It has yet to be proven whether the sympathetic nervous system plays an active role in the filling/storage phase of the bladder in humans; however, the presence of β-adrenergic receptors (AR) in human bladder muscle and urothelium prompted many attempts to increase bladder capacity with β adrenergic stimulation. Development of β-3 agonists came after the discovery that the human detrusor muscle contains a predominance of β-3 subtype ARs (97%) compared with β-1 (1.5%) and β-2 (1.4%) [122,123]. Detrusor muscle relaxation has been found to result from β-3 AR agonist therapy in animal models; furthermore, the effect appears to result in increased bladder capacity with no change in micturition pressure or residual urine volume [124,125]. Several selective β-3 agonists are being evaluated in clinical trials for the treatment of OAB. Acetanilide (YM178, mirabegron) was evaluated in patients with OAB in a RCT versus TOLT and placebo [126]. The treatment group experienced a significant reduction in micturition frequency, incontinence episodes and urgency symptoms, as well as an increase in volume voided. The drug was well tolerated in this study, with the most common side effects being headache and gastrointestinal effects. Further studies are under way to determine whether this class of drugs is equivalent or superior to currently available alternatives in terms of efficacy, tolerability and safety. These drugs are currently in the advanced stages of development in most developed countries; mirabegron has been approved for use in Japan. It is anticipated that when the product is approved in the USA it will carry a warning on its label to refrain from use in patients of reproductive age, based on finding in rats. The Japanese label carries this warning based on minimal available information in animals; we await the recommendations of the US FDA Advisory Committee Meeting for mirabegron for more information on this topic.

Surgical treatment of OAB

Surgical options for OAB have evolved slowly over recent years and are currently available to patients who have failed combination therapy with conservative measures and medication and to those who suffer from drug intolerance. The addition of neuromodulation and botulinum toxin to the armamentarium of treatment options for OAB has salvaged many suboptimally treated patients and has had a great impact on patient satisfaction and quality of life. These options come with heightened risk, as well as heightened cost, compared with conservative and medication therapy, but are becoming more and more common as patients seek effective and more tolerable treatment options for their OAB.

■ Neuromodulation

Modulation of neural reflexes has gained popularity in the treatment of several medical conditions utilizing a variety of nerve modulating techniques. For the treatment of OAB, nerve stimulation utilizing electrical pulses to stimulate the nerves or nerve roots involved in voiding function has become popular over recent years.

Sacral nerve stimulation

Sacral neuromodulation is well-established as a treatment modality for refractory urgency, frequency, UUI and idiopathic urinary retention. The mechanism of action remains unknown but theories include modulation of spinal cord reflexes and brain networks, primarily via somatic sensory afferent fibers [127]. It is thought that the modulation of abnormal involuntary reflexes from the bladder restores voluntary control. Sometimes referred to as a 'bladder pacemaker', this device includes a tined lead with four electrodes, an implantable neurostimulator, a physician programmer and a patient programmer. An electrical circuit is achieved that delivers electrical stimulation from the neurostimulator to the sacral nerve routes via the overlying tined lead electrodes. Implantation is a two-stage procedure, with the first stage being considered the trial or test drive period. Success rates vary based on the technique used for placement (with the two-stage approach having greater efficacy than the percutaneous nerve evaluation) and the indication for intervention (with slightly higher efficacy found among patients with idiopathic urinary retention compared with refractory OAB) [128]. Interstim® (Medtronic, Inc.; Minneapolis, MN, USA) is the only currently available sacral nerve stimulator; Interstim was approved in the USA in 1997 and to date over 100,000 patients have been treated worldwide.

Evolution in our understanding of neuromodulation has allowed expanded indications for treatment and alternative approaches for nerve stimulation. When unilateral sacral neuromodulation fails, options for salvage include contralateral lead placement with the potential for bilateral stimulation or utilization of an alternative approach to stimulation via the tibial or pudendal nerves (see below). In addition, previously excluded patients such as those with neurologic diseases such as multiple sclerosis or Parkinson's disease and patients with incomplete spinal cord injuries, have undergone successful treatment using neuromodulation and are being recognized as potential candidates [129,130]. The ICI rated the evidence a level 1 and grade A for recommendation for the impact of neuromodulation on improved urgency, frequency and urgency urinary continence [131].

Percutaneous tibial nerve stimulation

An alternative neuromodulatory approach is percutaneous tibial nerve stimulation (PTNS), a noninvasive way of modulating pelvic reflexes via projections from the posterior tibial nerve [132]. Urgent® PC (Uroplasty, Inc., MN, USA) is an office procedure approved by the FDA that is used to deliver stimulation to the posterior tibial nerve using a 34-gauge needle electrode placed slightly cephalad to the medial malleolus. The recommended course of treatment is 12 weekly sessions of 30 min each [133]. The OrBIT trial was a multicenter RCT that compared PTNS with TOLT ER. In total, 79.5% of patients in the PTNS arm reported cure or improvement in symptoms compared with 54.8% of the TOLT group, as measured by the Global Response Assessment ($p = 0.01$) [134]. Objective measures, including urinary frequency, UUI episodes, urgency severity, night-time voids and volume voided, showed similar improvement in the two groups. The authors concluded that PTNS was a "clinically significant treatment alternative for OAB." The ICI rated the level of evidence 3 for the impact of PTNS on increasing bladder capacity [134].

Pudendal nerve stimulation

A second alternative approach is stimulation of the pudendal nerve within Alcock's canal, by means of neurophysiological guidance [135]. This is a logical alternative to direct sacral root stimulations since many of the sensory afferent fibers of the sacral nerves originate in the pudendal nerve, which in fact innervates the pelvic organs [136]. Peters *et al.* reported a 71.4% response rate (>50% improvement) in a mixed population of patients with OAB, painful bladder syndrome, neurologic voiding dysfunction and nonobstructive urinary retention, of whom 52% had failed prior sacral stimulation [136]. In a previous comparative study, 30 patients

underwent simultaneous sacral and pudendal lead placement with subsequent blinded and randomized stimulation of each electrode [137]. In 79.2% of patients, the pudendal lead was chosen as superior, with a 63% reduction in symptoms (versus 46% reduction with sacral stimulation, p = 0.02). The ICI gavet the evidence a level 3 for the impact of pudendal nerve stimulation on increasing bladder capacity [134].

Botulinum toxin

Botulinum toxin (Botox®; Allergan, Inc., CA, USA) is a neurotoxin produced by *Clostridium botulinum* that acts as a potent presynaptic inhibitor of ACh release at the neuromuscular junction. It was approved by the FDA in 2011 for the treatment of refractory neurogenic OAB but continues to be used off label for the treatment of refractory idiopathic OAB in patients who are refractory to conventional antimuscarinic therapy or who do not tolerate it due to systemic side effects. It is applied directly to the bladder by cystoscopic injection into the detrusor muscle and/or suburothelium, producing a chemical denervation that is reversible after approximately 6 months. The mode of administration allows the agent to reach the bladder tissue without systemic administration and resultant unsuitable levels in other organs. The dose and injection protocol for Botox has not been universally agreed upon and several variations exist. In the initial description for the treatment of neurogenic OAB, 300 units (U) of Botox-A was diluted in normal saline to a concentration of 10 U/ml. Under direct cystoscopic visualization using a 6F injection needle, 30 injections of 1 ml each were administered to the bladder wall in 30 different locations above the trigone [138]. Since that description, several other authors have described varying doses, dilutions, numbers of sites and locations (trigone, suburothelial space and so on). The onset of Botox-A effects is seen within the first 2 weeks after injection [139]. Urgency, nocturia and frequency have been shown to improve as early as 2 days after injection [140]. The reported duration of Botox-A following the first injection was 6–9 months [139] and duration of effect along with beneficial clinical effect after subsequent injections is maintained [141]. In a double-blinded RCT including 34 patients with OAB refractory to antimuscarinics, the efficacy of 200 U of Botox-A was studied [142]. Significant improvements in maximum cystometric capacity, frequency and UUI episodes were seen at 4 and 12 weeks. Despite clinical improvement, 6 patients (37.5%) required clean intermittent catheterization to empty their bladder. In another RCT, 28 women with refractory OAB received Botox-A 200 U and 15 women received placebo [143]. Approximately 60% of the women who received Botox-A reported a clinical response with a mean duration of response of 373 days (compared with 62 days or less for placebo). Post-void residual urine was increased in 43% of women in the treatment group and urinary tract infections occurred in 75% of these women. The duration of retention following the first injection was approximately 2 months; however, following repeat injection, this duration increased to 5 months. Given the degree of voiding dysfunction seen after Botox injection in patients with OAB, dose reduction studies looking at 100 U have been carried out. In a prospective, nonrandomized study including 100 men and women, 100 U of Botox-A was injected in 30 locations [144]. At 4- and 12-week follow-up, 88% of patients showed significant improvement in bladder function in regard to subjective symptoms, urodynamic parameters and health-related quality of life. There were four cases of urinary retention. A more recent study suggests a dose–response relationship between bladder capacity and dose (50–300 U) for doses ≥100 U with improvement in both urodynamic and clinical parameters in patients with idiopathic OAB [145]. This study showed no impact of the presence of urodynamic detrusory overactivity on successful outcome. A subsequent study looked at low-dose Botox-A (50–150 U) versus placebo for idiopathic OAB [146]. This study found reasonable improvement in bladder symptoms with a low risk of incomplete bladder emptying at doses of 100 and 150 U. Botox appears to be a promising therapy in the treatment of neurogenic and idiopathic OAB. Further studies are needed to determine optimum dosages, locations and methods of injection. The case for usage in neurogenic OAB patients on clean intermittent catheterization who leak between catheterizations seems clearer than in patients with idiopathic OAB, in whom the post-void residual urine volume issue has yet to be clarified. The ICI rated the evidence a level 3 and grade B for recommendation for the impact of botulinum toxin A on idiopathic OAB [67].

Ongoing challenges & unmet needs

Clinical trials for OAB lack the scientific integrity to make evidenced-based treatment recommendations [66]. Several shortcomings have been identified, including design flaws and use of a vast array of outcome measures, making it difficult to compare trials. For example, some trials use primary end point of reduction in urgency episodes while others use reduction in UUI, frequency, nocturia, a change in urodynamics parameters, global impression of improvement, health-related quality of life and/or several other nonvalidated measures. Other shortcomings include the publication of theoretical edges in various drug trials (often sponsored by the drug company) that have not translated to true clinical edges. In addition, a variety of study designs, study populations and symptom severity makes comparison of trials impossible. For example, some trials use a single-agent open-label design while others use a randomized placebo-controlled design. Some enrolled patients are refractory to treatment while others are treatment naive; and some include male patients while others are only female. Some patients have very severe symptoms while others have milder and seemingly easier to treat symptoms. Some trials utilize patient recall to determine improvement in symptoms while others use real time electronic diaries. Some analyses use mean data while others use median data. Essentially, during analysis investigators and authors have selected parameters that make the study 'look good', at times redefining or inventing terms to show an effect. Comparative studies have cherry picked data from prior studies to show what they were hoping to show, at times using a best and worst study rather than meta-analyzing the data. Often, publication of statistically significant results has not translated to clinically significant results. Along these lines, poor persistence with therapy, whether conservative or pharmacologic, remains a major challenge in the evaluation of treatment. Patients often discontinue due to inadequate results, overly restrictive dietary changes, and/or poor drug tolerance. Further complicating matters is the magnitude of the placebo effect and spontaneous resolution of symptoms in all OAB studies, reinforcing the necessity to conduct double-blinded, placebo-controlled studies. Several unmet needs have been identified for research in OAB, including the need for patient centered outcome measures and a better understanding of what matters most to patients suffering from OAB. These important assessments are necessary to truly understand the impact of existing and evolving treatment modalities and to improve the quality of clinical trials in the future. Novel drug and treatment options are desperately needed for this prevalent, bothersome condition. Future studies must be designed fairly and evenly with parameters defined in exactly the same way to allow us to draw reasonable conclusions regarding the superiority of one treatment over another.

Executive summary

- Therapeutic options for overactive bladder (OAB) include behavioral modifications, pelvic floor muscle therapy, pharmacotherapy and neuromodulation.
- Variable levels of evidence exist for behavioral therapy with caffeine restriction, weight loss and bladder-training programs receiving the best grades from the International Consultation on Incontinence.
- Antimuscarinics are the mainstay of therapy for OAB with several agents receiving an A grade. Poor clinical trial design has limited evaluation of comparative efficacy and tolerability of these drugs.
- Surgical innovation with neuromodulation has expanded the armamentarium of treatments for OAB and will likely continue to evolve.
- Clinical trials in OAB lack sound scientific methodology and integrity.
- Effective patient reported outcome measures are needed in future trials.

Conclusion

Clinical trials in OAB have helped to shape the contemporary treatment paradigm. However, current recommendations lack sound scientific evidence to support their use. More work is needed to effectively evaluate treatment modalities in the hopes of providing level one evidence for the treatment of OAB. Recent advances in basic science, translational and clinical research has led to greater understanding of OAB and the potential mechanisms of action of antimuscarinic agents. Despite the great interest and vast number of research studies focusing on OAB, few novel pharmaceutical agents have made it to market and, with the exception of Botox and there have been few surgical innovations for the treatment of OAB.

Future perspective

The continuous evolution and development of innovative agents for the treatment of OAB stem from the fact that the ideal agent – one that is lower urinary tract selective, easily administered and relatively inexpensive – has yet to be found. This search continues, and although antimuscarinic drugs are still the mainstay for treatment of OAB, therapies with different mechanisms of action are currently being studied with some promise. Ongoing scientific research has provided us with greater sophistication and a clearer understanding of the mechanisms of therapeutic interventions for OAB and this – combined with improved outcome measures to assess efficacy and patient satisfaction, as well as high-quality clinical trials with proper design – should inevitably translate into more refined and directed therapies in future years.

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