Clinical trials and overactive bladder: lessons learned

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.

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

**Keywords:** β-3 adrenergic receptor agonists • antimuscarinics • frequency • neuromodulation • nocturia • overactive bladder • urgency • urgency incontinence • uroselectivity
Review: Clinical Trial Outcomes  
Smith & Wein

Clinical trials & overactive bladder: lessons learned

Review: Clinical Trial Outcomes

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. Consensus guidelines recommend treating OAB patients with fluid restriction, therapy and biofeedback. These therapies boost minimal to no side effects, but require substantial effort and due to its potential negative impact should only be recommended in those with excessive fluid intake (grade of recommendation: C) [18]. Box 1. Modified Oxford Guidelines: levels of evidence

Caffeine
Caffeine consumption is pervasive in ‘Western’ society, with >80% of US adults consuming at least 200 mg/day [36]. 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 [41]. In addition, 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 [37]. 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%) [42]. Withindank et al. found that reducing fluid intake was effective in reducing voiding frequency, urgency and incontinence episodes, but changing from caffeine to decaffeinated beverages did not improve symptoms [43]. Caffeine-decaffeinated 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 [44,45]. 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 [46]. 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 [46]. Fluid intake
Excessive fluid intake can certainly increase urinary frequency and exacerbate OAB symptoms [47]. 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 [48]. 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 [36]. The type of fluids ingested can have an important impact on bladder pain. Bladder irritation in response to 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 [48,49]. This is also important since nocturia can often be improved by restricting oral intake 3–6 h before bed [46]. The ICI found that fluid intake played a major 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) [46].

Obesity
Obesity, which is defined as a BMI ≥30kg/m2, was traditionally considered a risk factor for stress urinary incontinence only, but more recently has been appreciated as a risk factor for OAB and UIU as well [50]. 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 vescular perfusion and neural innervations may be the cause of OAB symptoms and incontinence [51]. Bump et al. showed improvement in both stress urinary incontinence and UIU following surgical weight reduction in morbidly obese women [52]. However, even moderate weight loss can improve bladder symptoms in overweight women. In fact, loss of 5–10% of body weight can improve incontinence episodes by as much as 50–60% [46]. 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 [46].

Smoking
Smoking, particularly nicotine, has been implicated as a risk factor for OAB and incontinence [53]. Potential etiologies are increased intra-abdominal pressure from chronic cough and increased nicotine induced detrusor overactivity (as shown in cats) [36]. 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 [46].

Constipation
Constipation is a common comorbid complaint among patients with OAB [54]. Several factors have been implicated, including reduced fluid intake (in attempts to control bladder symptoms), limited exercise, decreased dietary fiber intake [55,56]. Straining to defecate and chronic constipation have been implicated as contributors to both lower urinary tract symptoms and pelvic organ prolapse [57]. 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 [58]. Furthermore, a recent study by Panayi et al. reported that rectal distension using a rectal balloon significantly decreased several urodynamometric parameters, including volume at first sensation, volume at strong desire and maximum bladder capacity [59]. Presumably, bowel distension leads to increased pelvic afferent input and could be grouped with those factors leading ‘increasing afferent noise’, which is linked to increase spontaneous detrusor contractions and urgency [60]. 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 [46].

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 ICI rated the evidence a level 3 and the grade for recommendation C for the impact of timed voiding on bladder symptoms. The ICI rated the evidence a level 3 and the grade for recommendation 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 [54].

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 ret timing, bladder re-education or bladder drills, may be effective as the result of rewiring of complex circuitry between the
bladder and the brain [42]. 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 care-givers [43,44].

Utilization of relaxation techniques including slow, deep breathing and distraction techniques (mental concentration on other tasks) are most popular [44]. Additional strategies include: 

■ Biofeedback

Biofeedback incorporates instrumentation and tech-nology 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 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 [45]. 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. 

■ Pharmacologic therapy

Pharmacologic therapies, primarily antimuscarinic agents, have been the mainstay of treatment for OAB and have been studied in numerous clinical trials [46]. These drugs produce variable efficacy, a moderate rate of side effects and rare occurrences of cure. 

Years of experience have proven an 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 the detrusor muscle [47]. When effective, these agents produce symptomatic improvement by reducing urgency and thereby reducing UI and frequency, decreasing detrusor overactivity or involuntary contractions of the bladder muscle and increasing bladder capacity [47]. Andersson has shown, however, that at the doses used for the treatment of OAB symptoms, there is little reduction in detrusor contractility [48]. Furthermore, clinical experience has taught us that antimuscarinics reduce storage symptoms including urgency, urgency and urge incontinence and increase bladder capacity, suggesting a mechanism of action during the storage phase [49]. 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 antimuscarinics 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. The bladder capacity and compliance of the pouch have become a focus of scurvy interest, as it is known to release afferent signaling molecules in ACh and contain muscarinic receptors [50]. Yoshida et al. have shown that urothelium has a basal level of ACh release of non-neuronal origin that increases with bladder distention [51]. Further work has linked urothelial ACh to activation of both muscarinic and nicotinic receptors with subsequent release of ATP [52]. ATP acts on both purinergic and cholinergic receptors on afferent nerve terminals, possibly providing the important link between ACh and a sensory mechanism of action [53]. Given this foundation, antimuscarinic medications, which tend to produce a delay in storage, may inhibit incontinence 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 [54]. 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 of the agents. A patient's profile 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, pruritus, 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 sta-tistically significant results to translate to clinically significant outcomes. Several other criticisms exist, including inadequate drug comparison, primary drug comparison, or 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 [56].

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available formulation</th>
<th>Dosing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine (hyoscine)</td>
<td>0.125 mg sublingual tablet</td>
<td>1-2 tablets every 4 h</td>
</tr>
<tr>
<td>0.125 mg/ml oral drops</td>
<td>1-2 doses every 4 h</td>
<td></td>
</tr>
<tr>
<td>0.375 mg ER capsule</td>
<td>1-2 tablets twice daily</td>
<td></td>
</tr>
<tr>
<td>Bellodonna &amp; opium</td>
<td>16/20 mg, 16/20 mg suppository</td>
<td>1-2 times daily</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>7.5 or 15 mg tablet</td>
<td>Daily</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>4 or 8 mg tablet</td>
<td>Daily</td>
</tr>
<tr>
<td>Flavoxate</td>
<td>100 mg tablet</td>
<td>1-2 tablets 3- to 4-times daily</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>5 mg tablet</td>
<td>2- to 4-times daily</td>
</tr>
<tr>
<td>5 mg/5 ml syrup</td>
<td>2- to 4-times daily</td>
<td></td>
</tr>
<tr>
<td>5, 10, 15 mg ER tablet</td>
<td>2 times weekly</td>
<td></td>
</tr>
<tr>
<td>3.9 mg/day ER patch</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>100 mg/g transdermal gel</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Propapentine</td>
<td>15 mg tablet</td>
<td>1-2 tablets, 4-times daily</td>
</tr>
<tr>
<td>Propiverine</td>
<td>15 mg tablet</td>
<td>1-4 tablets, 3-times daily</td>
</tr>
<tr>
<td>30 mg ER capsule</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Solifenacin</td>
<td>5 or 10 mg tablet</td>
<td>Daily</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1 or 2 mg tablet</td>
<td>Twice daily</td>
</tr>
<tr>
<td>2 or 4 mg ER capsule</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Trospium</td>
<td>20 mg tablet</td>
<td>Twice daily</td>
</tr>
<tr>
<td>60 mg ER capsule</td>
<td>Daily</td>
<td></td>
</tr>
</tbody>
</table>

**ER:** Extended release.

**Drug Level**

* A indicates level of evidence; C indicates grade of recommendation for the various medications.

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

Atropine

Atropine, along with hyoscyamine and scopolamine, is an active belladonna alkaloid, derived from the toxic belladonna plant with anticholinergic properties [6]. Atropine has significant systemic side effects including ventricular fibrillation, tachycardia, dizziness, nausea, blurred vision, loss of balance, dilated pupils, photophobia, extreme confusion and disso- ciative 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 [6]. 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-blind RCTs was performed by Chapple et al. in 2005 [6]. A total of 1059 patients (85.5% female) with urgency, UI and frequency were treated with darifenacin 7.5 or 15 mg, or placebo daily for 12 weeks. Significant dose related improvements in micturition frequency and 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-blind, three-period crossover study with 129 patients 65 years of age or older [28]. 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) [29]. 5-HMT is metabolized in the liver and is eliminated primarily in the urine 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) [29]. 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 dual dosing regimens. Fesoterodine is indicated for the treatment of OAB at doses of 4 and 8 mg daily. In a multicenter, double-blind, double-dummy RCT with TOLT ER, 132 patients were enrolled and received treatment [21]. 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 [21]. Fesoterodine 8 mg performed better than the 4 mg dose in improving urgency and UI as recorded by 3-day bladder diary, offering the possibility of dose titration.

Propapentine bromide

The RCTs in the bienicke study comparing solifenacin for the lower urinary tract was propapentine bromide, a nonselective quaternary ammonium compound that is poorly absorbed after oral administration [44]. It has a short plasma half-life of less than 2 h and varying bioavailability. It is usually prescribed at 15–30 mg four-times daily but larger doses are often required [24]. Despite hav- ing 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 [44] and no difference from placebo in 154 and 23 patients, respectively [28-29]. By today’s standards, the effect of propapentine 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 selec- tivity over the M1 receptors [46]. It is a once-a-day antimuscarinic that is being marketed at 5- and 10-mg doses. Cardozo et al. performed a multinational renal function study comparing solifenacin 5 and 10 mg daily with placebo in 857 patients [46]. Both doses significantly improved clinical trial outcomes, urgency, voiding frequency 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 and 10 mg daily, which is comparably low in both groups.¶

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine (hyoscine)</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Flavoxate</td>
<td>2</td>
<td>D</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Propantheline</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Propiverine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>Trospium</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td>YM-178 (mirabegron)</td>
<td>2</td>
<td>B</td>
</tr>
</tbody>
</table>
therapeutic effect of the drug [a]. Both TOLT and its metabolite have plasma half-lives of 2–3 h, but their effects persist for up to 24 h. This effect seems to be more long-lasting [a]. 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 [b]. The ER form appears to be a very low incidence of gastrointestinal side effects with TOLT, which is likely due to the low lipophilicity of the drug and its metabolite, minimizing penetration into the CNS [c]. 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 [d]. 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 4 mg daily to OXY ER 10 mg daily in 790 women with OAB symptoms [e]. This was a double-blinded RCT with duration of 12 weeks. Improvements in UUI episodes were similar between the two treatment groups. The frequency 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 showing similar rates of discontinuation of treatment.

Trospium Trospium is a hydroporphic, quaternary amine with limited ability to cross the blood–brain barrier. This, in theory at least, should result in minimal cognitive related dysfunction [f]. 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 [g]. 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, Jürenmann and Al-Shukri et al. found trospium to be significantly more effective in decreasing the frequency of micturition than either TOLT or placebo [h]. Additionally, trospium caused a greater reduction in incontinence episodes with a similar rate of dry mouth as TOLT. A double-blind crossover 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 [i]. Urodynamics and patient recorded voiding diaries were performed at baseline, 26 and 52 weeks. Mean micturition frequency 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 urological symptoms, but trospium showed a reduction in micturition frequency 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 [j]. Intravesical installation of trospium was studied with a single center, single-blinded RCT with 84 patients [k]. Since intravesical trospium does not seem to be absorbed, an opportunity exists for treatment with minimal systemic antimuscarinic effects [l]. Compared with placebo, intravesical trospium produced a significant increase in maximum bladder capacity of 23% and a 34% mean reduction in detrusor pressure. No improvement in unimitted bladder contractions was seen. No adverse events were reported but, an increase in residual urine was noted.

Dual muscarinic relaxants: antimuscarinic agents Some agents have been identified that have dual mechanisms of action. They have antimuscarinic activity as well as direct muscarinic 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 and have the ability to inhibit phosphodiesterase type 4. The drug has also been found to possess modest calcium antagonistic activity, exhibit local anesthetic properties and have the ability to inhibit phosphodiesterase type 4. In rats and cats there is some evidence that flavoxate may also have central effects on the inhibition of the micturition reflex [m]. Clinical studies addressing the efficacy of flavoxate in the treatment of OAB have been mixed. In a double-blind crossover study comparing flavoxate 1200 mg and placebo daily in 41 women with idiopathic detrusor overactivity, both drugs had similar efficacy with flavoxate having fewer and milder side effects [n]. A very small study in the elderly population with non-neurogenic detrusor overactivity has also been reported. The drug is effective in reducing micturition frequency and improving quality of life. Flavoxate may also have central effects on the inhibition of dopamine D1 receptors, as suggested by its ability to reduce extracellular striatal dopamine levels [o]. 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- to 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 [p] and subsequent reports documented success in inhibiting idiopathic detrusor overactivity as well [q]. A meta-analysis summarizing 15 RCTs (n = 476) reported a 52% mean reduction in micturition frequency at 4 to 6 mg of drug per day [r]. The therapeutic effect of OXY IR is associated with a high incidence of side effects that are often dose limiting [s]. 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 [t]. Three different 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 [u]. 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 [v]. Dry mouth was a side effect seen with the previously approved OXY patch. The 1 mg application dose delivers approximately 4 mg of drug to the circulation with stable plasma concentrations and few side effects [w]. In a multicenter RCT (186 women) with urge predominant urinary incontinence were assigned to OXY gel or placebo once daily for 12

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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 conserva-
tive measures and medication and to those who suffer
drug intolerance. The addition of neuromodula-
tion to the armamentarium of drugs in the treatment
options for OAB has salvaged many subopt-
timally treated patients and has had a great impact
on patient satisfaction and quality of life. These options
can be considered as an additional treatment arm
in those patients with a greater treatment burden,
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.

New drug development: β-3 adrenergic receptor
agonists

It has yet to be proven whether the sympathetic ner-
vous system plays an active role in the filling/storage
phase of the bladder in humans; however, the pres-
ence of β-3 adrenergic receptors (AR) in human bladder
muscle and urothelium prompted many attempts to
increase bladder capacity with β adrenergic stimu-
lation. 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 (5.0%) and β-2 (1.4%) [122,123]. Detrusor mus-
cle relaxation has been found to result from -2 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 eval-
uated in patients with OAB in a RCT versus TOLT
and placebo [126]. The treatment group experienced a significant reduction in micturition frequency, incon-
tinence 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 alterna-
tives in terms of efficacy, tolerability and safety. These
drugs are currently in the advanced stages of devel-
oment 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 with
reproductive age, based on finding in rats. The
Japanese label carries this warning based on minimal
available information in animals; we await the rec-
ommendations of the US FDA Advisory Committee
Meeting for mirabegron for more information on this
topic.

Neuromodulation

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

Sacral nerve stimulation

Sacral nerve stimulation has been well-established as a treat-
ment modality for refractory urgency, frequency, UI
and idiopathic urinary retention. The mechanism of
action remains unknown but theories include mod-
ulation 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 timed lead with four electrodes, an
implantable neuromodulator, a physician program-
ner 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 percu-
taneous nerve evaluation) and the indication for inter-
vention (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 1995 and is available to over 100,000 patients
who have failed combination therapy with conserva-
tion and have been recognized as potential candidates
[129,130]. The ICI rated the evidence a level 1 and grade
A for recommendation for the impact of neuromod-
ulation for their OAB.

Percutaneous tibial nerve stimulation

An alternative neuromodulatory approach is percuta-
neous tibial nerve stimulation (PTNS), a noninvasive
way of modulating pelvic reflexes via projections from
the posterior tibial nerve (m). Urgent PC (Uroplasty,
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
superficial to the medial malleolus. The recom-
mended treatment is 12 weekly sessions, 30 min each
[131]. 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) [132]. Objective measures,
including urinary frequency, UI episodes, urgency
severity, night-time voids and voiding voided, showed
similar improvement in the two groups. The authors
concluded that PTNS was a ‘clinically significant
management alternative for OAB.’ The ICI rated the level
of evidence 3 for the impact of PTNS on increasing
bladder capacity [133].

Pudendal nerve stimulation

A second alternative approach is stimulation of the
pudendal nerve within Alcock’s canal, by means of
neurophysiological guidance [134]. This is a logical alter-
native 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 pel-
vic organs [134]. Peters et al. reported a 71.4% response
rate (50% improvement) in a mixed population of
patients with OAB, painful bladder syndrome, neuro-
logical voiding dysfunction and urinary retention, of
whom 52% had failed prior sacral stimula-
tion [135]. In a previous comparative study, 30 patients

weeks. Mean number of UIU episodes, as recorded in a
3 day voiding diary, were reduced by 3.0 episodes per
day in the propiverine group (p<0.001). Urinary
frequency was decreased by 2.7 episodes per day and
voided volume increased by 21 ml (p<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.
In addition, there was a 5% reduction in skin tolerance
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; person-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 [136].
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 increase in bladder capacity and a 77% subjective
improvement rate. Side effects were found in 14% of
subjects [137]. Several comparative studies have con-
ﬁrmed the efficacy of propiverine and suggested that
the drug may be equally efficacious in increasing blad-
der capacity and lowering bladder pressure, with fewer
side effects than OXY [138,139]. In 2006, Abrams et al.
reported data that refuted these prior studies [140].
In a double-blind, placebo-controlled crossover
study comparing propiverine 20 mg daily, propiverine
15 mg three-times daily, OXY 5 mg three-times daily
day 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, ran-
domized patients to solifenacin 5 or 10 mg, propiver-
line 10 mg group, with more dry mouth and constipation.
Increased volume voided compared with propiverine
was reported in 52% of patients with idiopathic urinary
retention compared with propiverine in 20% of patients
with OAB, painful bladder syndrome, neuro-
logical voiding dysfunction and urinary retention [136].
The ICI rated the evidence a level 1 and grade
A for the impact of PTNS on improving urgency, frequency and urgency
continence [133].
underwent simultaneous sacral and pudendal lead placement with subsequent blinded and randomized treatment allocation (146). 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 ICQI rated the evidence a level 3 for the impact of pudendal nerve stimulation on increasing bladder capacity (146).

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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 suburothelial, producing a chemical denervation that is relatively brief (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 (150). Urgency, nocturia and frequency have been shown to improve as early as 2 days after injection (149). The reported duration of Botox-A following the first injection was 6–9 months (138) 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 maximal cystometric capacity, frequency and UI were seen at 4 and 12 weeks. Despite clinical improvement, 6 patients (37.5%) required clean intermittent catheterization to empty their bladders (142). In the 28 women with refractory OAB received Botox-A 200 U and 15 women received placebo (142). Approximately 60% of the women who received Botox-A reported a clinical response with a mean duration of response of 373 days (compared with 67 days with placebo). 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 random first injection 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 reduction studies 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 met 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 number of patients, inappropriate 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 makes the condition least severe to most severe. 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.

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 one level evidence for the treatment of OAB. Recent advances in basic science, translational and clinical research has led to greater understanding of the disease and future research could provide the necessary tools for the development of more refined and directed therapies in the future.

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Papers of special note have been highlighted as:
- of interest
- important


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