

Recent advances in management of bladder overactivity

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Abstract

Pharmacologic therapies, primarily antimuscarinic agents, have been the mainstay of treatment for overactive bladder. These drugs produce variable efficacy, a moderate rate of side effects, and rare occurrences of cure. The search for newer and better formulations and derivatives of this class of medication as well as novel therapies is ongoing and primarily fueled by the high prevalence of overactive bladder and the tremendous number of health care dollars spent on current therapy. Surgical options for overactive bladder have evolved slowly and are currently reserved for medical treatment failures and drug intolerance. This article will highlight the new drugs and therapies brought into clinical use for the treatment of overactive bladder over the last few years as well as a promising new agent in the advanced stages of development.

Introduction and context

Overactive bladder (OAB) affects between 8.0-13.9% of the population in Western nations [1]. This variation in prevalence is thought to be due primarily to differences in the definition of OAB used across different study populations. The International Continence Society has defined OAB as 'urgency, with or without urge incontinence, usually with frequency and nocturia' [2] in attempts to standardize reporting of this highly prevalent and bothersome condition. The drugs most commonly prescribed for the treatment of OAB are the antimuscarinics; these drugs are proven efficacious and safe and are the mainstay of treatment for OAB [3]. These agents produce symptomatic improvement by reducing urgency and therefore urge urinary incontinence (UI) and frequency, decreasing detrusor overactivity and increasing bladder capacity [4]. There are several drugs available for use today, with some variability based on country of residence. As newer antimuscarinic agents have become available, some progress has been made in maximizing therapeutic efficacy while minimizing bothersome side effects; however, a large number of patients remain dissatisfied with the mix of efficacy and tolerability and discontinue therapy. Nevertheless, most physicians prescribe a trial of antimuscarinic therapy and behavioral

modification in patients with bothersome OAB, and if it is not effective, a second trial using a different drug or formulation is often instituted. When these drugs fail, the side effects become intolerable, or the category of drug is contraindicated, physicians have limited therapeutic options, including off-label use of other categories of drug or more invasive treatment options such as neuromodulatory agents or devices.

With recent advances in the science of OAB, it has become clear that the functioning and malfunctioning of the urinary bladder are much more complex than previously appreciated and that other targets besides the muscarinic receptors should be addressed. 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 (LUT)-selective, easily administered, and relatively inexpensive – has yet to be found. This search continues and therapies with different mechanisms of action are currently being studied with some promise.

Recent advances

Several new therapies have been added to the armamentarium of treatment options for OAB over the last couple

of years. These include oxybutynin (OXY) topical gel, fesoterodine, trospium extended release (ER), continued development of novel β_3 adrenergic receptor (AR) agonists, off-label use of phosphodiesterase (PDE) inhibitors, off-label use of intradetrusor botulinum toxin (BTX), and advances in neuromodulation. Some of these additions represent new drugs approved specifically for OAB and others represent new or off-label uses of previously approved therapies. Additionally, advances in the understanding of OAB through basic science research have not only opened the door to new categories of drug therapy but also enhanced our utilization of available antimuscarinics for the treatment of OAB in the setting of bladder outlet obstruction, an often concomitant disease process. Together, these recent advances have had a modest impact on clinical practice.

Oxybutynin topical gel

OXY topical gel is a new transdermal formulation that is applied once daily to the abdomen, thigh, shoulder, or upper arm area [5]. The 1 gram application dose delivers approximately 4 mg of drug to the circulation with stable plasma concentrations. In a multicenter randomized control trial (RCT), 789 patients (89% women) with urge-predominant UI were assigned to OXY gel or placebo once daily for 12 weeks. The mean number of urge UI episodes, as recorded by 3-day voiding diary, was reduced by 3.0 episodes per day versus 2.5 in the placebo arm ($P < 0.0001$). Urinary frequency decreased by 2.7 episodes per day and voided volume increased by 21 mL (versus 2.0 episodes [$P = 0.0017$] and 3.8 mL [$P = 0.0018$], respectively, in the placebo group). 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 transdermal patch 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. The evolution of the transdermal gel allows greater patient tolerability and improved compliance. Further data are needed to assess whether the decreased rate of side effects is at the expense of diminished efficacy. This would require a head-to-head trial with another antimuscarinic drug, a type of trial that occurs only rarely, creating a major challenge in evaluating the comparative efficacies of these agents.

Fesoterodine

Fesoterodine is a new oral antimuscarinic drug that is metabolized rapidly and extensively to 5-hydroxymethyl tolterodine (5-HMT), the same active metabolite of

tolterodine [6]. 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 [7]. 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 tolterodine ER, 1132 patients were enrolled and received treatment [6]. 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. There appears to be little difference between fesoterodine 4 mg and tolterodine ER. Only one subject from the fesoterodine 8 mg group and one subject from the tolterodine ER 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 [8]. Fesoterodine 8 mg performed better than the 4 mg dose in improving urgency and urge UI as recorded by 3-day bladder diary, offering the possibility of dose titration. Further studies are needed to determine whether patients prefer the more efficacious 8 mg dose despite the added side effects.

Trospium extended release

The development of a once-daily formulation of trospium chloride was a necessary step to maintain its place in the competitive antimuscarinic drug market. In addition to convenience and improved compliance, the ER deliver system was felt to lower maximum plasma concentration levels of the drug and thus decrease the incidence of side effects. Phase III data confirmed the efficacy of the ER formulation in reducing the number of voids per day and urge UI episodes per day [9]. Additionally, improvements in urgency severity, volume voided, and urgency voids per day were seen. Dry mouth incidence was 8.7% in the trospium ER group versus 3% in the placebo group; 8.7% is the lowest reported rate of dry mouth for this class of drug. Subsequent authors have confirmed the improved tolerability profile of trospium ER; constipation rates in this study were 7.5% versus 1.8% in placebo [10]. MacDiarmid *et al.* [11] tabulated an average dry mouth incidence of 20.1% with trospium immediate release (IR) versus 10.7% with trospium ER and average constipation rates of 9.6% with trospium IR and 8.5% with trospium ER.

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 ARs in human bladder muscle 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%) [12,13]. 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 [14,15]. Several selective β_3 agonists are being evaluated in clinical trials for the treatment of OAB. Acetanilide (YM178) was evaluated in patients with OAB in an RCT versus tolterodine and placebo [16]. 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.

Phosphodiesterase inhibitors

PDE inhibitors (sildenafil, tadalafil, and vardenafil) are generally prescribed for the treatment of erectile dysfunction (ED) and were found incidentally to improve LUT symptoms in men [17]. LUT smooth muscle undergoes relaxation in the presence of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), and PDE inhibitors block the degradation of cAMP and cGMP, resulting in greater intracellular concentrations [18]. This class of drug is not currently approved for the treatment of OAB or other LUT symptoms and its use for this indication is off-label. In an RCT evaluating the effects of sildenafil on ED and LUT symptoms in 189 men, significant improvements in International Prostate Symptom Score (IPSS) and health-related quality of life (HRQoL) were seen [19]. In the first RCT looking at sildenafil and voiding dysfunction in women, no significant differences were seen in patients with complete retention, partial retention, or obstructed voiding [20]. An RCT comparing tadalafil with placebo in 281 men with ED and LUT symptoms produced clinically meaningful and significant symptomatic improvement in LUT symptoms [21]. In another RCT, vardenafil 10 mg twice daily in men with ED and LUT symptoms showed a significant improvement in IPSS and HRQoL [22]. The PDE-1 inhibitor vinpocetine was evaluated in a multicenter, double-blind RCT in patients with urgency and urge UI with urodynamically documented detrusor overactivity who failed antimuscarinic therapy [23]. The patients received either vinpocetine

20 mg three times daily or placebo. The results showed a significant reduction in micturition frequency in men; however, the remainder of assessed outcomes showed a trend toward improvement without reaching significance. The lack of side effects in this study indicates that the dose delivered may have been too low. While large-scale studies in women using PDE inhibitors for OAB have yet to be done, the early data in men suggest a possible role in the treatment of bladder diseases. The mechanism of action to produce this beneficial effect in OAB remains unknown at this time.

Botulinum toxin

BTX (Botox®; Allergan, Inc., Irvine, CA, USA) is a neurotoxin produced by *Clostridium botulinum* and is a potent presynaptic inhibitor of acetylcholine release at the neuromuscular junction. It is applied directly by cystoscopic injection into the detrusor muscle, producing a chemical denervation that is reversible after approximately 6 months. The mode of administration allows high concentrations of the agent to reach the bladder tissue without systemic administration and resultant unsuitable levels in other organs. BTX is not approved for the treatment of OAB but is now widely used in patients who are refractory to conventional antimuscarinic therapy or who do not tolerate it due to systemic side effects.

The dose and injection protocol for BTX has not been universally agreed upon and several variations exist. In the initial description for the treatment of neurogenic OAB, 300 units (U) of BTX-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 [24]. 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 BTX-A effects is seen within the first 2 weeks after injection [25]. Urgency, nocturia, and frequency have been shown to improve as early as 2 days after injection [26]. The reported duration of BTX-A following the first injection was 6-9 months [25], and duration of effect along with beneficial clinical effect after subsequent injections is maintained [27].

In a double-blind RCT including 34 patients with OAB refractory to antimuscarinics, 200 U of BTX-A was studied [28]. Significant improvements in maximum cystometric capacity, frequency, and UI episodes were seen at 4 and 12 weeks. Despite clinical improvement, 6 patients (37.5%) required clean intermittent catheterization (CIC) to empty their bladder. In another RCT,

28 women with refractory OAB received BTX-A 200 U and 15 women received placebo [29]. Approximately 60% of the women who received BTX-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 (PVR) 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 BTX injection in patients with OAB, dose reduction studies looking at 100 U have been done. In a prospective, non-randomized study including 100 men and women, 100 U of BTX-A was injected in 30 locations [30]. At 4- and 12-week follow-up, 88% of patients showed significant improvement in bladder function in regard to subjective symptoms, urodynamic parameters, and HRQoL. There were four cases of urinary retention.

BTX 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 CIC who leak between catheterizations seems clearer than in patients with idiopathic OAB, in whom the PVR issue has yet to be clarified.

Neuromodulation

Sacral neuromodulation (SNM) is well established as a treatment modality for refractory urgency, frequency, urge UI, 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 [31]. 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 urgency/frequency and urge UI) [32]. Evolution in our understanding of neuromodulation has allowed expanded indications for treatment and alternative approaches for nerve stimulation. When unilateral SNM 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. In addition, previously excluded patients such as those with neurologic diseases like multiple sclerosis or Parkinson's disease and patients with incomplete spinal cord injuries have undergone successful treatment using

neuromodulation and are beginning to be recognized as potential candidates [33,34].

One alternative approach is percutaneous tibial nerve stimulation (PTNS), a non-invasive way of modulating pelvic reflexes via projections from the posterior tibial nerve [35]. Urgent® PC (Uroplasty, Inc., Minnetonka, MN, USA) is an office procedure approved by the US Food and Drug Administration and 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 minutes each [36]. The Overactive Bladder Innovative Therapy (OrBIT) trial was a randomized, multicenter, control trial that compared PTNS with tolterodine ER; 79.5% of patients in the PTNS arm reported cure or improvement in symptoms compared with 54.8% of the tolterodine group as measured by the global response assessment ($P = 0.01$) [35]. Objective measures, including urinary frequency, urge UI episodes, urge severity, nighttime voids, and volume voided, showed similar improvement in the two groups. The authors concluded that PTNS was a 'clinically significant treatment alternative for OAB'.

A second alternative approach is stimulation of the pudendal nerve within the Alcock canal by means of neurophysiological guidance [37]. 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 [38]. Peters *et al.* [38] reported a 71.4% response rate (>50% improvement) in a mixed population of patients with OAB, painful bladder syndrome, neurologic voiding dysfunction, and non-obstructive urinary retention, of whom 52% had failed prior sacral stimulation [38]. In a previous comparative study, 30 patients underwent simultaneous sacral and pudendal lead placement with subsequent blinded and randomized stimulation of each electrode [39]. In 79.2% of patients, the pudendal lead was chosen as superior, with a 63% reduction in symptoms (versus 46% reduction with sacral stimulation, $P = 0.02$).

Antimuscarinics and urinary retention

Advances in the understanding of the mechanisms of action of antimuscarinic agents and the pathophysiology of OAB through basic science research have enhanced our utilization of antimuscarinics for the treatment of OAB in the setting of bladder outlet obstruction, an often concomitant disease process. The use of these drugs in this setting was previously feared due to the theoretical risk of urinary retention, and in the past there was universal concern regarding the risk of acute retention

when prescribing antimuscarinic drugs. However, as Andersson and Wein [40] and Andersson *et al.* [41] propose, these drugs are usually competitive antagonists, implying that when there is massive release of acetylcholine during voiding, the relative effect of the drug should be diminished. If this did not occur, urinary retention would result from the inability of the bladder to contract. In fact, at high doses, urinary retention can occur but this is uncommon at the doses typically prescribed for OAB [40]. Our current understanding is that the dose range used for beneficial effects in OAB is much lower than that needed to produce a significant reduction in the voiding contraction. Monitoring PVRs in patients with prostatic enlargement or incomplete bladder emptying is still recommended; however, these diagnoses should not be considered absolute contraindications to the use of antimuscarinics.

Implications for clinical practice

Pharmacologic therapies, primarily antimuscarinic agents, have been the mainstay of treatment for OAB. For many patients, the side effects of oral administration 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. Fesoterodine offers another oral option to the long list of oral agents available. Its uniqueness lies in its optimum biopharmaceutics profile with decreased lipophilicity and permeability across biological interfaces, producing at least a theoretically lower incidence of side effects [42]. Additionally, there is less variability in the pharmacokinetics of this agent due to its metabolism by ubiquitous non-specific esterases, allowing a more narrow therapeutic window. Trospium ER offers a once-daily option with side effect rates lower than those of a previously approved and efficacious drug. 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 [43]. Contraindications for all of these drugs include uncontrolled narrow-angle glaucoma, urinary retention, gastric retention, or conditions with severely decreased gastrointestinal motility. Determining where these three new antimuscarinic options fit among the other available drugs in the same class is a challenge as head-to-head trials resulting in comparative efficacies of these agents have not been performed. As more clinical experience is reported for drugs like PDE inhibitors and BTX for the treatment of OAB, more practitioners are becoming comfortable offering off-label use of these agents, thus providing an alternative to antimuscarinic treatment. 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 BTX, there have been few surgical innovations for the treatment of OAB. The use of expanded indications (including patients with neurologic disease) and additional implantation routes have resulted in the successful treatment of countless refractory OAB patients with neuromodulation over the last couple of years. Neuro-modulation is considered ineffective and thus contraindicated in patients with complete spinal cord injury.

Ongoing scientific research has provided us with greater sophistication and a clearer understanding of the mechanisms of therapeutic interventions for OAB and this should inevitably translate to more refined and directed therapies in the future. There are several classes of drug currently in phase II and phase III testing which may have a great impact on the treatment of OAB in upcoming years.

Abbreviations

5-HMT, 5-hydroxymethyl tolterodine; AR, adrenergic receptor; BTX, botulinum toxin; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CIC, clean intermittent catheterization; ED, erectile dysfunction; ER, extended release; HRQoL, health-related quality of life; IPSS, International Prostate Symptom Score; IR, immediate release; LUT, lower urinary tract; OAB, overactive bladder; OXY, oxybutynin; PDE, phosphodiesterase; PTNS, percutaneous tibial nerve stimulation; PVR, post-void residual; RCT, randomized control trial; SNM, sacral neuromodulation; U, units; UI, urinary incontinence.

Competing interests

ALS declares that she has no competing interests. AJW is an advisor for Astellas (Tokyo, Japan), Novartis (Basel, Switzerland), Pfizer Inc. (New York, NY, USA), and Endo Pharmaceuticals (Newark, DE, USA).

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