The Future of Overactive Bladder Management: Anticholinergics and Beyond

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Purpose
Overactive bladder (OAB) remains a highly prevalent condition with a significant impact on a patient’s quality of life. Despite improvements in symptoms and lower incidences of side effects with newer formulations of anticholinergic agents, treatment discontinuation rates remain high over the long term. Suboptimal treatment is therefore a major challenge for the successful management of OAB. The chronic nature of the condition means that effective treatment must be long-term and continuous, and must be taken as prescribed. As a result, alternative therapeutic options are needed to treat patients from an efficacy and tolerability standpoint. The purpose of this report is to review emerging therapies in OAB that offer a new application or make use of an entirely novel mechanism of action. This report will address OAB treatments that are currently available to patients and those that are on the horizon.

Learning Objectives
• Review current therapeutic approaches to OAB
• Recognize the barriers and unmet needs associated with the current pharmacologic management of OAB
• Examine emerging therapies for the treatment of OAB and their future role in clinical practice

Understanding OAB and Identifying Current Barriers to Treatment Management

Overactive bladder (OAB) is a common syndrome that affects both men and women, and can be a chronic condition requiring long-term medical management and lifestyle changes.1,2 OAB is expected to affect approximately 546 million individuals worldwide by 2018.3
The potential negative impact of OAB on quality of life, through its effects on day-to-day activities, is well established.\textsuperscript{1,2,4} To ensure that bothersome symptoms do not go unnoticed, it is important for primary care physicians to screen, assess and treat OAB. OAB is defined by the International Continence Society and the Canadian Urological Association guidelines as urinary urgency that is frequently accompanied by urinary frequency and nocturia, with or without urgency urinary incontinence.\textsuperscript{1,5}

While conservative measures such as behavioural modification and pelvic-floor exercises remain first-line therapy for OAB, anticholinergics remain the mainstay of pharmacologic treatment.\textsuperscript{1,6} Both are effective in reducing OAB symptoms, and their combination may provide even better results than either used as a monotherapy.\textsuperscript{7,8} However, each of these therapies has its limitations. Behavioural therapy requires a motivated patient who: is interested in education about normal bladder function and healthy bladder habits; has a willingness to make dietary and lifestyle modifications; and has a willingness to perform urgency suppression techniques, such as conscious suppression and pelvic-floor muscle exercises. Although behavioural therapy may be quickly adopted initially, its overall success depends on persistent adherence to the behavioural changes. There are numerous anticholinergic agents that are currently approved by Health Canada for the treatment of OAB, with fesoterodine and topical oxybutynin as the newest anticholinergic agents (Figure 1, Figure 2).\textsuperscript{9-18}

A 2008 meta-analysis of 52 randomized clinical trials found that anticholinergic medications effectively improved OAB symptoms and health-related quality of life, and were generally well tolerated.\textsuperscript{19} Anticholinergics differ in molecular structure, molecular size, bladder muscarinic receptor selectivity, method of administration (\textit{i.e.}, oral, transdermal, once daily, twice daily), metabolism (CYP3A4 dependent or independent), tendency of crossing the blood-brain barrier, and incidence of side effects.\textsuperscript{6,20} However, they all share the same mechanism of action in preventing acetylcholine (ACh) from binding to muscarinic receptors in the detrusor muscle of the bladder.\textsuperscript{9-18}

Despite proven success rates in improving OAB-related symptoms, a significant proportion of patients may not tolerate prolonged anticholinergic therapy; and their use can often be limited because of insufficient response, loss of efficacy, contraindications, or intolerance to side effects (specifically dry mouth and constipation).\textsuperscript{21-25} This is important to note, as adverse events due to the pharmacologic actions of anticholinergics remain a primary limiting factor in their tolerability as an OAB treatment, regardless of whether they are new or
old. While fesoterodine’s pivotal Phase III trial with tolerodine ER was not a head-to-head comparison, it was evident that fesoterodine displayed an adverse-event profile typical of other anticholinergics. Dry mouth (placebo 7.1%, tolerodine ER 16.9%, fesoterodine 4 mg 21.7%, fesoterodine 8 mg 33.8%) and constipation (placebo 1.4%, tolerodine ER 2.8%, fesoterodine 4 mg 3.3%, fesoterodine 8 mg 4.5%) were the most commonly reported adverse events. The availability of topical oxybutynin introduced a new set of adverse events not associated with previous oral formulations. In the 14-week open-label extension of the Phase III study, treatment-related adverse events included application-site dermatitis (2.3%) and application site pruritus (2.3%). Even with improvements in the side-effect profiles of long-acting and more bladder-targeted formulations, discontinuation rates still remain high over the long term (Figure 3). Consistent with previous reports, in a recent systematic review of studies published since 1998 on the treatment of OAB with anticholinergic therapy, 43% to 83% of patients discontinued medication within the first 30 days, with rates continuing to rise over time (oxybutynin having the highest discontinuation rate among the drugs studied). In addition, a 2009 study determining 12-month adherence rates across multiple chronic conditions found OAB medications (35%) were lower than cardiovascular (61%), oral antidiabetic (72%), and oral osteoporosis (60%) therapies. The reasons underlying these low rates of persistence for OAB therapy in clinical practice are not clear. Few studies have reported either the predictors or the patient-reported reasons for OAB medication discontinuation. In surveys evaluating patient-reported reasons for discontinuing anticholinergic prescription medications for OAB, expectations about treatment efficacy and adverse events were the most important factors, with 45.4% of patients reporting unmet treatment expectations as the reason for discontinuation. Consistent with these surveys, a recently published 12-week observational study investigating factors that motivate physicians and patients to change their OAB treatment, found that reasons for last treatment change included lack of efficacy (60%) and adverse events (24%). In this respect, there is still a need to develop additional effective and well-tolerated therapies for the treatment of OAB.

Novel Class of Non-oral Medications—Botulinumtoxin

OnabotulinumtoxinA (botulinum toxin type A; BoNTA; BOTOX®) is a neurotoxin produced by the gram-positive organism Clostridium botulinum. The general mechanism of action of BoNTA involves blocking neuromuscular conduction through receptor binding on motor nerve terminals, and inhibiting the release of ACh. In the context of OAB treatment, an intradetrusor injection of BoNTA inhibits ACh release from the presynaptic nerve terminal, preventing stimulation of detrusor muscle muscarinic receptors, suppressing voluntary detrusor contractions (Figure 4).
Currently, intradetrusor injections of BoNTA are approved in Canada for patients with neurogenic detrusor overactivity associated with a neurological condition. Clinical efficacy in this population has been assessed in a double-blind, randomized, placebo-controlled, 52-week Phase III trial (n = 416). At week 6, results demonstrated a decrease in the mean number of urinary incontinence episodes per week for patients receiving 200 units (21 episode reduction; n = 135) and 300 units (23 episode reduction; n = 132) of BoNTA compared to a decrease of only 9 episodes per week in control patients (p < 0.001 for each dose). The most common adverse events in this trial were urinary tract infection (UTI) (34%, 49% and 50%, respectively, for placebo, BoNTA 200 U and 300 U) and urinary retention (3%, 20% and 17%, respectively, for placebo, BoNTA 200 U and 300 U). Of the patients who did not catheterize at baseline, 10% of the placebo group, 35% of the BoNTA 200 U group, and 42% of the BoNTA 300 U group initiated catheterization as a result of urinary retention.

Studies have also been conducted to demonstrate the efficacy of BoNTA injections in idiopathic OAB (iOAB) patients. A randomized, double-blind, placebo-controlled Phase II study observed the effects of BoNTA in 313 iOAB patients with urinary urgency incontinence (UUI). Patients were randomized to 50, 100, 150, 200 or 300 U of BoNTA or placebo. The primary outcome was weekly UUI episodes at week 12. The magnitude of reduction in weekly UUI episodes was greater for all dose groups of BoNTA than placebo starting at week 6. At 12 weeks, mean reduction from baseline in UUI episodes was –17.4, –20.7, –18.4, –23.0, –19.6, –19.4 for placebo and BoNTA dose groups of 50, 100, 150, 200 and 300 U, respectively. The study also demonstrated statistically significant improvements in mean weekly episodes of micturition, urgency, nocturia, and volume voided/micturition with BoNTA treatment at week 12 compared to placebo. The adverse-event profile was similar to what was observed in the neurogenic OAB population. The most common adverse events in this trial were urinary retention and UTI, both of which occurred significantly more frequently in the active treatment groups than placebo (p < 0.005). Mean post-void residual (PVR) values in all dose groups of BoNTA at week 6 were significantly higher than their respective baseline values. The proportion of patients that required PVR-related catheterization was higher in any of the BoNTA dose groups compared to placebo; 0.0%, 5.4%, 10.9%, 20.0%, 21.2%, 16.4% for placebo and BoNTA dose groups of 50, 100, 150, 200 and 300 U, respectively.

While the efficacy results of these and other similar trials are promising, the use of BoNTA intradetrusor injections for the iOAB population remains unapproved in Canada, and there is no universally accepted dose for this indication. Additionally, the adverse-event profile in both populations may be a limiting factor in the widespread use of BoNTA. Overall, more research is needed to determine the long-term viability of BoNTA as an OAB treatment, as safety and efficacy data beyond two intradetrusor treatments are currently limited.

### Novel Oral Medications—β3-Adrenoceptor Agonists

β3-adrenoceptor (AR) agonists are a novel treatment for OAB, with a mechanism of action that is distinct from anticholinergics. Mirabegron (YM-178; Astellas) is a novel, orally active, once-daily β3-AR agonist. Mirabegron is the first drug in...
its class to complete Phase III registration studies. It is currently approved for use in Japan, Europe and in the United States, and has been submitted for approval in Canada.\textsuperscript{36,37} Solabegron (GW427353; AltheRx) is also a $\beta_3$-AR agonist; however, it is still in the investigational stages of study.\textsuperscript{39} Unlike antimuscarinics, which target neural control of the voiding phase of micturition, mirabegron targets the storage phase of micturition, resulting in increased bladder capacity and lengthening the interval between voiding (Figure 5).\textsuperscript{36-38} It also does not prevent contraction during the voiding phase.\textsuperscript{36-38}

Three recently published Phase III trials provide evidence regarding the safety and efficacy of mirabegron.\textsuperscript{40-42} Khullar and colleagues (2012) conducted a multicentre, randomized, double-blind, parallel-group, placebo- and tolterodine-controlled study in 1,978 adult patients with symptoms of OAB for $\geq$ 3 months.\textsuperscript{40} Patients were randomized to treatment with placebo, mirabegron 50 mg, mirabegron 100 mg, or tolterodine extended release (ER) 4 mg orally, once daily, for 12 weeks.\textsuperscript{40} The mirabegron 50- and 100-mg groups demonstrated a statistically significant improvement in both the co-primary efficacy endpoints of mean change from baseline in number of incontinence episodes per 24 hours (–1.57 and –1.46, respectively vs. placebo –1.17; $p < 0.05$) and mean change from baseline in number of micturition episodes per 24 hours (–1.93 and –1.77, respectively, vs. placebo –1.34; $p < 0.05$).\textsuperscript{40} Tolterodine ER also demonstrated improvements in co-primary efficacy endpoints, however, these improvements did not reach statistical significance compared to placebo ($p = 0.011$ for both).\textsuperscript{40} The incidence of treatment-emergent adverse events was similar across all treatment groups. It is important to note that the incidence of dry mouth in the mirabegron 50-mg and 100-mg groups was similar to placebo (2.8%, 2.8% and 2.6%), while in the tolterodine ER 4-mg group, the incidence was about three-fold higher (10.1%).\textsuperscript{40}

Chapple and colleagues also conducted a randomized, double-blind, active-controlled trial to focus on the long-term safety and efficacy of mirabegron.\textsuperscript{42} After a four-week washout period, patients were randomized to receive mirabegron 50 mg, mirabegron 100 mg or tolterodine ER 4 mg for a 12-month treatment period.\textsuperscript{42} The primary outcome was incidence and severity of adverse events.\textsuperscript{42} The secondary outcome was clinical efficacy based on voiding diaries.\textsuperscript{42} A total of 2,444 patients with OAB were randomized.\textsuperscript{42} The number of reported adverse events was similar with mirabegron 50 mg (59.7%), mirabegron 100 mg (61.3%), and tolterodine ER (62.6%).\textsuperscript{42} However, the incidence of dry mouth was 2.8%, 2.3%, and 8.6% for mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER, respectively.\textsuperscript{52} Both doses of mirabegron and tolterodine ER demonstrated improvement in OAB parameters that was sustained throughout the 12-month treatment period.\textsuperscript{42} As previously mentioned, dry mouth has often been reported as a key factor in determining adherence to OAB treatments, suggesting the improved tolerability profile of mirabegron has the potential to improve patient adherence to OAB therapy.\textsuperscript{38,40,41} Although further studies are required to confirm the place of $\beta_3$-AR within clinical practice, the Phase III trials provide promising clinical data to support the safety and efficacy of mirabegron.\textsuperscript{40-42}

**Conclusion**

There is a strong need to develop additional effective and well-tolerated therapies for the treatment of OAB. While behavioural modification and pelvic-floor exercises continue to be the foundation of first-line OAB management strategies, anticholinergics remain the mainstay of pharmacologic therapy; however, a number of promising new treatments are on the horizon for OAB. The use of botulinum toxin for neurogenic detrusor overactivity is increasing and Health Canada may grant approval for its use in iOAB in the future. In addition, $\beta_3$-AR agonists have been identified as an effective therapeutic
class for OAB. The forerunner of this group, mirabegron, has documented clinical efficacy in several large Phase III trials and is likely to become a first-line option in the management of OAB.  

40-42 The excellent tolerability profile of mirabegron offers the potential to improve compliance with OAB treatment in clinical practice.  

40-42 Further studies are underway to confirm these results, along with other strategies, such as combination treatment with anticholinergics.

Development of this article was sponsored through an educational grant from Astellas Pharma Canada, Inc. The authors had complete editorial independence in the development of this article and are responsible for its accuracy. The sponsor exerted no influence in the selection of the content or material published.