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Review Article

Where will the next generation of medical treatments for overactive bladder syndrome come from?

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Abbreviations & Acronyms
AE = adverse event
NR = not reported
OAB = overactive bladder syndrome
QoL = quality of life

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Abstract: This review article discusses the medical need for improved medical treatments of overactive bladder syndrome, and the hurdles and research required to address that need. Currently, few overactive bladder syndrome patients stay on long-term treatment, largely because efficacy expectations are not met, and tolerability is considered insufficient for the chronic treatment of a non-life-threatening condition. Therefore, a medical need exists for improved tolerability and, even more importantly, improved efficacy. It is unlikely that major improvements of efficacy and tolerability can be achieved within the currently approved drug classes. Work in experimental animals suggests that many causes of overactive bladder syndrome exist – each with a distinct pathophysiology. This makes it unlikely that a single medication can address the pathophysiology and treatment needs of all overactive bladder syndrome patients; accordingly, any medication will appear to have only moderate efficacy in the overall group of overactive bladder syndrome patients, even if it fully eliminates symptoms within a subset of patients. It is proposed that only identification of subsets of patients with a defined pathophysiology (and biomarkers thereof) will allow the development and use of targeted treatment that can be highly effective in such subsets.

Key words: biomarker, drug development, overactive bladder syndrome, pathophysiology, patient stratification.

Introduction

OAB was defined in 2002 by the International Continence Society based on the presence of urgency, with or without incontinence, often accompanied by urinary frequency and nocturia.[1] This definition has been updated over time, but all versions consistently focus on the presence of urgency.[2,3] Furthermore, it is important to realize that OAB, as defined by the International Continence Society, is a symptom complex, not a disease entity; the term is intended for the initial management of patients. This definition implies that multiple pathologies might underly the diagnosis of OAB (see below). It follows that theoretical treatments that are highly effective against one cause of OAB are not necessarily similarly effective against other causes. Furthermore, the overall group of OAB patients is not only heterogeneous in its etiology, but also in its presentation: The pairwise correlation of OAB symptoms across patients is only moderate, with the possible exception of urgency and daytime frequency.[4]

Epidemiological estimates of the prevalence of OAB differ widely. This can in part be explained by investigators studying different populations and applying different definitions of the condition. A large multinational survey applying the OAB definition of the International Continence Society reported a prevalence of 11.8%.[5] However, all studies agree that OAB is a highly prevalent condition – irrespective of applied definition – and that its prevalence increases with age. Studies also agree that OAB adversely impacts QoL. This applies to various domains of QoL, including mental health.[6] However, the OAB symptoms of urgency, urgency incontinence, frequency and nocturia differ in their impact on QoL.[7,8] As the severity of specific OAB symptoms differs between patients, the impact on QoL is also expected to be different between them. Accordingly, individual patients suffering from OAB might have different therapeutic needs.

None of the existing medical OAB treatments is curative, but few patients stay on long-term treatment; the key reasons for poor long-term adherence include unmet expectations of

efficacy and lack of satisfaction with tolerability.[9] Against this background, this article discusses the medical need for improved medical treatments based on tolerability and on efficacy. It will discuss hurdles to future commercial drug development in this area and, based on this analysis, will propose future research priorities. The potential of other options, such as behavioral treatment[10] or neuromodulation,[11] will not be discussed here; of note, these other treatment modalities are not necessarily alternatives to medical treatment, but might also be seen as additions.

Defining the medical need: Tolerability

Safety and tolerability are key considerations in the treatment of non-life-threatening disorders, such as OAB. Although muscarinic receptor antagonists are generally considered to be well tolerated, AEs are one of the leading causes of discontinuation.[9] The most frequently observed AE in patients receiving treatment with a muscarinic receptor antagonist is dry mouth.[12] Other relevant AEs include constipation, increases in heart rate[13] and impairments of central nervous system functions. Among the latter, impaired cognition probably is the most important, but impaired sleep is also relevant.[14] Although the reported incidence of impaired cognition is low in most studies, this probably represents an underestimation, because most studies of muscarinic antagonists were not designed to systematically capture such events and/or were underpowered for meaningful results. Furthermore, many medications unrelated to OAB, but potentially present in such patients as comedications, also have antimuscarinic effects. These include anti-allergic, anti-emetic, obstructive airway and gastrointestinal drugs, as well as those targeting central nervous disease, such as anti-Parkinson and psychopharmacological medications. Therefore, the full impact of muscarinic antagonists on central nervous function can only be appreciated when the total antimuscarinic load is considered.[15]

The tolerability of mirabegron has been comparable to that of placebo in phase II and phase III studies;[16] it showed less dry mouth than tolterodine in a large actively controlled phase III study.[17] Although medically relevant changes in cardiovascular parameters were typically not observed in controlled studies, spontaneous post-marketing authorization AE reporting showed a risk for blood pressure elevations leading to hypertensive crisis, and cerebrovascular and cardiac events in some patients; this has led to a corresponding warning in the prescribing information, and a new contraindication for use in stage 2 hypertensive patients.[18] The mechanism behind the cardiovascular AE in some patients is not fully understood, but might relate to indirect sympathomimetic effects of mirabegron leading to the release of endogenous noradrenaline in the heart.[19] Data on other β_3-adrenoceptor agonists are currently too sparse to allow robust conclusions as to whether the observed cardiovascular AE of mirabegron are specific for this compound or extend to the entire drug class.

OnabotulinumtoxinA is an injectable treatment for OAB symptoms in patients where oral medication is insufficiently effective. Its main AEs include urinary retention and urinary tract infection.[20] Phosphodiesterase type 5 inhibitors, including sildenafil, tadalafil and vardenafil, have shown efficacy in the treatment of OAB symptoms, but none of them has received global regulatory approval for this indication.[21]

The above data show a medical need for improved tolerability of currently approved medications that can be used to treat OAB patients. However, it is questionable whether major improvements in tolerability can be achieved within these drug classes.

Defining the medical need: Efficacy

Muscarinic receptor antagonists as a class have proven effective in the treatment of OAB.[12] Although their effect relative to placebo was statistically significant in most adequately powered, randomized, controlled trials, the effect size typically was only moderate according to meta-analysis; for instance, the mean reduction in daily incontinence episodes and voids relative to placebo was <1 and <1.2, respectively, in most cases.[12] In contrast, a patient does not care whether the improvement of symptoms is at least partly due to active treatment. Accordingly, efficacy has been much greater in non-interventional studies (Table 1). The most likely differences between efficacy in placebo-controlled and non-interventional studies include the somewhat artificial setting of a clinical trial and the presence of a placebo run-in period before the start of active treatment, which might already have caused some improvement of symptoms. Almost all reported studies have focused on absolute or percentage changes of OAB symptoms with treatment (for examples from non-interventional studies, Table 1), but this information might not be informative to individual patients. A recent analysis based on two non-interventional studies with propiverine did not focus on mean symptom improvements, but rather on percentage of patients becoming free of a given symptom on treatment: after 12 weeks of treatment, 43–48% reached less than eight number of voids, 38–52% became free of incontinence, 18–22% free of urgency and 8–14% free of nocturia.[22] Thus, although many patients experienced at least some improvement, approximately half became symptom-free for frequency and incontinence, but only a minority became free of urgency or nocturia. The latter is not surprising, because nocturia is multifactorial, and muscarinic antagonists were not effective beyond the placebo effect in most controlled trials.[23] Poor efficacy against nocturia is relevant, because this is one of the OAB symptoms with the greatest impact on quality of life.[7,8]

At the conceptional level, limited efficacy of muscarinic antagonists is not surprising for two reasons. First, they are dosed in a way to reduce urgency, but to not inhibit voiding contractions of the detrusor. Second, by virtue of their mechanism of action, muscarinic agonists can only inhibit bladder effects of the endogenous agonist acetylcholine, regardless of whether release is from cholinergic nerves or non-neuronally from other cell types, such as urothelium. Although acetylcholine is the predominant transmitter of bladder contractions in healthy humans, other mediators, such as adenosine triphosphate and bradykinin, can become relevant in

Table 1 Efficacy of various OAB medications in real-life practice

Drug	*n*	Urgency	Incontinence	Frequency	Nocturia	Reference
Darifenacin†	3766	−45%	−38%	−35%	−45%	55
Propiverine	1849	−68%	−85%	−40%	−60%	56
Propiverine	1335	−71%	−82%	−41%	−59%	57
Propiverine	745	−65%	−70%	−36%	−48%	57
Solifenacin†	4450	−58%	−53%	−41%	−54%	58
Tolterodine	2250	−75%	−75%	−38%	NR	59
Tolterodine†‡	3824	−80%	−79%	−46%	−59%	60
Mirabegron	774	−52%	−53%	−34%	−49%	32

Data are from non-interventional studies carried out in Germany and shown as percentage reductions from baseline. †Recalculated from the reported mean before and after values. ‡A 9-month study (all others were 12–14 weeks of duration).

pathophysiological settings;[24] based on its mechanism of action, a muscarinic antagonist cannot inhibit the effects of these other mediators.

Although muscarinic receptor antagonists as a class have proven to be effective in the treatment of OAB, the same is not necessarily true for β_3-adrenoceptor agonists; mirabegron has consistently been found to be effective as compared with placebo across many studies.[16] In contrast, ritobegron failed to meet its primary end-point in the only completed phase III study.[25] Vibegron was effective in a phase III study in Japan.[26] Solabegron was effective in phase II studies,[27] but no phase III studies have been reported yet. Although mirabegron might be effective in some patients showing an insufficient response to a muscarinic antagonist, the efficacy of mirabegron across the overall group of OAB patients is comparable to that of muscarinic antagonists.[28] This finding has been surprising, because β_3-adrenoceptor agonists, in contrast to muscarinic antagonists, work not only against endogenously released acetylcholine, but also against contraction caused by other mediators.[29,30] One explanation for this might be the potential of agonists to cause desensitization. Although β_3-adrenoceptors were originally believed to be resistant to agonist-induced desensitization, it is now clear that these receptors at least in some tissues and cell types can undergo desensitization;[31] whether this also applies to the human bladder *in vivo* remains unclear. Similar to muscarinic antagonists, the efficacy of mirabegron relative to placebo was only moderate in controlled studies,[16] but considerably larger in a non-interventional study.[32]

Based on their different routes of administration and approved indications, randomized comparative trials between onabotulinumtoxinA and oral medications have not been reported. Randomized studies have shown effects in OAB patients that had experienced an insufficient therapeutic response to muscarinic antagonists, but the difference relative to placebo was moderate in most studies.[20] The placebo-controlled data for phosphodiesterase type 5 inhibitors in OAB patients are too limited to draw robust conclusions, but their efficacy appears to be similar to that of muscarinic antagonist or β_3-adrenoceptor agonists.[21]

Although there is a need for improved tolerability, these data showed that the largest unmet medical need in the treatment of OAB patients is probably related to efficacy. However, it is questionable whether major improvements in efficacy can be achieved within the existent drug classes.

Hurdles to drug development in OAB

Various novel targets have been proposed for the future treatment of OAB (Table 2). Some of them were proposed a long time ago, and either were not pursued further despite promising efficacy and safety data in phase II studies,[33] failed in clinical studies for efficacy[34] or tolerability reasons,[35] or have not been tested clinically. These include modulators of various types of K^+ channels,[34,35] rho kinase,[36] neurokinin receptors[37] and nitric oxide synthase/guanylyl cyclase.[38] More recently proposed targets include P2X3 receptors,[39] various members of the transient receptor potential family including TRPV1, TRPV4, TRPA1, TRPM4 and TRPM8,[40] and components of the endocannabinoid system, such as fatty acid amide hydrolase.[41] Furthermore, accumulating evidence from animal and patient studies points to a role of atherosclerosis as a predisposing or even causative factor in the development of OAB.[42,43] However, these also have not proceeded to clinical trials. Apparently, ligands for none of these potential targets appear to be in clinical development by major pharmaceutical companies. If an unmet medical need exists in OAB, particularly for more efficacious drugs, the question arises why there is limited interest for commercial drug development in this space. This might have both scientific and commercial reasons, and the two could be intertwined.

When considering the reasons for the limited efficacy of existing drug classes, the first question arising is whether we might not have identified the best drug class yet. Given that OAB is typically diagnosed considerably after the onset of symptoms, this implies the assumption that the pathophysiology of the condition is largely reversible. Although this has not been tested thoroughly in humans, animal models – for instance, in streptozotocin-induced diabetes[44] and in bladder outlet obstruction[45] – suggest that removal of the primary cause of bladder dysfunction largely restores normal morphology and function. The second major assumption is that there might be a master switch that causes OAB, which can restore normal storage of urine when it is reversed. Although the above examples of experimental diabetes and bladder outlet obstruction indicate that a single cause might explain

Table 2 Proposed targets for future treatments of OAB

Target	Comment	Reference
Proposed in the past and no longer pursued		
K^+ channel modulators	Ineffective at tolerated doses or poor tolerability	34,35
Rho kinase	Inhibitors approved for other indications in some countries, but not for OAB	36
Neurokinin receptors	e.g. NK1 receptor	37
Nitric oxide synthase/guanylyl cyclase		38
Currently under academic investigation		
Purinergic receptors	e.g. P2X3	39
Transient receptor potential channels	e.g. TRPV1, TRPV4, TRPA1, TRPM4 and TRPM8	40
Endocannabinoid system	e.g. Fatty acid amide hydrolase	41

detrusor overactivity in some settings, it is doubtful that a single master switch exists for OAB in general.

The original definition of OAB by the ICS characterizes OAB as a classification for initial treatment decisions, not a disease entity.[1] Thus, it is likely that other than neurogenic voiding dysfunction, a range of causes can lead to idiopathic OAB in patients. For instance, detrusor overactivity and non-voiding contractions are the closest proxy parameter of urgency in animal models.[46] They can be observed in a variety of animal models, including spontaneously hypertensive rats,[47] rats with renovascular hypertension[48] or congestive heart failure,[49] mice with sickle cell disease,[50] and various rodent models of type 1 and 2 diabetes.[51] If patients presenting with OAB represent a group of underlying pathologies, it is unlikely that a single master switch exists. Accordingly, it is also unlikely that a single drug target is promising to make the vast majority of patients with OAB symptom-free. A hypothetical example might clarify this idea: If it is assumed that 60% of OAB patients have underlying pathophysiology A, which is fully responsive to treatment X, 30% have pathophysiology B fully responsive to treatment Y and 10% have pathophysiology C fully responsive to treatment Z, it appears that drugs X, Y and Z can only make 60%, 30% and 10% of patients symptom-free. Of note, it is already an over-optimistic assumption that one drug can make even a group of patients fully symptom-free. If clinical studies are carried out in a group of unselected OAB patients, drugs X, Y and Z will reduce symptoms in the overall group by 60%, 30% and 10% respectively – despite being 100% effective in the respective subgroup A, B and C. Although a 60% reduction is in line with the current standard of care at least for incontinence and frequency (Table 1), a 30% reduction in group B would not look promising, and a 10% reduction in group C could probably not even be discriminated from placebo.

At the commercial level, muscarinic receptor antagonists have largely become or soon will be generics, which are or will be available cheaply. The same will apply to mirabegron a few years later. To be considered cost-effective by Healthcare Technology Assessment bodies, such as National Institute for Health and Care Excellence in the UK, and thereby likely to be reimbursable at a branded price, any new OAB medication would need to be considerably more effective than generic solifenacin or mirabegron. This is not a realistic scenario for the broad group of OAB patients. If at all, novel drugs have a chance to be considerably more effective than muscarinic agonists or β_3-adrenoceptor agonists in subsets of patients that show a specific pathology.

Future research needs

Novel classes of OAB medications are unlikely to become approved medicines without the involvement of the pharmaceutical industry. Their current interest in developing new treatment options in this disease area is limited, because it is unlikely that any new drug class with acceptable tolerability will show major improvements in efficacy against all four key symptoms (urgency, urge incontinence, frequency and nocturia) in the broad group of OAB patients. Theoretically, there are two, not mutually exclusive options to address this. First, it is possible to focus on one symptom rather than the overall symptomatology of OAB. Second, it is possible to focus on a subgroup of OAB patients. The potential of this approach is shown by the vasopressin receptor analog, desmopressin, in reducing nocturia in patients with nocturnal polyuria.[52] In contrast, phosphodiesterase type 5 inhibitors,[21] and the substance P and calcitonin gene-related peptide release inhibitor, cizolirtine,[33] were found to be effective and safe in phase II clinical studies, but not pursued further; a specific response subset of patients has not been identified for any of them. Thus, reawakening an interest of major pharmaceutical companies in OAB might only occur when academic research identifies not only potential therapeutic targets, but also biomarkers to identify patient populations in which responsiveness to addressing these targets is markedly enriched, and translational animals models for such pathophysiology-defined subsets (Table 3).[39–41] An example of this could be nerve growth factor,[53] but the evidence for this or

Table 3 Key priorities for future OAB research

Identify subsets of OAB patients based on specific pathophysiology
Identify/develop translational animal models for such subsets
Identify biomarkers allowing selective inclusion of subsets into clinical studies

other urinary markers at present is insufficiently robust to identify patient populations in which novel treatments might have greater efficacy than existing treatments.[54]

Conclusions

The tolerability of existing treatment options for OAB is largely good. Although there is room for some improvement, such improvement is unlikely to be achieved within the existing drug classes in clinical use. The major unmet medical need in OAB relates to efficacy, particularly the symptoms of urgency and nocturia. Addressing those needs will require identifying subpopulations of OAB patients in which a specific, pharmacologically addressable factor plays a major pathophysiological role, as well as biomarkers characterizing those subpopulations. Only progress in academic research in this area is likely to renew interest in OAB drug development in the pharmaceutical industry.

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Conflict of interest

In the field of OAB, the author is or has been a consultant and/or lecturer for the following companies in the past 5 years: Apogepha, Astellas, Dr. Willmar Schwabe, Ferring and Velicept. He is a shareholder of Velicept, and has been an employee of Boehringer Ingelheim (unrelated to the urinary bladder) from 2011 to 2016.

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