Chapter 13
Future Considerations in Overactive Bladder Pharmacotherapy

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Background

The latest approved treatments of lower urinary tract syndrome (LUTS)/overactive bladder (OAB)—mirabegron, tadalafil, and botulinum toxin—are, together with antimuscarinics and α-adrenoceptor (AR) blockers, currently the most widely used treatments for both neurogenic and non-neurogenic LUTS/OAB [1]. Still, as monotherapies they are not effective in all patients, and new alternatives are continuously being explored. Even if much nonclinical and clinical research is ongoing, there seem to be few new principles in the pipeline. What can be expected in the future seems to be introduction of new additions to existing drug classes and combinations of existing options. However, new pharmacological principles, based on factors involved in OAB pathophysiology [1–6], may be developed. This review discusses what is currently ongoing in drug treatment of OAB/LUTS but also speculates, on the basis of promising preclinical and clinical data, what drugs can be expected to be introduced clinically within the next few years.

Drugs in the Pipeline

Antimuscarinics

Despite many different antimuscarinics being available and recommended for clinical use [1], there is still an interest in new developments [2]. Tarafenacin a novel potent antimuscarinic agent highly selective for M_3 over M_2 receptors [7], was

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reported to have functional selectivity for the bladder over atrial tissues in the order of 200-fold in a mouse model. This may be of interest from a cardiac safety point of view. Song et al. [8] performed a multicenter, randomized controlled phase 2b trial on 235 OAB patients and showed that after 4 weeks tarafenacin at doses of 0.2 and 0.4 mg was superior to placebo in reducing the number of micturitions per day (primary endpoint). The drug showed a good safety profile, with very few cases of constipation. This may be surprising considering the profile of the highly M_3 receptor-selective darifenacin, which has constipation as a common adverse effect [1]. However, the most common side effect of tarafenacin was dry mouth, which at a dose of 0.4 mg occurred in 52 out of 76 randomized patients. It is therefore unlikely that this drug, even if proven efficacious in future studies, will offer any advantages over existing options [1, 9, 10]. OAB is a filling disorder, and even if it is well established that M_3 receptors are involved in detrusor muscle contraction, it is not necessarily by this mechanism that the beneficial effects on OAB symptoms are exerted [11].

To specifically reduce the adverse effect of tolterodine-induced dry mouth, THVD-201 (Tolenix™, twice-daily formulation) and THVD-202 (once-daily formulation) were designed. Both drugs are a combination of the muscarinic antagonist, tolterodine, with modified-release formulations of the muscarinic receptor agonist, pilocarpine, as a salivary stimulant. THVD-202 is advancing into phase 3 studies (Clinicaltrials.gov). The combination of tolterodine and pilocarpine has demonstrated efficacy comparable to twice-daily tolterodine; however, the combination showed statistically significant and clinically meaningful improvements in saliva production and dry mouth, as compared to the active-control tolterodine [12]. It is possible, but has to be demonstrated in further trials, that this advantage over tolterodine alone will be sufficient to motivate marketing of the drug.

β_3-Adrenoceptor Agonists

β_3-adrenoceptor (AR) agonists have generally been considered to improve OAB symptoms by relaxing the detrusor muscle, inhibiting spontaneous contractile activity in the detrusor, and reducing bladder afferent activity [13–15]. For example, Aizawa et al. [16] showed that single-unit afferent activities (SAAs) of both Aδ-fibers and C-fibers in response to bladder filling significantly dose-dependently decreased after mirabegron administration, the effect being more conspicuous for Aδ-fibers. During isovolumetric bladder conditions, the mean bladder pressure and the number of microcontractions decreased after mirabegron administration, whereas these parameters did not change with oxybutynin administration. However, recent evidence suggests that in addition to a direct effect on the smooth muscle, activation of prejunctional β_3-AR may result in downregulation of ACh released from cholinergic terminals, thereby exerting an additional inhibitory control of parasympathetic activity [17–20].

In addition to the only marketed β_3-AR agonist, mirabegron, there are reports on other β_3-AR agonists in development, e.g., ritobegron and solabegron. A phase 3 randomized, double-blind, placebo-controlled study of ritobegron in patients with OAB has been initiated and completed, but the results of this study have not been published, and a press release by the pharmaceutical company stated that preliminary analysis indicated that the study's primary efficacy endpoint was not met.

Efficacy and safety of solabegron (GW427353) have been recently reported in a phase 2 multicenter, randomized, proof-of-concept trial in 258 women with wet OAB [21]. Solabegron was well tolerated and at the dose of 125 mg produced a statistically significant difference in percent change from baseline to week 8 in incontinence episodes over 24 h (primary outcome) when compared with placebo ($p = 0.025$) [21]. Further studies are awaited.

There have been many early investigations of other novel and putative β_3-AR agonists for management of OAB, including CL-316243, TRK-380, AJ-9677, and BRL-37344 [22]. These agents have been reported as being in development, but no clinical data have been published. Thus, even if there are several β_3-AR agonists in the pipeline, it is uncertain which, if any, will come to market and be available for the management of OAB. A new agent, vibegron [23, 24], is a potent, selective full β_3-AR agonist across species, and it dose-dependently increased bladder capacity, decreased micturition pressure, and increased bladder compliance in rhesus monkeys [24]. The relaxation effect of vibegron was enhanced when combined with muscarinic receptor antagonists but differentially influenced by muscarinic receptor subtype selectivity. The effect was greater when vibegron was co-administered with tolterodine (nonselective antagonist), compared with co-administration with darifenacin (selective M3 receptor antagonist). Furthermore, a synergistic effect for bladder strip relaxation was observed with the combination of a β_3-AR agonist and tolterodine in contrast to simple additivity with darifenacin. The authors speculated that combination of β_3-AR agonists with non-receptor-selective antimuscarinics has the potential to redefine the standard of care for the pharmacological treatment of OAB. Yoshida et al. [25] performed a randomized, double-blind, placebo-controlled phase 3 study on 1232 patients, who were assigned to one of four 12-week treatment groups: vibegron (50 mg or 100 mg once daily), placebo, or imidafenacin (0.1 mg twice daily). The primary endpoint was change in the mean number of micturitions per day at week 12 from baseline, and secondary endpoints were changes from baselines in OAB symptom variables (daily episodes of urgency, urgency incontinence, incontinence, and nocturia and voided volume per micturition). The proportions of patients with normalization of micturition and resolution of urgency, urgency incontinence, and incontinence were significantly greater with vibegron than with placebo. Vibegron also significantly improved the quality of life (QoL), with high patient satisfaction. Incidences of drug-related adverse events with vibegron 50 mg and 100 mg were 7.6% and 5.4%, similar to placebo (5.1%) and less than with imidafenacin (10.3%). Since the duration of the study was just 12 weeks, a long-term study is needed to establish efficacy compared with other alternatives.

Even if several β_3-AR agonists have been reported as being in development, no clinical data have been published, except for solabegron and vibegron. Whether any of these agents will come to market and be available for the management of OAB remains to be established.

Botulinum Toxin A

Botulinum toxin A (BoNT-A) is a high-molecular-weight (150 kDa) neurotoxin that may not be able to gain access to the afferent nerves located immediately below the urothelium without needle injection. To improve intravesical treatment with botulinum toxins, novel therapeutic uses and formulations have been reported [26, 27]. New formulations seek to improve bioavailability at the site of action while decreasing adverse events, and several new approaches have been tested in animal models and, to some extent, in patients (e.g., increasing urothelial permeability with DMSO or protamine sulfate pretreatment, iontophoresis, low-energy shock waves, thermosensitive hydrogels and liposomes) [28].

One of the most promising approaches seems to be liposome-based [29]. Liposomes are vesicles composed of concentric phospholipid bilayers separated by aqueous compartments. Because they adsorb onto cell surfaces and fuse with cells, they are being used as vehicles for drug delivery and gene therapy. In order to have the therapeutic effects of BoNT-A on the urothelial afferent nerves without impairing detrusor contractility and to improve patients' acceptability of the treatment by overcoming the adverse effects of the cystoscope-guided needle injections, studies are ongoing exploring if liquid liposomes may deliver BoNT-A (liposome-encapsulated BoNT-A or lipotoxin) through the urothelium to the suburothelial space. In a rat model, intravesical lipotoxin cleaved SNAP-25, inhibited calcitonin gene-related peptide release from afferent nerve terminals, and blocked acetic acid-induced DO [30]. Kuo et al. [31] performed a study on 24 patients with OAB, who were nonresponsive to >3 months of therapy with traditional antimuscarinic agents. They were randomized 1:1 to receive intravesical instillation of lipotoxin or saline solution. In the lipotoxin group, 3-day urinary frequency and urgency episodes were significantly decreased at 1 month, whereas no change was reported in the control group. Importantly, no urinary tract infections or large post-void residual volumes were reported. However, only 50% of the 12 patients initially treated with lipotoxin showed a response, and only 4 had a maintained response at 3 months. Furthermore, of 12 non-responders who were subsequently treated or retreated with lipotoxin (6 from each cohort), only 1 showed a response at 3 months. Moreover, no change in urgency incontinence was found in either group, although the median baseline frequency of incontinence episodes was only 0.5 events in the lipotoxin cohort.

Chuang et al. [32] performed a prospective, multicenter, double-blind, randomized trial on 62 OAB patients inadequately managed with antimuscarinics. At 4 weeks after treatment, lipo-botulinum toxin instillation was associated with a

statistically significant decrease in micturition events per 3 days and with a statistically significant decrease in urinary urgency events with respect to baseline, but not placebo. There were no statistically significant decrease in urgency severity scores compared to placebo and no increased risk of urinary retention. However, the effects of lipo-botulinum toxin on urinary urgency incontinence were inconclusive.

The combination of genetic engineering and molecular biology techniques has enabled the possibility of developing recombinant biotherapeutic proteins incorporating the light chain (endopeptidase) and the HN translocation domain of BoNT, combined with a binding domain that binds to a specific target represented by a cell surface receptor [33]. A novel-targeted BoNT-A has already completed phase 1 studies and entered proof-of-concept phase 2 studies in postherpetic neuralgia and idiopathic OAB.

Despite mildly encouraging preclinical results, significant technology refinement and clinical testing will be required in order to define the safety and efficacy profile of new BoNT formulations and engineered variants.

Combinations

Treatment of disorders with multifactorial pathophysiology with combinations of drugs seems to be a logical approach—not only can more than one underlying mechanism be influenced (if the drugs have different mechanisms of action), but also the doses of drugs can be kept low making it possible to reduce the number of side effects. LUTS/OAB in both men and women is multifactorial, and there are many examples that combined treatment can be superior to monotherapy [1]. However, which combination should be given to which patients? How much can be gained? Is there really a cost/benefit in combining currently approved drugs with respect to efficacy and side effects, or is the field open for introduction of "minor players," i.e., drugs with some efficacy, but not efficacious enough to be given as monotherapy? A variety of such combinations have been evaluated. Several randomized, controlled trials demonstrated that the combination treatment of antimuscarinic drugs and α_1-AR antagonists was more effective at reducing LUTS than α_1-AR antagonists alone in men with OAB and coexisting BPO [1, 33–42].

A large-scale, multicenter, randomized, double-blind, placebo-controlled trial (the TIMES study) demonstrated the efficacy and safety of tolterodine ER alone, tamsulosin alone, and the combination of both in 879 men with OAB and BPO [33]. In the primary efficacy analysis, 172 men (80%) receiving tolterodine ER plus tamsulosin reported treatment benefits by week 12. In the secondary efficacy analysis, patients receiving tolterodine ER plus tamsulosin compared with placebo experienced small but significant reductions in urgency incontinence, urgency episodes, daytime frequency, and nocturia. However, there were no significant differences between tamsulosin monotherapy and placebo for any diary variables at week 12. Patients receiving tolterodine ER plus tamsulosin demonstrated significant improvements in total IPSS.

The efficacy and safety of solifenacin in combination with tamsulosin were assessed in several large-scale RCTs, including the VICTOR [35], SATURN [36], and NEPTUNE [37] trials. Based on these studies, it may be concluded that the combination of antimuscarinics and α_1-AR antagonists may be the most effective therapy in men with OAB symptoms in the presence of BPO.

Abrams et al. [38] reported results of a phase 2 trial (Symphony) of combination treatment with mirabegron and solifenacin in 1306 patients with OAB. The primary endpoint was change from baseline to end of treatment in mean volume voided per micturition (MVV). The drug combinations solifenacin 5 mg plus mirabegron 50 mg, solifenacin 10 mg plus mirabegron 25 mg, and solifenacin 10 mg plus mirabegron 50 mg demonstrated significant improvements compared to both solifenacin 5 mg and placebo. No severe adverse events were reported, and treatment was generally well tolerated. Similar results were obtained by Yamaguchi et al. [37] in a multicenter, open-label, phase 4 study (MILAI study) to assess the safety and efficacy of mirabegron in combination with solifenacin in OAB patients who were being treated with solifenacin 2.5 mg or 5 mg once daily for at least 4 weeks [37] and by Drake et al. [39–41] in a phase 3b trial (BESIDE) in incontinent OAB patients. Xu et al. [42] performing a meta-analysis to evaluate the efficacy and safety of mirabegron add-on therapy to solifenacin for patients with OAB concluded that mirabegron therapy as an add-on to solifenacin provides a satisfactory therapeutic effect for OAB symptoms with a low occurrence of side effects.

Although antimuscarinic agents are the first choice of treatment for patients with OAB symptoms, these drugs do not always lead to the desired effect of detrusor stability and continence. A combined antimuscarinic regimen was evaluated as a noninvasive alternative by Amend et al. [43] for patients who had neurogenic bladder dysfunction with incontinence, reduced bladder capacity, and increased intravesical pressure. They added secondary antimuscarinics to the existing double-dose antimuscarinics for patients who previously demonstrated unsatisfactory outcomes with double-dose antimuscarinic monotherapy. The study drugs were tolterodine, oxybutynin, and trospium. After a 4-week combined regimen, incontinence episodes decreased, and reflex volume, maximal bladder capacity, and detrusor compliance increased. Side effects were comparable to those seen with normal-dose antimuscarinics. Kosilov et al. [44–46] evaluated the effectiveness of cyclic therapy of combined high-dose trospium and solifenacin depending on severity of OAB symptoms in elderly men and women. They found that this therapy of high-dose solifenacin and trospium in elderly patients with moderate or severe symptoms of OAB enabled patients to maintain a longer therapeutic effect with an acceptable level of side effects [44]. The effectiveness of combination therapy with two different antimuscarinics was also evaluated in patients with severe symptoms of OAB and BPH [46, 47]. Patients in the experimental group for 2 months received treatment with a daily combination of solifenacin 5 mg and trospium 5 mg simultaneous with tamsulosin 0.4 mg. Patients in the control group were treated only with tamsulosin. The authors concluded that combination of trospium and solifenacin in standard doses is an efficient and safe method for managing severe symptoms of OAB over the course of treatment with tamsulosin in patients with OAB/BPH [47].

However, in patients with OAB/BPH, the efficacy and side effects of combination therapy using different antimuscarinics should be further evaluated.

Based on available results, it may be concluded that combined regimens are logical and seem to be effective when monotherapy fails. However, combinations need further investigation to verify their efficacy and cost/benefit as noninvasive alternatives to third-line treatments.

Agents for Possible Future Development

As described above, animal studies and preclinical and clinical research involving modifications of existing options or directed at identifying novel pharmacological principles involved in LUTS/OAB pathophysiology are ongoing. This has been extensively discussed in several reviews [1–6]. Based on published information, the International Consultation on Incontinence (ICI) classified drugs in development depending on negative or positive proof-of-concept studies or as promising based on animal data (Table 13.1) [1]. Currently, the most promising targets seem to be purinergic receptors [48–51] and different members of the TRP channel family [52–55]. However, even if P2X3receptor antagonists have a good rationale and are currently being developed for treatment of nonbladder diseases, clinical experiences in bladder disorders have not yet been reported. Several TRP channels, including TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1, are expressed in the bladder and urethra and may act as sensors of stretch and/or chemical irritation. There seem to be several links between activation of these channels and LUTS/OAB, and the therapeutic potential for TRPV1 channel agonists (capsaicin, resiniferatoxin), which

Table 13.1 Current status of possible future drugs/targets [1]

Negative proof of concept
Potassium channel openers
Prostaglandin receptor antagonists
Positive proof of concept
Neurokinin receptor antagonists
Vitamin D3 receptor agonists
Monoamine reuptake inhibitors
Opioid receptor agonists
Cox inhibitors
Promising based on animal data
Rho-kinase inhibitors
Drugs acting on GABA receptors
Purinergic system—P2X3 receptor antagonists
Cannabinoid system—exocannabinoids, FAAH inhibitors
TRP channel family—TRP channel antagonists

FAAH fatty acid amide hydrolase, *TRP* transient receptor potential

inactivate the channel, has been convincingly demonstrated. Several TRP channel antagonists are in clinical development for nonbladder indications [55]. However, published clinical experiences in lower urinary tract (LUT) dysfunction are scarce, and the adverse effect of hyperthermia of the first-generation TRPV1 antagonists has delayed development. Nevertheless, TRP channels still may be most exciting targets for future LUT drugs.

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