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Drug therapy of overactive bladder - What is coming next?

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After the approval and introduction of mirabegron, tadalafil, and botulinum toxin A for treatment of lower urinary tract symptoms/overactive bladder, focus of interest has been on their place in therapy versus the previous gold standard, antimuscarinics. However, since these agents also have limitations there has been increasing interest in what is coming next – what is in the pipeline? Despite progress in our knowledge of different factors involved in both peripheral and central modulation of lower urinary tract dysfunction, there are few innovations in the pipe-line. Most developments concern modifications of existing principles (antimuscarinics, β_3-receptor agonists, botulinum toxin A). However, there are several new and old targets/drugs of potential interest for further development, such as the purinergic and cannabinoid systems and the different members of the transient receptor potential channel family. However, even if there seems to be good rationale for further development of these principles, further exploration of their involvement in lower urinary tract function/dysfunction is necessary.

Keywords: Cannabinoids; Purinergic receptors; Transient receptor potential channels

INTRODUCTION

The places in therapy for the three new drug principles recently approved for treatment of lower urinary tract symptoms/overactive bladder (LUTS/OAB), the β_3-adrenoceptor (AR) agonist, mirabegron, the phosphodiesterase 5-inhibitor tadalafil, and the blocker of afferent and efferent neutotransmission, botulinum toxin (BoNT), still have to be established [1-4]. Even if these agents compared to animuscarinics may have advantages, they are not effective in all patients, and alternatives are continuously being explored. There has been increasing interest in both old and new therapeutic principles and in what is currently in the pipeline. Much nonclinical and clinical research is ongoing, both involving modifications of existing options and directed at identifying novel pharmacological principles involved in LUTS/OAB pathophysiology, and this has been extensively discussed in several excellent reviews [4-8].

The aims of this review is to briefly comment on what is ongoing and then speculate on the future of some of the many targets and drugs theoretically attractive for development.

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OAB DRUGS IN THE PIPELINE

1. Antimuscarinics

Several antimuscarinics with different profiles are in development and have been reviewed previously [6]. These include tarafenacin which is a novel potent antimuscarinic agent highly selective for M_3 over M_2 receptors [9]. In a mouse model, the drug was reported to have functional selectivity for bladder over atrial tissues in the order of 200 folds, which may be of interest from a cardiac safety point of view. In a multicenter, randomized controlled 2b trial (235 patients), Song et al. [10] showed that tarafenacin at doses of 0.2 and 0.4 mg was superior to placebo after 4 weeks in reducing the number of micturitions per day (primary endpoint) and showed an good safety profile. Interestingly, there were very few cases of constipation. However, the most common side effect was dry mouth, which at a dose of 0.4 mg occurred in 52 out of 76 randomized patients. Considering this, it is hard to believe that this drug, even if proven efficacious in future studies, will offer any advantages over existing options. OAB, defined either based on symptoms (OAB syndrome) or urodynamically (detrusor overactivity, DO), 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 inhibition this contraction that the beneficial effects of antimuscarinics 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. Tolenix is advancing into phase III studies and 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 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.

Another antimuscarinic claimed to have a different profile is afacifenacin (SMP-986), which combines the dual pharmacological actions of nonselective muscarinic receptor antagonism and inhibition of bladder afferent pathways through Na+ channel blockade [6]. Theoretically, Na+ channel blockade would produce a local anesthetic effect that might increase the risk for cardiac side effects [13,14]. This would not be in favor of the drug. However, since no clinical studies have been published, no efficacy or saftety profile is available.

2. β_3-Adrenoceptor agonists

The approval and clinical success of mirabegron has focused interest on β_3-AR agonism and on how to modify and further improve this therapeutic principle. β_3-AR agonists have generally been considered to relieve OAB symptoms by relaxing detrusor muscle, inhibiting spontaneous contractile activity in the detrusor (*in vitro*: microcontractions; *in vivo*: nonvoiding contractions), and reducing bladder afferent activity [15-19]. *In vitro*, Biers et al. [15] demonstrated that the β_3-AR agonist, solabegron, concentration-dependently inhibited microcontractions in strips of human detrusor muscle, and *in vivo*, several investigators have shown that β_3-AR agonists can decrease nonvoiding contractions in the obstructed bladder [10]. Effects on afferent bladder activity was shown by e.g., Aizawa et al. [20] who demonstrated that single-unit afferent activities of both Aδ-fibers and C-fibers in response to bladder filling significantly and dose-dependently decreased after mirabegron administration, the effect being more conspicuous for Aδ-fibers. However, in a series of studies, Gillespie and colleagues [21-24] have questioned the accepted view on the mode and site of action of β_3-AR agonists, and suggested that effects on neither spontaneous microcontractions, nor on nonvoiding contractions in e.g., obstructed rats, can fully explain the effects of mirabegron. Supporting the view that other mechanisms than effects on detrusor muscle may contribute, recent evidence showed that activation of prejunctional β_3-AR may result in down-regulation of ACh released from cholinergic terminals thereby exerting an additional inhibitory control of parasympathetic activity [25,26].

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 [7,18]. Phases II and III randomised, double blind, placebo controlled studies of ritobegron in patients with OAB has been initiated and completed, but the results of this study have not been published and it seems that the primary efficacy endpoint of the studies was not met [7]. Since preclinical studies were promising, the findings that ritobegron was not clinically successful are somewhat surprising.

Efficacy and safety of solabegron (GW427353) have been reported in a phase II multicenter, randomized, proof-of-concept trial in 258 women with wet OAB [27]. 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 hours

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(primary outcome) when compared with placebo (p=0.025) [27]. 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 [28], aryloxypropanolamine [29], conformationally restricted acetanilides [30], TRK-380 [31], AJ-9677 [32], and BRL37344 [33]. These agents have been reported as being in development, but no clinical data have been published. Thus, even if there are a number of 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.

3. BoNT A – recent developments

To improve intravesical treatment with BoNTs, novel therapeutic uses and formulations have been reported [34-37]. New formulations seek to improve bioavailability at the site of action while decreasing adverse events.

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 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 [38]. Kuo et al. [36] 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 postvoid residuals volumes were reported. However, only 50% of the 12 patients initially treated with lipotoxin showed a response, and only four had a maintained response at 3 months. Furthermore, of 12 nonresponders who were subsequently treated, or retreated with lipotoxin (six from each cohort), only one showed a response at 3 months. Moreover, no change in urgency incontinence was found in either group, although the median baseline frequency was only 0.5 events in the lipotoxin cohort.

Intravesical lipotoxin is an interesting and promising principle, but it may have some limitations. The obvious question is whether BoNT will be transported into the bladder wall far enough to affect not only the afferent nerves in the suburothelium, but also the afferent and efferent nerves in the detrusor muscle. Intravesical liposome carried BoNT may have fewer adverse effects, but is this obtainable at the price of reduced efficacy (compared to bladder wall injection)?

Combination of genetic engineering and molecular biology techniques have enabled the possibility of developing recombinant biotherapeutic proteins incorporating the light chain (endopeptidase) and the H_N translocation domain of BoNT, combined with a binding domain that binds to a specific target represented by a cell surface receptor [34,37]. A novel targeted BoNT-A (AGN-214868; senrebotase) has already completed phase I studies and entered proof-of-concept phase II studies in postherpetic neuralgia and idiopathic OAB [39]. This is an exciting and promising principle, but the results of clinical studies have to be awaited. Thus, despite 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.

4. 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 are multifactorial, and there are many examples that combined treatment can be superior to monotherapy. However, which combination to which patient? 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? There are many reviews of combinations used to treat male LUTS, with and without OAB as a dominating symptom [40-42]. Combination of mirabegron and solifenacin has shown promising results in a phase 2 study of OAB parients [43], and further phase 3 studies are ongoing, possibly resulting in a fixed combination for clinical use within a reasonable time frame.

Even if drug+drug combinations are promising, combination of drugs with nonpharmacological neuromodulation, for

example percutaneous tibial nerve stimulation, may be an interesting alternative, and the many possibilities of combining therapies opens the door for personalized therapy of LUTS/OAB [44].

PROMISING FUTURE TARGETS?

There are many agents with theoretically interesting profiles that have been or still are considered as promising, but currently do not seem to be in active development or where development is slow (Table 1). For example, nerve growth factor (NGF) and other neurotrophins have been suggested to be an interesting target for treatment and a biomarker for diagnosis and evaluation of treatment outcome [45-47]. However, even if the effects of a humanized NGF antibody (tanezumab) in patients with interstitial cystitis seemed promising [48], adverse effects found in nonbladder studies stopped further development [49]. However, developments in other areas than LUT, e.g., pain seem to have been resumed [50].

Prostaglandin E2, acting via EP1 receptors, stimulates bladder contractile activity by sensitization of afferent nerves, and is increased in urine from patients with LUTS [51]. Despite promising results in animal experiments, a double-blind, placebo-controlled phase II study in OAB patients concluded that the role of an EP1 receptor antagonist in the management of OAB syndrome is minimal [52].

Rho-kinase inhibition is a theoretically interesting principle for inhibition of bladder overactivity [53], since up-regulation of the Rho-kinase pathway has been associated with bladder changes in diabetes, outflow obstruction, and idiopathic DO. The vitamin D3 agonist, elocalcitol, was shown to have an inhibitory effect on the RhoA/Rho kinase pathway [54,55], and showed some promising effects in female patients with OAB [56]. However, whether or not vitamin D3 receptor agonism (monotherapy or in combination) will be a useful alternative for the treatment of LUTS/OAB, requires further randomized controlled trials.

K^+ channel openers have shown great promise in pre-clinical experiments [57], but so far the K^-channel openers studied clinically- have yielded disappointing results [58]. Injection of naked" Maxi-K DNA directly into detrusor may be an interesting future possibility [59].

Even if not discussed in this review, it should be noted that drugs with a central mode of action, such as neurokinin receptor antagonists, tramadol, and duloxetine have positive proof of concept documented in randomized controlled trials [60]. Currently, most of these drugs cannot for various reasons be recommended for general use in the treatment of LUTS/OAB, but they illustrate that agents with a target in the central nervous system have a potential to be therapeutically useful.

Presently, the most promising targets seem to be the purinergic [61-64] and cannabinoid [65-67] systems, and different members of the transient receptor potential (TRP) channel family [68-73]. However, even if P2X3-receptor 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. Clinical studies with the use of exocannabinoids on LUTS are scarce and essentially restricted to multiple sclerosis patients, and the results have so far not been convincing. However, amplification of the activity of endocannabinoids by fatty acid amide hydrolase inhibitors, inhibiting their degradation, may be an attractive approach [67,74], but again clinical proof of concept is lacking. 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) has been convincingly demonstrated. However, so far the potential of any of the channel antagonists developed for nonbladder indications has not been explored clinically in lower urinary tract (LUT) dysfunction, 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. LUT dysfunction may not have been given the highest priority in TRP drug development, but research carried out for non-bladder diseases may be possible to apply also to LUT disorders.

Table 1. Drugs and targets of potential interest

Nerve growth factor – Inhibitor
Prostanoid receptors – Antagonists
Rho-kinase – Inhibitors
Vitamin D3 receptor – Agonists
K^+ channels – K^+ channel openers
Centrally acting drugs
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.

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CONCLUSIONS

Despite the limitations of current OAB treatments, which would be expected to stimulate the search for new alternatives, there are few innovations in the pipe-line, and most developments concern modifications of existing principles (antimuscarinics, β_3-receptor agonists, BoNT A). Several new and old targets/drugs of potential interest for further development can be identified, however, further exploration of their involvement in lower urinary tract function/dysfunction is necessary.

CONFLICTS OF INTEREST

Consultancy and Advisory Boards: Allergan, Astellas, Ferring. Except for that, the author has nothing to disclose.

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