Future therapies: Early trials and basic science

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Abstract

Pharmacotherapeutic options for overactive bladder (OAB) include antimuscarinics and the beta3-adrenoceptor agonist mirabegron. Research and development of novel therapeutic options for OAB continues to be an active field. This review summarizes recent research with the existing therapies as well as the most promising agents in development.

Current options for the pharmacologic management of overactive bladder (OAB) include antimuscarinic agents and the beta3-adrenoceptor (β3-AR) agonist mirabegron. These therapies can provide symptom relief for many patients with OAB, but there is still considerable room for refining and expanding the therapeutic armamentarium. This brief review summarizes the current status of recent and ongoing research with novel therapeutic approaches, as well as recent evidence on ways to better treat OAB symptoms using the agents we already have at our disposal.

Antimuscarinic therapy

There is one new molecule, imidafenacin, that has become available in certain parts of the world. It was designed to be selective to the M1 and M3 receptors, with the aim of reducing anticholinergic side effects.[1] While its efficacy and safety are well documented from randomized clinical trials,[1] there do not appear to be any obvious advantages over other antimuscarinics. Imidafenacin is not currently available in Canada (or the United States).

Another method that is being explored to reduce the burden of antimuscarinic-related adverse effects is the use of a muscarinic receptor agonist, pilocarpine, in a fixed-dose combination with an antimuscarinic, tolterodine. In a phase II study, this combination was shown to reduce the incidence of dry mouth by 60% compared to tolterodine alone, while achieving significant improvements of OAB and urge urinary incontinence symptoms relative to placebo.[2] Research is ongoing with this combination.

There has also been some interesting basic research completed that may help explain why antimuscarinic therapy fails to control symptoms in many patients. Evidence from an animal model has shown that chronic administration of antimuscarinic agents (oxybutynin or fesoterodine) leads to loss of muscarinic receptor efficiency and induces a shift from muscarinic to purinergic transmission.[3] Should this prove to be true in humans as well, the implication might be that it could be more beneficial to administer antimuscarinic therapy on an intermittent basis.

Combination therapy

β3-AR agonists exert their therapeutic effects through stimulation of adenylyl cyclase and activation of potassium K+ channels. The former leads to an increase in cyclic adenosine monophosphate and the latter to hyperpolarization, both of which result in relaxation. The beneficial effects of modulation of these pathways are: inhibition of spontaneous activity, increased bladder compliance (decreased bladder tone during filling), greater distension needed to activate the micturition reflex (increased bladder capacity), and decreased afferent activity, with no effect on voiding contraction (no risk for urinary retention).

These mechanisms are distinct from those of antimuscarinic therapies used to treat OAB. As such, the combination of these two types of medications is being investigated to determine whether concomitant use can result in increased efficacy with an acceptable profile of safety and tolerability. At the 2013 meeting of the American Urological Association (AUA), researchers working with animal models concluded that the "combination of antimuscarinics and β3-adrenoceptor agonists can result in increased efficacy and potency and supports the hypothesis that combining these compound classes in the clinic could have beneficial effects in treating urinary bladder dysfunction."[4]

Indeed, at the same congress, researchers presented the results of a phase II clinical study (the Symphony study) evaluating the combination of solifenacin and mirabegron in 1307 patients with OAB.[5] The subjects were randomized to receive one of six combinations: mirabegron 25 or 50 mg in combination with solifenacin 2.5, 5 or 10 mg; monotherapy with mirabegron or solifenacin (at each of the same doses studied in the combinations); or placebo. The study duration was 12 weeks. The primary efficacy variable was change in mean volume voided (MVV) per micturition; secondary variables included change in micturition frequency (MF) and

incontinence episode frequency per 24 hours. The investigators reported that mirabegron combination therapy with solifenacin (the latter at a dose of >5 mg) demonstrated greater efficacy than solifenacin 5 mg alone on MVV and MF.[5] The enhanced efficacy with the combination is of a magnitude that is probably similar to the enhanced efficacy one might expect from uptitrating the dose of the antimuscarinic. However, the combination is not associated with the adverse effects one would expect to encounter with higher doses of antimuscarinics. In this study, all six combinations appeared to be well-tolerated and there appeared to be no safety concern or significant increase in adverse effects with the combination treatment compared with either monotherapy.[5]

Investigational therapies with other mechanisms of action

There are a number of different therapeutic pathways being explored in preclinical studies that have potential utility for the treatment of OAB (Table 1). These include purinergic receptor antagonism, TRP channel antagonism, cannabinoid receptor agonism, melatonin modulation and apoptosis-inducing agents.

To date, the only agents that have made it from the laboratory into clinical trials for urinary tract symptoms are the apoptosis-inducing agents NX-1207 and PRX302, which are administered as intraprostatic injections for men with benign prostatic hyperplasia. NX-1207 has been associated with prostate volume reduction, as well as with short- and long-term symptomatic improvement in phase II studies,[6] and is currently being studied in phase III clinical trials.

In a phase IIb trial involving 92 patients with International Prostate Symptom Score (IPSS) scores of 15 or higher at baseline, treatment with PRX302 was associated with a 9-point reduction in IPSS and an increase of 3 mL per second in peak urine flow (both changes statistically significant).[7]

Conclusions

Research and development of pharmacotherapies for the treatment of urinary tract symptoms is an active and dynamic field. In addition to identifying and exploring a number of new treatment pathways, researchers are also continuing to expand the knowledge base about the way currently available therapies work alone and in combination. Whether or not any of the strategies currently being investigated end up supplanting antimuscarinic therapy as the standard first-line therapy remains to be seen.

Table 1. Future drugs and targets for OAB

- Nerve growth factor
- Purinergic receptors – antagonists
- TRP channels – antagonists
- Prostanoid receptors – antagonists
- Rho-kinase – inhibitors
- Vitamin D3 receptor – agonists
- K+ channels – K+ channel openers
- PDEs – PDE inhibitors
- Cannabinoid system
- Melatonin
- Apoptosis-inducing agents – NX-1207, PRX302
- Centrally acting drugs

OAB: overactive bladder; TRP: transient receptor potential; PDE: phosphodiesterase.

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