

# Drugs and future candidates

Karl-Erik Andersson, MD, PhD

Institute for Regenerative Medicine, Physiology & Pharmacology, Urology, Molecular Medicine, Wake Forest University School of Medicine, Winston-Salem, NC

Cite as: *Can Urol Assoc J* 2011;5(5Suppl2):S131-S133; DOI:10.5489/cuaj.11182

## Abstract

Antimuscarinic drugs are still first-line treatment for the symptoms of overactive bladder (OAB) and are associated with good initial response rates. Adverse effects and decreasing efficacy over the longer term do, however, limit their overall effectiveness. As such, alternatives to antimuscarinics are needed. The recognition of the functional contribution of the urothelium, the spontaneous myocyte activity during bladder filling, and the diversity of nerve transmitters involved in the symptoms of the OAB has sparked interest in pharmacologic manipulation of both peripheral and central pathophysiology. Some of the treatments currently under investigation are discussed in this review.

Antimuscarinic drugs are first-line treatment for the overactive bladder syndrome (OAB). Despite having good initial response rates, however, adverse effects and decreasing efficacy cause long-term compliance problems. It is therefore desirable that alternative treatment methods be developed and made available. This is currently a rich field of research, as many compounds with potential efficacy for the treatment of OAB are undergoing preclinical and clinical testing. In OAB, there are many potential pathophysiologic targets for intervention, and this is reflected by the broad variety of mechanisms amongst the agents in development. Broadly speaking, drugs for OAB are designed to target mucosal (urothelial) signaling, myocyte signaling or the central nervous system.

This brief review presents the potential treatment pathways, discusses whether or not they hold promise and briefly summarizes the key evidence gathered to date.

## Drugs targeting mucosal (urothelial) signalling

### NGF antibodies

Although some have speculated that nerve growth factor (NGF) might have utility as a biomarker or treatment path-

way for OAB,<sup>1,2</sup> this does not appear to be a promising avenue of investigation. Intuitively, since OAB is such a non-specific condition, the use of specific biomarkers does not appear to be appropriate. As a target for treatment, use of biologic antibodies to block this pathway is possible, but because NGF is involved in many physiologic processes, one would expect there to be many potential side effects.

### Acetylcholine: muscarinic receptor antagonists

All of the muscarinic receptors are found in the urothelium and suburothelium, with predominant expression of M<sub>2</sub>, M<sub>3</sub> receptors. The density of M<sub>2</sub> and M<sub>3</sub> receptors is increased in detrusor overactivity (DO)<sup>3</sup> and there is a correlation between suburothelial muscarinic receptor density and urgency scores.<sup>4</sup>

Oxybutynin, a non-selective muscarinic receptor antagonist, and darifenacin, selective for M<sub>3</sub> receptors, have been demonstrated to modulate bladder afferent activity, both in C fibres and Adelta fibres.<sup>5</sup> Such an effect may be an important mechanism of action for antimuscarinics.

### ATP: P2X3-receptor antagonists

In pathologic bladder dysfunctional states, like OAB, there is a known increase in ATP-mediated contractions. ATP is also involved in the generation of afferent impulses.<sup>6</sup> One method of blocking the ATP afferent pathway is through the use of P2X3 receptor antagonists. In animal models, this strategy appears to work very well.<sup>6</sup> Whether this translates effectively to humans remains to be seen.

### K<sup>+</sup> channels: KCNQ/Kv7 openers

Potassium channels in both the urothelium and the detrusor are potential targets for OAB therapy. Retigabine, a KCNQ/Kv7 opener that is approved for the treatment of epilepsy, has been associated with urinary retention and has been successfully evaluated in rats, with a marked decrease in urinary frequency.<sup>7</sup> Once again, clinical research will be

required to determine whether these benefits can be replicated in humans. At the present time, the manufacturers of this compound do not seem to be actively exploring this potential indication.

### Prostaglandin E2: EP1-receptor antagonists

Prostaglandins are known to be increased in pathologic bladder conditions, including OAB. Prostaglandin E2 works primarily through the EP-1 receptor, which is expressed in both the urothelium and the suburothelial cells.<sup>8</sup> This receptor was therefore investigated a potential target for the treatment of OAB. In a study in cynomolgus monkeys, the EP-1 receptor antagonist ONO-8539 was found to significantly increase bladder capacity without increasing residual volume.<sup>9</sup> However, when it was evaluated in a phase 2 clinical trial in OAB, the investigators concluded that it had minimal impact.<sup>10</sup>

### TRP-channel antagonists

Another potential target for OAB treatment is the transient receptor potential (TRP) channel superfamily, which has been demonstrated to be involved in nociception and mechanosensory transduction in various organ systems. Studies of the lower urinary tract have indicated that several TRP channels, including TRPV1, TRPV2, TRPV4, TRPM8 and TRPA1, are expressed in the bladder and may act as sensors of stretch and/or chemical irritation.<sup>11</sup> Animal studies have shown that inhibition of these pathways can be effective for the reduction of bladder activity.<sup>12,13</sup> However, the roles of these individual receptors for normal function and in pathologic states have not been established. There seem to be several links between activation of different members of the TRP superfamily and OAB, and further exploration of the involvement of these channels in lower urinary tract function and dysfunction may be rewarding.

## Drugs targeting myocyte signalling

### Acetylcholine: muscarinic receptor antagonists

Research has suggested that antimuscarinic drugs exert their therapeutic benefit through effects on afferent activity during the filling phase and that there is no proof that, at approved doses, they reduce the ability to empty the bladder.<sup>14</sup> There is a theoretical potential of these agents to have an effect on voiding contraction, but the concentration of antimuscarinic required to achieve this effect would be limited by the potential for side effects.

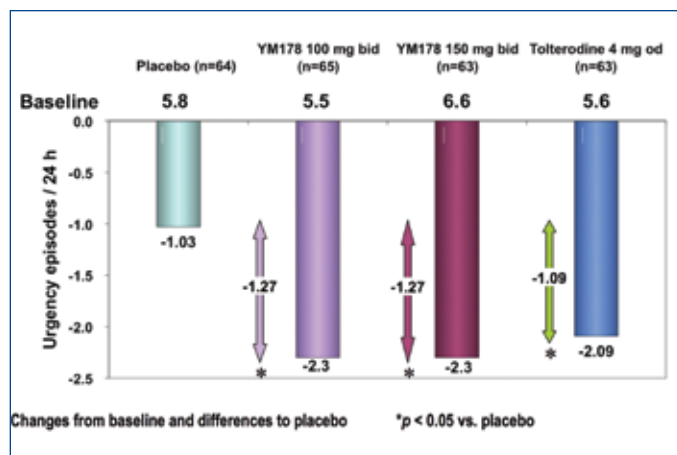


Fig. 1.  $\beta$ 3-Adrenoceptor (AR) agonist vs. placebo: reduction in urgency episodes/24-hr. Chapple et al.<sup>16</sup>

### $\beta$ 3-adrenoceptors (AR)

$\beta$ 3-AR agonists (e.g., mirabegron) are in Phase III trials after promising initial results.<sup>15-17</sup> The results of these studies indicate that this is indeed a useful treatment strategy for OAB. Figure 1 shows the results from one of the studies using mirabegron, which showed a significant reduction in urgency episodes for each of the doses evaluated.<sup>16</sup> These agents should be a welcome addition to the therapeutic armamentarium as a complementary strategy alongside the agents we already have at our disposal.

### Phosphodiesterases (PDE)

PDE type 5 inhibitors (sildenafil, tadalafil, vardenafil) have been shown to improve urinary symptom scores in men with erectile dysfunction and OAB, and this finding has been confirmed in several well-designed and conducted randomized controlled trials (RCTs).<sup>18-21</sup> However, their place in therapy has not been established, and whether or not these drugs are effective in females with OAB is not known.

### Rho kinase: rho kinase inhibitors

A theoretically interesting principle is Rho-kinase inhibition. Upregulation of this 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, and showed some promising effects in female patients with OAB.<sup>22</sup> However, whether or not vitamin D3 receptor agonism (monotherapy or in combination) will be a useful alternative for the treatment of OAB, requires further RCTs.

## Drugs targeting the central nervous system

Drugs with a central mode of action, such as GnRH antagonists,<sup>23</sup> tramadol<sup>24</sup> and duloxetine<sup>25</sup> have positive proof of concept documented in RCTs. Even if these drugs cannot currently be recommended for general use in the treatment of OAB, they illustrate that agents with a target in the central nervous system can be therapeutically useful.

## Combination therapy

Combinations might theoretically provide improved symptom relief. One such example is the combination of  $\alpha$ 1-AR antagonists with 5- $\alpha$  reductase inhibitors, which has proven to improve clinical outcomes and reduce the incidence of BPH and LUTS progression measured as symptom worsening, retention or progression to surgery. Other combinations have also been tested with varying degrees of success. Traditionally, muscarinic receptor antagonists have been contraindicated in patients with BPH due to fears of urinary retention. However, this dogma has been questioned and several studies have been performed in which  $\alpha$ 1-AR antagonists are combined with muscarinic receptor antagonists with promising results.

## Conclusions

Although antimuscarinic drugs remain the first-line treatment of the overactive bladder, and their favourable efficacy/tolerability safety ratio has been confirmed, new drugs are needed. Promising new alternatives are emerging and future controlled studies will decide their place in the therapeutic arsenal.

**Competing interests:** Dr. Andersson has received honoraria or speaker fees from Allergan, Astellas, Endo, Ferring, GlaxoSmithKline, Lilly, Novartis, ONO and Pfizer.

This paper has been peer-reviewed.

## References

- Kuo HC, Liu HT, Chancellor MB. Can urinary nerve growth factor be a biomarker for overactive bladder? *Rev Urol* 2010;12:e69-77.
- Liu H-T, Wang Y-S, Chancellor M, et al. Nerve growth factor levels in urine correlate with expression in urothelium but not suburothelium in the bladder tissues of overactive bladder syndrome [abstract]. *J Urol* 2010;183(4 Suppl):e644-5.
- Bschleipfer T, Schukowski K, Weidner W, et al. Expression and distribution of cholinergic receptors in the human urothelium. *Life Sci* 2007;80:2303-7.
- Mukerji G, Yianguo Y, Grogono J, et al. Localization of M2 and M3 muscarinic receptors in human bladder disorders and their clinical correlations. *J Urol* 2006;176:367-73.
- De Laet K, De Wachter S, Wyndaele JJ. Systemic oxybutynin decreases afferent activity of the pelvic nerve of the rat: new insights into the working mechanism of antimuscarinics. *NeuroUrol Urodyn* 2006;25:156-61.
- Ford AP, Cockayne DA. ATP and P2X purinoceptors in urinary tract disorders. In: KE. Andersson, MC Michel (editors). *Handbook of Experimental Pharmacology* 202; 2011:485-526.
- Iijima K, De Wachter S, Wyndaele JJ. Effects of the M3 receptor selective muscarinic antagonist darifenacin on bladder afferent activity of the rat pelvic nerve. *Eur Urol* 2007;52:842-7.
- Rahnama'i MS, van Koeveeringa GA, Essers PB, et al. Prostaglandin receptor EP1 and EP2 site in guinea pig bladder urothelium and lamina propria. *J Urol* 2010;183:1241-7.
- Okada H, Konemura T, Maruyama T. ONO-8539, a novel EP1 receptor antagonist, suppresses bladder hyperactivity via excessive production of prostaglandin E2 (PGE2) induced by intravesical instillation of ATP in urodynamic evaluation of cynomolgus monkeys [abstract]. *Eur Urol Suppl* 2010;9:72.
- Chapple C, Abrams P, Andersson KE, et al. A Randomised, Double-blind, Placebo-controlled Phase II Study to Investigate the Efficacy and Safety of the EP-1 Receptor Antagonist, ONO-8539, in Overactive Bladder Syndrome. Presented at the 2011 American Urological Association Annual Meeting [late breaking science forum].
- Streng T, Axelsson HE, Hedlund P, et al. Distribution and function of the hydrogen sulfide-sensitive TRPA1 ion channel in rat urinary bladder. *Eur Urol* 2008;53:391-9.
- Avelino A, Cruz C, Nagy I, et al. Vanilloid receptor 1 expression in the rat urinary tract. *Neuroscience* 2002;109:787-98.
- Charrua A, Cruz CD, Narayanan S, et al. GRC-6211, a new oral specific TRPV1 antagonist, decreases bladder overactivity and noxious bladder input in cystitis animal models. *J Urol* 2009;181:379-86.
- Finney SM, Andersson KE, Gillespie JJ, et al. Antimuscarinic drugs in detrusor overactivity and the overactive bladder syndrome: motor or sensory actions? *BJU Int* 2006;98:503-7.
- Aizawa N, Igawa Y, Nishizawa O, et al. Effects of CL316,243, a beta 3-adrenoceptor agonist, and intravesical prostaglandin E2 on the primary bladder afferent activity of the rat. *NeuroUrol Urodyn* 2010;29:771-6.
- Chapple C, Wyndaele JJ, Van Kerrebroeck P, et al. Dose-ranging study of once-daily mirabegron (YM178), a novel selective  $\beta$ 3-adrenoceptor agonist, in patients with overactive bladder (OAB) [abstract]. *Eur Urol Suppl* 2010;9:249.
- Biers SM, Reynard JM, Brading AF. The effects of a new selective beta3-adrenoceptor agonist (GW427353) on spontaneous activity and detrusor relaxation in human bladder. *BJU Int* 2006;98:1310-4.
- Sairam K, Kulinskaya E, McNicholas TA, et al. Sildenafil influences lower urinary tract symptoms. *BJU Int* 2002;90:836-9.
- McVary KT, Monnig W, Camps JL Jr, et al. Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. *J Urol* 2007;177:1071-7.
- McVary KT, Roehrborn CG, Kaminetsky JC, et al. Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol* 2007;177:1401-7.
- Stief CG, Porst H, Neuser D, et al. A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur Urol* 2008;53:1236-44.
- Morelli A, Vignozzi L, Filippi S, et al. BXL-628, a vitamin D receptor agonist effective in benign prostatic hyperplasia treatment, prevents RhoA activation and inhibits RhoA/Rho kinase signaling in rat and human bladder. *Prostate* 2007;67:234-47.
- Colli E. Gonadotropin-Releasing Hormone Antagonists: From Basic Science to the Clinic in Patients With Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms. *UroToday Int J* 2010;3(5); doi:10.3834/uij.1944-5784.2010.10.14
- Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of idiopathic detrusor overactivity: a double-blind, placebo-controlled, randomized study. *Br J Clin Pharmacol* 2006;61:456-63.
- Steers WD, Herschorn S, Kreder KJ, et al. Duloxetine compared with placebo for treating women with symptoms of overactive bladder. *BJU Int* 2007;100:337-45.

**Correspondence:** Dr. Karl-Erik Andersson, Institute for Regenerative Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157; keanders@wakehealth.edu