

## INCONTINENCE

# $\beta_3$ -adrenoceptor agonists synergize with antimuscarinics

Antimuscarinics have been the standard-of-care pharmacological approach for the noninvasive management of patients with a range of storage lower urinary tract symptoms (LUTS) for several decades. However, despite these agents being effective in most patients, the adverse event profile often precludes long-term use.

In 2012, the FDA approved the  $\beta_3$ -adrenoceptor agonist mirabegron for the treatment of overactive bladder syndrome. Treatment with this agent results in fewer, and better-tolerated adverse events than treatment with antimuscarinics. However, some urologists remain sceptical about the efficacy of mirabegron.

Subsequent clinical trials, such as the BESIDE study, revealed that patients treated with a 5 mg dose of the antimuscarinic solifenacin plus 50 mg mirabegron had similar efficacy outcomes compared with those treated with 10 mg solifenacin alone, with substantially fewer incidences of dry mouth, one of the most bothersome side effects of antimuscarinics. Despite compelling clinical evidence for use of this combination therapy, an important physiological question remains: is the apparent effectiveness of these agents when administered in combination the result of a synergistic effect? Data from two recently published studies serve to address this question using experimentally induced spinal cord injury (SCI) or cold stress to induce bladder dysfunction in rats.

“the combination of antimuscarinics with  $\beta_3$ -adrenoceptor agonists is a rational approach”

In the SCI model, researchers investigated the effects of oxybutinin (a widely used antimuscarinic agent), mirabegron or the combination of these two agents. Researchers found no significant changes in a range of urodynamic parameters, including intercontraction interval, time to first nonvoiding contraction, non-voiding contraction integral, bladder compliance or voiding efficiency in rats that received either oxybutinin or mirabegron, compared with controls. However, in rats treated with a combination of these two agents, at concentrations that were largely ineffective as monotherapies, statistically significant improvements in all of these parameters were observed, strongly suggesting an improved level of continence.

Similarly, in spontaneously hypertensive rats exposed to cold stress, this stimulus resulted in detrusor overactivity as indicated by increased basal pressure, a decrease in voiding interval and decreased bladder capacity. These parameters were, again, largely unaffected by solifenacin or mirabegron alone; however, rats that received the combination of these two agents had statistically significant improvements in the majority of these parameters. In addition to these significant improvements in bladder function, significant improvements in bladder elastin concentrations were observed in SCI rats treated with oxybutinin alone, or with combination therapy, suggesting



a bladder-preserving effect of oxybutinin, but not mirabegron.

Taken together, these findings, from two distinctly different models of bladder dysfunction, indicate a synergistic effect of mirabegron with antimuscarinic agents. These findings, although encouraging, offer few hints of the possible mechanisms of action of these effects. Despite this lack of mechanistic data, the authors of both studies speculate that, based on evidence published elsewhere, both agents might have effects on bladder afferent activity in addition to their established effects on receptors located on detrusor smooth muscle.

These data provide confirmation that, physiologically, the combination of antimuscarinics with  $\beta_3$ -adrenoceptor agonists is a rational approach to the noninvasive management of patients with a range of storage LUTS.

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**ORIGINAL ARTICLES** Imamura, T. et al. Combined treatment with a  $\beta_3$ -adrenergic receptor agonist and a muscarinic receptor antagonist inhibits detrusor overactivity induced by cold stress in spontaneously hypertensive rats. *NeuroUrol. Urodyn.* <http://dx.doi.org/10.1002/nau.23061> (2016) | Wada, N. et al. Combinational effects of muscarinic receptor inhibition and  $\beta_3$ -adrenoceptor stimulation on neurogenic bladder dysfunction in rats with spinal cord injury. *NeuroUrol. Urodyn.* <http://dx.doi.org/10.1002/nau.23066> (2016)