

# New developments in the management of overactive bladder: focus on mirabegron and onabotulinumtoxinA

Karl-Erik Andersson

Institute of Regenerative Medicine,  
Wake Forest University School of  
Medicine, and Department of Urology,  
Wake Forest Baptist Medical Center,  
Winston Salem, NC, USA

**Abstract:** In the last few years, much new information has been generated on the pathophysiology, possible therapeutic targets, and pharmacologic treatment of overactive bladder (OAB). Antimuscarinic drugs are still first-line pharmacologic treatment for OAB and often have good initial response rates, but adverse effects and decreasing efficacy cause long-term compliance problems, prompting a search for new therapeutic alternatives. Mirabegron and onabotulinumtoxinA, two drugs with different mechanisms of action, and with adverse effect profiles different from those of antimuscarinics, were recently approved for treatment of OAB. However, their place in the treatment of this disorder has not yet been established. In this short review, the mechanisms of action, clinical efficacy, and safety profiles of these drugs are discussed and compared with those of the current gold standard, antimuscarinic agents.

**Keywords:** antimuscarinics, mirabegron, onabotulinumtoxinA

## Introduction

The overactive bladder (OAB), defined either symptomatically as the OAB syndrome or urodynamically as detrusor overactivity, is a multifactorial bladder disorder.<sup>1</sup> OAB syndrome and detrusor overactivity are not synonymous, but share therapeutic options and underlying pathophysiologic mechanisms. At least two afferent signaling pathways in the bladder have been defined,<sup>2</sup> ie, the “myogenic” and the “urothelial” pathways, and even if many mechanisms contribute to the pathogenesis of OAB,<sup>3,4</sup> these pathways seem to be ultimately involved.<sup>5</sup> However, only a few drugs (representing different principles) have been demonstrated to have efficacy and safety profiles acceptable for regulatory approval and clinical use. Antimuscarinic drugs are still first-line pharmacologic treatment of OAB/detrusor overactivity, and even if the sites and mechanisms of action of these drugs have not been definitely established,<sup>6</sup> it is now widely accepted that effects on afferent signaling are important for their clinical efficacy. This may also be the case for the two novel drugs that have recently been approved for treatment of OAB/detrusor overactivity, ie, mirabegron and onabotulinumtoxinA.<sup>5</sup> These drugs have different pharmacologic mechanisms, ie,  $\beta_3$ -adrenoceptor agonism and inhibition of nerve release of efferent and afferent transmitters, respectively, and their clinical efficacy and safety profiles in the treatment of OAB/detrusor overactivity have been well documented in clinical trials. However, their position in the management of patients has not yet been established. In the present review, the pharmacologic basis for the use of these drugs will be discussed. In addition, their efficacy and safety profiles are compared with those of the current gold standard, antimuscarinic drugs.

Correspondence: Karl-Erik Andersson  
Institute for Regenerative Medicine,  
Wake Forest University School of  
Medicine, Medical Center Boulevard,  
Winston Salem, NC 27157, USA  
Tel +1 336 713 1195  
Fax +1 336 713 7290  
Email keanders@wfubmc.edu

## Antimuscarinic agents

Current guidelines recommend the use of oral antimuscarinics (anticholinergics) as first-line pharmacologic therapy for the management of OAB/detrusor overactivity.<sup>7,8</sup> Generally, these drugs are recognized as safe and effective in the treatment of these conditions.<sup>9–11</sup>

## Mechanism of action

Antimuscarinics competitively inhibit the effects of acetylcholine at post-junctional muscarinic receptors on detrusor muscle cells, as well as on other structures in the bladder wall, such as the urothelium, interstitial cells, and afferent nerves.<sup>12</sup> In addition, they block muscarinic receptors outside the bladder. How antimuscarinic drugs exert their beneficial effects in the treatment of OAB has been extensively discussed. OAB is a filling disorder, and recent focus has been on afferent mechanisms as a main target for these agents. There is experimental evidence from animal as well as human bladder/tissue studies suggesting that during filling there is a release of acetylcholine from non-neuronal as well as neuronal sources.<sup>6</sup> Afferent activity induced by bladder distension is the normal initiator of the voiding reflex.<sup>13</sup> However, urothelially derived acetylcholine, probably via release of adenosine triphosphate, may also generate afferent activity (“afferent noise”) from the bladder, contributing to OAB. Afferent noise may also be generated by local acetylcholine release within the detrusor muscle. Both types of afferent activity can be inhibited by antimuscarinics at the low concentrations obtained with doses recommended for clinical use in OAB. Within this therapeutic window, antimuscarinics may decrease OAB syndrome and detrusor overactivity without affecting voiding contraction. Changes in afferent activity and in muscarinic receptor function have been demonstrated with aging and in various comorbidities associated with OAB.<sup>12</sup>

## Efficacy

Even if the efficacy of antimuscarinic drugs relative to placebo has been questioned,<sup>14</sup> large meta-analyses of studies performed with the currently most widely used drugs show clearly that antimuscarinics are of significant clinical benefit.<sup>10,15</sup>

If antimuscarinics are acceptably effective and tolerated in randomized, controlled clinical trials, a relevant question is: why is the persistence with prescribed antimuscarinic therapy so conspicuously low?<sup>16–18</sup> Gomes et al compared persistence with oxybutynin or tolterodine therapy among patients newly prescribed one of these drugs in a retrospective cohort study

of Ontarians aged 66 years and older.<sup>19</sup> Persistence with treatment was defined on the basis of refills for the drug within a grace period equivalent to 50% of the prescription duration. The authors identified 31,996 patients newly treated with oxybutynin and 24,855 patients newly treated with tolterodine. After 2 years of follow-up, persistence with oxybutynin (9.4%) was significantly lower than with tolterodine (13.6%,  $P < 0.0001$ ). The median time to discontinuation of oxybutynin and tolterodine was 68 and 128 days, respectively. Wagg et al analyzed prescription data for patients receiving these drugs for treatment of the OAB syndrome over a 12-month period.<sup>18</sup> At 12 months, they found that the proportions of patients still on their original treatment were: solifenacin 35%, tolterodine extended-release 28%, propiverine 27%, oxybutynin extended-release 26%, trospium 26%, tolterodine immediate-release 24%, oxybutynin immediate-release 22%, darifenacin 17%, and flavoxate 14%. The longest persistence was reported for solifenacin (a mean of 187 days versus 77–157 days for the other treatments).

The most common causes of low persistence seem to be lack of efficacy and emergence of intolerable adverse effects. The failure of the drugs to fulfill expectations may also be a contributing factor. However, whether there is a fading of efficacy with time has never been established, and the durability of the effects is not known. Furthermore, the symptom relapse rate after discontinuation of treatment has not been systematically studied. In a prospective, randomized, open-label trial, Lee et al studied what happened 3 months after their patients had been successfully treated for one, 3, or 6 months.<sup>20</sup> The relapse rate was 62%, and the request for further treatment was 65%, indirectly suggesting efficacy of treatment.

## Tolerability and adverse effects

The common adverse events of antimuscarinic drugs are expected and well known, and result from blockade of muscarinic receptors in, eg, the salivary gland, colon, and ciliary smooth muscle, inducing dry mouth, constipation, and blurred vision, respectively.<sup>10</sup>

Madhuvrata et al analyzed 86 trials including 31,249 adults with OAB symptoms in order to compare preferences for various antimuscarinics.<sup>21</sup> In their analysis, an important effect determining drug preference was occurrence of dry mouth. Thus, when the prescribing choice is between oral immediate-release oxybutynin and tolterodine, tolterodine might be preferred for reducing the risk of dry mouth. For the same reason, an extended-release preparation of oxybutynin or tolterodine might be preferred to

an immediate-release preparation. When solifenacin and immediate-release tolterodine were compared, solifenacin seemed to be preferred because of its superior efficacy and lower risk of dry mouth. Likewise, fesoterodine might be preferred over extended-release tolterodine for superior efficacy, but may have a higher risk of withdrawal because of adverse events, mainly dry mouth.

Kessler et al analyzed 69 trials enrolling 26,229 patients with OAB with the aim of comparing the adverse events of antimuscarinics using a network meta-analytic approach that overcomes the shortcomings of conventional analyses.<sup>22</sup> They found similar overall adverse event profiles for darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride, but not for oral oxybutynin, when currently used starting doses were compared. They concluded that most currently used antimuscarinics seem to be equivalent first-choice drugs to start the treatment of OAB, except for oral oxybutynin dosages  $\geq 10$  mg/day, which may have a more unfavorable adverse event profile.

Despite antimuscarinics being associated with many adverse effects, they are generally considered to be “safe” drugs. However, concerns have been raised with regard to adverse cardiac effects, particularly QT prolongation, induction of polymorphic ventricular tachycardia (torsade de pointes), and increases in heart rate.<sup>23,24</sup> QT prolongation and its consequences are not related to blockade of muscarinic receptors, but rather linked to inhibition of the hERG potassium channel in the heart. The potential of the different antimuscarinic agents to increase heart rate and/or prolong the QT interval has not been extensively explored for all agents in clinical use. Differences between drugs cannot be excluded, but risk assessments based on available evidence are not possible. However, based on experiences both from clinical trials and extensive clinical use, the cardiovascular safety of antimuscarinics is generally considered acceptable.

## Mirabegron: a $\beta_3$ -adrenoceptor agonist

Mirabegron is the only  $\beta_3$ -adrenoceptor selective agonist approved for treatment of OAB. It has been approved in Japan (Betanis<sup>®</sup>, Astellas Pharma Inc, Tokyo, Japan) US (Myrbetriq<sup>®</sup>, Astellas), and Europe (Betmiga<sup>®</sup>, Astellas). However, several pharmaceutical companies are developing selective  $\beta_3$ -adrenoceptor agonists for treatment of OAB.<sup>25,26</sup> Except for the proof-of-concept studies of solabegron<sup>27</sup> and ritobegron,<sup>25</sup> clinical experiences with these agents are limited. Therefore, the focus in this paper is on mirabegron.

## Pharmacokinetics

Mirabegron is rapidly absorbed after oral administration, the time to maximum plasma concentration ( $T_{max}$ ) being about 2 hours.<sup>28,29</sup> The drug circulates in plasma as the unchanged active form and as inactive metabolites. Most of an administered dose is excreted in the urine, mainly as the unchanged form, and one third is recovered in feces, almost entirely as the unchanged form.<sup>30</sup> Mirabegron is highly lipophilic, and is metabolized in the liver via multiple pathways, but mainly by cytochrome P450, ie, CYP3A4 and CYP2D6.<sup>31,32</sup> The terminal elimination half-life was approximately 23–25 hours.<sup>28,29</sup>

## Mechanism of action

As mentioned previously, OAB is a filling disorder, which makes afferent activity in the bladder during filling an interesting treatment target. Distension of the bladder initiates activity in “in series”-coupled, low-threshold mechanoreceptive ( $A\delta$ ) afferents.<sup>13</sup> If compliance of the bladder is increased, the response to distension is decreased, and greater filling volumes are needed to recruit sufficient afferent activity to initiate micturition, so bladder capacity increases. One determinant of bladder compliance is spontaneous (autonomous) bladder activity during filling. Experimental studies both in the human<sup>33–35</sup> and animal (mainly rat<sup>36,37</sup>) bladder have documented the inhibitory effects of  $\beta_3$ -adrenoceptor agonists on autonomous activity in vitro, and on “nonvoiding contractions” in vivo. Gillespie et al found that mirabegron inhibited only nonvoiding activity in the rat, while tolterodine (an antimuscarinic agent) inhibited nonvoiding activity as well as the amplitude of voiding contractions.<sup>38</sup>

Effects on bladder compliance may be the basis for the finding in numerous preclinical studies, and also in clinical trials, that  $\beta_3$ -adrenoceptor agonists increase bladder capacity without a change in micturition pressure or residual volume. Evidence that such effects can be linked to reduced bladder afferent activity during filling has been presented by Aizawa et al,<sup>39</sup> who showed in rats that the  $\beta_3$ -adrenoceptor agonist, CL316,243, could inhibit filling-induced activity not only in mechanosensitive  $A\delta$  fibers, but also in C fiber primary bladder afferents, provided that these fibers were stimulated by prostaglandin E2. Similar findings were reported for mirabegron.<sup>40</sup> Voiding contraction is caused by a massive release of contractant transmitters (acetylcholine and adenosine triphosphate), which may be the reason why bladder emptying does not seem to be impaired by  $\beta_3$ -adrenoceptor agonists.

## Efficacy

Several randomized, controlled, Phase II clinical trials have shown that mirabegron consistently improves mean numbers of micturitions and continence episodes in 24 hours in patients with OAB.<sup>41,42</sup> Mirabegron was further evaluated in three pivotal, randomized, controlled, 12-week Phase III clinical trials in patients with OAB symptoms of urgency urinary incontinence, urgency, and urinary frequency<sup>43–45</sup> (Tables 1–3). These trials had a basically similar design. The inclusion criteria required that patients had symptoms of OAB for at least 3 months, at least eight micturitions per day, and at least three episodes of urgency with or without incontinence over a 3-day period. The majority of patients were Caucasian (94%) and female (72%), with a mean age of 59 (range 18–95) years.

In a study by Nitti et al, 1329 patients were randomized to receive placebo, mirabegron 50 mg, or 100 mg once daily for 12 weeks.<sup>43</sup> Coprimary endpoints were the change from baseline to final visit (study end) in mean numbers of incontinence episodes and micturitions per 24 hours. At the final visit, mirabegron 50 mg and 100 mg showed statistically significant improvements in the coprimary efficacy endpoints and mean volume voided/micturition compared with placebo.

Khullar et al performed a similarly designed study, enrolling 1978 patients.<sup>44</sup> The study included a fourth arm in which tolterodine sustained-release 4 mg was used as a comparator. As in the study reported by Nitti et al,<sup>43</sup> mirabegron caused a statistically significant improvement from baseline compared with placebo in the numbers of urgency incontinence episodes and micturitions per 24 hours. For these two key symptoms of OAB, mirabegron 50 mg and 100 mg were statistically superior to placebo, whereas tolterodine was

not, but the study was not powered for head-to-head evaluation.

In a third Phase III study, in which Van Kerrebroeck et al evaluated the effects of mirabegron 25 mg and 50 mg, both doses were associated with significant improvements in efficacy measures of incontinence episodes and micturition frequency.<sup>45</sup>

Nitti et al<sup>46</sup> reported the effects of mirabegron on maximum urinary flow rate and detrusor pressure at maximum flow rate in a urodynamic safety study in male patients with bladder outlet obstruction and lower urinary tract symptoms. Two hundred men with OAB symptoms and a bladder outlet obstruction index > 20 were randomized to receive placebo, mirabegron 50 mg, or mirabegron 100 mg once daily for 12 weeks. Mirabegron did not adversely affect flow rate, detrusor pressure at maximum flow rate, or bladder contractile index, and was well tolerated.

Chapple et al<sup>47</sup> compared the safety and efficacy of long-term administration of mirabegron 50 mg and 100 mg and tolterodine in a 12-month, three-arm, parallel-group study (with no placebo arm). A total of 812 (50 mg) and 820 (100 mg) patients were randomized to receive mirabegron, and 812 patients received tolterodine extended-release 4 mg. The primary variable was incidence and severity of treatment-emergent adverse events, and secondary variables were change in key OAB symptoms from baseline at months 1, 3, 6, 9, and 12. Both mirabegron and tolterodine improved key OAB symptoms from the first measured time point of 4 weeks, and efficacy was maintained throughout the 12-month treatment period.

## Tolerability and adverse effects

In a proof-of-concept study of mirabegron 100 mg and 150 mg twice daily,<sup>41</sup> adverse events were experienced by

**Table 1** Effects of mirabegron on number of incontinence episodes per 24 hours

| Parameter   | Nitti et al <sup>43</sup> |                    | Khullar et al <sup>44</sup> |                    | Van Kerrebroeck et al <sup>45</sup> |                    |                    |
|---|---------------------------|--------------------|-----------------------------|--------------------|-------------------------------------|--------------------|--------------------|
|   | Placebo                   | Mirabegron 50 mg   | Placebo                     | Mirabegron 50 mg   | Placebo                             | Mirabegron 25 mg   | Mirabegron 50 mg   |
| <b>Incontinence episodes per 24 hours (n)<sup>a</sup></b> |                           |                    |                             |                    |                                     |                    |                    |
| n   | 291                       | 293                | 325                         | 312                | 262                                 | 254                | 257                |
| Baseline (mean)   | 2.67                      | 2.83               | 3.03                        | 2.77               | 2.43                                | 2.65               | 2.51               |
| Change from baseline (adjusted mean) <sup>†</sup>         | –1.17                     | –1.57              | –1.13                       | –1.47              | –0.96                               | –1.36              | –1.38              |
| Difference from placebo (adjusted mean) <sup>†</sup>      | –                         | –0.41              | –                           | –0.34              | –                                   | –0.40              | –0.42              |
| 95% confidence interval                                   | –                         | (–0.72, –0.09)     | –                           | (–0.66, –0.03)     | –                                   | (–0.74, –0.06)     | (–0.76, –0.08)     |
| P value   | –                         | 0.003 <sup>#</sup> | –                           | 0.026 <sup>#</sup> | –                                   | 0.005 <sup>#</sup> | 0.001 <sup>#</sup> |

**Notes:** <sup>a</sup>Week 12 is last observation on treatment; <sup>†</sup>least squares mean adjusted for baseline, gender, and geographical region; <sup>a</sup>for incontinence episodes per 24 hours, the analysis population is restricted to patients with at least one episode of incontinence at baseline; <sup>#</sup>statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment. Data from Mirabegron prescribing information.<sup>48</sup>

**Table 2** Effects of mirabegron on number of micturitions per 24 hours

| Parameter  | Nitti et al <sup>43</sup> |                     | Khullar et al <sup>44</sup> |                    | Van Kerrebroeck et al <sup>45</sup> |                    |                    |
|--|---------------------------|---------------------|-----------------------------|--------------------|-------------------------------------|--------------------|--------------------|
|  | Placebo                   | Mirabegron 50 mg    | Placebo                     | Mirabegron 50 mg   | Placebo                             | Mirabegron 25 mg   | Mirabegron 50 mg   |
| <b>Micturitions per 24 hours (n)</b>                 |                           |                     |                             |                    |                                     |                    |                    |
| n  | 480                       | 473                 | 433                         | 425                | 415                                 | 410                | 426                |
| Baseline (mean)                                      | 11.71                     | 11.65               | 11.51                       | 11.80              | 11.48                               | 11.68              | 11.66              |
| Change from baseline (adjusted mean) <sup>†</sup>    | -1.34                     | -1.93               | -1.05                       | -1.66              | -1.18                               | -1.65              | -1.60              |
| Difference from placebo (adjusted mean) <sup>†</sup> | –                         | -0.60               | –                           | -0.61              | –                                   | -0.47              | -0.42              |
| 95% confidence interval                              | –                         | (-0.90, -0.29)      | –                           | (-0.98, -0.24)     | –                                   | (-0.82, -0.13)     | (-0.76, -0.08)     |
| P value  |                           | <0.001 <sup>#</sup> |                             | 0.001 <sup>#</sup> |                                     | 0.007 <sup>#</sup> | 0.015 <sup>#</sup> |

**Notes:** <sup>†</sup>Week 12 is last observation on treatment; <sup>†</sup>least squares mean adjusted for baseline, gender, and geographical region; <sup>†</sup>for incontinence episodes per 24 hours, the analysis population is restricted to patients with at least one episode of incontinence at baseline; <sup>#</sup>statistically significantly superior compared with placebo at the 0.05 level with multiplicity adjustment. Data from Mirabegron prescribing information.<sup>48</sup>

45.2% of patients, and the incidence was similar among those treated with placebo (43.2%) and mirabegron (43.8%–47.9%). The most commonly reported adverse events were treatment-related gastrointestinal disorders, including constipation, dry mouth, dyspepsia, and nausea. There was no patient-reported acute retention. No significant difference in electrocardiographic parameters was demonstrated between the groups. However, a small but significant increase in mean pulse rate was observed after mirabegron 100 mg and 150 mg (1.6 and 4.1 beats per minute, respectively), but was not associated with an increase in cardiovascular adverse events in this study. The overall discontinuation rate owing to adverse events was 3.2% (placebo 3.0% versus mirabegron 2.4%–5.3%).

In a study reported by Khullar et al,<sup>44</sup> the incidence of adverse effects was similar across the placebo, mirabegron 50 mg and 100 mg groups (50.1%, 51.6%, and 46.9%, respectively). The most common ( $\geq 3\%$ ) adverse events in any treatment group were hypertension (6.6%, 6.1%, and

4.9%, respectively), urinary tract infection (1.8%, 2.7%, and 3.7%), headache (2.0%, 3.2%, and 3.0%), and nasopharyngitis (2.9%, 3.4%, and 2.5%). The incidence of dry mouth was similar in the placebo and mirabegron groups (2.6% versus 2.8%), and lower than that observed in patients receiving tolterodine sustained-release (10.1%). The incidence of constipation was similar in all treatment groups (placebo 1.4%, mirabegron 1.6%), including tolterodine (2.0%).

In the 12-month safety and efficacy study of mirabegron referred to earlier,<sup>47</sup> the incidence and severity of treatment-emergent serious adverse effects (primary outcome parameters) were similar across the mirabegron 50 mg (59.7%), mirabegron 100 mg (61.3%), and tolterodine sustained-release 4 mg (62.6%) groups. The most frequent treatment-emergent adverse effects were hypertension, dry mouth, constipation, and headache, which occurred at a similar incidence across all treatment groups, while the incidence of dry mouth was more than three-fold lower than in the tolterodine sustained-release 4 mg group.<sup>47</sup>

**Table 3** Effects of mirabegron on voided volume per micturition

| Parameter  | Nitti et al <sup>43</sup> |                     | Khullar et al <sup>44</sup> |                    | Van Kerrebroeck et al <sup>45</sup> |                  |                     |
|--|---------------------------|---------------------|-----------------------------|--------------------|-------------------------------------|------------------|---------------------|
|  | Placebo                   | Mirabegron 50 mg    | Placebo                     | Mirabegron 50 mg   | Placebo                             | Mirabegron 25 mg | Mirabegron 50 mg    |
| <b>Volume voided (mL) per micturition</b>            |                           |                     |                             |                    |                                     |                  |                     |
| n  | 480                       | 472                 | 433                         | 424                | 415                                 | 410              | 426                 |
| Baseline (mean)                                      | 156.7                     | 161.1               | 157.5                       | 156.3              | 164.0                               | 165.2            | 159.3               |
| Change from baseline (adjusted mean) <sup>†</sup>    | 12.3                      | 24.2                | 7.0                         | 18.2               | 8.3                                 | 12.8             | 20.7                |
| Difference from placebo (adjusted mean) <sup>†</sup> | –                         | 11.9                | –                           | 11.1               | –                                   | 4.6              | 12.4                |
| 95% confidence interval                              | –                         | (6.3, 17.4)         | –                           | (4.4, 17.9)        | –                                   | (-1.6, 10.8)     | (6.3, 18.6)         |
| P-value  |                           | <0.001 <sup>#</sup> |                             | 0.001 <sup>#</sup> |                                     | 0.15             | <0.001 <sup>#</sup> |

**Notes:** <sup>†</sup>least squares mean adjusted for baseline, gender, and geographical region; <sup>#</sup>statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment. Data from Mirabegron prescribing information.<sup>48</sup>



One concern with the use of  $\beta_3$ -adrenoceptor agonists has been the possibility of negative cardiovascular effects. In healthy subjects, mirabegron 50–300 mg/day for 10 days increased blood pressure in a dose-dependent manner.<sup>48</sup> However, in the studies of patients with OAB, the mean increases in systolic/diastolic blood pressure after therapeutic doses of mirabegron once daily compared with placebo was approximately 0.5–1 mmHg, and was reversible upon discontinuation of treatment.

In a study of healthy volunteers, mirabegron increased heart rate in a dose-dependent manner. Maximum mean increases in heart rate from baseline for the 50 mg, 100 mg, and 200 mg dose groups compared with placebo were 6.7, 11, and 17 beats per minute, respectively, in healthy volunteers.<sup>48</sup> However, in the clinical efficacy and safety studies, the change from baseline in mean pulse rate for mirabegron 50 mg was approximately one beat per minute and reversible upon discontinuation of treatment.

The cardiac safety of mirabegron was evaluated in a thorough QT/QTc (heart rate-corrected QT interval) study, including supratherapeutic dose. This was a randomized, placebo-controlled, and active-controlled (moxifloxacin 400 mg) parallel crossover study with four treatment arms,<sup>49</sup> and the design followed the recommendations made by the International Conference on Harmonisation. Equal numbers of male and females were enrolled in each treatment group, and the pharmacokinetic and pharmacodynamic analyses comprised 333 and 317 subjects, respectively. The effect of multiple doses of mirabegron 50 mg, 100 mg, and 200 mg once daily on QTc interval was studied, and according to International Conference on Harmonisation E14 criteria, mirabegron did not cause prolongation of the QTc interval at the 50 mg therapeutic or 100 mg supratherapeutic doses in men or women. Mirabegron prolonged the QTc interval at the 200 mg supratherapeutic dose (upper one-sided 95% confidence interval > 10 msec) in women, but not in men.

Even if the cardiovascular effects of mirabegron observed in clinical studies have been minimal and not clinically relevant, effects on heart rate and blood pressure need to be monitored when the drug is generally prescribed and patients with cardiovascular morbidities are treated.

## Botulinum toxin

Botulinum toxin, the neurotoxin produced by *Clostridium botulinum*, has been used clinically for the treatment of neurogenic detrusor overactivity since 1999, and onabotulinumtoxinA was approved by the US Food and Drug Administration for this indication in 2011. In December 2012 it was

approved in Europe and in January 2013 in the US also for the treatment of OAB.

Botulinum toxin comprises seven subtypes, of which subtype A (botulinum toxin A), which has the longest duration of action, is clinically the most important. Botulinum toxin A is available in three different commercial forms, ie, onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA. Although there are differences in potency between the forms, there is no reason to believe that their basic mechanisms of action are different. The potency of each one is usually expressed in units; however, the doses are not interchangeable. Unfortunately, clinical dose conversion studies are not available for the lower urinary tract. Most of the information available preclinically and clinically derives from the use of onabotulinumtoxinA.

## Mechanism of action

Details of the mechanism of action of botulinum toxin in the nerve terminal are well outlined elsewhere.<sup>50,51</sup> Briefly, this entails cleavage of the attachment proteins involved in the mechanism of fusion of synaptic vesicles to the cytoplasmic membrane, which is necessary for neurotransmitter release. Attachment proteins (the SNARE complex) include synaptosome-associated protein 25 kD (SNAP 25), synaptobrevin (vesicle-associated membrane protein), and syntaxin. Botulinum toxin A cleaves SNAP 25, rendering the SNARE complex inactive. In striated muscle, paralysis is produced by inhibition of release of acetylcholine from cholinergic motor nerve endings.<sup>50</sup> In the human bladder, SNAP-25 expression has been demonstrated in parasympathetic, sympathetic, and sensory fibers.<sup>52</sup> It has been well documented that botulinum toxin A can inhibit release of transmitters from sensory nerves both in the central nervous system and peripherally.<sup>52–56</sup> Botulinum toxin A was found to reduce afferent firing from bladder afferents and antidromic release of neuropeptides.<sup>57</sup>

Although SNAP-25 immunoreactivity has not been detected in urothelial cells,<sup>58</sup> urothelial function also seems to be influenced after administration of botulinum toxin A, given that botulinum toxin A has been shown to inhibit release of adenosine triphosphate from the urothelium in animal models of spinal cord injury.<sup>58,59</sup> Takahashi et al studied the direct effects of botulinum toxin A on rat detrusor muscle, and demonstrated inhibitory effects on L-type voltage-gated  $\text{Ca}^{2+}$  channels.<sup>60</sup> The inhibitory potency was similar to that on efferent nerves and higher than that on afferent nerves. Botulinum toxin A, injected into the bladder wall, also seems to influence effects mediated via, eg, P2X3 and TRVP1<sup>61</sup> and muscarinic receptors.<sup>62</sup> The available evidence suggests that

botulinum toxin A has multiple sites of action in the bladder, including inhibition of transmitter release from both efferent and afferent nerves, and direct inhibitory effects on the urothelium and detrusor muscle.

## Efficacy

Several randomized controlled clinical trials have documented the clinical effects of onabotulinumtoxinA in neurogenic and idiopathic detrusor overactivity, where the drug decreases incontinence episodes, frequency, and urgency, and improves quality of life.<sup>63–66</sup> The drug was also shown to be effective in patients with OAB syndrome.<sup>67</sup> Successful treatment of OAB syndrome with botulinum toxin A does not appear to be related to the existence of detrusor overactivity. No differences in outcomes were found between those with and those without baseline detrusor overactivity.<sup>68,69</sup>

Nitti et al<sup>67</sup> reported the results of the first large placebo-controlled Phase III trial ( $n = 557$ ) of onabotulinumtoxinA in patients with OAB. To be included, patients had to have at least three urge urinary incontinence episodes in three days and at least eight micturitions per day. They were randomized 1:1 to receive an intradetrusor injection of onabotulinumtoxinA 100 U or placebo (saline). Coprimary endpoints were change from baseline in urge urinary incontinence episodes per day and proportion of patients with a positive response on the Treatment Benefit Scale at week 12 post-treatment. Secondary endpoints included other OAB symptoms and health-related quality of life. OnabotulinumtoxinA significantly reduced the daily frequency of urge urinary incontinence episodes versus placebo ( $-2.65$  versus  $-0.87$ ,  $P < 0.001$ ), and 22.9% versus 6.5% of patients, respectively, became completely continent. A larger proportion of onabotulinumtoxinA-treated patients than those on placebo reported a positive response on the Treatment Benefit Scale (60.8% versus 29.2%,  $P < 0.001$ ). All other symptoms of OAB improved versus placebo ( $P \leq 0.05$ ). OnabotulinumtoxinA improved health-related quality of life in patients across multiple measures ( $P < 0.001$ ).

The finding that onabotulinumtoxinA 100 U was consistently effective, with a 2–4-fold improvement over placebo in all symptoms of OAB is important, in that an effect of this magnitude versus placebo does not seem to have been reported previously with antimuscarinics or  $\beta_3$ -adrenoceptor agonists.

## Adverse effects

In the study reported by Nitti et al,<sup>67</sup> the majority of adverse effects occurred in the first 12 weeks (15.5% with

onabotulinumtoxinA versus 5.9% with placebo). The most frequently reported adverse event was uncomplicated urinary tract infection with no upper urinary tract involvement. Other adverse effects were dysuria (12.2%) bacteriuria (5.0%), and urinary retention (5.4%). Post void residual urine volume significantly increased with onabotulinumtoxinA versus placebo, with the highest volume recorded at week 2 post-treatment, and 8.7% of patients had an increase from baseline of  $\geq 200$  mL in post void residual urine volume at any time following the initial toxin treatment (versus none with placebo). The proportion of patients who initiated clean intermittent catheterization at any time during treatment cycle 1 was 6.1% versus none in the placebo group; the duration of clean intermittent catheterization was  $\leq 6$  weeks in over half the patients who initiated this (10/17). This value is lower than that reported in previous studies of idiopathic detrusor overactivity.<sup>63,64,66,70</sup> In the study by Nitti et al,<sup>67</sup> discontinuation rates due to adverse effects were low in both the onabotulinumtoxinA (1.8%) and placebo (1.4%) groups.

## Combined treatment

A combination of an antimuscarinic agent and mirabegron (or another  $\beta_3$ -adrenoceptor agonist) seems rational and theoretically attractive, but clinical studies supporting use of this combination are still lacking. Assuming that both drugs have reduction in afferent activity as the main mechanism of action, the question is whether there is a ceiling for this effect, and if this ceiling can be reached by any of the drugs given as monotherapy. If this is the case, only modest increases in efficacy can be expected by a combination. However, it is possible that the differences in safety profiles can confer advantages to a combination and increase the efficacy/adverse effect ratio, leading to a better persistence rate by, eg, reducing antimuscarinic-induced dry mouth.

Combination of onabotulinumtoxinA with either an antimuscarinic or a  $\beta_3$ -adrenoceptor agonist may not be expected to increase efficacy. However, combinations can possibly prolong the interval between onabotulinumtoxinA injections by contributing to efficacy when the effects of the treatment are fading. Combinations do not seem to have any advantages with respect to adverse effects, because the potential negative effects of onabotulinumtoxinA are not eliminated.

## Conclusion

OAB is a filling disorder in which abnormal sensations lead to urinary urgency, frequency, and incontinence. The afferent signaling pathways that regulate micturition play a central role in the pathogenesis of OAB, and thus represent important

targets for therapy. The three types of drugs discussed, ie, antimuscarinics,  $\beta_3$ -adrenoceptor agonists (mirabegron), and onabotulinumtoxinA, all have well documented efficacy in the treatment of OAB and acceptable safety profiles, although the long-term cardiovascular effects of mirabegron are not as yet known. Antimuscarinic drugs remain the first-line pharmacologic treatment for OAB. According to prescription recommendations, onabotulinumtoxinA may be given after failure of antimuscarinic drugs, so it remains a second-line pharmacologic alternative. If it seems logical to use a  $\beta_3$ -adrenoceptor agonist (currently mirabegron) as an alternative to antimuscarinics, particularly when these drugs have failed, a  $\beta_3$ -adrenoceptor agonist may be tried as a first-line treatment. The question is whether it is necessary to try both antimuscarinics and a  $\beta_3$ -adrenoceptor agonist or a combination of these drugs before administering onabotulinumtoxinA. More clinical experience is needed before optimal pharmacologic management of OAB can be defined.

## Disclosure

Professor Andersson is a consultant to Allergan, Astellas, Ferring, Pfizer, TheraVida. There are no further conflicts of interest in this work.

## References

- Roosen A, Chapple CR, Dmochowski RR, et al. A refocus on the bladder as the originator of storage lower urinary tract symptoms: a systematic review of the latest literature. *Eur Urol*. 2009;56(5):810–819.
- Kanai A, Andersson KE. Bladder afferent signaling: recent findings. *J Urol*. 2010;183(4):1288–1295.
- Andersson KE. LUTS treatment: future treatment options. *Neurourol Urodyn*. 2007;26(Suppl 6):934–947.
- Cerruto MA, Asimakopoulou AD, Artibani W, et al. Insight into new potential targets for the treatment of overactive bladder and detrusor overactivity. *Urol Int*. 2012;89(1):1–8.
- Hood B, Andersson KE. Common theme for drugs effective in overactive bladder treatment: inhibition of afferent signaling from the bladder. *Int J Urol*. 2013;20(1):21–27.
- Andersson KE. Antimuscarinic mechanisms and the overactive detrusor: an update. *Eur Urol*. 2011;59(3):377–386.
- Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. American Urological Association; Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction. *J Urol*. 2012;188(Suppl 6):2455–2463.
- Lucas MG, Bosch RJ, Burkhard FC, et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. *Eur Urol*. 2012;62(6):1130–1142.
- Abrams P, Andersson KE. Muscarinic receptor antagonists for overactive bladder. *BJU Int*. 2007;100(5):987–1006.
- Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *Eur Urol*. 2008;54(3):543–562.
- Andersson KE, Chapple CR, Cardozo L, et al. Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. *Curr Opin Urol*. 2009;19(4):380–394.
- Andersson KE. Muscarinic acetylcholine receptors in the urinary tract. *Handb Exp Pharmacol*. 2011;202:319–344.
- Iggo A. Tension receptors in the stomach and the urinary bladder. *J Physiol*. 1955;128(3):593–607.
- Herbison P, Hay-Smith J, Ellis G, Moore K. Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. *BMJ*. 2003;326(7394):841–844.
- Novara G, Galfano A, Secco S, et al. Systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. *Eur Urol*. 2008;54(4):740–763.
- Basra RK, Wagg A, Chapple C, et al. A review of adherence to drug therapy in patients with overactive bladder. *BJU Int*. 2008;102(7):774–779.
- Sears CL, Lewis C, Noel K, Albright TS, Fischer JR. Overactive bladder medication adherence when medication is free to patients. *J Urol*. 2010;183(3):1077–1081.
- Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU Int*. 2012;110(11):1767–1774.
- Gomes T, Juurlink DN, Mamdani MM. Comparative adherence to oxybutynin or tolterodine among older patients. *Eur J Clin Pharmacol*. 2012;68(1):97–99.
- Lee YS, Choo MS, Lee JY, Oh SJ, Lee KS. Symptom change after discontinuation of successful antimuscarinic treatment in patients with overactive bladder symptoms: a randomised, multicentre trial. *Int J Clin Pract*. 2011;65(9):997–1004.
- Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJ. Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Syst Rev*. 2012;1:CD005429.
- Kessler TM, Bachmann LM, Minder C, et al. Adverse event assessment of antimuscarinics for treating overactive bladder: a network meta-analytic approach. *PLoS One*. 2011;6(2):e16718.
- Andersson KE, Olshansky B. Treating patients with overactive bladder syndrome with antimuscarinics: heart rate considerations. *BJU Int*. 2007;100(5):1007–1014.
- Andersson KE, Campeau L, Olshansky B. Cardiac effects of muscarinic receptor antagonists used for voiding dysfunction. *Br J Clin Pharmacol*. 2011;72(2):186–196.
- Igawa Y, Michel MC. Pharmacological profile of  $\beta(3)$ -adrenoceptor agonists in clinical development for the treatment of overactive bladder syndrome. *Naunyn-Schmiedeberg's Arch Pharmacol*. 2013;386(3):177–183.
- Kanie S, Otsuka A, Yoshikawa S, et al. Pharmacological effect of TRK-380, a novel selective human  $\beta_3$ -adrenoceptor agonist, on mammalian detrusor strips. *Urology*. 2012;79(3):744. e1–e7.
- Ohlstein EH, von Keitz A, Michel MC. A multicenter, double-blind, randomized, placebo-controlled trial of the  $\beta_3$ -adrenoceptor agonist solabegron for overactive bladder. *Eur Urol*. 2012;62(5):834–840.
- Eltink C, Lee J, Schaddelee M, et al. Single dose pharmacokinetics and absolute bioavailability of mirabegron, a  $\beta_3$ -adrenoceptor agonist for treatment of overactive bladder. *Int J Clin Pharmacol Ther*. 2012;50(11):838–850.
- Krauwinkel W, van Dijk J, Schaddelee M, et al. Pharmacokinetic properties of mirabegron, a  $\beta(3)$ -adrenoceptor agonist: results from two Phase I, randomized, multiple-dose studies in healthy young and elderly men and women. *Clin Ther*. 2012;34(10):2144–2160.
- Takusagawa S, van Lier JJ, Suzuki K, et al. Absorption, metabolism and excretion of [(14)C]mirabegron (YM178), a potent and selective  $\beta(3)$ -adrenoceptor agonist, after oral administration to healthy male volunteers. *Drug Metab Dispos*. 2012;40(4):815–824.
- Takusagawa S, Yajima K, Miyashita A, Uehara S, Iwatsubo T, Usui T. Identification of human cytochrome P450 isoforms and esterases involved in the metabolism of mirabegron, a potent and selective  $\beta(3)$ -adrenoceptor agonist. *Xenobiotica*. 2012;42(10):957–967.
- Takusagawa S, Miyashita A, Iwatsubo T, Usui T. In vitro inhibition and induction of human cytochrome P450 enzymes by mirabegron, a potent and selective  $\beta_3$ -adrenoceptor agonist. *Xenobiotica*. 2012;42(12):1187–1196.



33. 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(6):1310–1314.
34. Takasu T, Ukai M, Sato S, et al. Effect of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide (YM178), a novel selective beta3-adrenoceptor agonist, on bladder function. *J Pharmacol Exp Ther.* 2007;321(2):642–647.
35. Svalø J, Nordling J, Bouchelouche K, Andersson KE, Korstanje C, Bouchelouche P. The novel  $\beta(3)$ -adrenoceptor agonist mirabegron reduces carbachol-induced contractile activity in detrusor tissue from patients with bladder outflow obstruction with or without detrusor overactivity. *Eur J Pharmacol.* 2012;699(1–3):101–105.
36. Hatanaka T, Ukai M, Watanabe M, et al. In vitro and in vivo pharmacological profile of the selective  $\beta(3)$ -adrenoceptor agonist mirabegron in rats. *Naunyn Schmiedeberg Arch Pharmacol.* 2013;386(3):247–253.
37. Hatanaka T, Ukai M, Watanabe M, et al. Effect of mirabegron, a novel  $\beta(3)$ -adrenoceptor agonist, on bladder function during storage phase in rats. *Naunyn Schmiedeberg Arch Pharmacol.* 2013;386(1):71–78.
38. Gillespie JJ, Palea S, Guilloteau V, Guerard M, Lhuil P, Korstanje C. Modulation of non-voiding activity by the muscarinic antagonist tolterodine and the  $\beta(3)$ -adrenoceptor agonist mirabegron in conscious rats with partial outflow obstruction. *BJU Int.* 2012;110(2 Pt 2):E132–E142.
39. Aizawa N, Igawa Y, Nishizawa O, Wyndaele JJ. 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(5):771–776.
40. Aizawa N, Homma Y, Igawa Y. Effects of mirabegron, a novel  $\beta_3$ -adrenoceptor agonist, on primary bladder afferent activity and bladder microcontractions in rats compared with the effects of oxybutynin. *Eur Urol.* 2012;62(6):1165–1173.
41. Chapple CR, Yamaguchi O, Ridder A, et al. Clinical proof of concept study (Blossom) shows novel  $\beta_3$  adrenoceptor agonist YM178 is effective and well tolerated in the treatment of symptoms of overactive bladder. *Eur Urol Suppl.* 2008;7(3):29:239. Abstr 674.
42. Chapple C, Wyndaele JJ, van Kerrebroeck P, Radziszewski P, Dvorak V. Dose ranging study of once-daily mirabegron (YM178), a novel selective  $\beta_3$  adrenoceptor agonist, in patients with overactive bladder (OAB). *Eur Urol Suppl.* 2010;9(2):249. Abstr 774.
43. Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized Phase III trial of mirabegron in patients with overactive bladder. *J Urol.* 2012;S0022–5347(12):05216–05210.
44. Khullar V, Amarencu G, Angulo JC, et al. Efficacy and tolerability of mirabegron, a  $\beta(3)$ -adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. *Eur Urol.* 2013;63(2):283–295.
45. Van Kerrebroeck P, Barkin 2, Castro-Diaz D, et al. Randomised, double-blind, placebo-controlled Phase III study to assess the efficacy and safety of mirabegron 25 mg and 50 mg once daily in overactive bladder (OAB). Presented at the 42nd Annual Meeting of the International Continence Society, Beijing, China, October 15–19, 2012.
46. Nitti V, Rosenberg S, Mitcheson HD, et al. Randomized, multicenter phase II study evaluating the urodynamic safety of mirabegron in males with lower urinary tract symptoms (LUTS) and bladder outlet. *J Urol.* 2012;187(Suppl 4):e756.
47. Chapple CR, Kaplan SA, Mitcheson D, et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a  $\beta(3)$ -adrenoceptor agonist, in overactive bladder. *Eur Urol.* 2013;63(2):296–305.
48. Mirabegron prescribing information. Available from: <http://www.us.astellas.com/docs/myrbetriq-full-pi.pdf>. Accessed February 26, 2013.
49. Malik M, van Gelderen EM, Lee JH, et al. Proarrhythmic safety of repeat doses of mirabegron in healthy subjects: a randomized, double-blind, placebo-, and active-controlled thorough QT study. *Clin Pharmacol Ther.* 2012;92(6):696–706.
50. Humeau Y, Doussau F, Grant NJ, Poulain B. How botulinum and tetanus neurotoxins block neurotransmitter release. *Biochimie.* 2000;82(5):427–446.
51. Chancellor MB, Fowler CJ, Apostolidis A, et al. Drug insight: biological effects of botulinum toxin A in the lower urinary tract. *Nat Clin Pract Urol.* 2008;5(6):319–328.
52. Coelho A, Cruz F, Cruz CD, Avelino A. Spread of onabotulinumtoxinA after bladder injection. Experimental study using the distribution of cleaved SNAP-25 as the marker of the toxin action. *Eur Urol.* 2012;61(6):1178–1184.
53. Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. *Neurotoxicology.* 2005;26(5):785–793.
54. Rapp DE, Turk KW, Bales GT, Cook SP. Botulinum toxin type A inhibits calcitonin gene-related peptide release from isolated rat bladder. *J Urol.* 2006;175(3 Pt 1):1138–1142.
55. Meng J, Wang J, Lawrence G, Dolly JO. Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by botulinum toxins reflects their anti-nociceptive potential. *J Cell Sci.* 2007;120(Pt 16):2864–2874.
56. Lucioni A, Bales GT, Lotan TL, McGehee DS, Cook SP, Rapp DE. Botulinum toxin type A inhibits sensory neuropeptide release in rat bladder models of acute injury and chronic inflammation. *BJU Int.* 2008;101(3):366–370.
57. Ikeda Y, Zabarova I, Birder L, et al. Botulinum neurotoxin serotype A suppresses neurotransmitter release from afferent as well as efferent nerves in the urinary bladder. *Eur Urol.* 2012;62(6):1157–1164.
58. Khara M, Somogyi GT, Kiss S, Boone TB, Smith CP. Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. *Neurochem Int.* 2004;45(7):987–993.
59. Smith CP, Gangiano DA, Munoz A, et al. Botulinum toxin type A normalizes alterations in urothelial ATP and NO release induced by chronic spinal cord injury. *Neurochem Int.* 2008;52(6):1068–1075.
60. Takahashi R, Yunoki T, Naito S, Yoshimura N. Differential effects of botulinum neurotoxin A on bladder contractile responses to activation of efferent nerves, smooth muscles and afferent nerves in rats. *J Urol.* 2012;188(5):1993–1999.
61. Apostolidis A, Popta R, Yiangou Y, et al. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. *J Urol.* 2005;174(3):977–982.
62. Datta SN, Roosen A, Oullen A, et al. Immunohistochemical expression of muscarinic receptors in the urothelium and suburothelium of neurogenic and idiopathic overactive human bladders, and changes with botulinum neurotoxin administration. *J Urol.* 2010;184(6):2578–2585.
63. Sahai A, Khan MS, Dasgupta P. Efficacy of botulinum toxin A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial. *J Urol.* 2007;177(6):2231–2236.
64. Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinumtoxin A for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. *J Urol.* 2010;184(6):2416–2422.
65. Mangera A, Andersson KE, Apostolidis A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of Botox (onabotulinumtoxinA) and Dysport (abobotulinumtoxinA). *Eur Urol.* 2011;60(4):784–795.
66. Tincello DG, Kenyon S, Abrams KR, et al. Botulinum toxin A versus placebo for refractory detrusor overactivity in women: a randomized blinded placebo-controlled trial of 240 women (the RELAX study). *Eur Urol.* 2012;62(3):507–514.
67. Nitti VW, Dmochowski R, Herschorn S, et al; EMBARK Study Group. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a Phase 3 randomized placebo-controlled trial. *J Urol.* 2012;pii:S0022–5347(12):05849-1.

68. Rovner E, Kennelly M, Schulte-Baukloh H, Zhou J, Haag-Molkenteller C, Dasgupta P. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. *Neurourol Urodyn*. 2011;30(4):556–562.
69. Kanagarajah P, Ayyathurai R, Caruso DJ, Gomez C, Gousse AE. Role of botulinum toxin-A in refractory idiopathic overactive bladder patients without detrusor overactivity. *Int Urol Nephrol*. 2012;44(1):91–97.
70. Brubaker L, Richter HE, Visco A, et al. Refractory idiopathic urge urinary incontinence and botulinum A injection. *J Urol*. 2008;180(1):217–222.

### Therapeutics and Clinical Risk Management

Dovepress

### Publish your work in this journal

Therapeutics and Clinical Risk Management is an international, peer-reviewed journal of clinical therapeutics and risk management, focusing on concise rapid reporting of clinical studies in all therapeutic areas, outcomes, safety, and programs for the effective, safe, and sustained use of medicines. This journal is indexed on PubMed Central, CAS,

EMBase, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/therapeutics-and-clinical-risk-management-journal>