Ther Adv Drug Saf
2016, Vol. 7(5) 204–216
DOI: 10.1177/2042098616659412



# Mirabegron in overactive bladder patients: efficacy review and update on drug safety

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***Abstract*:** Overactive bladder is a common condition, which significantly affects people's quality of life. The use of anticholinergic medication has been the mainstay of managing overactive bladder when conservative measures are not enough. Many patients stop anticholinergic medication because of the side effects and more recently the concerns about the effect of an anticholinergic burden and the development of dementia have been studied. Activation of β3 adrenoceptors has been shown to relax the detrusor muscle and subsequently lead to the development of the first β3 adrenoceptor agonist. Mirabegron is the first drug in this class to be approved for the use in overactive bladder. It has been extensively studied in phase II and III trials and has significant improvement in key overactive bladder parameters when compared with placebo. The incidence of side effects such as constipation, hypertension and tachycardia were comparable to anticholinergic medication but there was significantly less dry mouth incidence in the mirabegron groups. Mirabegron has been shown to be used safely in combination with solifenacin and tamsulosin. Head-to-head studies comparing efficacy and safety of mirabegron with anticholinergic medication would further help in the management strategy for overactive bladder.

***Keywords:*** anticholinergic, β3 agonist, mirabegron, overactive bladder

## Introduction

Overactive bladder (OAB) is a common and bothersome symptom complex, which significantly affects patients' quality of life. Approximately 400 million people worldwide suffer with symptoms of urgency and frequency (dry OAB) and a proportion will have associated urgency incontinence (wet OAB). The prevalence of OAB increases with age with approximately 30–40% of the population over 75 being affected [Irwin *et al.* 2006]. The International Continence Society defines the OAB syndrome as urinary urgency, usually with frequency and nocturia with or without urgency urinary incontinence [Abrams *et al.* 2009]. NICE guidelines [NICE, 2013] provide a structured approach to managing patients with incontinence and as part of these recommendations a treatment ladder for those patients with OAB syndrome. Taking a history allows differentiation between incontinence that is urgency, stress or mixed urgency/stress. All patients should have a bladder diary to complete in addition to a symptom scoring and quality of life questionnaire. Urine dipstick testing and flow tests make up part of the initial assessment with urodynamics being reserved for those who have failed conservative therapy including drug treatment. Initial management is bladder training, weight loss and fluid management. The next step in the ladder is antimuscarinic treatment starting at the lowest dose initially and titrating according to the patient's response and side effects. NICE also supports the use of intravesical botulinum toxin injections and neurostimulation for management of refractory OAB before considering surgical intervention such as augmentation cystoplasty. Antimuscarinics are a well-established treatment for OAB and have been shown to reduce the bothersome symptoms of urgency, frequency and incontinence. However, their use is often restricted by limited efficacy and intolerable adverse events. Approximately 50% of patients discontinue treatment at 3 months [Wagg *et al.* 2012]. Common side effects are dry eyes, dry mouth, blurred vision and constipation.

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## Anticholinergic burden

Anticholinergic medications, as a treatment for OAB, have been utilized effectively for many years. They have provided successful treatment for many OAB patients, but have well-recognized side-effect profiles, including cognitive dysfunction, which can be particularly concerning in an elderly patient population. Since the 1980s it has been possible to measure the serum anticholinergic activity level. The first study investigating short-term cognitive dysfunction in relation to anticholinergic medication was in a community-based population in 2003. This study investigated serum levels of anticholinergic activity in 201 patients with a mean age of 78.2 years who were randomly selected from an epidemiological community study [Mulsant *et al.* 2003]. In this study higher serum anticholinergic activity levels were found to significantly correlate with poorer mini mental test results.

However, anticholinergic medication for an OAB is not the only medication with anticholinergic activity. There have been concerns that polypharmacy with multiple anticholinergic medications that have some anticholinergic action may lead to a significantly raised anticholinergic burden and reduced cognitive function or dementia in the long term.

Various options that have been described for assessing anticholinergic burden include the use of assessment tools, such as the Anticholinergic Cognitive Burden (ACB) Scale. This gives an individual score based upon use of medications from a master list with probable or definite anticholinergic activity, defined by anticholinergic serum activity. Shah and colleagues used the ACB scale to investigate decline in cognitive function associated with use of anticholinergic medication over a 10-year period, in a longitudinal epidemiological study of aging, and found that higher scores significantly correlated with a steeper decline in cognitive function over the study period [Shah *et al.* 2013].

Several papers have also linked anticholinergic burden to dementia or Alzheimer's disease [Jessen *et al.* 2010; Carriere *et al.* 2009]. A recent paper by Gray and colleagues followed 3434 participants from the Adult Changes in Thought study, a prospective population-based cohort study, for 10 years [Gray *et al.* 2015]. The patients had their anticholinergic exposure expressed as a total standardized daily dose over the 10 years and compared this with the finding of dementia over the 10-year period, as assessed using standard diagnostic criteria. The group found that a 10-year cumulative dose–response relationship existed between anticholinergic use and the risk of developing dementia. No difference in risk was found between recent use and past use, suggesting that the risk of dementia may persist despite discontinuation of treatment.

Not only has a high anticholinergic burden been linked to cognitive dysfunction but a recent paper has also linked a higher anticholinergic burden (as assessed by ACB) with increased mortality and cardiovascular risk [Myint *et al.* 2015]. Ongoing long-term data is needed to further assess these risks, however there is certainly enough evidence emerging that these risks should become part of a discussion with the patient prior to considering starting anticholinergic medication for an OAB, particularly in the presence of other anticholinergic medication and other alternative medication such as mirabegron should be considered.

## Pharmacology of mirabegron

The beta-adrenoceptors are distributed in adipose tissue, heart, vascular systems and the bladder. Studies in the pathophysiology of OAB have demonstrated three subtypes of beta-adrenoceptors in the detrusor muscle and urothelium. The β3 subtype was identified in 1989 and is the predominate adrenoceptor in the bladder and direct stimulation is responsible for mediating detrusor relaxation in humans and can increase bladder capacity. At a molecular level the β3 adrenoceptor activation leads to opening of big conductance calcium activated potassium channels or activation of adenylyl cyclase with subsequent formation of cyclic adenosine monophosphate. The development of a β3 adrenoceptor agonist to cause detrusor relaxation is a further weapon in the armamentarium of both primary care physicians and specialist urologists, geriatricians and urogynaecologists. Two types of contraction have been observed in the human detrusor muscle: voiding and spontaneous involuntary contractions (IDCs) during bladder filling. Preclinical and clinical studies showed β3 adrenoceptor agonists have no significant negative effect on the voiding contraction therefore limiting the risk of urinary retention [Michel *et al.* 2011]. β3 adrenoceptor agonists have shown a pronounced effect on spontaneous contractile activity in the detrusor muscle *in vitro* therefore reducing the bladder tone and afferent input which is

related to the storage symptoms of the OAB syndrome [Andersson *et al.* 2013].

Mirabegron is the first β3 adrenoceptor agonist to be approved for the treatment of OAB symptoms and is the first in a new class of therapy for OAB symptoms for over 30 years. It is licensed in Japan, USA, Europe and Canada. The dose recommendation varies from country to country with a starting dose of 25 mg in the USA and Canada increasing to 50 mg whereas the UK and Japan use a starting dose of 50 mg reducing it in patients with renal or hepatic impairment. Mirabegron has a particular affinity for β3 adrenoceptors and improves the storage capacity of the bladder with little effect on the contractile ability of the bladder. It is rapidly absorbed after oral administration, has a $t_{max}$ of 3–4 hours, half-life of 40 hours and a bioavailability of 35% at the 50 mg dose. It circulates in plasma in its unchanged form, as glucuronic acid conjugates and other inactive metabolites. Mirabegron is highly lipophilic and is metabolized in liver by cytochrome p450. A total of 55% is excreted in urine and 34% recovered in faeces, both in its unchanged form. Mirabegron has little or no effect on commonly used drugs such as the oral contraceptive pill, warfarin, metformin, digoxin and solifenacin. Caution should be exercised with CYP6D6 substrates with a narrow therapeutic index because of the cytochrome P450 metabolism pathway. For example, the maximum plasma concentration of tamsulosin is increased by 60% in the presence of mirabegron [Rossanese *et al.* 2015].

## Efficacy and safety of mirabegron

Mirabegron has been studied extensively in the last few years within the context of phase II and III trials. The trials had standard inclusion criteria enrolling men and women over the age of 18 years of age with OAB symptoms for >3 months.

The initial BLOSSOM study [Chapple *et al.* 2013a] was a phase IIA proof of concept study. A total of 314 patients with OAB symptoms were included of whom 262 were randomized into four groups: placebo, mirabegron 100 mg bd, mirabegron 150 mg bd or tolterodine 4 mg qds for a 4-week treatment. The primary endpoint was efficacy and the primary efficacy endpoint was a change in number of micturitions per 24 hours from baseline to 4 weeks. The two mirabegron groups showed significant improvements *versus* placebo (−2.19 and −2.21, respectively). The mean voided volume dose dependently increased in the mirabegron groups and the change attained significance in the mirabegron 150 mg group. An increase in heart rate of 5 beats per minute (bpm) was noted but was not associated with clinically significant increase in adverse events. The drug appeared to be safe and well tolerated.

Chapple and colleagues carried out the phase IIB trial (DRAGON). This was a dose ranging study with extended release once-daily dose of mirabegron 25 mg, 100 mg, 150 mg, 200 mg or placebo or tolterodine 4 mg extended release (ER) for a 12-week period. A total of 928 patients were randomized. The primary endpoint was to evaluate the dose–response relationship for efficacy in terms of mean number of micturitions per 24 hours. Secondary endpoints included change in volume voided per micturition, mean number of urgency urinary incontinence and urgency episodes per 24 hours, severity of urgency, nocturia and quality of life measures. Baseline to end of treatment micturition frequency decreased in a dose-dependent fashion and were statistically significant for mirabegron 50 mg, 150 mg and 200 mg *versus* placebo. The mean volume voided per micturition increased in a dose-dependent fashion and the increases were significant for doses of above 50 mg. There was a statistically significant improvement with mirabegron *versus* placebo for most secondary endpoints including quality of life variables. Adverse events and discontinuation rates were similar to placebo in all groups [Chapple *et al.* 2013b].

There have been a number of phase III trials assessing efficacy and safety of mirabegron [Herschorn *et al.* 2013; Khullar *et al.* 2013a; Nitti *et al.* 2013a; Yamaguchi *et al.* 2014]. The four largest studies included patients >18 years of age who had OAB symptoms >3 months. They each had a 3-day diary to show they had more than eight micturitions in 24 hours and more than three urgency episodes with or without incontinence (or one episode of urgency or more than one episode of urgency incontinence in 24 hours in the Yamaguchi study). Exclusion criteria were the presence of stress incontinence, mixed incontinence or total urine volume >3000 ml in 24 hours. They were randomized, parallel-group, placebo-controlled, double-blind multicentre studies with a 2-week placebo run-in period. SCORPIO included tolterodine 4 mg ER and compared this with placebo but no direct

**Table 1.** Phase III trials of mirabegron.

| Trial | Arms of study | Primary endpoint | Study size |
|---|---|---|---|
| CAPRICORN 2013<br>to assess the efficacy and safety of mirabegron in patients with OAB<br>Europe and North America | 25 mg mirabegron<br>50 mg mirabegron<br>placebo | Change from baseline to final visit in mean number of incontinence episodes per 24 hours and micturitions per 24 hours | $n = 1306$<br>baseline demographics similar |
| SCORPIO 2013<br>to assess tolerability, efficacy, safety of mirabegron<br>Europe and Australia | 50 mg mirabegron<br>100 mg mirabegron<br>placebo<br>4 mg tolterodine | Change from baseline to final visit in mean number of incontinence episodes per 24 hours and micturitions per 24 hours | $n = 1987$<br>baseline demographics similar |
| ARIES 2013<br>US and Canada | 50 mg mirabegron<br>100 mg mirabegron<br>placebo | Change from baseline to final visit in mean number of incontinence episodes per 24 hours and micturitions per 24 hours | $n = 1329$<br>baseline demographics similar |
| Yamaguchi 2014<br>Japan | 50 mg mirabegron<br>placebo<br>tolterodine 4mg | Change in mean number of micturition episodes per 24 hours | $n = 1105$<br>baseline demographics similar (82% female) |

**Table 2.** ARIES efficacy results.

| Baseline to final visit | Placebo | 50 mg Mirabegron | 100 mg Mirabegron |
|---|---|---|---|
| **Incontinence episodes/24 hours** | **−1.13** | **−1.47*** | **−1.63*** |
| **Micturitions/24 hours** | **−1.05** | **−1.66*** | **−1.75*** |
| Change in mean voided volume/micturition (ml) | +7.0 | +18.2* | +18.0* |
| Grade 3 or 4 urgency episodes/24 hours | −0.82 | −1.57 | −1.76 |
| Nocturia episodes/24 hours | −0.38 | −0.57 | −0.57 |

*$p < 0.05$.

comparison was made between tolterodine and mirabegron. Likewise, the Yamaguchi study included tolterodine but did not directly perform statistical analysis comparing tolterodine and mirabegron. Follow-up visits were at baseline, and weeks 4, 8 and 12. Primary and secondary efficacy endpoints and treatment emergent adverse events, including serious cardiac events, were recorded. Lab assessments, vital signs, ECG and post-void residual volumes were measured at each visit. An adverse event of hypertension was recorded if systolic blood pressure (SBP) was higher than 140 mmHg or diastolic blood pressure (DBP) was above 90 mmHg, or both, on two consecutive visits, in patients who were not hypertensive at baseline [Table 1].

In the ARIES trial, both mirabegron treatment groups were associated with significantly greater reduction from baseline to final visit *versus* placebo in mean number of incontinence episodes and micturitions per 24 hours. There was a significant increase in volume voided in both mirabegron groups. Of the secondary endpoints, there was also a significant improvement with both mirabegron groups *versus* placebo in number of incontinence, urgency and nocturia episodes. Both mirabegron groups showed improvements at week 4 and maintained it at week 12 [Table 2].

In the SCORPIO trial the primary comparison was between placebo and mirabegron with a secondary comparison between placebo and tolterodine [Table 3]. There was a statistically significant decrease in number of incontinence episodes and micturitions per 24 hours in both mirabegron groups compared with placebo. Efficacy was assessed using either full set analysis (FAS) or patients with at least one episode of incontinence at baseline (FAS-I).

**Table 3.** SCORPIO efficacy results.

| Baseline to final visit | Mirabegron 50 mg | Mirabegron 100 mg | Placebo | Tolterodine 4 mg |
|---|---|---|---|---|
| **Incontinence episodes per 24 hours** | **–1.57*** | **–1.46*** | **–1.17** | |
| **Number of micturitions per 24 hours** | **–1.93*** | **–1.77*** | **–1.34** | |
| Mean increase in volume voided (FAS) ml | 24.2 | 25.6 | 12.3 | 25 |
| Change in number of incontinence episodes (FAS1) | –1.04 | –1.03 | –0.65 | –1.00 |
| Mean number of urgency episodes (FAS) | –2.25 | –1.96 | –1.65 | –2.07 |
| Responder analysis reduction in incontinence episodes (FAS1) | 72% | 67.6% | 60.1% | 68.3% |
| Responder analysis for zero incontinence episodes at final visit (FAS1) | 45.1% (not statistically significant higher than placebo) | 43.8% | 40.5% | 47.3% |

*$p < 0.05$.

**Table 4.** CAPRICORN efficacy results.

| Baseline to final visit | Mirabegron 25 mg | Mirabegron 50 mg | Placebo |
|---|---|---|---|
| **Incontinence episodes per 24 hours** | **–1.36*** | **–1.38*** | **–0.96** |
| **Number of micturitions per 24 hours** | **–1.65** | **–1.60** | **–1.18** |
| Mean volume/micturition (ml) | +12.8 (not significant) | +20.7* | |
| Number of incontinence episodes per 24 hours (FAS-I) | –0.96 (both significant *versus* placebo) | –1.13* | |
| Responders for >50% reduction in incontinence episodes | 72.8% | 70% | 59.2% |
| Percentage with zero incontinence episodes | 45.7% | 47.1% | 39.7% |

*$p < 0.05$ compared with placebo.

Key secondary efficacy endpoints included mean volume voided per micturition and percent of responders with greater than 50% decrease from baseline in mean number of incontinence episodes per 24 hours and percentage of responders with no incontinence at final visit.

Results showed statistically significantly improved baseline to final visit in mean numbers of incontinence episodes and micturition seen in mirabegron 50 mg and 100 mg *versus* placebo which was seen from week 4 and maintained over time. Mirabegron 50 mg showed statistically significant improvement from baseline *versus* placebo to final visit in urgency incontinence episodes in 24 hours, urgency episodes in 24 hours, and mean level of urgency. Tolterodine showed non-statistical improvement in urgency incontinence episodes, but showed statistical improvements in mean volume voided and urgency episodes in 24 hours. All active treatments achieved statistically significant differences in mean volume voided per micturition. Mirabegron 50 mg showed a statistically significant improvement from baseline to final visit in number of episodes of urgency. All three active treatments demonstrated statistically significant improvement from baseline to final visit compared with placebo on patient quality of life questionnaire reporting. A *post hoc* analysis of this data separately analysing the patients who had not had previous antimuscarinic treatment and those that had showed similar improvements in endpoints in patients with OAB who were treatment naïve and those who had previously stopped other antimuscarinic therapy [Khullar *et al.* 2013b].

**Table 5.** Yamaguchi efficacy results.

| Baseline to final visit | Mirabegron 50 mg | Placebo | Tolterodine 4mg |
|---|---|---|---|
| **Number of micturitions per 24 hours** | **−1.67*** | **−0.86** | **−1.4** |
| Mean number of urgency episodes per 24 hours | −1.85* | −1.37 | −1.66 |
| Mean number of incontinence episodes per 24 hours | −1.12* | −0.66 | −0.97 |
| Mean number of urgency incontinence episodes per 24 hours | −1.01* | −0.60 | −0.95 |
| Mean volume voided per micturition (ml) | +24.3* | +9.7 | 28.8 |

*$p < 0.05$ compared with placebo.

In the CAPRICORN trial, both mirabegron groups demonstrated statistically significant improvements for coprimary endpoints *versus* placebo. Incontinence was reduced by approximately 50% in the mirabegron groups *versus* placebo. Mirabegron 50 mg was effective at week 4 with a significant reduction in episodes of incontinence and this was maintained at week 12. The 25 mg dose had a numerically smaller effect *versus* 50 mg for the mean level of urgency and number of urgency episodes [Table 4].

In the Yamaguchi study tolterodine was used as an active comparator but without testing for non-inferiority of efficacy and safety [Table 5].

Mirabegron was associated with a significantly greater reduction from baseline to final visit in number of micturitions per 24 hours *versus* placebo. Secondary endpoints showed significant improvement in the mirabegron group *versus* placebo in reduction in number of urgency and incontinence episodes. All the primary and secondary efficacy endpoints showed improvement with mirabegron *versus* placebo at week 4 of the study. Seven out of the nine quality-of-life domains improved with mirabegron compared with placebo.

Each phase III study reported treatment-related adverse events.

The majority of treatment emergent adverse events (TEAEs) were mild in severity in the Yamaguchi study [table 6]. There were no treatment-related serious adverse events. The incidence of cardiovascular-related adverse events (tachycardia, palpitations, increased heart rate, increased blood pressure and ECGs) was similar to placebo. There was a slight increase in mean pulse rate (2 bpm) for the mirabegron group at 4 weeks but this did not increase with time. The pulse rate returned to normal after treatment was stopped.

Tolerability is important in the treatment of a chronic condition and this study showed low incidence of side effects in mirabegron group *versus* placebo. Only one patient with pre-existing cardiovascular disease received mirabegron and had no adverse events.

Mirabegron was well tolerated in the CAPRICORN study with the incidence of TEAEs in both mirabegron groups similar to that of placebo. Most TEAEs were mild or moderate. The severe adverse event occurrence was higher in the placebo group.

The ARIES safety assessment also revealed similar frequency of TEAEs between the mirabegron and placebo groups [table 7]. Less than 2% in all groups had dry mouth. There were no TEAEs of QTc prolongation, ventricular tachycardia or ventricular fibrillation. Cardiac arrhythmias (tachycardia, atrial fibrillation) were reported in 0.9% of the placebo group, 2% of the mirabegron 50 mg group and 2.3% mirabegron of the 100 mg group. Hypertension TEAEs were reported in 7.1%, 7.5% and 6.2% of the placebo, mirabegron 50 mg and mirabegron 100 mg groups. There were no serious hypertension TEAEs reported. A small increase in pulse rate was observed *versus* placebo (up to 2.6 bpm in the mirabegron 100 mg group). The difference in post-void residual volume was comparable across all three groups. No patient had more than 300 ml residual. The number of patients who discontinued due to adverse events were 3.7% in the placebo group, 4.1% in the 50 mg mirabegron group and 4.4% in the 100 mg mirabegron group.

The SCORPIO trial again showed the incidence of TEAES was similar across the placebo, mirabegron (50 and 100 mg) and tolterodine groups [table 8]. Dry mouth was significantly higher in the tolterodine group. The incidence of cardiovascular-related events was monitored with hypertension-related

TEAEs found to be higher in the placebo and tolterodine group than the mirabegron groups. The small dose-dependent rise in pulse rate, compared with placebo, in the mirabegron groups was found to be similar compared with the tolterodine group. Mean changes in blood pressure from baseline was less than 1.5 mmHg for both diastolic and systolic measurements.

Chapple and colleagues [Chapple *et al.* 2013c] carried out a phase III randomized double-blind active controlled study to assess safety and efficacy of mirabegron in OAB over a 12-month period (TAURUS) [table 9 and 10]. The primary objective was to assess safety and tolerability of 12-month treatment with once-daily 50 or 100 mg mirabegron in parallel with tolterodine. Patients with frequency of more than eight times in 24 hours and three or more episodes of urgency were randomized to mirabegron 50/100 mg or 4 mg tolterodine. Patients completed bladder diaries at baseline, and months 1, 3, 6, 9 and 12 and recorded morning and afternoon blood pressure and pulse rate. The primary endpoint safety variable was incidence of TEAEs. Each patient was examined and had bloods, vital signs and ECG carried out at each visit.

Efficacy endpoints were secondary and were changes from baseline at months 1, 2, 6, 9 and 12 recorded in a bladder diary of key OAB symptoms. In addition, two responder analyses based on incontinence were included: responders were defined as those with greater than 50% decrease from baseline in number of incontinence episodes, or those with zero incontinence episodes at final visit. A total of 2444 patients with similar baseline demographics were randomized.

Common TEAEs included hypertension, dry mouth, constipation and headache. The incidence was similar across all groups with the exception of dry mouth being higher in the tolterodine group. The incidence of cardiovascular arrhythmias was higher in the tolterodine group. There was a small increase from baseline to final visit of SBP and DBP in the mirabegron groups. The increase in pulse rate was small and similar in the mirabegron 100 mg and tolterodine groups.

There were no safety concerns during or at the end of the study across the treatment groups.

The safety profile was found to be similar to that of the earlier 12-week studies. They also noted the improvements in efficacy found at month 1 was sustained throughout the 12-month follow up.

**Table 6.** Yamaguchi safety results.

| | Mirabegron | Placebo | Tolterodine |
|---|---|---|---|
| TEAEs | 24.5% | 24% | 34.9% |
| Constipation | 3.5% | 2.6% | 3.5% |
| Dry mouth | 2.6% | 2.9% | 13.3% |

TEAE, treatment-emergent adverse event.

Chapple and colleagues [Chapple *et al.* 2015] used pooled data from SCORPIO, ARIES, CAPRICORN to examine the efficacy of mirabegron for treatment of OAB by severity of incontinence at baseline. The effect of once-daily mirabegron 50 mg was compared with placebo for frequency of micturition, urgency episodes and volume voided per micturition in the subgroup who were incontinent at baseline. They also compared the effect on these variables stratified by the severity of the incontinence (at least two episodes a day and at least four episodes a day). There were 878 patients in the placebo group and 862 patients in the mirabegron group. Mirabegron resulted in statistically significant improvements in domains of mean number of incontinence episodes, mean number of micturitions, mean number of urgency episodes and mean volume voided compared with placebo and this treatment effect was increased in the group with the more significant incontinence at baseline.

Given the prevalence of OAB in an aging population with other comorbidities, the potential cardiovascular effects of stimulating the β3 adrenoceptors needs considering. A recent systemic literature review was performed on the cardiovascular effects of β3 adrenoceptor agonists [Rosa *et al.* 2016]. Data from the placebo and mirabegron arms of SCORPIO, ARIES, CAPRICORN and TAURUS were pooled and cardiovascular events of interest noted. These included hypertension, QT prolongation and cardiac arrhythmias. Hypertension was the most commonly reported TEAE occurring in 8.7% of the pooled mirabegron group *versus* 8.5% of the placebo group. The mean change in SBP and DBP was less than 1 mmHg from baseline to week 12. Patients with poorly controlled hypertension, arrhythmias or cardiac heart failure were excluded from the studies so data is

**Table 7.** ARIES safety results.

| | Mirabegron 25 mg | Mirabegron 50 mg | Placebo |
|---|---|---|---|
| TEAEs | 48.6% | 47.3% | 50.1% |
| SAEs | 1.9% | 1.8% | 3.7% |
| Dry mouth | 1.9% | 1.6% | 2.1% |
| Hypertension | 6.9% | 7% | 5.3% |
| Headache | 0.9% | 0.9% | 2.1% |
| PVR >300 ml | 0 patient | 1 patient | 2 patients |
| Tachycardia | 1.6% | 1.6% | 0.9% |
| Discontinuation due to AEs | 3.9% | 2.7% | 3.5% |

AE, adverse event; PVR, post-void residual volume; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

**Table 8.** SCORPIO safety results.

| | Mirabegron 50 mg | Mirabegron 100 mg | Placebo | Tolterodine |
|---|---|---|---|---|
| Dry mouth | 2.8% | 2.8% | 2.6% | 10.1% |
| Hypertension | 5.9% | 5.4% | 7.7% | 8.1% |
| Pulse rate increases *versus* placebo | Am +0.8<br>Pm +0.7<br>Both groups similar to tolterodine *versus* placebo | Am +1.6<br>Pm +2.0 | | |
| Number of patients with notable shift in PVR >300 ml | 1 | 2 | | 1 |
| Discontinuing due to TEAE | 4.9% | 3.2% | 2.6% | 4.4% |

PVR, post-void residual volume; TEAE, treatment-emergent adverse event.

**Table 9.** Safety results of TAURUS.

| | Mirabegron 50 mg n=812 | Mirabegron 100 mg n=820 | Tolterodine 4mg n=812 |
|---|---|---|---|
| TEAEs | 59.7% | 61.3% | 62.6% |
| Dry mouth | 2.8% | 2.3% | 8.6% |
| Discontinuation | 6.4% | 5.9% | 6.0% |
| SAEs | 5.2% | 6.2% | 5.4% |
| AUR requiring catheter | 0 patients | 1 patient | 1 patient |
| Cardiac arrhythmias | 3.9% | 4.1% | 6% |
| Major adverse cardiovascular events | 0.7% | 0% | 0.5% |
| Changes in SBP from baseline to final (mmHg) | +0.2 (am)<br>−0.3 (pm) | +0.4 (am)<br>+0.1 (pm) | −0.5 (am)<br>0 (pm) |
| Change in pulse rate from baseline (bpm) | +0.9 (am)<br>+0.4 (pm) | +1.6 (am)<br>+1.3 (pm) | +1.5 (am)<br>+1.9 (pm) |

AUR, acute urinary retention; SAE, serious adverse event; TEAE, treatment–emergent adverse event.

lacking on this group and blood pressure and pulse should be monitored after commencing mirabegron.

There is a lack of head-to-head comparisons of mirabegron with other antimuscarinic agents. Maman and colleagues carried out a quantitative

**Table 10.** Efficacy results of TAURUS.

| | Mirabegron 50 mg | Mirabegron 100 mg | Tolterodine 4mg |
|---|---|---|---|
| Change in number of micturitions in 24 hours from baseline | −1.27 | −1.41 | −1.39 |
| Change in number of incontinence episodes from baseline | −1.01 | −1.24 | −1.26 |
| Change in mean volume voided/micturition (ml) | +17.5 | +21.5 | +18.1 |
| Percentage of responders with >50% decrease in mean number incontinence episode per 24 hours | 63.7% | 66.3% | 66.8% |
| Percentage of responders for zero incontinence | 43.4% | 45.8% | 45.1% |
| Discontinuation due to lack of efficacy | 3.6% | | 5.5% |

synthesis of the literature to compare the clinical efficacy and safety of the most widely used pharmacological agents used to treat OAB and more specifically to estimate the efficacy and safety of mirabegron compared with other antimuscarinics [Maman *et al.* 2014]. The review considered all randomized controlled trials studying the efficacy or safety of pharmacological agents used to treat OAB and included darifenacin, fesoterodine, oxybutinin, solifenacin, tolterodine, trospium and mirabegron. A Bayesian mixed treatment comparison was conducted to estimate the relative efficacy and safety of mirabegron *versus* other OAB agents. They included 44 trials with a total of 27,309 patients. A total of 26 studies examined micturition frequency and found the effect of mirabegron was not significantly different to other OAB agents. Solifenacin 10 mg was more effective; it had 100% probability for being more effective in reducing the number of micturitions in 24 hours. A total of 17 trials examined improvement in number of daily incontinence episodes; again, mirabegron was not significantly better than other agents. A total of 18 studies combined found mirabegron was significantly less efficacious than solifenacin 10 mg in terms of urgency urinary incontinence and did not differ from other antimuscarinics. All 44 studies reported on dry mouth with mirabegron having a similar dry mouth incidence to placebo. All other antimuscarinics had significantly higher rates of dry mouth compared with mirabegron. Mirabegron had a similar incidence of constipation to placebo, compared with the other antimuscarinics which had a significantly higher incidence.

One randomized double blind phase IIIb noninferiority study enrolled 1887 patients who had failed antimuscarinic therapy and randomized them to solifenacin 5 mg or mirabegron 50 mg for 12 weeks [Batista *et al.* 2015]. The primary efficacy endpoint was change in baseline to end of study in mean number of micturitions per 24 hours. Noninferiority of mirabegron to solifenacin was not demonstrated for the primary endpoint. Both drugs improved key OAB symptoms including number of incontinence episodes, urgency episodes and urgency incontinence episodes but no difference between the drugs was demonstrated.

The majority of patients studied using mirabegron have had pure OAB symptoms but, in practice, many men with have a combination of storage and voiding symptoms with urgency being a most bothersome symptom. Nitti and colleagues [Nitti *et al.* 2013b] investigated urodynamic parameters in men with lower urinary tract symptoms and bladder outflow obstruction treated with mirabegron. A total of 200 men were randomized to receive placebo, mirabegron 50 mg or mirabegron 100 mg. Primary urodynamic parameters assessed were the change from baseline to end of treatment in maximum urinary flow rate and detrusor pressure. The study showed that mirabegron did not adversely affecting voiding parameters such as the bladder contractility index *versus* placebo compared with placebo after 12 weeks of treatment.

Otsuki and colleagues [Otsuki *et al.* 2013] investigated the safety and efficacy of mirabegron for patients with OAB unresponsive to previous antimuscarinic treatment and OAB related to 'benign prostatic hyperplasia' in 143 patients. They found mirabegron is as effective as antimuscarinics for

newly diagnosed OAB and effective for OAB that is resistant to antimuscarinics. They found no negative impact on voiding or detrusor contraction in the group with 'BPH' (prostate volume >30 ml).

There is an increasing aging population affected by OAB. They often have multiple comorbidities and are taking other anticholinergic medication. Wagg and colleagues used results from the phase III studies including both the 12-week and 12-month follow up and carried out a subgroup analysis of the patients group over the age of 65 and 75 [Wagg *et al.* 2016]. Their results showed the incidence of dry mouth occurred with a six-fold higher incidence in the tolterodine ER 4 mg group compared with mirabegron 25 or 50 mg and a threefold higher incidence with tolterodine ER *versus* mirabegron over 1 year. Patients over the age of 65 were not any more likely to experience cardiovascular adverse events.

## Efficacy in combination

Management of OAB symptoms in the future may involve utilizing combinations of medications. There are emerging trials that have been investigating the combination of an anticholinergic and a β3 agonist. The first of these was the SYMPHONY study: a phase II study investigating use of mirabegron in various doses in combination with solifenacin. This study showed greater improvements in mean voided volume, frequency and urgency with combination therapy as opposed to monotherapy with solifenacin [Abrams *et al.* 2015]. More recently a phase IV study has been published from a Japanese group (the MILAI study), looking at mirabegron as add-on therapy to solifenacin in patients with OAB symptoms that have not been controlled just by solifenacin [Yamaguchi *et al.* 2015]. Short-term results (16 weeks) were presented, showing that adding 25 mg of mirabegron to patients already taking either 2.5 or 5 mg of solifenacin, with an option to increase to 50 mg mirabegron at 8 weeks, led to significant improvements in efficacy but with an increased side-effect profile. This was contradicted in a paper by Kosilov and colleagues investigating the use of short-term combination therapy of solifenacin and mirabegron in older male and female patients with an OAB [Kosilov *et al.* 2015]. The paper states that combination therapy for 6 weeks was the most effective management for urgency incontinence and urinary frequency as compared with monotherapy, and failed to show an increase in the side effects in this population. Longer-term results are awaited from other studies that are ongoing, such as the BESIDE study which is investigating effect on urgency incontinence with a combination of solifenacin and mirabegron. Given that OAB is a chronic disease, it will be important to see longer-tem efficacy and safety of combinations along with tolerability data.

OAB often coexists in men with voiding symptoms secondary to benign prostatic obstruction. There are only two papers investigating this combination. The first study was an open-label randomized two-arm, two-sequence study to investigate the safety profiles of dual therapy with both medications, in particular assessment of cardiovascular side effects [van Gelderenvan *et al.* 2014]. There were no clinically relevant cardiovascular side effects noted. The second study investigated the combination of mirabegron with tamsulosin in male patients with mixed OAB and voiding lower urinary tract symptoms [Ichihara *et al.* 2015]. This was a randomized multicentre Japanese study of 96 men, which showed a significant improvement in urgency, urgency incontinence and nocturia with combination therapy as compared with monotherapy. These two studies show the safety of using mirabegron as add-on therapy in combination with tamsulosin in male patients with benign prostatic obstruction.

## The future

Future developments and research in the arena of OAB treatment will include other types of β3 agonist. Two other β3 agonists have been reported in the literature: solabegron and ritobegron. Solabegron has been investigated in a phase II trial and has shown good results [Ohlstein *et al.* 2012], whilst ritobegron has not yet been reported in human trials but has been shown to exhibit potent and selective β3 agonist activity in monkeys [Maruyama *et al.* 2012].

OAB guidelines, such as those from the European Association of Urology [Lucas *et al.* 2015] and the National Institute of Clinical Excellence [NICE, 2010], currently recommend an anticholinergic as first-line medical treatment and recommend mirabegron as second-line medical treatment. However, this may change in the future, particularly given that studies have shown good responses in the treatment-naïve groups.

## Conclusions

Mirabegron is the first β3 adrenoceptor agonist licensed for use in the treatment of OAB. It is a safe, effective and well-tolerated new class of drug. The tolerability profile of mirabegron offers potential to improve patients' adherence with treatment for OAB as dry mouth is often the reason cited for stopping antimuscarinic treatment. The incidence of dry mouth with mirabegron is similar to placebo in all trials. It has consistently demonstrated its efficacy and tolerability in phase III randomized controlled trials. It has shown statistically significant improvements in the mean number of incontinence episodes per 24 hours and micturitions per 24 hours when compared with placebo. Secondary endpoints showed significant improvements with mirabegron *versus* placebo in voided volume and urgency-related outcomes. These improvements are generally significant at week 4 after starting treatment and are maintained at 12 months. There is a lack of head-to-head comparison between mirabegron and other anticholinergic drugs. Future studies should compare directly, and as urgency is one of the most bothersome symptoms of OAB, studies using this as a primary endpoint would be clinically relevant. Long-term data is also needed to see whether the initially promise of mirabegron's efficacy and tolerability is maintained beyond 12 months.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Conflict of interest statement

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: KW and HB have no conflicts of interest to declare. PA has previously received personal fees from Astellas, Ferring, Ipsen and Pfizer and had support for research projects from Astellas.

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