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Mirabegron, alone and in combination, in the treatment of overactive bladder: real-world evidence and experience

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Abstract: Overactive bladder (OAB), the syndrome characterized by urgency, with or without urgency incontinence, usually with frequency and nocturia, in the absence of infection or other pathology, is a common, distressing and often debilitating condition with a high prevalence in the general population. For many years, the only available pharmacological treatment for OAB were the antimuscarinic agents. More recently, mirabegron, a selective agonist of the β3 adrenergic receptor, has become available. In this article we review the current evidence and experience of its use.

Keywords: overactive bladder, urinary incontinence, mirabegron, beta-3 agonist, pharmacotherapy, lower urinary tract symptoms

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Background

Lower urinary tract symptoms (LUTS), including urgency, frequency and nocturia, are common in the general population and increase in prevalence with ageing.[1,2] Overactive bladder (OAB), the clinically defined symptom complex of urgency, with or without urgency incontinence, usually with frequency and nocturia, in the absence of infection or other pathology,[3] is the most common cause of incontinence in both men and women, and the prevalence of OAB increases with age.[1] OAB and other forms of urinary incontinence (UI) are stigmatizing conditions with significant impacts on quality of life[4,5] and are commonly under-reported by patients for multiple reasons,[6] including belief that incontinence is normal post-partum or as part of ageing, or that treatment is not available.[7] OAB is a disorder of the filling phase of the bladder, characterized by the presence of urgency, the sudden, compelling desire to void which is difficult to defer.[3] The exact underlying cause of urgency and of OAB remains the subject of much debate in the literature, with there being evidence for the urothelium,[8] detrusor,[9] and brain[10] being involved in the pathophysiology of OAB. In those without lower urinary tract dysfunction, voiding is under voluntary control and continence is maintained by a complex interaction between the bladder and numerous areas of the brain, including the frontal and prefrontal cortices, the periaqueductal grey matter and the pontine micturition centre.[11] Neurological diseases, including the accumulation of white matter hyperintensities on MRI, cerebrovascular disease and dementia are all strongly associated with the development of LUTS in later life.[12–14] As such, OAB cannot be considered simply as a disease of the bladder and lower urinary tract. Although conservative management options consider a whole-person approach, encompassing fluid intake, urgency suppression and bladder retraining, pharmacological agents are all directed at the bladder itself.

Treatment of OAB

The earliest account of treatment for incontinence was written by Pliny the Elder in AD77, who advocated giving children boiled mice in their food as a treatment for bedwetting.[15] Beyond this, for many years the only available pharmacological options for treating OAB were anticholinergic drugs. Oxybutynin, a non-selective antagonist of the muscarinic receptor,[16] became available in the 1970s[17] and has been shown in multiple randomized controlled trials (RCTs) to be effective in reducing

symptom burden in OAB,[18–21] and experience of its use means that clinicians are well-versed in its efficacy, tolerability and side-effect profile. It has been long recognized that oxybutynin carries a significant burden of adverse drug reactions, with anticholinergic side-effects being common, including constipation, dry mouth and blurred vision.[18,22] Dry mouth occurs in up to 80% of those taking oxybutynin,[23] and discontinuation rates are high, with a systematic review of OAB drugs in 2011 finding discontinuation rates up to 31% at 12 weeks in RCTs, up to 80% in analyses of claims data, and with half of patients not refilling their prescriptions after the first script issued.[24] Despite this, oxybutynin is recommended as first-line pharmacotherapy in several national guidelines, including those of the National Institute of Health and Clinical Excellence in the UK.[25] This is most likely on cost grounds, as oxybutynin has the lowest acquisition cost of the available medications for OAB.[26] Newer and more selective anticholinergics for the treatment of OAB have been developed, including tolterodine in the 1990s,[27] with solifenacin,[28] darifenacin[29] and fesoterodine[30] becoming available for clinical use in the 2000s. The newer anticholinergics are more selective for the M2 and M3 receptor subtypes[31] and were developed in the hope that this increased selectivity would improve efficacy and reduce side-effects. A Cochrane review of the available anticholinergics for OAB suggested that tolterodine conferred a lower risk of xerostomia than oxybutynin, that solifenacin demonstrated superior efficacy to tolterodine, and that fesoterodine likewise was more efficacious than tolterodine.[32]

Anticholinergic concerns

Exposure to drugs with anticholinergic effects has been lined to cognitive decline in older adults[33] with cumulative exposure to anticholinergic drugs being linked to an increased risk of dementia.[34] Normal ageing is associated with changes to the blood–brain barrier, with increased permeability to inflammatory mediators and drugs,[35] and lipophilic drugs such as oxybutynin are inherently able to cross the blood–brain barrier relatively freely.[36] This may be why oxybutynin in particular, of the bladder antimuscarinics, has been shown, in high doses, to be associated with impaired cognitive performance.[37,38] There is evidence that the newer and more M2/M3-specific antimuscarinics have little or no impact on cognition, with cognitive safety data available for trospium,[39] darifenacin,[40] solifenacin[41] and fesoterodine[42] in cognitively intact older people. It has therefore been suggested that the use of oxybutynin should be avoided in the elderly, and in particular the frail elderly.[43] Anticholinergic side-effects, and in particular dry mouth, are the most commonly cited reasons for discontinuing treatment for OAB with antimuscarinic drugs.[24] Older adults are also more likely to be subjected to polypharmacy, the prescription of five or more medications,[44] which exponentially increases the risk of drug–drug interaction and potential for harm.[45] There is evidence from case-control studies that exposure to drugs with an Anticholinergic Cognitive Burden Scale (ACB) of 3 confers higher odds of developing dementia, with an odds ratio of 1.11 [95% confidence interval (CI) 1.08–1.14] when compared to no anticholinergic exposure.[46] However, 'gastrointestinal' and 'antipsychotic' drugs with an ACB score of 3 did not demonstrate this association, and no dose–response effect was demonstrated. Furthermore, the 'urological' drugs were considered as a class, without the differential cognitive risks, lipophilicity, CNS penetration and receptor subtype affinity being considered. In addition, objective serum anticholinergic activity has been found to have no link to cognitive impairment in randomized studies.[47] At present, therefore, there is no evidence to suggest the complete avoidance of the newer antimuscarinics in older people is necessary.

Across patient groups, the typical anticholinergic side-effects of dry mouth and constipation are particularly bothersome, which is reflected in the poor adherence rates with anticholinergics. Therefore, national and international guidelines for the treatment of OAB emphasize conservative methods such as bladder retraining, fluid intake normalization and urgency suppression techniques prior to the use of pharmacotherapy,[48] and much research has focused on finding alternative, non-anticholinergic drugs for the treatment of OAB.

Development of mirabegron

Initial interest in β3 receptors centred around their role in thermogenesis in adipose tissue and potential for development as a treatment for obesity,[49] which proved a therapeutic dead end. However, investigation of the role of β3 in detrusor relaxation suggested that β3 agonists could be a useful therapeutic option for OAB,[50] and mirabegron was developed by Astellas Pharma Inc., Japan.[51] Mirabegron is currently the only available β3 agonist. It was approved for clinical use in

the USA in 2012, and is a potent and selective agonist of the β3 adrenoreceptor.[52] Mirabegron has been studied as both monotherapy and as combination therapy as a treatment for OAB. At present, mirabegron is the only available β3 agonist, although a second agent, vibegron, is undergoing phase III trials.[53]

Mirabegron as monotherapy

Following development and testing in phase I and II trials,[51] mirabegron as monotherapy for OAB was studied in numerous phase II and III RCTs, with both placebo and active controls.

The SCORPIO trial compared mirabegron to placebo and tolterodine in people with OAB in Europe and Asia.[54] Khullar and colleagues randomized a total of 1978 adults with OAB in a 1:1:1:1 ratio comparing placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine ER 4 mg. [54] Tolterodine was included as an active control but formal statistical comparisons with tolterodine were not performed. The mirabegron groups had statistically significant reduction in the number of incontinence episodes per 24 h from baseline (−1.57 and −1.46 for 50 mg and 100 mg respectively) compared to placebo and in number of micturitions per 24 h, with 1.93 and −1.99 fewer for mirabegron 50 mg and 100 mg respectively compared to 1.34 fewer in the placebo arm. Similarly, in the ARIES trial, Nitti and colleagues randomized 1329 adults in North America to receive placebo, mirabegron 50 mg, or mirabegron 100 mg in a 1:1:1 ratio.[55] Over the 12 week follow-up period there was a significantly greater improvement in the key end-point, incontinence episodes per 24 h, in the mirabegron groups (−1.47 and −1.63 for 50 mg and 100 mg respectively) compared to the placebo group (−1.13). As often seen in OAB trials, there was a significant placebo effect.[56] Secondary endpoints, including severity of urgency, nocturia and OAB-q bother scores also improved, with more in the mirabegron groups than the placebo arm. The third phase III trial, Capricorn, compared mirabegron 25 mg and 50 mg to placebo in 1305 adults with OAB in Europe and North America, across 151 sites.[57] They reported significantly greater improvements for mirabegron 25 mg and 50 mg daily compared to placebo for mean number of incontinence episodes per day (−1.36 and −1.38 respectively), as well as improvements in number of micturitions and improvements in quality of life measures.

Looking specifically at older adults, Wagg and colleagues performed a prospective subgroup analysis of these three trials analysing those aged ⩾65 and ⩾75 years of age.[58] There were no statistically significant differences across the age groups. The frequency of treatment emergent adverse events (TEAEs) was also similar across the age groups, with no increase in TEAEs in older adults with mirabegron. Unsurprisingly, the incidence of dry mouth was significantly higher in the tolterodine groups, with a sixfold higher occurrence rate than in the mirabegron groups.

All three of the initial phase III studies were of relatively short duration, each being 12 weeks in length. Longer-term studies, with follow-up periods of up to a year, have also been reported. Chappel and colleagues reported a 12-month trial of mirabegron, 50 mg and 100 mg, *versus* tolterodine extended release 4 mg, randomizing 2444 adults with OAB.[59] They collected efficacy and safety data at 1, 3, 6, 9 and 12 months, and demonstrated similar efficacy across the three groups, including a reduction in number of incontinence episodes per 24 h (−1.01, −1.24, and −1.26 for mirabegron 25 mg, 50 mg, and tolterodine respectively), and micturitions per 24 h (−1.27, −1.41, and −1.39, respectively). Serious TEAE rates were likewise similar for the three groups, at 5.2% for mirabegron 50 mg, 6.2% for mirabegron 100 mg, and 5.4% for tolterodine. TEAEs of all levels of severity were reported in 59.7%, 61.3% and 62.6%, respectively, and were most commonly hypertension, gastrointestinal disturbance (predominantly constipation), and headache, which occurred equally across the three groups. They conclude that mirabegron demonstrated an acceptable safety and tolerability profile with improvements in OAB symptoms at the first measurable time point of month 1, with sustained improvement throughout 12 months, and that the effect size was similar to those of antimuscarinic therapy.

Ciu and colleagues performed a systematic review of trials of mirabegron in 2014,[60] including four RCTs with a total of 5791 participants. They reported the standardized mean difference (SMD) from baseline to study completion, comparing mirabegron to the placebo arm, and found that mirabegron was effective in treating OAB, with a greater reduction in incontinence episodes of 0.44 episodes/day for mirabegron *versus* placebo, as well as reduced micturitions per day and episodes of urgency. They also analysed TEAEs,

finding similar rates of discontinuation for TEAEs in the active and placebo groups, with pooled odds ratio of 1.22 (95% CI 0.84–1.76), and the authors therefore concluded that mirabegron is an efficacious and well-tolerated treatment option for OAB.

It is a feature of OAB trials that the primary endpoints, such as micturitions per 24 h, incontinence episodes and voided volumes often show modest improvements, and it has been suggested that health-related quality of life (HRQoL) outcomes are a more valid measure of success.[61] In view of this, Castro-Diaz and colleagues[62] performed a post-hoc responder analysis of pooled data from three randomized, 12-week placebo controlled trials.[54,55,57] They defined a responder as a $\geqslant$50% decrease from baseline to final visit in mean number of incontinence episodes per 24 h incontinence episodes for incontinence, and a patient with $\leqslant$8 micturitions per 24 h at final assessment for urinary frequency. Within these groups, there was a statistically significantly greater improvement for patient-reported outcomes over placebo for patient perception of their bladder condition, and statistically significant improvements from baseline to final visit relative to placebo in OAB-q total HRQoL and the OAB-q subscales of coping, concern and sleeping, but not social interaction, suggesting that as well as having measurable impact on objective indices, mirabegron as monotherapy has a positive impact on quality of life.

Wagg and colleagues reported a longer-term and real-world study of mirabegron, using persistence with therapy as a marker of efficacy and tolerability.[63] They reported a 12 month retrospective cohort study of 6189 patients in the United Kingdom prescribed either an antimuscarinic or mirabegron. Their data suggested that antimuscarinics as a group were taken for less time than mirabegron, with the median days on therapy for antimuscarinics ranging from 27 days for oxybutynin IR and tolterodine IR to 55 for fesoterodine and 56 for solifenacin, compared to 101 days for mirabegron. Similarly, the mean duration of treatment was 86 days for oxybutynin IR, 130 days for solifenacin and 160 days for mirabegron. As a retrospective review of prescription data, these data were influenced by the practice of issuing prescriptions 1 month at a time, and there was a significant discontinuation rate for all agents at 30 days. Commonly reported side-effects of mirabegron were hypertension (9.1%), nasopharyngitis (4.1%) and urinary tract infection (3.1%). The authors conclude that mirabegron was associated with significantly longer time to discontinuation, greater persistence at 1 year, and better adherence with therapy than the antimuscarinic agents.

Mirabegron has not been compared to intravesical onobotulinumtoxin A in a head-to-head trial. However, Freemantle and colleagues conducted a network meta-analysis of 19 available trials to construct a network meta-regression comparing the two agents.[64] They concluded that onobotulinumtoxinA and mirabegron were both more efficacious than placebo in the treatment of idiopathic OAB, and that onabotulinumtoxinA may be superior to mirabegron in improving symptoms of UI, urgency and frequency.

The use of mirabegron in combination with other agents

There has also been interest in using mirabegron in combination with antimuscarinic drugs for treatment-resistant OAB. Given that the two groups have different modes of action, it is reasonable to think that combination therapy would have advantages over monotherapy.

The Symphony trial, a multinational phase II double-blind RCT, compared 1306 people with OAB across 12 groups, 6 combination groups (solifenacin 2.5, 5 or 10 mg plus mirabegron 25 or 50 mg), 5 monotherapy groups (solifenacin 2.5, 5 or 10 mg, or mirabegron 25 or 50 mg), or placebo,[65] with a 2 week placebo run-in period. Compared to solifenacin 5 mg monotherapy, at 12 weeks follow up those treated with mirabegron 25 mg or 50 mg in combination with solifenacin 2.5 mg, 5 mg and 10 mg had significantly reduced numbers of micturitions per 24 h, with a trend for increasing effect with increasing doses of solifenacin and mirabegron. All treatment groups, including placebo, demonstrated a reduction in the number of urgency episodes from baseline, and none of the active treatment groups significantly reduced incontinence episodes compared with placebo.

Following this, the SYNERGY study was a larger phase III trial comparing solifenacin 5 mg in combination with mirabegron 25 mg and 50 mg with solifenacin 5 mg, mirabegron 25 mg and mirabegron 50 mg as monotherapy and placebo.[66] Conducted at 425 sites in 42 countries, a total of 3398 participants were randomized in a

2:2:1:1:1:1 ratio to the combination groups and monotherapy/placebo groups respectively. Participants completed 2 weeks of placebo run-in prior to 12 weeks of therapy. As with Symphony, all the treatment groups demonstrated a reduction in UI episodes per 24 h, with a greater reduction in the combination therapy groups than monotherapy or placebo, with reductions of −1.34 for placebo, −1.7 and −1.76 for mirabegron 25 mg and 50 mg respectively, −1.79 for solifenacin 5 mg, −2.04 for mirabegron 25 mg with solifenacin 5 mg, and −1.98 for mirabegron 50 mg with solifenacin 5 mg. However, although the combined solifenacin 5 mg/mirabegron 50 mg arm was superior to solifenacin 5 mg monotherapy for UI episodes (mean adjusted difference of −0.2 episodes/24 h, 95% CI −0.44−0.04, $p = 0.033$), superiority to mirabegron 50 mg was *not* demonstrated (mean adjusted difference −0.23 95% CI −0.47, 0.01, $p = 0.052$). Prespecified subgroup analysis demonstrated a small but statistically significant improvement for reduction in micturition episodes per 24 h and incontinence episodes per 24 h for both combination groups (mirabegron 25 mg and 50 mg with solifenacin 5 mg) compared to mirabegron and solifenacin monotherapy, with all active treatment groups having greater improvements in UI episodes/24 h *versus* placebo, with effect sizes for the combined therapy groups (combined solifenacin and mirabegron 25 mg group: −0.70 episodes/24 h and solifenacin/mirabegron 50 mg group −0.65 episodes/24 h) that were higher than those obtained with monotherapy (range −0.37 episodes/24 h for mirabegron 25 mg to −0.45 episodes/24 h for solifenacin 5 mg). It is interesting to note that there was no additional benefit from the higher dose of mirabegron when comparing the two combination arms, and taken as a whole the data from this trial did not show a consistent and clinically significant benefit from combining mirabegron with solifenacin.

The BESIDE study specifically recruited adults with OAB who had not responded to 4 weeks of therapy with solifenacin.[67] Following single-blind 5 mg solifenacin run-in, those participants who reported at least one episode of incontinence on a three-day diary were randomized to receive either solifenacin 5 mg, solifenacin 10 mg or solifenacin 5 mg with mirabegron 25 mg, increasing to 50 mg after 4 weeks. A total of 2174 people entered the second phase of the study, and were randomized in a 1:1:1 ratio and followed for 12 weeks. The primary outcome measure was reduction in incontinence episodes from baseline, and secondary end-points included number of urgency episodes, mean voided volume, and nocturia, and patient perception of bladder condition score. There was a greater reduction in incontinence episodes per 24 h for the combination group than the solifenacin 5 mg group (–1.80 *versus* –1.53 respectively), and the combination was non-inferior to solifenacin 10 mg for the majority of the reported end-points. The incidence of TEAEs was lowest in the solifenacin 5 mg group (33.1%) and highest with solifenacin 10 mg (39.4%), with the combination group falling between these two at 35.9%. Classical anticholinergic effects, constipation and dry mouth, were the commonest TEAEs reported, and these were unsurprisingly highest in the solifenacin 10 mg group and similar in the combination and solifenacin 5 mg groups. This suggests that, although the effect of adding mirabegron and increasing the solifenacin dose were similar, the bothersome anticholinergic side-effects of higher-dose solifenacin could be avoided by adding mirabegron.

Given the well-reported issues concerning anticholinergic use in older adults,[34] a pre-specified subgroup analysis of the BESIDE study was reported, analysing the results in the over-65 and over-75 age groups.[68] Of the initial BESIDE group, 30.9% were aged 65 or over, and 8.9% were 75 or over. In the efficacy analysis there were no significant interactions between age group and treatment group for the $\geqslant$65 group ($p = 0.825$) or $\geqslant$75 group ($p = 0.96$), suggesting that age did not influence the efficacy of any of the three treatment arms. The older groups were more likely to have TEAEs, and in particular constipation was reported slightly more commonly in the $\geqslant$75 group in all three treatment arms, and the incidence of cardiovascular effects was $<$2% across the board. Cognitive adverse events were not specifically reported in this study. Additionally, a responder analysis to the BESIDE trial has also been reported,[69] exploring if the reported changes to objective symptoms were translated to significant improvements in patient-reported outcomes (PRO). The authors defined PRO responders as those who achieved a change from baseline to end of treatment that exceeded the predefined minimally important difference on the OAB Questionnaire[70] or the Patient Perception of Bladder Condition questionnaire.[71] There were differences in favour of the combination arm compared to both solifenacin groups in the proportion of responders who reported a 50% reduction in

incontinence episodes and normalization of micturition frequency, and those receiving combination treatment had greater odds of achieving complete cure of incontinence [OR 1.47 (95% CI 1.17–1.84)] compared to solifenacin 5 mg monotherapy. It is worth noting that all the trials using mirabegron as a combination therapy have used solifenacin, as both agents share a common manufacturer. There are no trials using mirabegron in combination with other antimuscarinics or with onabotulinumtoxinA.

Conclusion

Taken as a whole, the available data suggest that mirabegron is broadly as effective as monotherapy for OAB across the age range when compared to antimuscarinic agents. Rates of TEAEs with mirabegron are similar to antimuscarinics, although the rates of anticholinergic side-effects, which are often cited by patients as being most bothersome, are significantly lower, which may explain the improved adherence and treatment longevity with mirabegron. Clinical experience and the responder analyses suggest that, for unknown reasons, some patients do not respond to antimuscarinics for OAB, and for these patients the availability of a new class of drug provides a valuable alternative therapeutic option. The results when using mirabegron in combination with solifenacin have been disappointing, with much less of an additional benefit than may have been hoped for based on the experience of monotherapy. However, responder analyses do suggest again that for some, selected, patients, the addition of mirabegron to an antimuscarinic will achieve a meaningful improvement in their symptoms, and that higher doses of antimuscarinics can be avoided by adding mirabegron to existing treatment. As such, mirabegron is proving to be a useful addition to the available treatment options for people with OAB, and in particular in people in whom anticholinergics may be undesirable, such as the elderly and those with preexisting neurological disease.

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