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Review Article

How to choose appropriate medication for overactive bladder: Findings from the largest integrated clinical trial database analysis of mirabegron studies

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Abstract

Medical treatment of overactive bladder (OAB) includes antimuscarinic agents, beta-3 adrenoceptor agonist (mirabegron), or combination with both drugs. Recently, a meta-analysis reported the integrated clinical trial data from 10 phase 2–4, double-blind, 12-week mirabegron monotherapy studies. The results confirmed that mirabegron is as effective as the previously used antimuscarinic agent to treat OAB. The treatment-emergent adverse events were similar across subgroups. This article comments on this largest integrated clinical trial data analysis, and reviews the recently published literature and tries to reveal how to choose the appropriate medication for OAB. For OAB patients, starting from antimuscarinic agent is feasible. However, if the patients have risk of cognitive dysfunction, a history of constipation, dry mouth, and urinary retention, starting with mirabegron 50 mg might be more safe and appropriate. In the elderly patients with low detrusor contractility, with central nervous system lesion, and men with benign prostatic hyperplasia, starting from 25 mg mirabegron is recommended. If the treatment result is not satisfactory to the 25 mg mirabegron, increase dose to 50 mg mirabegron is appropriate. In patients who have failed from the first OAB medication either with antimuscarinics or mirabegron 50 mg, the exchange of the OAB medication to each other should be tried first. If the treatment result is still not satisfactory, a combination of antimuscarinics and mirabegron is recommended.

Keywords: *Adverse events, Antimuscarinics, Mirabegron, Overactive bladder, Pharmacotherapy*

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Introduction

Overactive bladder syndrome (OAB) is defined by its symptoms with urgency with or without urgency incontinence as the key symptom, usually accompanied by nocturia and frequency [1]. The prevalence of OAB has been estimated to be 12%–16% of the adult population and affects >400 million people worldwide [2]. The treatment of OAB should start with behavior modification and drinking habit changes. If OAB persists and is bothersome, antimuscarinics have conventionally been the first-line oral medication [3]. The success rate of antimuscarinics pharmacotherapy for OAB is around 70%. Some patients might have suboptimal responses or develop adverse events to antimuscarinics, such as dry mouth, constipation, or blurred vision [4]. Therefore, patients often discontinue antimuscarinics due to ineffectiveness or adverse events. Less than 25% of patients can maintain treatment for >1 year [5].

In the urinary bladder, beta-3-adrenergic receptors are responsible for detrusor muscle relaxation. During the bladder storage phase, the balance between parasympathetic and sympathetic activity should be maintained to ensure a stable bladder without phasic detrusor contractions, which cause the urgency sensation [6]. Mirabegron is the first β_3-adrenoceptor agonist that has a therapeutic effect on detrusor overactivity during the storage phase and has been approved for the treatment of OAB.

The efficacy and safety of mirabegron in the treatment of OAB have been confirmed by several previous phase III trials in Europe, Australia, and North America [7-9]. The adverse events (AEs) of mirabegron differ from those of antimuscarinics. Since dry mouth and constipation are the chief causes of discontinuation of antimuscarinic treatment, the pooled safety data have indicated that mirabegron is a valuable therapeutic option for OAB patients [10]. The mirabegron treatment

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response is similar to that of other OAB agents such as darifenacin, fesoterodine, oxybutynin transdermal delivery systems, propiverine extended-release (ER), solifenacin, tolterodine ER and immediate release, and trospium. Patients treated with mirabegron showed statistically significant improvements in health-related quality-of-life measures versus placebo [11].

A recently published pooled data analysis from 10 phase 2–4, double-blind, 12-week mirabegron monotherapy studies in adults with OAB further confirmed the safety and efficacy profiles of mirabegron, solifenacin, and tolterodine in different age groups and both sexes [12]. Since its safety and efficacy were assessed in different subgroups, such as male and female, and younger and older OAB patients, in several phases 2–4 clinical studies, mirabegron has been documented as the first choice for OAB treatment. Treatment-emergent adverse events (TEAEs) were similar across subgroups, and most AEs were mild and moderate. In this article, we examine the individualized and appropriate choice of oral medication for OAB patients based on a literature review and analysis of this clinical trial database.

Key findings of the large integrated clinical trial database

Analysis of this large integrated phase 2–4 clinical trial database of 11261 patients with OAB receiving mirabegron, antimuscarinics, or placebos revealed that the efficacy of mirabegron is not inferior to antimuscarinics such as solifenacin or tolterodine [12]. Results of the analysis showed mirabegron 25 mg, mirabegron 50 mg, solifenacin 5 mg, and tolterodine ER 4 mg were associated with greater improvements in the mean daily micturition, incontinence episodes, urgency episodes, volume voided, and nocturia episodes from baseline versus placebos. The magnitude of changes in these measured variables versus placebo was higher in older patients, women, and patients who had received prior OAB medication [Table 1].

In this integrated clinical trial data analysis, more TEAEs were reported for the antimuscarinics group (21.4%) versus the mirabegron group (17.0%). The incidence of dry mouth was noted in 8.7% of the antimuscarinics group, 2.7% in the mirabegron group, and 2.4% in the placebo groups. The frequency of constipation was similarly low between groups (placebo 1.7%, mirabegron 2.1%, and antimuscarinics 2.4%). The frequency of treatment, emergent hypertension, urinary tract infection, and tachycardia was low and similar in all three groups. Urinary retention was <1% for all groups [Table 1]. The overall frequency of TEAEs was higher in older patients and higher for women than for men. Constipation was more frequently observed in older patients in the antimuscarinic group. However, the frequency of dry mouth in the antimuscarinic group was similar for older and younger age groups and for both sexes. The hypertension TEAEs occurred more frequently in older patients and in men, but the incidence was similar across different treatment groups. Frequencies of tachycardia and urinary retention were <1% in all treatment groups and age groups and for both sexes.

Since the pharmacological mechanisms of antimuscarinics and mirabegron are different, the effects on salivary glands, gastrointestinal motility, cardiovascular system, detrusor contractility, and cognitive function are also different. Therefore, higher TEAE incidence in antimuscarinics groups is reasonable. Interestingly, although mirabegron may cause hypertension and tachycardia more, and antimuscarinics might affect detrusor contractility more, in this analysis, the frequency of tachycardia and urinary retention are low and similar between groups, indicating that both OAB medications are safe. As most of the enrolled patients had received prior antimuscarinic therapy for OAB, they might feel less urge sensation during the storage phase and perceive less dry mouth while taking mirabegron trial, these subjective perception will increase the satisfaction to trial medication, especially in the elderly and women.

Special efficacy of mirabegron in the treatment of overactive bladder in elderly patients and patients with low detrusor contractility

The role of beta-3 adrenergic receptors involves facilitating bladder urine storage by inducing detrusor muscle relaxation [13]. In human urinary bladders, the beta-3 adrenoceptor was the predominant beta-receptor subtype [6]. Beta-3 adrenoceptor agonists relax the detrusor smooth muscle, inhibit detrusor rhythmic contractions during the bladder storage phase, and result in an increase in bladder capacity [14]. In animal models, beta-3 adrenoceptor agonists increase bladder capacity with no change in micturition pressure, residual volume, or voiding contraction. The effect of the beta-3 adrenoceptor agonists on detrusor contractility occurs mainly in the storage phase and not the voiding phase [15]. Therefore, unlike the effect of antimuscarinic agents, which reduce detrusor contractility during micturition, in clinical practice, beta-3 adrenoceptor agonists can increase bladder capacity without accompanying changes in the voiding detrusor pressure,

Table 1: Key findings of the large integrated clinical trial database [11]

Baseline hypertension and diabetes were more frequent across treatment groups in the older versus younger age groups and in men versus women
Within sexes, frequencies were similar between treatment groups. Some differences were observed in baseline characteristics, including type of incontinence and medical history between sexes
No previously unreported safety concerns were identified
Improvements in efficacy (mean number of incontinence episodes/24 h, micturitions/24 h, urgency episodes/24 h, volume voided/micturition, and nocturia episodes) versus placebo were observed in all treatment groups
Significant treatment-by-subgroup interactions included change from baseline in the mean number of incontinence episodes/24 h by age (<65 vs. ≥65 years), nocturia by age (<65 vs. ≥65 and <75 vs. ≥75 years), and urgency episodes by previous OAB medication
Mirabegron 25 and 50 mg, solifenacin 5 mg, and tolterodine ER 4 mg were associated with greater improvement from baseline versus placebo

OAB: Overactive bladder, ER: Extended release

increase of postvoid residual (PVR) volume, or decrease of detrusor contractions [16]. This specific therapeutic effect is the reason for mirabegron's popularity as the initial medication for patients with low detrusor contractility and in male OAB patients with benign prostatic hyperplasia.

Elderly patients, with primary OAB or secondary to bladder outlet obstruction, usually have low detrusor contractility, low maximum flow rate, and increased PVR volume. OAB treatment using antimuscarinics in these patients might increase the risk of large PVR and subsequent urinary tract infection. However, our recent study revealed the use of mirabegron 25 mg/day in elderly patients is safe and effective in the improvement of OAB symptoms with no increase in PVR after 3 months of treatment. Interestingly, we also found that younger patients experienced more minor AEs than older patients (41.9% vs. 24.6%) during the treatment period [17]. In a postmarket clinical study of the safety and efficacy of mirabegron 25 mg on elderly patients with urodynamic detrusor hyperactivity with impaired contractility (DHIC), both groups showed improvement in the subjective perception of bladder function compared to the baseline, but the efficacy was lower in DHIC patients. Although PVR did not increase after mirabegron treatment, 16% of DHIC patients developed PVR >180 mL [18].

Recent evidence has shown that the long-term use of antimuscarinic agents increases the risk of cognitive dysfunction in elderly patients or patients with OAB due to Alzheimer's disease [19]. Since mirabegron has no effect on cognitive function, it might be considered as the first choice of OAB medication for elderly OAB patients with central nervous system (CNS) lesions. A high success rate has been achieved using antimuscarinic agents in elderly patients with OAB due to CNS lesions such as cerebrovascular accidents, Parkinson's disease, or early dementia. However, the risks of impaired bladder emptying and impaired cognitive function also increase in long-term treatment with nonselective antimuscarinic agents [20]. Mirabegron 25 mg once daily has been shown to effectively decrease the urgency symptoms in elderly OAB patients with CNS lesions after the 12-week treatment period. The AEs were mild and only noted in few cases [21].

In a recent study assessing the therapeutic efficacy and safety of directly switching from antimuscarinics to mirabegron in patients with OAB receiving stable antimuscarinic treatment, improvement of OAB symptoms was noted in 57.1% of patients, and AEs also decreased after switching medications [22]. These results suggest OAB patients treated with antimuscarinics might be in suboptimal condition and having certain intolerable AEs. Switching from antimuscarinics to mirabegron provides OAB patients a chance to experience new therapeutic effects and less AEs. The same treatment outcomes were also observed in this large integrated clinical trial database, the treatment efficacy was similar between mirabegron and antimuscarinics, but the magnitude of changes in variables from baseline was higher in older patients, women, and those who had previous OAB medication.

Combination with antimuscarinics in initial treatment failure with mirabegron

Although OAB treatment using antimuscarinics or mirabegron is equally effective, not all patients can be completely symptom-free after medication monotherapy. In patients who fail the initial OAB medication monotherapy, a satisfactory result can be achieved by increasing the medication dose, increasing the treatment duration, shifting from one to another type of medication, combining two subtypes of the antimuscarinic agent, adding-on mirabegron, or considering botulinum toxin A injection [23]. In a recent phase 2 clinical trial, the combination medication with mirabegron 25 or 50 mg and different doses of solifenacin significantly increased the maximum volume voided, and reduced frequency and urgency episodes, in comparison with solifenacin monotherapy [24]. Because the pharmacological mechanism of mirabegron and antimuscarinics are compensatory to each other, it seems reasonable to use combinations of mirabegron and antimuscarinic agents in OAB patients who fail first-line treatment with an antimuscrinic agent or mirabegron alone. Increasing evidence has emerged, demonstrating that combination pharmacotherapy with mirabegron and solifenacin is safe and effective for OAB patients with moderate to severe symptoms [25].

What is the appropriate initial dose of mirabegron for overactive bladder patients?

The recommended dose of mirabegron for OAB was 50 mg/day in Europe, Japan, and most other countries. Although the risk of hypertension in mirabegron vs. placebo does not increase based on the previous clinical trials and integrated clinical trial data analysis, due to the potential risk of hypertension as an AE, a starting dose of 25 mg of mirabegron was recommended in the United States, Taiwan, Singapore, and some Asian countries, especially for patients who have a history of hypertension. If the initial treatment with mirabegron 25 mg fails, the dose can be raised to 50 mg for a better treatment outcome. From the results of a recent study, we found the number of patients with improvement of urgency severity scores was significantly higher in patients receiving escalating doses of mirabegron from 25 mg for 1 month to 50 mg for 2 months compared with those who were persistently treated with mirabegron 25 mg for 3 months (34.5% vs. 15.6%, $P = 0.031$) [26]. The urgency incontinence episodes also significantly decreased after escalating mirabegron dose from 25 mg to 50 mg, without increasing the rate of AEs. In the largest integrated clinical trial database [12], the efficacy of mirabegron 25 mg and 50 mg was similar in the mean micturition diary variables from baseline to the end of treatment, including daily incontinence episodes (−1.49 vs. −1.45), daily micturition number (−2.05 vs. −2.12), daily urgency episode (−2.58 vs. −2.60), volume voided (15.94 vs. 23.17), and nocturia episodes (−0.50 vs. −0.53). It seems rational to treat OAB patients with a mirabegron dose of 25 mg and increase the dose to 50 mg if the initial treatment with a lower dose fails. However, if there is only one choice for selecting mirabegron in the

hospital, a 50 mg dose would be appropriate as a starting medication.

Based on the results from previous clinical trials and this integrated clinical trial data analysis, a flow chart of the algorithm of the appropriate OAB medication is established [Figure 1]. For OAB patients, starting from anti-muscarinic agent is feasible. However, if the patients have risk of cognitive dysfunction, a history of constipation, dry mouth, and urinary retention, starting with mirabegron 50 mg might be more safe and appropriate. In the elderly patients with low detrusor contractility, with CNS lesion, and men with benign prostatic hyperplasia, starting from 25 mg mirabegron is recommended. If the treatment result is not satisfactory to the 25 mg mirabegron, increase dose to 50 mg mirabegron is appropriate. In patients who have failed from the first OAB medication either with antimuscarinics or mirabegron 50 mg, the exchange of the OAB medication to each other should be tried first. If the treatment result is still not

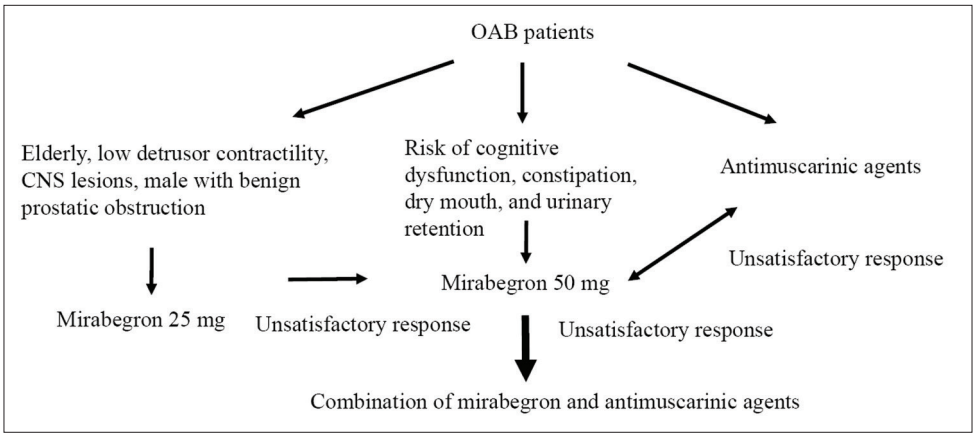

Figure 1: The algorithm of appropriate choice of medications for patients with overactive bladder syndrome

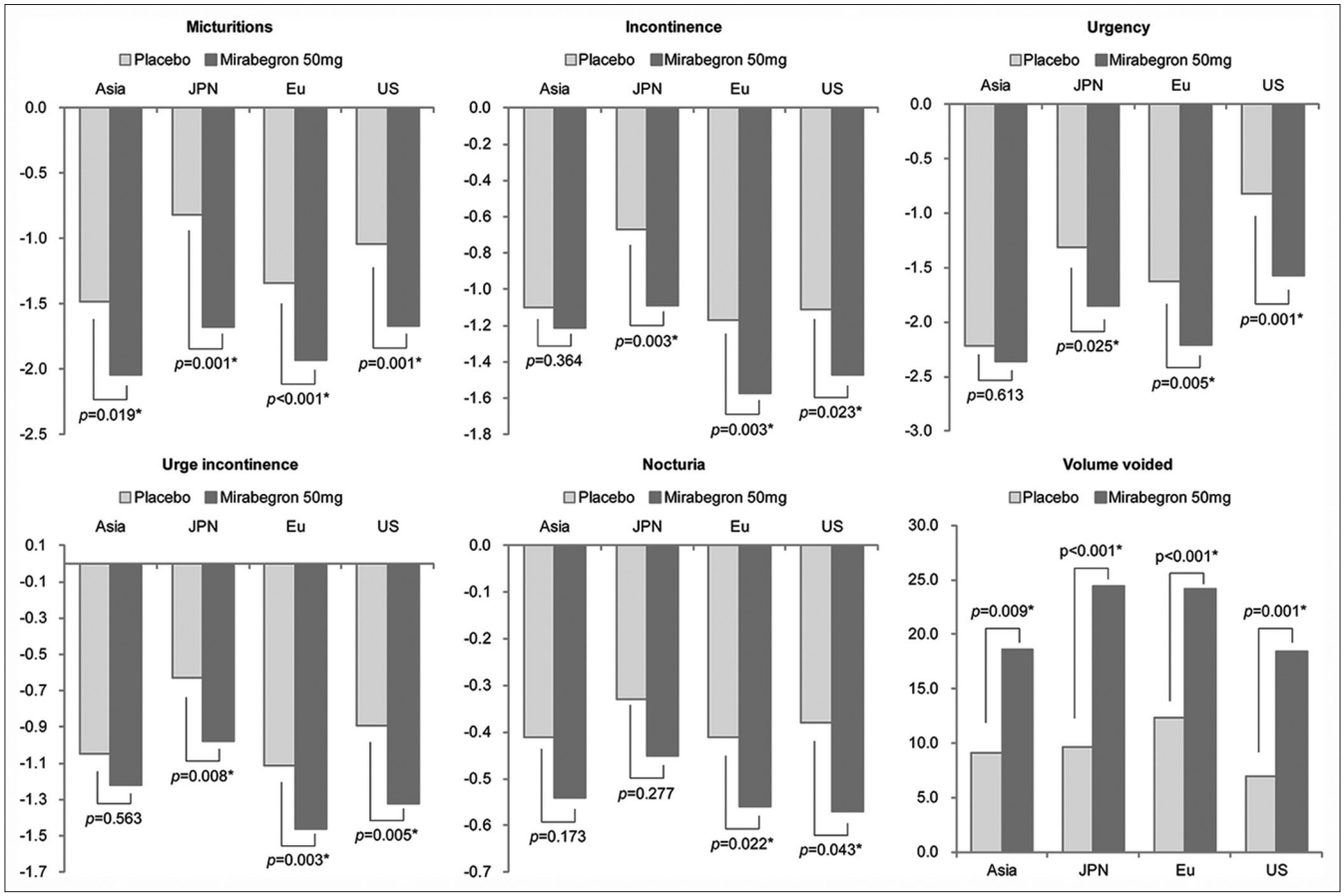

Figure 2: Comparison of the measured efficacy variable of mirabegron versus placebo from baseline to the end of treatment among Asian, Japan, European, and US pivotal clinical trials

satisfactory, a combination of antimuscarinics and mirabegron is recommended.

Comparison of mirabegron efficacy and safety among Asian and Other worldwide clinical trials

In this large integrated clinical trial database, the safety and efficacy of mirabegron of 25 mg and 50 mg have been well documented. Although the change of measured efficacy and safety variables showed slight differences between men and women, older patients and younger patients, and between previous OAB medication treated and treatment naïve patients, this pool provides the largest database for clinicians considering the use of mirabegron as an initial pharmacotherapy for OAB patients.

Interestingly, we found differences in the variable changes from baseline to the end of treatment between clinical trials from different regions. In the Asian trial conducted in Taiwan, Korea, India, and China, changes from baseline in daily urgency episodes, incontinence episodes, and urgency incontinence episodes were not significantly reduced compared with those in the placebo group [27]. The changes of these variables, however, were significantly reduced in clinical trials in Japan [28], Europe [8], and the United States [9]. Nevertheless, the changes from baseline of daily micturition number and volume voided were significantly greater than the placebo group in the Asian, Japanese, European, and US clinical trials [Figure 2].

The regional difference in the treatment outcomes of mirabegron versus placebo is difficult to explain. The definition of urgency and urgency incontinence might be different between different regional clinical trials. Younger OAB dry patients might have a higher incidence of bladder hypersensitivity rather than detrusor overactivity. It is possible that a considerably high percentage of patients enrolled in the Asian trial might not have true OAB, which might contribute to the high placebo effect. A high placebo effect has been noted in other previous studies of antimuscarinic agents, and this effect is commonly observed in OAB clinical trials [29]. The high placebo effect might be attributable to the specific characteristics of Asian people who might have unrealistically high expectations of the new test drug after the failure of previous OAB medication. In addition, patients participating in the clinical trial might already have drinking habit modification that increases the placebo response and diminishes the therapeutic effect of mirabegron in the study [30].

Conclusion

The large integrated clinical trial database reported that the pooled safety and efficacy profiles of beta-3 adrenoceptor agonist, mirabegron, in the treatment of OAB patients are similar to that of antimuscarinic agents such as solifenacin or tolterodine. Mirabegron is feasible as a first-line medication for OAB patients and doses starting from 25 mg/day are as effective as 50 mg/day, especially in elderly OAB patients, with low detrusor contractility, and patients with CNS lesions. In patients who have less favorable responses or AEs to antimuscarinics therapy, switching to mirabegron may have better outcomes. The AEs of mirabegron, such as dry mouth, constipation, or hypertension, are usually mild to moderate and tolerable in most OAB patients. For patients with suboptimal treatment results to mirabegron 25 mg, escalating to 50 mg or a combination of mirabegron and solifenacin can improve therapeutic efficacy and health-related quality of life.

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Conflicts of interest

Dr. Hann-Chorng Kuo, an editorial board member at *Tzu chi Medical Journal*, had no role in the peer review process of or decision to publish this article.

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