Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

journal home page : https://ijpsdronline.com/index.php/journal

Review Article

From Research to Practice: The Role of Mirabegron in Managing Overactive Bladder

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ARTICLE INFO

Article history:

Received: 10 November, 2024

Revised: 30 December, 2024

Accepted: 08 January, 2025

Published: 30 January, 2025

Keywords:

Overactive bladder, Mirabegron, Antimuscarinic agents.

DOI:

10.25004/IJPSDR.2025.170114

ABSTRACT

Millions of people in the world suffer from overactive bladder (OAB). It is characterized by urinary incontinence, increased frequency, and nocturia, which leads to a compromise in the quality of the patient's life. Traditional treatments comprised of antimuscarinic agents have limitations due to the side effects and reduced long-term effectiveness which creates a demand for alternative therapies. Treatment strategy for overactive bladder (OAB) has changed from antimuscarinics to β3-adrenergic receptor agonists after the discovery of mirabegron in 2012. This review examines the effectiveness of mirabegron in OAB patients and its integration into clinical practice. New advances in disease management mostly depend on the appropriate use of clinical data in guidelines for clarity. This is evident in OAB management with mirabegron. The landscape has changed, providing new options for healthcare professionals. This review discusses the latest data on mirabegron use, efficacy, safety, cost-effectiveness, and its potential use in combination therapies. In addition to its position in OAB management, the futuristic use of this β3-adrenergic receptor agonist will also be explored.

Introduction

Overactive bladder (OAB) syndrome is defined as incontinence with urgency or without urgency and it is usually linked to increased frequency in the daytime (more than 7) as well as nocturia (awakening at night to urinate).[1,2] Urinary urgency is the main focus of treatment among OAB patients. OAB affects an estimated 12 to 17% of the world's population, which means that tens of millions of people worldwide are living with it.[3] Urgency incontinence is more likely to occur with other OAB symptoms. Age is an important factor linked to OAB and prevalence increases with aging, especially for those living in care environments.[4] Other factors linked with OAB include poor general health or a large number of comorbidities, sedentary lifestyle, obesity, female sex, postmenopausal hormone therapy, and urologic surgery.[5] Several studies have suggested that OAB has a psychological or social impact with a compromised standard of living.[6,7] A large community-based telephonic survey found that people with moderate to severe urgency incontinence were likely to report overall poor health.[8] Further, OAB patients with moderate symptoms and severe symptoms were found to be depressed and had limitations in their daily activities for living and social functioning.[6,7] In a qualitative study among patients with incontinence, many individuals reported that it affected their emotional well-being, including feelings of helplessness, fear, anguish, worry, anger, and frustration. Moreover, incontinence negatively impacts their social and physical well-being. Although the impact of OAB has been acknowledged, few studies have addressed the treatment options of OAB, specifically using well-designed randomized clinical trials.[9] The prevalence rates for OAB are important in terms of the rationale for treatment.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Definition and Prevalence of OAB

The standard definition of OAB includes several symptoms such as uncontrollable urge for urination;[10] urinary incontinence commonly known as the leakage of urine;[11] an increase in urinary frequency means voiding at intervals of less than every 2 hours after consuming the last beverage[2] nocturia[12] and these symptoms are not caused by proven infection, inflammation, or any other pathologies. Moreover, OAB symptoms are mostly subjective and may be present with some level of variation. It occurs in both female and male patients at any age.[1]

A demonstrated global type of disease state, OAB is an extremely common urological condition that affects all age groups. Concerning the prevalence rates, OAB is demonstrated to impact 11 to 20% of the adult population of the entire world.[3] Furthermore, it is estimated that at least 400 out of 1000 adults may exhibit at least one OAB symptom at least weekly. Moreover, in a population study, around 42.8% of the population aged younger than 50 years and around 50% of the population aged older than 70 years exhibited OAB symptoms twice per week or more.[1,13] Overall, it is reported that female adults present with the highest prevalence of OAB at approximately 16.9%, followed by a study that showed a prevalence rate of 16.6% in male adult patients.[14] Notably, OAB is linked with several conditions, such as older patients as well as comorbid diseases.

Symptoms and Impact on Quality of Life

OAB presents an array of clinical symptoms including a strong urge for urination, incontinence, daytime frequency increases and nocturia.[1,2] Urgency incontinence occurs when urgency is followed by early sudden leakage of urine when it cannot be controlled at all. The primary symptom of OAB remains a strong urge for urination with or without incontinent episodes.[16] This condition may lead to embarrassment, interfere with daily activities, and affect social, sexual intercourse, and professional schedules.

Several studies have shown that the quality of life of OAB patients is greatly affected.[15] Living standards and overall well-being as a patient-reported outcome measure is also very crucial. These patients often seek medical guidance to improve emotional and mental well-being, physical vitality, and social security. OAB can lead to a range of changes in people's behavior, including less intake of fluid, and reduced physical and social activity.[1] Isolation, loss of self-confidence, and depression also contribute to reduced social contact, thereby affecting the effectiveness of social interactions. Data from valid and relabelled QoL studies in different therapeutic contexts in OAB address the need for appropriate and effective treatment.

Current Treatment Options for OAB

There are various therapeutic approaches for managing OAB. This includes both pharmacological and non-pharmacological strategies. Antimuscarinic agents are relatively easy to use and universally accepted and have historically been the first line of treatment.[16] Several anticholinergic drugs are prescribed for the management of OAB symptoms. Although several studies have reported the beneficial effects of anticholinergic treatment in the reduction of symptoms in OAB patients, the dose-dependent adverse effects such as cognition problems in the elderly, and reduction in efficacy after long-term use compared with the placebo group have always been an issue.[17] However, it should be noted that the number of patients who take medication is slightly lower than expected.

Behavioral therapies are the first choice of treatments, as they are non-invasive and can be implemented in large numbers of patients.[18] Modification of lifestyle is also recommended as supportive therapy in patients who are overweight or have an unhealthy diet and constipation.[19] A combination of these therapies is recommended as initial treatment in a step-wise manner.[20] To tailor the treatment for each patient, the severity of symptoms, underlying disease condition, sex differences, and the resting bladder volume should always be considered. Although actual OAB medicines should not be effective for all OAB patients, it would increase the treatment success rate to select appropriate patients based on these factors.[21] There is currently no single treatment that can meet the criteria such as low risk, high effectiveness, and good compliance.[22] Therefore, if the symptoms are not sufficiently controlled by some medications, a multi-modality approach should be adopted.

Antimuscarinic Agents

Antimuscarinic agents are widely used and appear to be effective in comparison to the other established drug classes for the management of OAB.[23] Several antimuscarinic agents now exist, such as darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, and trospium.[16] The mechanism of action of all antimuscarinic agents involves blocking the effects of acetylcholine on the bladder wall to decrease bladder smooth muscle contractions responsible for OAB symptoms.[24] Muscarinic receptors are blocked on the bladder by these agents is a long-term process that requires the accumulation of a sufficient concentration of drug in the bladder to prevent acetylcholine from binding to and stimulating muscarinic receptors in the bladder wall.[25]

Clinical studies for all currently available antimuscarinics have shown improvements compared to baseline values in symptoms associated with OAB, for example, urge for urination, incontinence, number of voiding episodes, nocturia, and urinary volume voided in both men and women.[26] However, in clinical practice, less than 50% of patients are dry on these medications and up to 50% of patients discontinue therapy within 3 months due to adverse effects. This scenario supports the necessity of

offering different oral OAB treatments to patients who have either not responded or are unable to tolerate adverse effects.[27]

Beta-3 Adrenergic Agonists

For decades, antimuscarinics have been used as a pillar of OAB treatment, and the introduction of beta-3 adrenergic agonists signified a groundbreaking shift in the treatment landscape.[27] These agents function differently from antimuscarinics. Antimuscarinics bind to bladder muscarinic receptors, thus blocking the activity of acetylcholine and leading to bladder relaxation. In contrast, beta-3 adrenergic agonists target adrenergic beta-3 receptors located in the detrusor muscles, which helps in their relaxation and increases the storage volume of the bladder.[28]

Clinical trials in the multi-year process of clinical research supporting mirabegron's benefit compared with placebo found statistically significant changes in the primary endpoint and other core OAB symptoms in mirabegron-treated patients.[29] Previous research has also documented the efficacy of this agent as a supplementary therapy in patients with persistent OAB symptoms, despite the use of an antimuscarinic.[30] The efficacy and safety profile of vibegron has also been evaluated in phase III clinical trials, while other beta-3 adrenergic receptor agonists remain under investigation.[31,32] A meta-analysis outlined the tolerability profile of mirabegron based on studies published before a certain date. According to this data, beta-3 adrenergic receptor agonists are relatively well-tolerated and have less adverse effects in comparison to the antimuscarinic agents, that are effective in the treatment of most OAB symptoms.[33] Results from post-hoc trials suggest that patients who may particularly benefit from a beta-3 adrenergic agonist over an antimuscarinic include those with intolerance to the latter class of agent, which is most commonly due to dry mouth.[34] Since consistent therapeutic efficacy is vital for assessing its clinical effectiveness and maximizing its potential benefits, any factors that might hinder adherence must be carefully addressed. Multiple research studies have highlighted that longer durations of therapy and worse scores on the patient's insight into their bladder condition are associated with poor persistence.[35,36] Furthermore, persistence was shown to decrease when the frequency of dosing increased.[37] Combining all these data provides considerable insight into the issues surrounding treatment adherence and persistence, and emphasizes the need for appropriate patient counseling when initiating therapy using antimuscarinic agents or β3-adrenoceptor agonists to optimize patient adherence and maintain the therapeutic benefits of treatment. Considering these factors, the addition of a beta-3 adrenergic agonist to the treatment spectrum represents an easy, practical option that may diversify the armamentarium for managing OAB.

Mirabegron: Mechanism of Action

The non-adrenergic protocol of nerve activity leading to detrusor contraction has sparked in researchers the idea of targeting the overactive detrusor *via* a mechanism that is independent of antimuscarinic receptor effects. It was thus not until mirabegron was approved as a novel therapeutic option for OAB, debuting a new therapeutic class called β3-adrenoceptor agonists. Postulated as an "adrenergic replacement" earlier by phosphodiesterase inhibitors and tamsulosin, mirabegron complements this concept by acting on the receptor downstream of the cholinergic effects.[38] It has been described that β-adrenoceptors are present in human and animal bladders with plenty of β2-adrenoceptors.[39] Yet, it is the vast presence of β3-adrenoceptors that has attracted several researchers who have demonstrated the presence and function of β3-adrenoceptors on the human detrusor.[40]

The time to reach peak plasma concentration is approximately 3 hours when taken orally, and urinary excretion as parent drug (approximately 42.2%) peaks within 4 hours of a single oral dose.[41] A linear dose exposure relationship has been described for doses between 25 and 200 mg, with a terminal half-life of 50 hours.[29] The drug is mainly excreted as metabolites, with little or no unchanged drug found in urine.[42] The substrate, CYP enzymes involved in the biotransformation that gives rise to active metabolites of mirabegron are CYP2D6 and CYP3A4.[43] Furthermore, mirabegron is also primarily excreted via the feces as an active drug.[29] Many single-dose studies conducted over generations and in the elderly have indicated that a steady state is attained following the first dose or on day 3 for this long-acting preparation.[44]

Efficacy of Mirabegron in Treating Overactive Bladder

Administration of β3-adrenoceptor agonist resulted in dose-dependent activation in the lower urinary tract which results in improvement in voiding patterns, and sustained increases in the first involuntary detrusor contraction volume.[29,40] This work shows that mirabegron effectively reduces the rate of urgency episodes in OAB patients.[29] A randomized study in patients with OAB assessed the effectiveness, tolerability and safety of mirabegron daily for 12 weeks *versus* placebo. The OAB patients enrolled were over 18 years old, with a confirmed OAB diagnosis, urinary symptoms of more than 8 micturitions per day, and 3 or more urges to urinate. Among the studies where mirabegron was compared to antimuscarinic agents, one study showed that 50 and 100 mg of mirabegron daily dosages, resulted in a greater mean decline rate in the daily urge episodes compared to tolterodine extended-release at 12 weeks, with a difference in mean of 0.7 and 0.9 for 50 and 100 mg of mirabegron compared to tolterodine.[45-47]

Safety of Mirabegron in the Clinical Trials and its Place Nowadays

The phase III study showed no significant cardiovascular events, with a low increase in diastolic and systolic pressure after treatment.[48] According to the studies on the safety of mirabegron, the cardiovascular effects of mirabegron cannot likely be considered a class effect, as it is well defined with OAB treatment. According to mirabegron safety, the currently available clinical trials for mirabegron showed good short- and mid-term safety and tolerability, and no significant effect on manual blood pressure measurements, which might not increase the risk for hypertension.[49] Therefore, for select patients with a contraindication to antimuscarinic pharmacotherapy, mirabegron should be considered a potential option.[50] However, future studies with large groups of patients will determine the chronic adverse effects and the consequences of blood pressure safety in elderly patients.

Guidelines and Recommendations for Using Mirabegron in the Management of OAB

Current guidelines recommend initiating pharmacotherapy for OAB patients with at least three episodes of incontinence associated with urinary urgency within a period of 3 days.[51] When discussing OAB treatment with patients, healthcare professionals can utilize clinical practice guidelines to inform and support clinical decision-making; guidelines are also designed to encourage best practices in patient care.[52] This resource serves as a summary of current clinical practice guidelines for the initiation of mirabegron in patients experiencing OAB symptoms. Techniques for tailoring the discussion and treatment to the goals and needs of the patient are not included in this review.

Real-World Evidence and Long-Term Outcomes of Mirabegron Use

Real-world evidence provides information on the practical benefits of mirabegron in managing OAB. Observational studies demonstrate that numerous prescribers from different healthcare settings evaluate the effectiveness of mirabegron in diverse patient populations outside a trial.[29] Previously published studies in routine clinical practice predominantly focused on either failure of antimuscarinic therapy or suggested mirabegron as a second option.[53] Collectively, evidence is scarce concerning mirabegron's effectiveness as monotherapy or additional therapy in clinical practice, outside clinical trials.[29] However, the research presents evidence concerning monotherapy with mirabegron_or as an additional therapy over the entire management of patients.[54] With a focus on long-term outcomes, the utilization of real-world evidence can provide insights into the sustainability of positive findings from short-term randomized controlled trial efficacy outcomes. In terms of patient benefit, long-term outcomes explore a patient's satisfaction, adherence, and symptom management over time.

In various settings, real-world data identifies there is no difference in patient outcomes based upon patient demographics including age and comorbid conditions, although using real-world evidence, non-adherence has been reported to be lower in a study of patients.[55] Although research studies identify no difference in response based on the line of therapy used, there may be a marginal advantage in initiating treatment with mirabegron compared to an antimuscarinic agent, if the expectation is to achieve a therapeutic effect within the first week.[56]

Combination Therapy with Mirabegron and Antimuscarinic Agents

Mirabegron is well known to be an effective monotherapy for OAB.[29] However, recent preclinical and translational studies have pointed out several clinical rationales mainly associated with detrusor activation to support the use of mirabegron with antimuscarinic agents.[29] Antimuscarinic agents act on muscarinic receptors, and mirabegron acts on β3-adrenoceptors in different ways; it has been suggested that they show a synergistic effect on increased cAMP levels to relieve bladder dysfunction symptoms, especially OAB symptoms and storage phase-related symptoms.[57] Although there are currently no studies that support the synergistic effect of this combination, clinical studies, and clinical trial results suggest that mirabegron with an antimuscarinic medication is more effective for symptomatic relief in a subgroup of patients prescribed an antimuscarinic in combination therapy.[58]

The efficacy of combination therapy has been confirmed in many clinical studies using changes in the OAB symptom index, alteration in the daily micturition, changes in the_number of urgency episodes per day and changes in average volume voided on uroflowmetry per day. However, little has been done in combination therapy when it comes to quality of life.[59] Regardless, mirabegron does show a positive trend of improvement over monotherapy for quality of life as well. However, combination therapy is an off-label regimen, and reporting potential adverse effects and monitoring by clinicians may not be done properly on a large scale. Even though several patients are unsatisfied with antimuscarinics showing no symptomatic improvement and therapeutic effect in monotherapy, it may have some limitations; in such cases, some patients may request antimuscarinic medication adjustment or may consider changing their medication.[56] Therefore, clinicians who can advise patients should notify them, to a certain extent, of the appropriate candidates and those who appear to have insufficient effects and responses by objective methods with monotherapy. Moreover, a clinician may consider selecting patients who would show improved

responses with a combination therapy clinical trial.

Cost-Effectiveness and Health Economic Considerations of Mirabegron

Clinical success is not the only consideration when it comes to a cost-benefit evaluation of a certain management strategy. In the context of treatment options for OAB, such as mirabegron, the affordability and cost-effectiveness of management strategies should also be evaluated. According to current evidence, mirabegron appears less expensive in comparison to other medications.[59] Because of the small differences in medication costs that should be expected as a result of mirabegron being available in the free market, healthcare professionals should approach the use of mirabegron in managing OAB as a resource that is likely to manage symptoms with improvement in quality of life and potentially decrease healthcare utilization. The cost-effectiveness of a new strategy must be assessed in economic evaluations. Similarly, an assessment of health economic outcomes is needed.

A potential place in therapy can be secured for mirabegron if it is shown to be cost-effective. There is no large near-future trial comparing OAB medications and assessing cost-effectiveness parameters. However, recent papers were published to inform on the long-term population-based expected values of mirabegron.[29] The importance of making evidence-based decisions is emphasized, presenting the evidence currently available regarding the cost-effectiveness of mirabegron. Mandatory registration of clinical trials has to include the cost comparison of new treatment versus current treatment.

Future Directions in OAB Management and Potential Developments in Mirabegron

The evolving landscape of OAB management is underpinned by a deeper understanding of the underlying pathology and irritative symptoms, as well as innovations in drug delivery systems. This review has highlighted many areas for future research. How these could drive the evolution of clinical practice is an area yet to be fully understood. Research into mirabegron therapy is ongoing, with trials further exploring short- and long-term usage. Emerging fields of interest in OAB research focus on a paradigm that does not tailor treatments to symptoms, but rather to disease mechanisms. Interest in combination therapies is high, with further trial data anticipated. One area for growth that has not been discussed here is digital health and the role of telemedicine in OAB care. This area has grown during COVID-19 as areas of healthcare have moved online. Patients in healthcare also report many other barriers that reduce their ability to access care, not least geographical limitations and costs. Finally, even where drugs exist, a significant proportion of patients may find it challenging to obtain them due to cost restrictions. Opportunities for addressing these barriers can only be fully realized by communicating with and learning from patients, clinicians, healthcare systems, digital health providers, and all other stakeholders that could directly or indirectly benefit from measures to increase access to and improve the affordability of treatments. The future directions of OAB management cannot therefore be dictated solely based on scientific and clinical advances, but through collaboration with numerous other fields and experts, including those with strategic knowledge of policy, access to care, and patient experiences.

Conclusion

OAB is commonly found in urology and affects the quality of life in patients. Ideal medical treatment needs to improve all aspects and symptoms of OAB without requiring dosage adjustments. Antimuscarinic agents are the standard treatment but often cause side effects. The new agent, mirabegron, is moderately effective and has fewer side effects like dry mouth or constipation. It helps OAB patients maintain their quality of life and reduces symptoms. Mirabegron also has benefits like less risk of cognitive impairment and salivary gland function preservation. However, common adverse events include elevated blood pressure, nasopharyngitis, UTI, and headache. Blood pressure increase is a concern, particularly in the elderly with heart failure or coronary artery disease. Daily use of mirabegron is reasonable and safe with caution for those with cardiovascular disease.

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HOW TO CITE THIS ARTICLE: Ghosh A. From Research to Practice: The Role of Mirabegron in Managing Overactive Bladder. Int. J. Pharm. Sci. Drug Res. 2025;17(1):98-104. **DOI:** 10.25004/IJPSDR.2025.170114