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Mirabegron in the treatment of neurogenic detrusor overactivity: pharmacological and clinical aspects

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ABSTRACT

The main cause of the impaired storage function of the bladder in patients with neurogenic dysfunctions of the lower urinary tract is detrusor overactivity, clinically manifested by symptoms of an overactive bladder. The article presents data on the epidemiology, pathogenesis, clinical course and modern approaches to the treatment of detrusor overactivity in neurological patients. It is emphasized that the most important aspect of the clinical course of neurogenic detrusor overactivity is the high risk of upper urinary tract dysfunction, and reducing the threat of kidney damage is the main goal of treating such patients. Pharmacological and clinical aspects of the use of the β3-adrenoreceptor agonist mirabegron in patients with neurogenic bladder dysfunctions are presented. The results of experimental and clinical studies of its use in the treatment of neurogenic detrusor overactivity are presented. A high safety profile of the drug is noted. It is shown that the mechanisms of the therapeutic effect of mirabegron in neurogenic detrusor overactivity include a decrease in detrusor tone, inhibition of spontaneous myocyte contractions, and a decrease in myogenic and urotheliogenic mechanosensory afferent activity. The features of the clinical and urodynamic effects of mirabegron in patients with neurogenic detrusor overactivity in various neurological diseases — multiple sclerosis, Parkinson's disease, spinal cord injury — are highlighted. The leading role of the results of urodynamic research in choosing the treatment tactics for patients with neurogenic detrusor overactivity is emphasized.

Keywords: overactive bladder; neurogenic detrusor overactivity; neurogenic bladder; mirabegron; β3-adrenoceptor agonists.

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Мирабегрон в лечении нейрогенной детрузорной гиперактивности: фармакологические и клинические аспекты

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АННОТАЦИЯ

Основной причиной нарушения накопительной функции мочевого пузыря у пациентов с нейрогенными дисфункциями нижних мочевыводящих путей является детрузорная гиперактивность, клинически проявляющаяся симптомами гиперактивного мочевого пузыря. В статье приведены данные относительно эпидемиологии, патогенеза, клинического течения и современных подходов к лечению детрузорной гиперактивности у больных неврологического профиля. Подчеркнуто, что важнейшим аспектом клинического течения нейрогенной детрузорной гиперактивности является высокий риск нарушения функции верхних мочевыводящих путей, а снижение угрозы поражения почек — основная задача лечения таких пациентов. Представлены фармакологические и клинические аспекты применения агониста β3-адренорецепторов мирабегрона у пациентов с нейрогенными дисфункциями мочевого пузыря. Приведены результаты экспериментальных и клинических исследований его использования при лечении нейрогенной детрузорной гиперактивности. Отмечен высокий профиль безопасности препарата. Показано, что механизмы лечебного эффекта мирабегрона при нейрогенной детрузорной гиперактивностью включают снижение тонуса детрузора, торможение спонтанных сокращений миоцитов и уменьшение миогенной и уротелиогенной механосенсорной афферентной активности. Выделены особенности клинического и уродинамического эффектов мирабегрона у пациентов с нейрогенной детрузорной гиперактивностью при разных неврологических заболеваниях — рассеянном склерозе, болезни Паркинсона, травме спинного мозга. Подчеркнута ведущая роль результатов уродинамического исследования при выборе тактики лечения таких пациентов.

Ключевые слова: гиперактивный мочевой пузырь; нейрогенная детрузорная гиперактивность; нейрогенный мочевой пузырь; мирабегрон; агонист β3-адренорецепторов.

Как цитировать

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INTRODUCTION

Neurogenic lower urinary tract dysfunction (NLUTD) refers to abnormal continence function and voiding difficulty, which is a secondary complication of neurological disorders [1]. The prevalence of NLUTD is high, with urinary disorders observed in most neurological patients. Among individuals with multiple sclerosis, *spina bifida*, and spinal cord injury, the proportion of patients affected by urinary disorders is reported to be as high as 90% [1–4]. In the Russian population, more than 900,000 individuals are diagnosed with NLUTD [5]. The significance of NLUTD arises not only from its high prevalence and substantial deterioration in the quality of life, but also from the risk of life-threatening complications [6]. Moreover, there is a significant economic effect of this problem that must be addressed. In Russia, the estimated financial burden of NLUTD is approximately 85 billion rubles annually [5]. In this context, the development of novel, effective treatments for NLUTD constitutes a pivotal medical and socio-economic priority.

CLINICAL ASPECTS OF NEUROGENIC DETRUSOR OVERACTIVITY

The primary underlying factor contributing to the impaired bladder continence function in patients with NLUTD is detrusor overactivity, which is characterized by involuntary contractions of the detrusor muscle. Clinical presentations of detrusor overactivity include symptoms consistent with overactive bladder (OAB), such as urinary urgency with or without urge incontinence, often accompanied by frequent daytime and/or nighttime urination [7]. Urge incontinence has been observed in more than half of patients with neurogenic detrusor overactivity [8]. Symptoms of OAB, particularly urge incontinence, have a significant impact on patients' quality of life [9]. Neurogenic OAB has been demonstrated to exert a more substantial deleterious effect on patients' quality of life compared with the idiopathic form of the disease [10].

Neurogenic detrusor overactivity is most frequently observed in patients with suprasacral lesions of the central nervous system (CNS) [6]. Neurogenic detrusor overactivity has been observed in 65% of patients with cervical spine injury, 78% of patients with thoracic spine injury, and 49% of patients with lumbar spine injury [11].

The most significant aspect of the clinical course of NLUTD in general, and of neurogenic detrusor overactivity in particular, is the high risk of complications. Among these complications, upper urinary tract dysfunction is of the greatest concern. The primary goal of therapeutic interventions in such patients is to mitigate the risk of renal injury [1, 6]. It has been established that the major risk to the upper urinary tract is an increase in the intravesical pressure. Therefore, treatment should be aimed at reducing it to safe levels [6]. However, the safe level of the intravesical pressure remains controversial. The maximum detrusor pressure (P_{detmax}) during the storage phase and the detrusor leak point pressure of >40 cm H_2O, P_{detmax} during the voiding phase of >80 cm H_2O in males and >60 cm H_2O in females, a decrease in the bladder compliance of <20 mL/cm H_2O, a decrease in the maximum cystometric capacity of <200 mL, and an increase in the post-void residual volume of >100 mL or >30% of the functional bladder capacity are considered risk factors for renal injury in patients with NLUTD [12, 13]. The highest risk of upper urinary tract complications occurs in patients who present with detrusor overactivity combined with detrusor sphincter dyssynergia, a condition in which the detrusor pressure reaches its peak values.

TREATMENT OF NEUROGENIC DETRUSOR OVERACTIVITY

Therapeutic interventions for patients with neurogenic detrusor overactivity and OAB are based on a range of approaches, including conservative strategies, minimally invasive procedures, and surgical treatment. The conservative approach entails a combination of pharmacotherapy and non-pharmacological interventions [6]. The latter include lifestyle modification (e.g., the adjustment of fluid intake patterns, particularly targeting the first half of the day for higher fluid consumption among individuals with severe nocturia, and the restriction of diuretic foods) and pelvic floor exercises. Their effect is attributed to the suppression of the detrusor activity during pelvic muscle contraction [14]. However, a large proportion of neurological patients demonstrate an inability to perform these exercises correctly.

Anticholinergic drugs play a pivotal role in the pharmacotherapy of neurogenic OAB [15–18]. Oxybutynin was a first-in-class pharmaceutical agent developed for the treatment of OAB. It has been used for 50 years since 1975. Thereafter, a range of other M-cholinoblockers became available, which have gained extensive clinical application. These include tolterodine, solifenacin, trospium chloride, and fesoterodine. These agents vary in their pharmacokinetic and pharmacodynamic properties, clinical efficacy, and safety profile [16]. Anticholinergic drugs have the potential to effectively improve clinical symptoms and urodynamic outcomes [15, 16]. The detrusor contraction has been demonstrated to be regulated by M-cholinergic receptors. The inhibition of these receptors prevents their activation by acetylcholine, thereby reducing the myocyte contractile activity [15]. The bladder has mainly two of the five identified M-cholinergic

receptors, i.e., M2 and M3 subtypes with a 4:1 ratio [19]. In healthy individuals and patients with idiopathic urinary tract dysfunction, the detrusor contraction is regulated by M3-cholinergic receptors. NLUTD is associated with a higher density of M2-cholinergic receptors and, more importantly, their functional changes. Along with M3 receptors, M2 are directly responsible for the bladder contraction [20]. Consequently, the number of M-cholinergic receptors that are responsible for the detrusor contraction increases significantly, which is the underlying cause of the suboptimal efficacy of standard doses of muscarinic antagonists in patients with NLUTD. Therefore, high doses of M-cholinoblockers and combinations of two drugs of this class are recommended for such patients, although these treatments are associated with a higher frequency and severity of adverse effects, which often results in treatment discontinuation [6].

The potential of muscarinic antagonists to cross the blood-brain barrier and produce CNS adverse effects, particularly cognitive and emotional disorders, is a significant concern for patients with NLUTD [21, 22]. Furthermore, the administration of M-cholinoblockers can induce a substantial reduction in the detrusor contractile function during voiding events, potentially resulting in decreased urine output from the bladder or even urinary retention. Therefore, anticholinergic therapy is recommended to be initiated with low doses, which can be gradually increased as long as the treatment is well-tolerated, and the post-void residual volume should be closely monitored [23, 24]. This is especially crucial for patients who present with a combination of detrusor overactivity and detrusor sphincter dyssynergia, as these conditions are known to contribute to infravesical obstruction. The pharmacological treatment of NLUTD is a long-term intervention, and in certain cases, lifelong medication is necessary. However, the suboptimal efficacy of M-cholinoblockers at standard doses along with the unfavorable safety profile at higher doses contributes to the relatively low adherence of patients with neurogenic OAB to treatment compared with those with idiopathic forms of the disease. Manack et al. [25] analyzed the medical records of 26,922 patients with NLUTD and reported that 38% of them discontinued anticholinergic therapy within the first year [25]. If the efficacy of pharmaceutical treatment is found to be inadequate, the treatment is poorly tolerated, or there are contraindications, then the second-line therapy is initiated. This includes minimally invasive procedures, with botulinum toxin being the primary treatment option [26]. In contrast to patients with idiopathic overactivity, the therapeutic response in those with neurogenic detrusor overactivity is primarily informed by urodynamic rather than clinical criteria, and largely by the achieved degree of the detrusor pressure reduction [6].

MIRABEGRON FOR TREATMENT OF OVERACTIVE BLADDER

Until recently, M-cholinoblockers were recognized as the only pharmaceutical agents available for the treatment of OAB. In the early 2010s, the range of pharmaceutical treatments used in clinical practice was replenished with mirabegron, a β3-adrenergic agonist. The molecule was developed by Japanese researchers, and Japan was the first country to approve the drug for the treatment of OAB in 2011. In 2012, mirabegron received U.S. and European approval; in 2015, it was authorized in Russia.

Numerous preclinical and clinical studies have demonstrated the high efficacy and safety of mirabegron in the treatment of OAB [27, 28]. Consequently, it has been included in both Russian and international clinical guidelines [29, 30]. A substantial advantage of the drug is its favorable safety profile, which is attributed to the pharmacokinetic and pharmacodynamic properties. After oral dosing, mirabegron is rapidly absorbed, with approximately 71% of the active substance binding to plasma proteins and the time to maximum plasma concentration being 3–4 hours [31]. The drug is not associated with the adverse effects commonly observed with M-cholinoblockers. Consequently, it can be considered a suitable initial treatment option for OAB in patients with a high anticholinergic burden, cognitive impairment, and elderly patients [29, 30]. Mirabegron is also indicated for patients with non-neurogenic OAB, where M-cholinoblockers have shown the suboptimal efficacy [29, 30]. Liao and Kuo [32] reported that mirabegron improved symptoms in 57.1% of patients with OAB who were unresponsive to anticholinergic therapy [32].

The study findings have demonstrated the clinical efficacy and cost-effectiveness of mirabegron in patients with OAB, supporting its potential as a viable treatment option [33]. This is attributable to its efficacy and good tolerance, with minimal costs for the relief of emerging adverse symptoms [34].

MECHANISM OF PHARMACOLOGICAL ACTION OF MIRABEGRON

The therapeutic effect of mirabegron is attributed to its ability to activate β3-adrenergic receptors in the bladder, thereby inducing detrusor relaxation and reducing afferent nerve activity. In the late 1990s, studies discovered that β3-adrenergic receptors, which account for 97% of all β-adrenergic receptors in the bladder, were expressed in the detrusor and mediated the relaxation of smooth muscle cells [35, 36]. The stimulation of β3-adrenergic receptors activates the enzyme adenylate cyclase, which catalyzes the conversion of sodium adenosine triphosphate into cyclic adenosine

monophosphate. This contributes to a decrease in the concentration of intracellular Ca^{2+} and the relaxation of detrusor myocytes [37].

In the storage phase of the micturition cycle, the detrusor smooth muscle cells experience spontaneous activity, which is induced by their distension. Usually, the nervous system suppresses the spontaneous contraction; however, when the suppression mechanisms are compromised, the contraction may increase the afferent activity of the bladder and induce detrusor overactivity [38]. This scenario is consistent with that observed in patients with CNS disorders, who demonstrate a reduced or absent ability to regulate this spontaneous activity. The therapeutic effect of β3-adrenergic agonists is based on their ability to suppress the detrusor contractile activity in the storage phase [39]. Therefore, mirabegron exerts its effect by suppressing the spontaneous myogenic activity of the bladder, reducing its mechanosensory afferent activity.

In addition to bladder wall myocytes, β3-adrenergic receptors are expressed in the urothelium, interstitial cells of Cajal, types Aδ and C fibers, and blood vessels (Fig. 1) [40]. It has been hypothesized that the activation of β3-adrenergic receptors residing outside the myocytes contributes to a decrease in the bladder afferent activity [38, 41].

Some studies have suggested that the effect of beta-3-adrenergic agonists in patients with detrusor overactivity may be largely attributable to the inhibition of acetylcholine release in cholinergic nerve terminals of the parasympathetic nervous system, rather than to the direct relaxation of the bladder smooth muscles [42, 43]. Based on this hypothesis, β3-adrenergic agonists selectively suppress the abnormal cholinergic overactivity of the detrusor in the storage phase compared with the physiological detrusor contraction during bladder voiding. This observation has significant clinical implications, as it demonstrates that mirabegron exerts its primary effect on the contractile activity in the storage phase, without compromising the voiding function of the bladder.

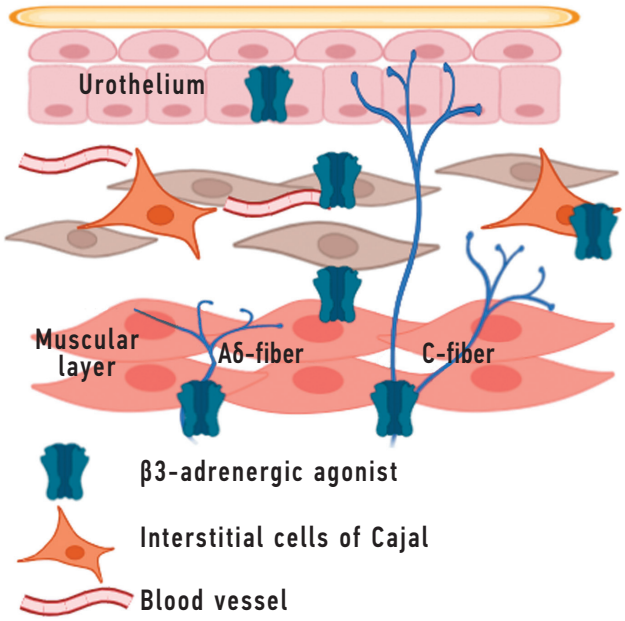

Fig. 1. Localization of β3-adrenoceptors in the bladder wall.
Рис. 1. Локализация β3-адренорецепторов в стенке мочевого пузыря.

The hypothesized mechanisms of the therapeutic effect of β3-adrenergic agonists in patients with detrusor overactivity and OAB are shown in Fig. 2. These mechanisms include the detrusor relaxation, contributing to a decrease in the bladder tone; the suppression of the myocyte spontaneous contraction; and a decrease in the myogenic and urotheliogenic mechanosensory afferent activity [44].

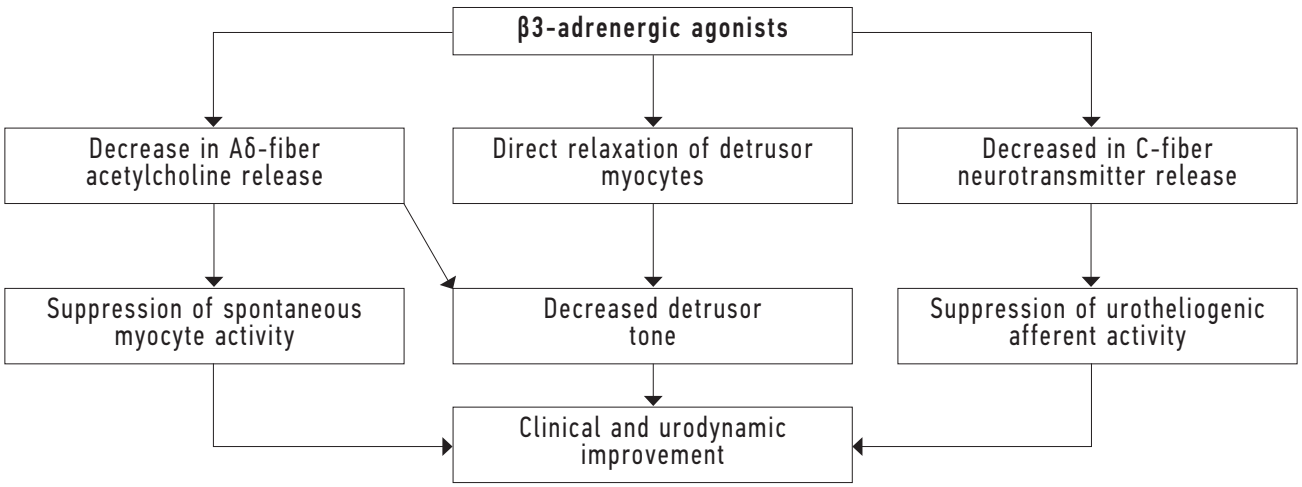

Fig. 2. Mechanism of the therapeutic effect of β3-adrenoceptor agonists in patients with detrusor overactivity and overactive bladder.
Рис. 2. Механизм лечебного эффекта агонистов β3-адренорецепторов у пациентов с детрузорной гиперактивностью и гиперактивным мочевым пузырем.

MIRABEGRON FOR TREATMENT OF NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

The use of mirabegron in patients with neurogenic urinary dysfunction has been the focus of numerous studies and discussions. Considerable attention is given to the efficacy of β3-adrenergic agonists in this patient population, as their safety profile is well-established and has been substantiated by the findings of multiple studies. A significant potential benefit of β3-adrenergic agonists as compared with M-cholinoblockers is their ability to induce their effect during the storage phase of the micturition cycle without compromising the urine output from the bladder. This benefit of mirabegron is extensively relied upon in the treatment of patients with non-neurogenic OAB and infravesical obstruction [45].

Experimental Findings

As demonstrated by the initial experimental studies, β3-adrenergic agonists effectively increase the functional bladder capacity without reducing the intravesical pressure during urination or increasing the post-void residual volume [46]. Therefore, the activation of β3-adrenergic receptors induced bladder relaxation in the storage phase of the micturition cycle without affecting the voiding phase. In experimental models of neurogenic detrusor overactivity, the administration of β3-adrenergic agonists has been observed to result in a dose-dependent increase in the bladder capacity without any increase in the post-void residual volume [35, 46]. In patients with detrusor overactivity caused by spinal cord injury, β3-adrenergic agonists have been shown to reduce the frequency and number of the involuntary detrusor contractions without significantly altering the amplitude of the contraction [47, 48]. The efficacy of an M-cholinoblocker in combination with a β3-adrenergic agonist for the treatment of experimental neurogenic detrusor overactivity was superior to the efficacy of each drug alone [48].

Clinical Evaluation of Mirabegron Efficacy for the Treatment of Neurogenic Detrusor Overactivity

Several systematic reviews and meta-analyses have summarized the cumulative experience of using mirabegron for the treatment of NLUTD [49–51]. The first of these reviews was conducted by El Helou et al. [49], who analyzed treatment outcomes of 302 patients diagnosed with neurogenic OAB in seven studies, only two of which were randomized clinical trials (RCTs). All patients had previously received anticholinergic therapy, which was discontinued due to its low efficacy or poor tolerance. The authors highlighted that mirabegron demonstrated the favorable safety profile, improved clinical symptoms, and increased the maximum cystometric capacity and bladder compliance. These findings supported the conclusion that mirabegron is effective as a second-line treatment for OAB in patients who have not responded to prior anticholinergic therapy [49]. In another review, Elkhashab et al. [50] summarized the results of 6 RCTs comparing the efficacy and safety of mirabegron to placebo or muscarinic antagonists. Although mirabegron was generally well-tolerated, its efficacy was found to be suboptimal. The authors recognized the limitations of their research, which were attributed to the heterogeneous patient population and differences in the criteria for evaluating therapeutic success. In contrast, Zhou et al. [51] reported more favorable outcomes for mirabegron, analyzing the results of nearly all 23 RCTs conducted to date, which included 1,697 patients with NLUTD. The authors concluded that mirabegron had a positive effect on both clinical symptoms and urodynamic outcomes. Mirabegron therapy significantly reduced the urinary frequency and the number of incontinence events, improved patients' quality of life, increased the bladder storage volume during the initial involuntary detrusor contraction, and increased the bladder compliance. However, in contrast to M-cholinoblockers, mirabegron treatment was not associated with a decrease in P_{detmax} during the storage phase. The tolerance of mirabegron was significantly superior to that of anticholinergic drugs. Furthermore, there was no increase in the post-void residual volume or the frequency of urinary retention events.

Neurogenic detrusor overactivity occurs secondary to a variety of CNS diseases, including multiple sclerosis, Parkinson disease, spinal cord injury, cerebrovascular diseases, etc. The severity of clinical and urodynamic abnormalities varies significantly with the extent, severity, and nature of the CNS involvement, and is clearly influenced by the underlying etiology of NLUTD. Consequently, treatment protocols and their efficacy are likely to vary. In this context, it seems reasonable to consider the clinical and urodynamic efficacy of mirabegron based on the underlying cause of NLUTD.

Mirabegron for the Treatment of Neurogenic Lower Urinary Tract Dysfunction in Patients with Multiple Sclerosis

The conducted studies have demonstrated the clinical efficacy of mirabegron in patients with multiple sclerosis. Brucker et al. [52] concluded that mirabegron was non-inferior to solifenacin in alleviating OAB symptoms. In a randomized study by Glykas et al. [53], there was no significant difference in the reduction of symptoms of neurogenic OAB or improvement in patients' quality of life between mirabegron and anticholinergic drugs. However, mirabegron had significantly better tolerance.

The treatment outcomes of 22 patients diagnosed with neurogenic OAB secondary to multiple sclerosis were documented by Mut et al. [54]. The initial therapy included solifenacin 10 mg for 4 weeks. Further, mirabegron

was administered to 11 patients who did not respond adequately to the initial treatment. A significant reduction in OAB symptoms was observed in all patients who received combination therapy. The authors concluded that combination treatment had a higher efficacy than M-cholinoblockers alone in this specific category of patients. Zachariou et al. [55] reported significant clinical improvement in patients treated with a combination of mirabegron and desmopressin, as evidenced by lower urination frequency, urinary urgencies, and urinary incontinence events. There was a statistically significant increase in the mean urination volume, from 104 to 189 mL (p <0.01).

In the systematic review, Akkoc presented the findings of studies evaluating the use of mirabegron as a second-line treatment. The review concluded that the clinical efficacy of mirabegron in patients with neurogenic detrusor overactivity caused by multiple sclerosis was comparable to that of anticholinergic drugs, although mirabegron was found to be significantly better tolerated [56].

Mirabegron for the Treatment of Neurogenic Lower Urinary Tract Dysfunction in Patients with Parkinson disease

Several studies have investigated the efficacy of mirabegron in patients with OAB and Parkinson disease. In 2018, Peyronnet et al. [57] published the retrospective study that demonstrated the high efficacy and good tolerance of mirabegron in this population. Their findings indicated the long-term effect maintained in more than half of the patients even after the end of treatment. In the study by Gubbiotti et al. [58], mirabegron was administered to 30 patients with Parkinson disease complicated by OAB with urge incontinence, which did not respond to M-cholinoblockers. The treatment proved effective in most patients, with incontinence resolved in seven cases (23.3%). The authors observed the favorable tolerance profile of the treatment.

In 2021, the first multicenter, randomized, placebo-controlled study evaluating the efficacy and safety of mirabegron in treating OAB symptoms in patients with Parkinson disease was published. The study enrolled a total of 136 patients, with 117 of them being randomized [59]. Patients received mirabegron 50 mg once daily for 12 weeks. Mirabegron demonstrated significantly higher efficacy compared to placebo. Adverse events were reported in 23.1% of patients from the treatment group and were largely mild in severity, with only a small proportion of events being treatment-related. Moussa et al. [60] reported comparable findings in the RCT with 110 patients with Parkinson disease. The study documented the high clinical efficacy and good tolerance of mirabegron in the treatment of OAB. A combination of mirabegron and pelvic floor exercises has been shown to yield favorable outcomes [61]. Cheng et al. [62] performed a systematic review and meta-analysis of previous RCTs, confirming the high efficacy of mirabegron in the treatment of neurogenic OAB in patients with Parkinson disease.

Mirabegron for the Treatment of Neurogenic Lower Urinary Tract Dysfunction in Patients with Spinal Cord Injury

The first report on the use of mirabegron in patients with spinal cord injury and neurogenic detrusor overactivity was published in 2016. In this report, Wöllner and Pannek analyzed medical records of 15 patients who had been treated with mirabegron. The authors observed both clinical (reduced urinary frequency and urge incontinence) and urodynamic improvements. As compared to baseline, the therapy produced an increase in the bladder capacity from 365 to 419 mL, a decrease in P_{detmax} during the storage phase from 45.8 to 30 cm H_2O, and an increase in the bladder compliance from 28 to 45 mL/cm H_2O. However, the authors highlighted the small sample size and the retrospective design among the study limitations [63].

In 2018, two placebo-controlled RCTs evaluating the efficacy of mirabegron in patients with spinal cord injury and detrusor overactivity were published [64, 65]. In the study by Welk et al. [64], the administration of mirabegron was associated with the reduction in the severity of clinical symptoms compared with placebo. However, no significant urodynamic improvements were observed, including the maximum cystometric capacity, bladder storage volume at the time of the first involuntary contraction, and P_{detmax} during the storage phase. Comparable findings were reported in another RCT. As reported by Krhut et al. [65], significant clinical improvement was observed in patients receiving mirabegron; however, the urodynamic effect of mirabegron was not as evident. The authors documented an increase in the bladder volume during the initial involuntary contraction and an improvement in the bladder compliance. However, no improvement was observed in the critical parameters such as the maximum cystometric capacity and P_{detmax}.

The findings of Trbovich et al. [66] and Vasudeva et al. [67] demonstrated a decline in the severity of clinical symptoms in patients with spinal cord injury and neurogenic detrusor overactivity. Vasudeva et al. [67] suggested that mirabegron produced similar urodynamic improvement. The authors observed an increase in the maximum cystometric capacity and a decrease in P_{detmax} during the storage phase. Although the value of P_{detmax} decreased from an average of 54 to 41 cm H_2O after mirbegron therapy, it remained above the safe threshold (40 cm H_2O), indicating a high risk of upper urinary tract injury.

In 2022, Akkoc published a systematic review that summarized 11 studies, which included a total of 488 patients with detrusor overactivity secondary to spinal injury and multiple sclerosis [56]. The length of mirbegron

therapy ranged from 4 weeks to 12 months, with the drug administered as a second-line treatment after M-cholinoblockers. Mirabegron has been observed to reduce the severity of clinical symptoms in patients with spinal cord injury. However, no significant urodynamic improvement was observed in two RCTs with the assessment of treatment outcomes. It was concluded that the use of mirabegron in patients with spinal cord injury was clinically effective, though it failed to produce urodynamic improvement. Furthermore, the efficacy of mirabegron in patients with detrusor overactivity following spinal cord injury was inferior to that observed in patients diagnosed with multiple sclerosis. The author also highlighted the favorable tolerance profile of mirabegron treatment [56].

When administered in combination with anticholinergic drugs, mirabegron demonstrated a significantly higher urodynamic efficacy in patients with spinal cord injury and detrusor overactivity. This is evidenced by Han et al. [68] and Krebs et al. [69], who demonstrated that combination treatment produced a decrease in P_{detmax} during the storage phase, an increase in the maximum cystometric capacity, and an improvement in the bladder compliance.

Thus, the study findings demonstrate conflicting outcomes in patients with spinal cord injury and detrusor overactivity treated with mirabegron. This treatment has been shown to improve clinical symptoms, reduce the urinary frequency and the severity of incontinence. Furthermore, the treatment has been found to be well-tolerated by patients. However, no significant effect was observed on the most critical urodynamic parameters, which determine the risk of upper urinary tract injury.

Mirabegron for the Treatment of Neurogenic Lower Urinary Tract Dysfunction in Pediatric Patients

Mirabegron has demonstrated the clinical and urodynamic efficacy in pediatric patients with neurogenic detrusor overactivity. In the retrospective study by Park et al. [70], the administration of mirabegron to patients with *spina bifida* aged under 18 years was associated with a reduction in the severity of OAB symptoms, resolution of urinary incontinence, and cystometric improvement. Mirabegron demonstrated efficacy in children with neurogenic detrusor overactivity who had not responded to muscarinic antagonists [71–73]. In this patient population, mirabegron showed significant urodynamic benefits, as evidenced by a decrease in P_{detmax} during the storage phase, an increase in the cystometric capacity, and an improvement in the bladder compliance. Mirabegron was well-tolerated, with no cases of discontinuation due to adverse events. These findings supported the U.S. Food and Drug Administration (FDA) approval of mirabegron for the treatment of neurogenic detrusor overactivity in pediatric patients aged 3 years and older.

CLINICAL AND URODYNAMIC CRITERIA FOR EVALUATING THERAPEUTIC EFFICACY IN PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY

The reduction in the severity of clinical symptoms associated with neurogenic detrusor overactivity, particularly the resolution of urinary incontinence, has been shown to improve patients' quality of life. However, the clinical efficacy achieved through pharmacological treatment is not always supported by improved urodynamic outcomes. In contrast to patients with idiopathic forms of dysfunction, the primary criterion for the efficacy of treatment in patients with NLUTD is the achievement of the normal urodynamics in the lower urinary tract [6]. This is attributable to the fact that abnormal urodynamic patterns are the primary cause of renal injury and subsequent renal failure. The primary focus of treatment for patients with NLUTD is the prevention of these complications. The most significant urodynamic abnormalities are observed in patients with spinal cord injuries, who also demonstrate the highest incidence of complications related to upper urinary tract injury [74]. Patients with multiple sclerosis, Parkinson disease, and cerebrovascular diseases have a significantly lower risk of renal injury associated with abnormal urodynamics.

The currently available data on the use of mirabegron in patients with NLUTD suggest its clinical efficacy and good tolerance, with any neurological disorder contributing to neurogenic detrusor overactivity. However, the urodynamic effect of the drug varies based on the type of neurological impairment. Whereas the urodynamic effects of mirabegron appear to be relatively favorable in patients with Parkinson disease, multiple sclerosis, and *spina bifida*, patients with spinal cord injury demonstrate the opposite patterns. The primary therapeutic goal in the management of patients with NLUTD is to reduce the storage phase P_{detmax} values to safe levels and to achieve normal ranges of other urodynamic parameters to prevent upper urinary tract injury. None of the studies involving patients with NLUTD and spinal cord injury who were treated with mirabegron demonstrated a decrease in P_{detmax}, which is a primary risk factor for the deterioration of renal function. For these patients, mirabegron is usually administered in combination with an M-cholinoblocker or botulinum toxin rather than generally regarded as the primary component of pharmacotherapy. However, patients with neurogenic detrusor overactivity associated with neurological diseases, such as multiple sclerosis and Parkinson disease, have experienced clinical and urodynamic benefits from mirbegron treatment. Therefore, this β3-adrenergic agonist may be considered a potential alternative to M-cholinoblockers. In this regard, RCTs must be planned with a focus on the clinical

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and urodynamic efficacy of the pharmacotherapy for neurogenic detrusor overactivity, distinguishing between patients with different neurological diseases. Therefore, the treatment options for NLUTD may vary based on the underlying cause. This observation is particularly relevant for patients with spinal cord injury.

The reasons why the urodynamic efficacy of mirabegron varies with the neurological etiology of detrusor overactivity remain to be elucidated. The following hypothesis may be proposed. Based on de Groat's concept (1997), neurogenic detrusor overactivity may arise from a combination of factors, including a decrease in the suppression of detrusor activity during the storage phase and an increase in the micturation reflex [75]. A decrease in the suppression of detrusor activity can be observed in patients with brain and spinal cord injury. The etiology of increased micturition reflex includes the abnormal activation of the afferent nerves in the bladder [76] and the increased stimulation associated with neural remodeling [75]. Mirabegron, a β3-adrenergic agonist, suppresses myogenic and urotheliogenic afferent activity caused by bladder distension (Fig. 2). Clinically, this is characterized by an increase in the intervals between urination, a decrease in the urinary frequency, and an elevation in the urination volume. However, there was no observed decrease in P_{detmax} during the storage phase in response to mirabegron therapy, nor was there a change in other parameters that describe the detrusor contractile activity. It can be hypothesized that mirabegron produces its effects in patients with OAB and detrusor overactivity associated with the more active micturition reflex, rather than the reduced suppression of the detrusor tone by the CNS. The latter phenotype includes detrusor overactivity induced by spinal cord injury, for which the urodynamic effect of mirabegron demonstrates the lowest efficacy.

CONCLUSION

Mirabegron has been demonstrated to be a highly effective pharmaceutical agent for the treatment of OAB and detrusor overactivity, with the favorable safety profile. Mirabegron effectively reduces the severity of clinical symptoms in neurogenic forms of these diseases. The research findings suggest that the drug is highly effective in treating detrusor overactivity in adult patients with multiple sclerosis, Parkinson disease, cerebrovascular diseases, and in pediatric patients. The urodynamic effects of mirabegron vary with the underlying neurological disease, causing detrusor overactivity. Before the initiation of treatment, urodynamic assessment must be performed, and mirabegron may be administered only if P_{detmax} value in the storage phase remains within the established safety limits. Otherwise, it is advisable to consider an alternative treatment option. In light of these findings, further investigation into the clinical and urodynamic evaluation of the efficacy of mirabegron in treating OAB and neurogenic detrusor overactivity associated with various neurological diseases is warranted.

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Вклад автора. И.В. Кузьмин — концепция и дизайн исследования, анализ данных литературы, написание текста статьи. Автор одобрил версию для публикации, а также согласился нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой ее части.

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