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INCREASING THE DOSE OF A SELECTIVE ANTIMUSCARINIC MEDICATION HELPS IMPROVE THE KEY SYMPTOMS OF OVERACTIVE BLADDER

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Abstract
Overactive bladder (OAB) is a serious urinary disorder affecting at least 17% of individuals over the age of 40. In most cases, treatment for OAB begins with pharmacological therapy. Currently, medications that block muscarinic receptors in the bladder are most commonly used. Among these medications, solifenacin stands out due to its high selectivity for the bladder compared to other muscarinic antagonists. The studies presented in this article demonstrate that a flexible dosing approach with solifenacin can effectively improve OAB symptoms with minimal impact on tolerability. Based on numerous studies, both the positive effect of increasing the solifenacin (Vesicare) dose on the key symptoms of OAB and the relevance of starting therapy with a 10 mg dose are confirmed. Unlike oxybutynin, this medication does not significantly affect cognitive function in elderly patients. Thus, solifenacin 10 mg, with its optimal balance of efficacy and safety, provides better treatment adherence compared to other muscarinic antagonists.

Keywords: Overactive bladder, muscarinic antagonists, solifenacin 5/10 mg.

Introduction

Overactive bladder (OAB) is a serious urinary disorder affecting at least 17% of the population over the age of 40, with the majority being women (56%) [1]. The causes and mechanisms underlying imperative urinary disorders associated with

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overactive bladder remain unclear; however, several hypotheses exist regarding the development of the condition. One common factor is nerve degeneration. It is believed that detrusor hyperactivity may be caused by age-related changes not only in the urinary tract but also in the central nervous system. As people age, the frequency of symptoms increases, reaching 30% in those over 65 years old and up to 40% in individuals over 70 years old. Among men with infravesical obstruction (IVO) due to benign prostatic hyperplasia (BPH), 52–80% experience overactive bladder, and 38–47% continue to have symptoms even after surgical removal of the obstruction [2]. The prevalence of frequent urination and imperative urges is almost the same in both men and women, but imperative urinary incontinence is more commonly found in older women. For 70% of women, the onset of these symptoms is linked to menopause [1], making it one of the main risk factors for OAB in women.

Particular attention in the pathogenesis of OAB is given to the disruptions in parasympathetic and sympathetic innervation of the bladder. Currently, five molecular subtypes of muscarinic receptors are identified, and their distribution in tissues may vary. The most crucial role is played by the M3 muscarinic receptors, responsible for detrusor contraction, and the M2 receptors, whose activation inhibits the relaxation of the detrusor's smooth muscle. The majority of muscarinic receptors in the bladder belong to the M2 subtype (around 80%) [3]. Stimulation of M3 receptors by acetylcholine leads to the hydrolysis of phosphoinositol, an increase in intracellular calcium, and contraction of the smooth muscle. Activation of M2 receptors, on the other hand, suppresses adenylate cyclase and facilitates the relaxation of the smooth muscle of the bladder, ensuring effective voiding. It is believed that these receptors may play a significant role in the age-related increase in α1-adrenergic receptor activity in bladder tissues, and that the enhancement of the contractile response related to α1-adrenergic receptors could be one of the causes of overactive bladder in elderly individuals.

Detrusor hypertrophy, which develops as a result of infravesical obstruction (IVO), leads to an increase in the metabolic needs of the tissues while simultaneously reducing blood flow, resulting in anoxia and neuronal damage [4].

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Studies have shown that the density of cholinergic nerve fibers in the detrusor of patients with benign prostatic hyperplasia (BPH) and IVO is 60% lower than in patients of the same age without IVO [5]. This reduction in nerve fiber density in response to IVO may disrupt neuromuscular control of the bladder. The physiological aging process in both men and women is typically accompanied by impaired blood supply, suggesting that hypoxia could be a cause of damage to the intramural neurons and changes in the function of the smooth muscle of the bladder in patients with detrusor overactivity. Ischemia leads to apoptosis of smooth muscle cells and impaired nerve conduction, and since nerve tissue is more sensitive to ischemia than smooth muscle, some of these damages can be almost irreversible. P. Abrams (1985) hypothesized that detrusor overactivity in BPH is not a result of IVO but rather a consequence of age-related changes in the bladder wall.

Despite the contradictory findings, it should be acknowledged that both age and IVO may contribute to postsynaptic denervation of the bladder, highlighting the crucial role of the nervous system in regulating the storage function of the bladder. Regarding the development of OAB in women during menopause, significant attention is paid to the role of estrogen deficiency and the related atrophy of the urothelium and detrusor dystrophy [6, 7]. This may explain the emergence of "sensory symptoms," such as pollakiuria, nocturia, and urgent urges to urinate, which are characteristic of "dry" OAB. The influence of hereditary factors on the development of OAB is also being explored, and several modern studies indicate potential genetic changes associated with this condition [8, 9]. Clinically, detrusor overactivity manifests itself in urgent urges to urinate, pollakiuria (frequent urination more than 6 times during the day), nocturia (more than 1-2 times per night), and urgent urinary incontinence (imperative incontinence). In addition to these symptoms, stranguria may also develop. These symptoms, which appear unexpectedly and often in inconvenient places, significantly disturb patients. Urgent urinary incontinence is the involuntary loss of urine accompanied by a strong, imperative urge to urinate. However, urgent incontinence is not mandatory for the diagnosis of OAB, as half of the patients experience only "sensory" symptoms, such as frequent daytime and nighttime

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urination and urgent urges. This symptom complex is referred to as "dry" OAB. When urgent incontinence is added to the symptoms, the diagnosis is classified as "wet" or "moist" OAB [10]. Overactive detrusor function refers to the involuntary contraction of the detrusor during the filling phase of the bladder. These contractions can be spontaneous or provoked (e.g., during rapid filling, changes in body position, coughing, walking, jumping, etc.), while the patient attempts to suppress them. This condition can only be diagnosed through urodynamic testing, which shows sudden fluctuations in detrusor pressure of more than 15 cm of water. Neurogenic detrusor overactivity (previously referred to as detrusor hyperreflexia) is characterized by excessive detrusor activity associated with neurological disorders, such as spinal cord injuries, spinal diseases, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and others. This diagnosis is confirmed by the presence of neurological pathology along with detrusor overactivity, requiring confirmation through urodynamic testing. If spontaneous contractions of the bladder occur without the sensation of urgency, a neurological disorder should be suspected, and a consultation with a neurologist is warranted. It has been proposed to replace the term "detrusor overactivity" with "overactive bladder." Currently, the term "overactive bladder" is used when the diagnosis is based on disease symptoms, while "detrusor overactivity" is used when the diagnosis is confirmed by urodynamic studies.

The mechanism behind detrusor overactivity symptoms is linked to the loss of voluntary control over urination and the decreased adaptive capacity of the detrusor muscle. However, the reflex arc, which includes the micturition centers in the sacral region and the pons of the brainstem, remains intact. As a result, despite the preservation of the ability to initiate urination, accumulating a sufficient volume of urine in the bladder becomes impossible. The International Continence Society (ICS) defines overactive bladder (OAB) as a symptom complex characterized by urgent urinary urges, with or without urinary incontinence, and frequent urination [10]. A comprehensive evaluation of patients suspected of having OAB includes taking a medical history, physical examination, urine analysis, and assessment of clinical symptoms. It is important to note that, to date, there are no specific laboratory markers for diagnosing

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detrusor overactivity. However, a two-time analysis of urine sediment is a mandatory part of the diagnostic process for patients with suspected detrusor overactivity. This analysis serves as a screening test rather than a diagnostic tool, helping to identify patients whose frequent or urgent urination is related to inflammatory diseases of the lower urinary tract. In patients with true overactive bladder, urine analysis typically shows no pathological changes. Further diagnostic testing, including urodynamic studies and cystoscopy, is necessary if symptoms such as hematuria without signs of infection, difficulty initiating urination (delayed onset of urination, weak stream, residual urine), neurological disorders, or metabolic diseases are present, or if the patient shows no positive response to treatment over a 2-3 month period. Pharmacotherapy is the most common treatment approach for OAB. According to established guidelines, pharmacological therapy is the first line of treatment, followed by behavioral therapy, physiotherapy, and other methods if necessary.

The advantage of pharmacotherapy lies in its rapid effectiveness, the absence of the need for specialized behavioral skills, the reduced time required from the physician, and the minimal participation required from the patient, making it an attractive treatment option for many. Key advantages of this approach include the accessibility of medications, the possibility of long-term use, and the flexibility in adjusting dosage and therapy regimen. Pathogenetic pharmacotherapy must take into account the potential myogenic and neurogenic mechanisms involved in OAB. Its primary goal is to alleviate the main symptoms of the condition, directly improving urodynamic parameters such as reducing detrusor activity and increasing bladder capacity.

The requirements for drugs used in the pharmacological correction of OAB include selective action on the bladder, good tolerability, the possibility of long-term use, and effective relief of primary symptoms such as urinary incontinence. Currently, the most commonly used medications for OAB are those that target muscarinic receptors in the bladder. It has been proven that the stimulation of M3 receptors by acetylcholine plays a key role in both normal and unstable detrusor contractions [11]. However, many of these medications cause side effects, which necessitate careful consideration of the benefits and drawbacks of each treatment.

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Common side effects of antimuscarinic drugs include dry mouth, constipation, accommodation disorders, and drowsiness. These drugs are contraindicated in patients with impaired urine flow from the bladder, intestinal obstruction, ulcerative colitis, glaucoma, or myasthenia. Additionally, the use of these medications may result in delayed reaction times, which requires caution when driving or operating potentially dangerous machinery [12].

Table-1

The selectivity of various m-anticholinergic drugs for the bladder [13].			
medication	increased intravesical pressure	saliva secretion	bladder selectivity
Solifenacin	0,023 (0,010-0,039)	0,15 (0,1-0,24)	6,5
Tolterodine	0,010 (0,008-0,014)	0,024 (0,016-0,047)	2,4
Oxybutynin	0,027 (0,015-0,045)	0,030 (0,024-0,038)	1,1

In a normal bladder, the connections between the bundles of muscle fibers ensure that diffuse activity does not cause an increase in bladder pressure. However, in overactive bladder (OAB), these connections are enhanced, leading to the generation of a wave of diffuse excitation, urgent urges, and uncontrolled (unstable) detrusor contractions. This hypothesis explains the effectiveness of antimuscarinic drugs in treating urgent urinary incontinence. If part of the ganglia is directly stimulated by sensory nerves, suppressing this effect should result in a reduction of both the urgent urges and the unstable contractions [7].

Currently, the following muscarinic antagonists are used in Russia for the treatment of overactive bladder (OAB): solifenacin (Vesicare), oxybutynin (Driptan), trospium chloride (Spasmex), and tolterodine (Detrusitol). Previously, oxybutynin chloride (Driptan, Ditropan) was considered the "gold standard" of therapy. It possesses antimuscarinic, antispasmodic, and local anesthetic properties, although not all of these effects manifest at therapeutic doses. Oxybutynin has a short half-life of 2–4 hours, which allows for its short-term use, such as before social events, but it is not recommended for long-term use. The medication requires individual dose adjustments, which takes some time. The optimal dose is considered to be the one that provides the desired effect with

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minimal side effects. Solifenacin and tolterodine are more selective for the bladder, with solifenacin having the highest selectivity among them [13]. In the STAR study [14], the efficacy and safety of solifenacin at doses of 5 and 10 mg were demonstrated in comparison to tolterodine ER (extended-release) at a dose of 4 mg taken once daily for 4 weeks in patients with overactive bladder (OAB). Urinary retention was observed in 59% of patients taking solifenacin and in 49% of those taking tolterodine ER. After 4 weeks of treatment, 48% of solifenacin patients and 51% of tolterodine ER patients requested an increase in dose. Solifenacin (Vesicare) has good tolerability, making it a preferred choice for elderly patients suffering from urgent urinary disorders. This is particularly important as elderly patients often have comorbidities that limit the use of drugs with high side-effect profiles.

According to the results of an international, multicenter, randomized, double-blind phase III study, solifenacin at doses of 5 and 10 mg significantly reduced urgency and other symptoms of OAB with good tolerability [15]. In another study conducted across 17 European centers, solifenacin 5 and 10 mg showed a significant advantage in all efficacy parameters compared to tolterodine ER 4 mg [16]. There was no statistically significant difference in the frequency of urination episodes and nocturia. However, solifenacin 5 and 10 mg demonstrated significant improvements in incontinence scores, surpassing tolterodine ER 4 mg. The 5 mg dose of solifenacin also significantly reduced the number of incontinence episodes and the number of pads used by the fourth week of treatment. According to the study design, after a two-week placebo run-in period, patients who met inclusion criteria were randomized to receive either 5 mg solifenacin or 4 mg tolterodine ER once daily. After 4 weeks of therapy, patients could either increase the dose or remain on the same dosage, depending on their satisfaction with the treatment results. The dose of tolterodine ER 4 mg could not be increased, as it was the maximum allowable dose, while the solifenacin dose could be increased to 10 mg.

According to a retrospective analysis of prescription medications in the United Kingdom, based on long-term patient data to assess adherence to darifenacin, flavoxate, oxybutynin (both extended-release and immediate-release

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formulations), propiverine, solifenacin 5 mg, solifenacin 10 mg, tolterodine (ER/IR), and trospium chloride, it was found that solifenacin (Vesicare) at a dose of 10 mg demonstrates the best balance of efficacy and safety among all muscarinic antagonists [17]. In this group of medications, solifenacin 10 mg showed the longest duration of use, averaging 216 days, which significantly exceeded the use of other medications, such as solifenacin 5 mg (158 days), tolterodine (152 days), trospium chloride (138 days), and oxybutynin (119 days). Discontinuation of treatment more than 1.5 times longer than the last dose was considered as non-adherence. The analysis only included patients who started treatment for the first time (i.e., those who had not received relevant treatment or doses of these medications for at least 6 months prior to the study).

According to the data from a multicenter, randomized, double-blind phase III study on the efficacy and safety of solifenacin succinate 10 mg in the treatment of overactive bladder syndrome, solifenacin significantly reduced the average number of daily micturitions, urgency episodes, and urge urinary incontinence ($p=0.001$ for all compared to placebo) [18]. The study involved 634 adult patients with OAB symptoms who were randomized into two groups: one received 10 mg solifenacin (n=318), and the other received placebo (n=316). Over a period of 12 weeks, the dynamics of micturition frequency, urgency episodes, and nocturia were assessed using a 3-day voiding diary. Solifenacin led to a significant reduction in daily micturitions, urgency episodes, and nocturia ($p<0.001$ for all compared to placebo). These improvements were observed as early as 4 weeks and were sustained throughout the study period. The side effects were predominantly mild or moderate in severity. Therefore, 10 mg solifenacin was found to be a well-tolerated and effective treatment for the primary symptoms of OAB, including urge urinary incontinence.

The results of another study focusing on the safety of solifenacin, oxybutynin, and placebo regarding cognitive function in healthy elderly patients also revealed interesting findings. Administration of 10 mg solifenacin did not show a significant effect on cognitive function, unlike 10 mg oxybutynin, which significantly impaired attention span just 2 hours after administration ($p<0.05$)

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[19]. However, after 6 hours, no differences in attention strength and duration were observed between the 10 mg solifenacin and placebo groups.

Antimuscarinic drugs, as studies have shown, are effective and well-tolerated treatments for overactive bladder (OAB). Research also confirmed that flexible dosing can be beneficial for improving disease symptoms with minimal impact on tolerability. In a study by L. Cardozo and colleagues [22], using doses of 5 mg and 10 mg solifenacin, it was found that increasing the dose of solifenacin from 5 mg to 10 mg in patients with more severe OAB symptoms could provide better outcomes. In this 16-week study, patients with OAB symptoms were randomized to receive either solifenacin or placebo. By the 8th week, all patients had the option to request a dose increase, which allowed for the examination of dose adjustments. Out of 591 patients, 275 (46.5%) requested a dose increase to 10 mg, and among those who continued treatment with the 10 mg dose, there was a significant reduction in urgency episodes compared to patients who remained on the 5 mg dose (a decrease of 0.9 and 0.4, respectively), though this difference was not statistically significant. Nevertheless, among patients who increased the dose to 10 mg, a statistically significant improvement in efficacy was observed, as evidenced by a reduction in micturition frequency and a decrease in OAB symptoms.

Thus, increasing the solifenacin dose to 10 mg showed additional improvement in OAB symptoms in patients who requested a dose increase after 8 weeks of 5 mg therapy. The results also confirm the need for starting therapy with 10 mg solifenacin to achieve optimal outcomes in the treatment of OAB.

The scientific studies conducted allow the following conclusions to be drawn:

- Solifenacin (Vesicare) 10 mg effectively eliminates all symptoms of OAB [20].
- Solifenacin 5/10 mg reduces urgency by 89% [21].
- Solifenacin 5/10 mg is more effective than tolterodine in reducing urgency and urge urinary incontinence [14].
- Increasing the solifenacin dose to 10 mg allows for better outcomes in the treatment of OAB patients [22].
- The use of 10 mg solifenacin is associated with effectiveness, a favorable safety profile, and good tolerability [22].

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- Solifenacin 10 mg does not significantly affect cognitive function in elderly patients, unlike oxybutynin [19].
- Solifenacin 10 mg provides better treatment adherence compared to other muscarinic antagonists, due to an optimal balance of efficacy and safety [17].

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