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An examination of Overactive Bladder Syndrome: present comprehension, methods of treatment, and innovative approaches

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ABSTRACT
Introduction
Overactive bladder syndrome poses a major challenge to healthcare, as an accurate estimate of its prevalence proves elusive due to patients' reluctance to disclose the embarrassing symptoms that accompany the disorder. Symptoms such as frequent urination, nocturia and incontinence are not only distressing but also significantly impair patients' quality of life. Effective diagnosis and treatment require the identification of associated risk factors, and behavioural therapy serves as the basis for implementing lifestyle modifications. This comprehensive study delves into the managing of overactive bladder syndrome, shedding light on recent advances in diagnosis and treatment. In particular, it looks at the integration of minimally invasive techniques and new medications that promise to not only alleviate symptoms, but also significantly improve patients' overall quality of life.

Aim of the study
This review aims to identify risk factors, symptoms, methods of diagnosis of overactive bladder syndrome and solutions in its treatment process. The main aim is to present treatment methods with the latest developments.
Material and method
This article presents the current state of knowledge about overactive bladder syndrome in various scientific articles. Publications describing overactive bladder syndrome, its symptoms, impact on life comfort and treatment options, including recent reports in the field, were reviewed using the PubMed platform. The search included the keywords 'overactive bladder', 'urgency urinary incontinence', 'anticholinergics', 'mirabegron', 'nocturia'.

Keywords
overactive bladder; urgency urinary incontinence; anticholinergics; mirabegron; nocturia

Introduction
Overactive bladder syndrome (OAB) is a common syndrome that can affect patients of all ages. Millions of individuals worldwide suffer from OAB, however the actual prevalence may be underestimated because many of these patients choose not to seek medical assistance. Studies have shown that the problem of overactive bladder affects 12.8 % of women and 10.8 % of men [1]. Other studies report that the phenomenon can affect up to 16.6% of the European population [2]. It has a significant impact on patients' quality of life and although treatments exist, the condition often remains under-diagnosed, under-estimated and under-treated [1].
It is worth emphasising that an overactive bladder is not a single disease entity with a specific pathophysiology, but a set of clinical symptoms [1].

Aetiology, symptoms and risk factors
There are multiple hypotheses regarding the aetiology of OAB, which is likely multifactorial. The process of urination is controlled by the cerebral cortex, spinal cord, cerebellum and peripheral autonomic pathways. Bladder contraction is primarily caused by the release of acetylcholine, which activates muscarinic receptors M3 and M2. There are two observed theories regarding the pathophysiology of Overactive Bladder (OAB) - neurogenic and myogenic. In the neurogenic hypothesis of overactive bladder, the sensation of urgency is thought to result from decreased inhibition of the micturition reflex due to neurological damage, both in the peripheral and central nervous systems. The myogenic theory suggests that there is a disruption in the innervation of the smooth muscle of the bladder, resulting in a modification of the proper muscle structure and an increased tendency of the bladder to spontaneously contract [3].
OAB is characterised by urinary urgency, often accompanied by frequent urination and nocturia, with or without urge incontinence, in the absence of urinary tract infection or the exclusion of other pathologies [4]. Patients with a bladder over-reactivity problem most commonly consult their doctor with a discomforting sensation of urinary urgency and urge incontinence. Studies suggest that >10% of the population struggles with urge incontinence, and the problem is twice as common in patients aged >65 years [5]. There are two types of clinical symptoms - OAB-wet and OAB-dry. Patients with wet overactive bladder experience more severe symptoms, stronger bladder contractions, and a higher rate of coexisting

urodynamic stress incontinence, in comparison to those with dry OAB. Currently, therapeutic options for patients with OAB-wet and OAB-dry are almost the same [6].
It is important to classify and identify the risk factors for this syndrome, as their prevention is an important part of the initial treatment of this disorder [5]. Analysing studies, the most important risk factor for overactive bladder is age. The frequency of OAB increases with age [5,7]. Gender also matters - the disorder is more common in women [2,5]. Other studies have analysed the association between OAB and lifestyle, especially smoking, alcohol consumption and diet, and found that controlling these factors improved or prevented the occurrence of OAB [8,9]. The risk of OAB is also increased by obesity, postmenopausal age, genital prolapse in women, benign prostatic proliferation in men, the presence of bladder stones, consumption of highly caffeinated drinks and carbonated beverages [5]. It is important in clinical practice that, where possible, treatment for overactive bladder should be implemented along with a change in modifiable risk factors for this condition. Patients should be advised to stop consuming alcohol, smoking, drinking highly caffeinated and carbonated beverages. It is important to maintain a normal body weight in the OAB patient and to reduce it when necessary.

Impact of OAB on quality of life
The quality of life for individuals with OAB is influenced by several aspects, mostly related to the severity and frequency of the disease's symptoms as well as how much it interferes with the patient's everyday activities [10]. Every area of a patient's life might be affected, involving spheres such as mental health, social interactions and sex behaviours [11]. Patients with OAB avoided sexual contact, which affected their relationships and reduces self-confidence. Their comfort and productivity during the day were negatively impacted by the considerable reduction in sleep quality caused by nycturia [11]. Depression affects 30% of individuals with Overactive Bladder, and those who have depression experience more intense symptoms of incontinence [10]. Patients with OAB frequently experience anxiety and persistent concern regarding their ability to reach a bathroom in time to prevent urge incontinence [10,12].

Diagnosis including differential diagnosis
OAB is a clinical diagnosis based on the frequency and severity of symptoms - frequent urination and daytime urgency, with or without urge incontinence [2].
In the process of diagnosis, we should start with physical examination. An interview with the patient about the symptoms is crucial - note how long they have been occurring, whether they are sudden, what factors cause or relieve them, whether there has been any previous treatment and what the results have been. Physical examination should include examination of the genitourinary tract as well as rectal imaging and examination of the prostate gland in men and gynaecological examination in women [2]. Physical examination may attract our attention to genital prolapse, prostatic proliferation, bladder overflow and other symptoms that may be useful in the differential diagnosis, also a neurological examination is crucial [11]. An important part of the diagnosis of a patient with an overactive bladder is keeping a micturition diary in which the patient records frequency and the volume of micturition. It is assumed that a three-day diary is sufficient for a clinical assessment of the patient's symptoms. It significantly facilitates the collection of an accurate history regarding micturition frequency, nycturia and urine volume [13, 14].
In all patients with symptoms of overactive bladder, we perform a general urinalysis. If we exclude hematuria and urinary tract infection during additional examinations, treatment targeting OAB can be initiated. Ultrasound examination can be useful in the differential diagnosis, in addition, it allows for a non-invasive measurement of the residual urine in the

bladder after micturition, which can guide the diagnosis to the existence of an obstruction to urinary outflow [13].
Use of urodynamic study (UDS) in the diagnosis of an overactive bladder is quite controversial. On one hand, it is considered the gold standard in the assessment of lower urinary tract symptoms, but on the other hand it is an invasive test that is associated with the risk of developing urinary tract infection (UTI). Currently, urodynamic testing is indicated in diagnostically questionable cases that are refractory to treatment or prior to invasive treatments [15, 16]. To summarise, cystoscopy, renal/bladder ultrasound, computed tomography (CT)/magnetic resonance imaging (MRI), and UDS are not advised for the initial evaluation of the patient with uncomplicated OAB [10].
It has been shown that in clinical practice, biomarkers e.g. NGF (neuronal growth factor) [17], prostaglandin E2 (PGE2), MCP-1 (monocyte chemotactic protein-1) and monocyte chemotactic protein-1 (scd40L) can be used to monitor treatment efficacy and support the diagnosis of OAB [13].
Differential diagnosis should be considered when diagnosing overactive bladder syndrome. In particular, it should be noted that neuropathic bladder due to central nervous system disease can result in neurogenic over-reactivity of the urinary detrusor muscle, which can produce symptoms similar to OAB. Such condition may occur in patients after stroke, with multiple sclerosis, dementia, diabetic neuropathy or after spinal injury [5]. Similarly, urothelial carcinoma of the bladder can cause, through irritation of the bladder, symptoms identical to those of OAB. It is important to remember that clinical symptoms, i.e. nycturia, urinary urgency, incontinence, may be the first signs of high-grade bladder cancer [5]. OAB-like symptoms may also be caused by the existence of a bladder obstruction - e.g. in benign prostatic hyperplasia, the presence of a foreign body in the urinary tract or recurrent urinary tract infections. They can also be caused by taking diuretics, anticholinergics and drugs [5].

Treatment of Overactive Bladder Syndrome including behavioural therapy, pharmacotherapy and invasive procedures

There are 3 lines of therapy for overactive bladder syndrome - the first line of treatment is behavioural therapy - lifestyle modification, pelvic floor physical therapy and bladder training. Pharmacological intervention is a second-line treatment. Invasive treatments are used as a third line of treatment.
If possible, treatment should go from the least to the most invasive. If a single therapeutic technique is unsuccessful, different modalities might be combined [18].

Behavioural treatment

All patients who begin treatment of OAB should start with some form of behavioural therapy and changing existing habits [19]. Because behavioural therapies and lifestyle changes can be combined with other treatments for OAB, they should be part of the treatment of every OAB patient [10]. Patients with OAB are recommended to change their daily micturition habits - the goal of these therapies is to increase the intervals between micturition episodes, reduce discomfort from episodes of urgency and nycturia, and prevent incontinence. Patients are advised to perform bladder training, which involves establishing a micturition schedule and attempting to lengthen the intervals between urinary episodes until these intervals are normalised [10]. Pelvic floor muscle training is also recommended as it improves urethral stabilization, which helps to reduce OAB symptoms [2,10]. These methods can be very effective. Up to 30% of patients have been relieved of their symptoms by exercise, and in some patients uncontrolled urine leakage has been reduced by 50-80% [20]. Patients with OAB are instructed to limit their fluid intake to 1-1.5 l per day. It has been proven that reducing fluid intake by 25% significantly alleviated OAB symptoms [2, 21, 22].

Appropriate treatment of comorbidities and avoidance of OAB risk factors is also important - treatment regimens that avoid diuretics, adequately control chronic cough and constipation are recommended. Patients should be advised to stop drinking alcohol, smoking and consuming large amounts of highly caffeinated beverages [14]. Weight loss in obese patients is also beneficial. It has been proven that in obese women, after weight loss, the number of incontinence episodes within one week decreased by 46% and the number of urges by 42% (compared to 28% and 26%, respectively, in the control group) [10, 23]. Regular physical activity has been shown to strengthen the pelvic floor muscles, which can alleviate OAB symptoms [10]. It is worth remembering that these forms of therapy require commitment and effort from the patient [19].

Pharmacological treatment

Controlling and decreasing the symptoms of urgency, frequency, and urine incontinence are the main objective of pharmacological treatment of OAB [10]. The two main drug groups in the pharmacotherapy of overactive bladder syndrome are beta-3 adrenergic receptors agonists and anti-muscarinic agents [10, 18].

Anti-Muscarinics

Acetylcholine (ACh)-induced activation of muscarinic receptors on bladder smooth muscle cells is the cause of bladder detrusor muscle contractions [24]. The mechanism of anti-muscarinics is based on an antagonistic effect on muscarinic receptors. The relieving of symptoms of overactive bladder syndrome by these medications is based on relaxing contractions of the bladder detrusor muscle and improving afferent sensory transmission by blocking M2 and M3 receptors in the bladder and urothelium [10]. This group of medicines is represented by drugs such as Oxybutynin, Tolterodine, Darifenacin, Trospium, Solifenacin, Propiverine, Fesoterodine [10, 18]. These agents come in different formulations and methods of application, e.g. oxybutynin in transdermal form or oral immediate/extended release form [10]. Tolterodine and oxybutynin are the most widely used drugs for the treatment of OAB and they are still the first or second most prescribed drugs in many countries [25]. The study showed that OAB patients who took antimuscarinics received improvements in average urine volume, episodes of urgency and frequency of micturition. The drugs also improved quality of life in patients with this syndrome [26]. This makes these drugs one of the most commonly used treatments for urgency and urgency incontinence, and they are recommended for patients with OAB [10, 18].

A number of antimuscarinic drugs are metabolised by the P450 enzymatic pathway to their metabolites [18]. Because of their metabolism, there is a possibility of drug interactions, so the patient needs to be informed before prescribing an antimuscarinic drug. The most commonly reported side effects of antimuscarinics were dry mouth, constipation and pruritus [10,18,26]. Patients may also experience problems with their eyesight, tachycardia, sleepiness and headaches. The higher the dose of antimuscarinics, the risk of side events increases [18]. Urinary retention, gastrointestinal motility disorders and narrow-angle glaucoma are the main contraindications to antimuscarinic therapy [10].

The new anticholinergic drugs tarafenacin and afacifenacin are in the research phases. The study revealed that administering a dosage of 0.4 mg of tarafenacin reduced the occurrence of urine incontinence following a 12-week treatment period. Additionally, the medicine exhibited good tolerability among the participants [27].

Beta-3 adrenergic receptors agonists

Currently, two beta-3 adrenergic receptors agonists are available - mirabegron and a second substance, recently approved for the treatment of OAB in the US, vibegron [18, 28]. Mirabegron is a beta-agonist, that activates beta-3 adrenergic receptors and helps relax the

detrusor muscle in the bladder [10]. The study showed that mirabegron was successful in reducing the number of incontinence incidents, the mean number of micturitions, the average volume of urine passed at each micturition and the number of urinary urgency episodes per 24-hour period in patients with OAB [29]. Research has shown that mirabegron has a high-level safety profile [18, 30]. The most frequent side effects of mirabegron were high blood pressure, nasopharyngitis and infection of the urinary tract [10]. Compared to treatment with antimuscarinic drugs, side effects are statistically less common [2, 31]. The total number of side effects in people taking mirabegron was 17.0%, compared with 21.4% in patients who were treated with anticholinergics [18]. Mirabegron is not recommended in patients with uncontrolled high blood pressure. Patients taking this medication should monitor their blood pressure regularly [18]. The newest drug to be licenced for treating OAB patients is called vibegron. It also belongs to the family of beta-3 adrenergic receptor agonists. Administering a daily dosage of 75 mg of vibegron resulted in notable reductions in the key symptoms of overactive bladder. Vibegron treatment had a favourable safety profile and high tolerability among elderly people, women and patients with or without urine incontinence [32]. Treatment with Vibegron reduced the number of urgency incontinence incidents in patients with ≥1 incidents/day and the number of voids/day. More research is needed to compare the efficacy and safety profile of vibegron with that of mirabegron [18]. Solabegron and ritobegron are two new beta-3 adrenergic receptors agonists under study for the treatment of OAB. The study indicated that solabegron effectively decreased symptoms of overactive bladder (OAB) and was well-tolerated. Preclinical investigations on ritobegron, a different beta-3 adrenergic receptors agonist, were carried out on cynomolgus monkeys and rats. The results indicate that this medication holds potential for clinical management of OAB [27].

In patients who are resistant to monotherapy, combination therapy (antimuscarinic and beta3-agonist) may be recommended. Combined therapy seems to improve effectiveness with a minimal increase in the adverse events profile [2]. In OAB patients in whom the use of solifenacin did not give satisfactory results, mirabegron was included. The combination of the two drugs was more effective than treatment with solifenacin alone and resulted in less adverse effects [33].

Third-line of treatment - invasive procedures

OnabotulinumtoxinA

In patients with OAB in whom pharmacological treatment has failed, intramuscular administration of OnabotulinumtoxinA is a promising alternative [10]. The treatment reduces the spasticity of the bladder muscles, which results in a decrease of bladder pressure [34]. This method showed significant relief of all symptoms of overactive bladder and health-related quality of life in patients who received inadequate anticholinergic treatment [35]. Patients with OAB who received OnabotulinumtoxinA treatment had increased satisfaction levels and improved therapeutic goal attainment in comparison to those who received a placebo [36]. The actual method used to treat OAB is the administration of 100 units of onabotulinum toxin A dissolved in 10 ml of physiological saline, the product is applied at 20 points of the posterior bladder wall, avoiding the ureteral oricifes and the bladder triangle. The procedure is performed under cystoscopy guidance [2, 34]. Negative aspects of this method include the necessity to repeat the injection every six months and an increased risk of urinary tract infections [2].

Sacral neuromodulation (SNM)

SNM is a highly effective and minimally invasive solution for treating refractory OAB [37]. This therapy has been shown to be an effective treatment for OAB, as evidenced by a reduction in the number of voids, an increase in bladder capacity and fewer leakage events [38]. There are several theories describing the mechanism of action of sacral

neuromodulation in overactive bladder syndrome - one of which is the direct inhibitory effect of SNM on the bladder. In this method, both urine leakage and bladder over-reactivity are reduced as a result of inhibition of the defence reflex and reduced spasticity of the pelvic floor muscles [38]. To restore normal voiding behaviours, an electrode implant is placed in the sacral foramen with fluoroscopic monitoring to stimulate the S3 or S4 nerve roots [2, 38]. Sacral neuromodulation is most effective with the right patient selection. This treatment method has the biggest effect on patients with wet OAB and provides greater benefits to younger patients [38]. Pain at the implant site and an unwanted change in stimulation were the most frequently reported side-effects [2].

Peripheral tibial nerve stimulation (PTNS)

This procedure is used to manage symptoms of overactive bladder and has been reported to be a safe and effective method to treat OAB. Percutaneous tibial nerve stimulation (PTNS) is a procedure that is based on electrical stimulation of the posterior tibial nerve (PTN) at a location above the patient's medial malleolus [39]. Through the PTN, electrical stimulation is delivered to the sacral micturition centers [2]. Most studies of PTNS have shown improvements in the symptoms of incontinence and urinary frequency and the absence of unpleasant adverse effects (discomfort and minimal pain at the time of stimulation, bleeding at the implant location) [10]. It has been reported that the sacral nerve plexus, which regulates bladder function, receives retrograde neuromodulation in response to stimulation of the posterior tibial nerve [40]. The improvement in urodynamic parameters is probably based on neuromodulation of the afferent and efferent nerve fibres, which results in inhibition of the activity of the urinary detrusor muscle [41].

If a patient has contraindications to the presented therapeutic choices or if these approaches are ineffective, intermittent or permanent catheterization may be an appropriate option to consider. Nevertheless, this approach is linked to some adverse outcomes. Chronically catheterized patients experience a higher occurrence of urinary tract inflammation, as well as injuries to the urethra. This approach requires cooperation with either the patient or the person who cares for them [10].

Surgery is only considered as a therapy for OAB in extremely few situations. The most common procedures used for this are urinary diversion or augmentation cystoplasty. These therapies are mostly used for groups of paediatric and neurogenic patients. Surgical intervention should be only considered for patients who have exhausted all alternative therapies or have had an unsatisfactory quality of life as a result of those treatments [10]. Laparoscopic and robotic augmentation cystoplasty procedures are now possible with minimal morbidity due to technological advancements [42].

New treatments

There are currently some categories of novel medications undergoing different phases of testing to treat Overactive Bladder (OAB).

As a potential treatment for OAB, pharmaceuticals that act on ion channels in the detrusor muscle (e.g., calcium channel blockers and potassium channel openers) are presently under investigation. Bladder muscle relaxation is achieved by drugs that activate K+ ion channels, which open K+ channels in the cell membranes of smooth muscle cells. This leads to the outflow of K+ ions and the hyperpolarization of the cell membrane. As a consequence, the membrane-bound voltage-dependent calcium channels (VDCCs) are deactivated, causing a reduction in the levels of intracellular Ca2+. This ultimately leads to the relaxation of the bladder muscles [27, 43]. Studies have demonstrated that nicorandil, by opening ATP-sensitive K+ channels, effectively suppresses the contraction response to acetylcholine (ACh), potassium chloride, and electrical stimulation in isolated urinary detrusor muscle in rats. The researchers demonstrated that nicorandil induces relaxation in isolated human detrusor muscle that has been constricted by the injection of potassium chloride. Additional ATP-

sensitive K+ channel openers that have been demonstrated to ease the detrusor muscle include minoxidil and pinacidil [27].
Calcium channel blockers (CCBs) are a group of medications that can relax the detrusor muscle by preventing the entry of calcium ions (Ca2+) into the cell through voltage-gated calcium channels (VGCC) from outside the cell. As a result, there is a decrease in the concentration of Ca2+ within the cells, leading to the relaxation of the muscles. The study demonstrated that nifedipine effectively eliminated the contraction of the isolated human detrusor muscle [27].
Another category of medications that may inhibit the contraction of the detrusor muscle and potentially be used to treat an overactive bladder (OAB) are those that target particular enzymes. Forskolin, an activator of adenylyl cyclase, increases intracellular levels of cyclic adenosine monophosphate (cAMP) and induces notable relaxation of porcine detrusor strips [27].
Phosphodiesterase 5 (PDE5) inhibitors have demonstrated efficacy in relieving symptoms of overactive bladder by inducing relaxation of smooth muscle cells in the genitourinary tract through the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP)/PDE5 pathway and by enhancing the control of bladder fusion and neuronal activity [44]. Preclinical and Phase I clinical trials have demonstrated the potential efficacy of PDE-5 inhibitors, such as tadalafil and sildenafil, in the treatment of OAB [27, 44].
The enzyme Rho kinase suppresses the activity of myosin light chain phosphatase, therefore promoting the contraction of smooth muscle. Preclinical investigations have demonstrated that Rho kinase inhibitors (eg. fasudil) induce relaxation of the detrusor muscle [27].
Research has demonstrated that a combination of acupuncture and pharmacological therapy provides a more advantageous outcome for overactive bladder compared to drug therapy alone. The limited sample size and significant bias risk, however, result in a low degree of proof. For acupuncture to be used in the treatment of OAB, further research will be required in the future to gather stronger evidence [45].

Conclusion

Overactive bladder syndrome is a disease that affects a significant percentage of patients in the global population. There are many risk factors that contribute to the development of this condition, such as age, gender, obesity, postmenopausal age and unhealthy dietary habits of patients. Symptoms including incontinence or urgency can be very distressing for patients and affect both their physical and psychological health. Physician needs to be aware that patients often tend to neglect or mask their symptoms as a result of which the therapeutic process is delayed. It is important to exclude other disease entities that may give similar complaints, with special attention to tumours or neurological conditions. An crucial part of treatment in any patient with this syndrome is behavioural therapy with changes in daily habits, including bladder training, weight reduction or effective management of co-morbidities. Antimuscarinics and beta-3 receptor agonists are among the many forms of therapy available for this condition. New substances are constantly being researched that may improve the quality of life of patients with overactive bladder syndrome. Invasive treatments are also available, including botulinum toxin injection or procedures involving neuromodulation. The approach to a patient with this condition should be comprehensive and include both medical and psychological aspects. Compliance is vital to minimize the time elapsed between diagnosis and satisfactory therapeutic outcome.

Author's contribution

Conceptualization, Zuzanna Kotowicz; methodology, Zuzanna Kotowicz; software, Jakub Pabiś; check, Zuzanna Kotowicz, Jakub Pabiś and Piotr Podgórski; formal analysis, Jakub Pabiś; investigation, Zuzanna Kotowicz; resources, Piotr Podgórski; data curation, Jakub

Pabiś; writing - rough preparation, Zuzanna Kotowicz; writing - review and editing, Zuzanna Kotowicz; visualization, Jakub Pabiś; supervision, Piotr Podgórski; project administration, Zuzanna Kotowicz, Piotr Podgórski; receiving funding, Zuzanna Kotowicz, Jakub Pabiś;

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