VIA MEDICA

The Urogynecology Section of the Polish Society of Gynecologists and Obstetricians guidelines on the management of non-neurogenic overactive bladder syndrome in women

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ABSTRACT

Objectives: The aim of the publication was to present the interdisciplinary guidelines of the Urogynecology Section of the Polish Society of Gynecologists and Obstetricians (PSGO) for the treatment of overactive bladder (OAB) syndrome based on the available literature, expert knowledge, and everyday practice.

Material and methods: A review of the literature, including current recommendations for the treatment of overactive bladder syndrome, urinary incontinence, urgency and mixed urinary incontinence, as well as the earlier recommendations of the PSGO Urogynecology Section, was conducted.

Results: Management of the patients with OAB is presented. Four lines of therapy were identified: 1) educating the patient, behavioral therapy with pelvic floor muscle training, 2) pharmacotherapy, 3) botulinum toxin injection and tibial nerve stimulation; and sacral nerve stimulation even though so far it has been used only in selected populations, 4) surgical intervention. The literature reports which provided supporting evidence and presented various aspects of the therapy were discussed. OAB pharmacotherapy-related issues which are vital in everyday clinical practice were presented.

Conclusions: A systematic review of the available guidelines and an analysis of OAB (including urgency urinary incontinence) management were conducted. The Polish Society of Gynecologists and Obstetricians issued the guidelines for the therapeutic management of OAB patients. The need for an individualized approach was emphasized.

Key words: overactive bladder; pharmacotherapy; behavioral therapy; physiotherapy; botulinum toxin; urinary incontinence

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INTRODUCTION

The mission of the Urogynecology Section of the Polish Society of Gynecologists and Obstetricians (PSGO) is to promote the development of urogynecology in Poland, support education, and set evidence-based standards for the management of urogynecologic diseases. The Urogynecology Section issues certificates and awards credit points. The present update of the Guidelines concerns the treatment of the overactive bladder (OAB) syndrome.

Various fields of medicine benefit from guidelines and recommendations for the management of numerous diseases issued by expert groups and associations. The aim of these guidelines is to set evidence-based standards and to present the current management of different diseases and conditions, in accordance with the global trends. Their content is based on the analysis of the available literature, having taken into consideration the specificity and resources of a given country.

The guidelines present the current management of the disease, which may be modified and altered in justifiable cases and after a detailed analysis of the clinical situation, which in turn might lead to future updates of the recommendations. Both, the patient and the treatment always require an individualized approach. Also, it is possible to apply other than recommended, and in some cases even off-label, therapies.

The available literature on the overactive bladder syndrome mostly relates to patients with mixed urinary incontinence or with urinary incontinence (UI). The authors of the present study aimed to review the up-to-date guidelines and recommendations and to analyze the management protocols for OAB patients, including cases with urgency urinary incontinence.

The present recommendations are supposed to serve as a guide to therapeutic management both, for gynecologists and other specialists. Considering the continuous advances in the field of pathophysiology and pharmacotherapy, the strategies presented herein will need to be updated in due course.

Overactive bladder is a symptom complex associated with the phase of urine storage. The International Continence Society defines OAB as a urinary urgency, typically with frequency and nocturia, with or without urinary incontinence. The diagnosis can be made after ruling out urinary tract infections, post-void urine retention, or changes such as cancer, urinary calculi or pelvic tumors modeling the bladder [1]. Pelvic organ prolapse (POP) may be the cause of OAB symptoms in the affected women. In the experience of the authors, the diagnosis of OAB should be made after excluding POP as the cause of OAB symptoms. On the other hand, numerous specialists believe that symptomatic POP should not influence the diagnosis and treatment of OAB.

A detailed diagnostic process is necessary to confirm the diagnosis of OAB before treatment. Also, other disorders, which might constitute the underlying causes for the reported symptoms, should be excluded. The following methods may be used in the diagnostic process: medical history, physical examination, urinalysis, urine culture, urine cytology, evaluation of post-void urinary retention, micturition diary, ultrasound examination, cystoscopy, urodynamic examination, and validated questionnaires to diagnose UI types, OAB severity, and health-related quality of life [2–4]. Importantly, a urodynamic examination is not necessary during the initial assessment and is not the essential condition to initiate treatment. The diagnostic process and test selection are tailored to the individual needs and symptoms of the patient. Guidelines for the diagnostic process of patients with OAB will have been presented elsewhere.

Objectives

The aim of the Urogynecology Section of the Polish Society of Gynecologists and Obstetricians (PSGO) was to develop interdisciplinary recommendations for the management of overactive bladder (OAB) syndrome, based on the available literature reports, expert knowledge, and everyday practice. The up-to-date standards, indications and expert opinions on the clinical management of OAB are presented.

MATERIAL AND METHODS

In 2005, 2006 and 2010, the panel of PSGO experts developed guidelines for the diagnosis and treatment of urogynecologic conditions. The present publication is an update of those recommendations, based on the literature reports published between 2010 and 2019, as well as the recommendations of the American Urological Association, the European Association of Urology, and the Canadian Urological Association [2–7].

The literature, including the current international recommendations for the management of overactive bladder, urinary incontinence, urgency urinary incontinence and mixed urinary incontinence, was reviewed.

Special attention has been paid to the level of evidence and degree of recommendation of the available data sources. If the literature source seemed insufficient, expert opinions and management protocols were included.

RECOMMENDATIONS
First-line treatment: behavioral therapy with pelvic floor muscle training

According to the recommendations of the American Urological Association (AUA) [2], education of the patient (resulting in active involvement in the therapy), lifestyle modifications, and various types of behavioral therapy combined with pelvic floor muscle training (PFMT),
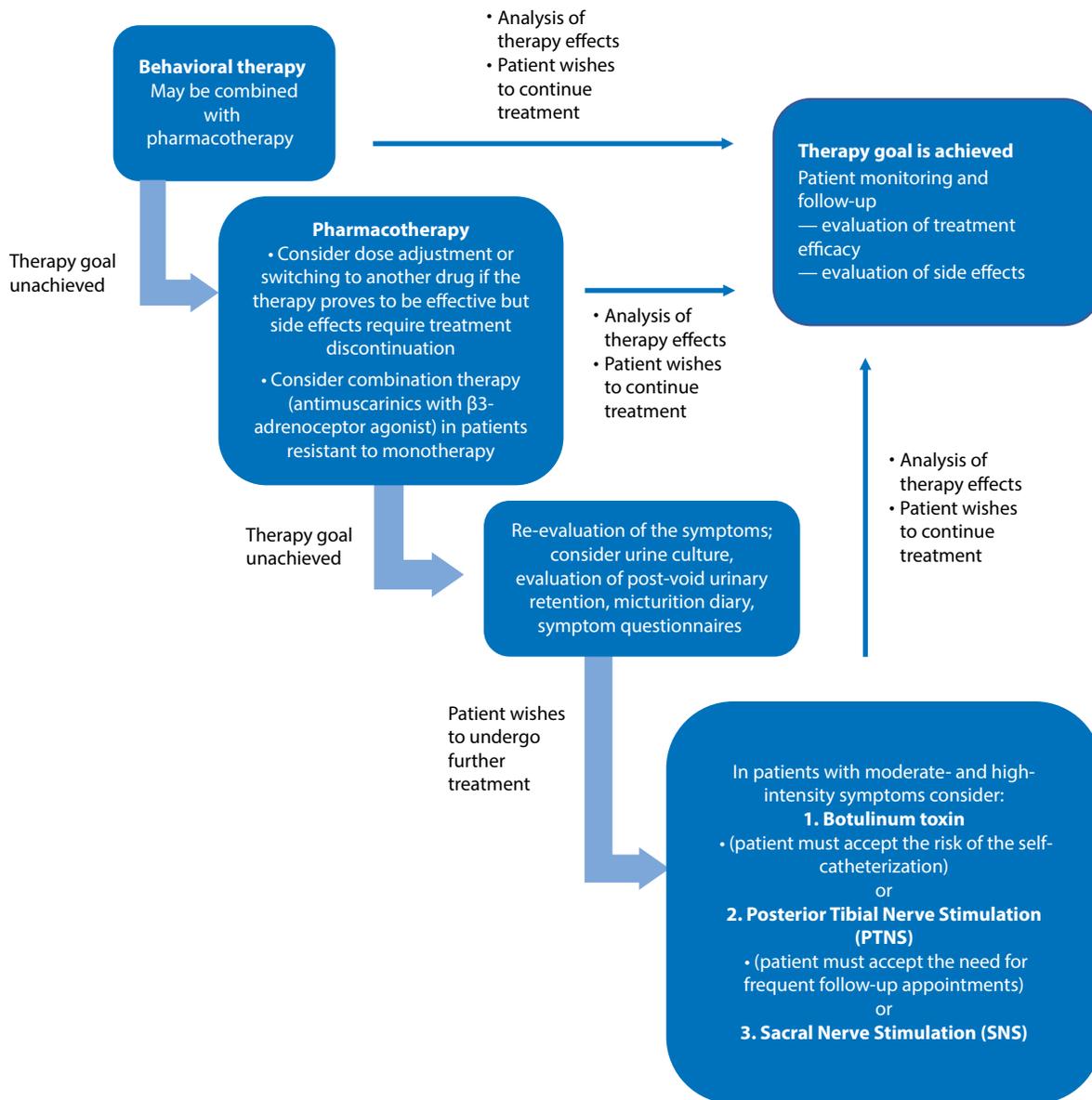
Figure 1. Management of patients with non-neurogenic overactive bladder syndrome [by M.E. Grzybowska, on the basis of Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and Treatment of Non-Neurogenic Overactive Bladder (OAB) in Adults: an AUA/SUFU Guideline (2019). Published 2012; Amended 2014, 2019. https://www.auanet.org/guidelines/overactive-bladder-(oab)-guideline (access: 2020.01.10)]

should constitute the first-line treatment for the OAB syndrome. It is important to establish if the cognitive abilities of the patient will allow for an effective implementation of the management. From the very beginning of the therapy, the first line of treatment may be combined with pharmacotherapy, *i.e.*, the second line. In everyday practice, both lines of treatment are often used simultaneously from the start. Patient motivation is of utmost importance as it determines lifestyle changes and strict adherence to treatment regime, which directly affects the efficacy of the treatment (Fig. 1).

Behavioral therapy includes:

a) actions aimed at improving bladder function, *i.e.*, scheduled voiding at time intervals and bladder training, allowing for gradual increase of the time intervals between voids
b) control of fluid intake and reduction of caffeine intake
c) lifestyle modifications, including weight control, cessation of smoking, and bowel regularity to prevent constipation.

Pelvic floor muscle training is an example of physical therapy used to treat OAB. In certain cases, it is also advisable to use biofeedback (real-time ultrasonography feedback, EMG-biofeedback) and electrostimulation.

The choice of treatment depends on the symptoms and patient preferences. Most patients do not experience complete symptom resolution after the first line of treatment.

Second-line treatment: oral and vaginal pharmacotherapy

In everyday clinical practice, pharmacotherapy is typically initiated together with the first-line treatment as it is already applicable in the initial stages of OAB therapy.

After reviewing the available recommendations for OAB treatment, it seems prudent to follow the guidelines issued by the American Urological Association [2], with minor modifications.

1. Oral antimuscarinics or β3-adrenoceptor agonists are used as the second-line treatment.
2. If both, immediate release (IR) and extended release (ER) drugs are available, ER drugs are preferred due to lower risk for dry mouth.
3. In the event of insufficient symptom control and/or serious side effects after administering an antimuscarinic drug, the dose may be modified or another antimuscarinic drug or a β3- adrenoceptor agonist may be initiated.
4. A combination therapy (antimuscarinics combined with β3-adrenoceptor agonists) may be considered for patients who failed on antimuscarinic or β3-adrenoceptor agonist monotherapy.
5. Antimuscarinics are contraindicated in patients with narrow-angle glaucoma. Patients with glaucoma should be referred to an ophthalmologist for a consultation before anticholinergic drugs are considered.
6. Antimuscarinics should be used with caution in patients with impaired gastric emptying or history of urinary retention.
7. Adequate fluid intake, bowel management, dose modification or switching to another antimuscarinic or mirabegron should be recommended to patients with constipation who are satisfied with the effects of the OAB treatment with antimuscarinics before treatment discontinuation.
8. Adequate fluid intake, hydration of the oral cavity, dose adjustment or switching to another antimuscarinic or mirabegron should be recommended to patients with dry mouth who are satisfied with the effects of the OAB treatment with antimuscarinics before treatment discontinuation.
9. Before antimuscarinic therapy is initiated, patient use of other drugs with anticholinergic properties should be taken into consideration.
10. Mirabegron is effective and safe in older populations. Caution is advised when prescribing antimuscarinic drugs to frail patients.
11. Vaginal estrogen therapy may effectively alleviate OAB symptoms in postmenopausal women. It is recommended to combine β3-adrenoceptor agonists or antimuscarinics with estrogens in that group of patients.
12. The efficacy of pharmacotherapy may be assessed after 4–8 weeks. Then, the effects of the treatment should be evaluated, and the necessary adjustments should be introduced, if needed.
13. Patients with behavioral and pharmacologic therapy resistant OAB should be referred to a specialist for further diagnostic procedures and therapeutic options.

Third-line treatment: botulinum toxin and neuromodulation (posterior tibial nerve stimulation and sacral nerve stimulation)

Botulinum toxin

1. Patients with first- and second-line therapy resistant OAB may be offered bladder wall injection of botulinum toxin A.
2. Patients should be informed about the limited duration of drug action and the risk for both, urinary tract infections and the need for self-catheterization (it is important to ensure the patient will cooperate and be willing to perform it, if necessary). The patient is required to report for post-void residual volume evaluation after the procedure.
3. The next bladder wall injection of botulinum toxin should be performed no sooner than three months after the pervious injection.

Posterior tibial nerve stimulation (PTNS)

In some patients, posterior tibial nerve stimulation (PTNS) may be used as third-line treatment. Transcutaneous PTNS is performed by a physiotherapist using adhesive surface electrodes. Percutaneous needle PTNS, performed by a physician, consists in stimulation with a slim needle electrode. In both cases, the electrodes are placed just above the medial condyle of the ankle.

Sacral nerve stimulation (SNS)

Sacral nerve stimulation (SNS) may be offered as third-line treatment to carefully selected patient populations with severe therapy resistant OAB symptoms or those who are not eligible for second-line treatment but are willing to undergo surgery.

Fourth-line treatment

Augmentation cystoplasty or other types of urine diversion may be considered in rare and complicated cases of therapy resistant OAB [2].

Patient care

Care and monitoring should be exercised during therapy to assess patient adherence to their treatment recommen-

dations and efficacy of the therapy, or to consider other therapeutic options.

Additional therapeutic procedures

Indwelling catheters (transurethral, suprapubic, etc.) are not recommended in the management of OAB due to the unfavorable risk-to-benefit ratio, with some exceptions [2].

As for manual therapy, the following techniques may be used: myofascial relaxation of the pelvic floor muscles and the lumbar-pelvic-iliac complex, joint mobilization/manipulation of the spine and the pelvis, and nerve neuromobilization. Manual therapy allows the normalization of pelvic floor and anterolateral abdominal wall muscle tone, which affects nerve conduction within the pelvis. The literature offers limited amount of data on the matter. Based on the expert knowledge and experience of the authors of the present study, manual therapy is a useful tool in OAB therapy.

OVERVIEW OF THE RECOMMENDATIONS
First-line treatment: behavioral therapy combined with pelvic floor muscle training
Actions improving the urinary bladder function

Timed voiding (at fixed intervals) — initiated by the affected patients or their caretakers — improves urinary continence, especially in older people with cognitive impairment (LE1b — level of evidence) [3].

Bladder training, typically combined with pelvic floor muscle training, is one of the basic elements of behavioral therapy. It gradually extends the time intervals between voiding, increases the bladder volume and reduces the number of urgency urinary incontinence (UUI) episodes (LE1b). The goal of the bladder training is for the patient to adhere to a voiding schedule, with gradually delayed voiding (by 15–30 minutes/week) until the goal of a 2–3--hour interval is achieved. Bladder training is used to correct urination habits. Combined with an anticholinergic and/or β3-agonist therapy, bladder training may be a more effective way of dealing with the symptoms of frequency and nocturia than any of these therapies alone (LE1b) [3].

According to a Cochrane analysis of 23 studies and 3685 patients, symptom resolution was more frequently observed in patients receiving antimuscarinics as compared to bladder training alone (RR 0.74, 95% CI 0.61–0.91), and in patients receiving antimuscarinics in combination with bladder training than bladder training alone (RR 0.57, 95% CI 0.38–0.88) [8].

Fluid intake management

Caffeine is found in beverages such as coffee, tea and cola. **Reduced caffeine intake** may diminish the symptoms of urgency and frequency (LE2b) [3].

Modification of fluid intake, depending on the initial balance of fluid intake and output, has been advised. In a randomized controlled trial (RCT), limitation of the fluid intake by 25% reduced the symptoms of urgency, frequency and nocturia in patients with OAB [3].

Caution should be exercised when recommending fluid restriction, as this strategy is often self-initiated by the affected patients to reduce the symptoms, before seeking medical help. Minimum daily fluid intake should be approximately 1500 mL or 30 mL/kg of body weight. In order to reduce the symptoms of nocturia, patients can be advised to limit their fluid intake after 6 p.m. (or 3–4 hours before bedtime) and to redirect fluid intake to the morning and afternoon hours [4, 9].

Lifestyle modification

In RCT, an 8% **weight reduction** in obese women resulted in a 42% reduction in the episodes of UUI as compared to 26% in the control group [2, 10]. The literature offers reports which confirm that the increase in the body mass index (BMI) corresponds to the increase in the incidence of UUI. Obesity (BMI > 30 kg/m^2) is believed to be an independent risk factor for OAB [3, 11, 12].

Smoking cessation seems to be weakly correlated with symptom alleviation in patients with urinary frequency [3, 11]. Nicotine, being an irritant, is considered a risk factor for OAB symptoms in both, former and current smokers (LE3) [13].

The literature offers a considerable number of reports on higher prevalence of chronic constipation in patients with OAB [4, 14]. Charach et al., demonstrated that the **treatment of constipation** reduces the symptoms of urgency and frequency in older patients (LE4) [4, 15]. However, according to the recommendations of the European Association of Urology (EAU), no evidence supports the alleviation of OAB symptoms after reduction of constipation [3]. High-fiber diet is standard medical approach to the management of constipation [3, 4].

Pelvic floor muscle training

Pelvic floor muscle training combined with urgency suppression techniques is often based on biofeedback (real-time ultrasonography feedback, EMG-biofeedback) with electrostimulation. The patients learn how to respond to urgency, which in turn reduces its intensity and delays the need to void. Six to ten quick pelvic contractions may be performed. If done correctly, and in the absence of parasympathetic and sympathetic dysfunction, they allow the detrusor to be temporarily relaxed. The contractions must be performed at optimal times to ensure optimal benefit (LE3) [4, 16].

Summary

Although most patients do not experience complete symptom resolution after behavioral therapy, significant

Table 1. Recommendation grade for behavioral therapy [31]	
Therapeutic method	**Grade**
Lifestyle modifications (BMI reduction, smoking cessation, adequate diet, fluid management, bowel management)	A–C
Bladder training, scheduled voiding	B

BMI — body mass index

Table 2. Recommendation grade for physiotherapy [31]	
Physiotherapeutic method	**Grade**
Pelvic floor muscle training	A
Pelvic floor muscle training with biofeedback	B
Electrostimulation	B
Posterior tibial nerve stimulation (PTNS)	A

reduction in symptom intensity and improved quality of patient life have been reported. The absence of side effects which might accompany the pharmacotherapy in the next stages of treatment is an important benefit. Eight to twelve weeks is the optimal duration of behavioral therapy, after that time the effects of the treatment should be evaluated and modified, if necessary [2].

Promotion of healthy habits associated with the functioning of the lower urinary tract, including the bladder, should become an element of routine medical care. Lifestyle modifications and other behavioral techniques should always be discussed with the patient, not only to optimize treatment results but also to educate the patient. The grades of recommendations for behavioral and physiotherapy are presented in Tables 1 and 2.

Second-line treatment: pharmacological therapy
1. Oral medications

Pharmacotherapy of OAB aims to reduce urgency, frequency, and urgency urinary incontinence, thus improving the quality of patient life. Increased 'warning time', *i.e.*, time from the onset of the urgency to void or incontinence, is one of the most important outcomes of the drug therapy. Currently, antimuscarinic drugs and β3-adrenoceptor agonist (mirabegron) are the most used medications in OAB therapy. Combination pharmacotherapy which uses drugs with different mechanisms of action alleviates OAB symptoms more effectively as compared to monotherapy, with a comparable rate of side effects, and is recommended in patients with insufficient clinical response. An ideal medication should be safe, effective, well-tolerated, and the patients should comply with the treatment regime for the required amount of time.

The following antimuscarinic drugs are available for OAB treatment: trospium, oxybutynin, tolterodine — im-

mediate release (IR) and extended release (ER), fesoterodine, darifenacin, and solifenacin. Their mechanisms of action and half-life are presented in Table 3. All the above- mentioned medications have a high grade (Grade A) of recommendation, though some of them are not currently available in Poland. The effects of various antimuscarinics were compared in a systematic review and the conclusions are presented below. The efficacy and side effects of the therapy were evaluated. The daily number of micturitions, urgency and leakage episodes were analyzed, as well as patient-reported subjective assessment of the treatment efficacy. Most of the available studies analyzed the treatment efficacy after a relatively short period of time — 12 weeks.

Conclusions from the Cochrane review [17]

Out of immediate release drugs, tolterodine is preferred over oxybutynin — despite similar efficacy rates — due to the lower risk for side effects, especially dry mouth. The recommended dose is 2 mg twice daily, but 1 mg may be equally effective, with a lower risk for side effects. Extended-release medications are preferred due to significantly reduced risk for mucosal dryness. Tolterodine ER should be the drug of choice compared to oxybutynin and tolterodine IR (LE1a). Fesoterodine demonstrated better effectiveness as compared to tolterodine ER but was associated with higher therapy discontinuation rates due to its adverse effects and (mainly) dry mouth. The recommended dose of solifenacin is 5 mg daily and may be increased to 10 mg daily, with elevated risk for dry mouth. Solifenacin was more effective and had lower rates of dry mouth as compared to tolterodine IR (LE1a). Solifenacin (10 mg) and tolterodine (8 mg) were more effective than their doses of 5 mg and 4 mg, respectively [4, 17].

Drug characterization
Oral medications
Oxybutynin

Oxybutynin has a mixed action. It blocks the calcium channel, and has an anticholinergic as well as a local anesthetic effect, although the latter is relevant only in case of intravesical instillation therapy. Oxybutynin is a non-selective antagonist of the muscarinic (M) receptors, with higher affinity for M1 and M3 receptor subtypes than M2. M3 receptors are in the salivary glands, which is the reason for high incidence of dry mouth reported by patients using immediate-release oxybutynin [18]. Only a small number of patients continue the treatment for longer than six months due to the side effects (dry mucous membranes, constipation, blurred vision, somnolence, etc.) [18, 19].

Oral drugs with extended release and the transdermal patches and gels are available, but not in Poland. The transdermal route allows to lower the total dose and

Table 3. Overactive bladder syndrome — drug characterization

International name	Half-life	Mechanism of action	Dosing	Grade of recommendation
Antimuscarinic drugs				
Trospium	18.3 h	Non-selective anticholinergic action	2 × 20 mg/day	A
Oxybutynin	2 h	Non-selective anticholinergic action (higher affinity for M1 and M3 than M2) blocks the calcium channel Local anesthetic effect	3 x 5 mg	A
Tolterodine	2–3 h 5-HMT (Tolterodine metabolite) 3–4 h	Non-selective anticholinergic action	2 × 1–2 mg Extended release: 1 × 2–4 mg	A
Fesoterodine	Pro-drug Metabolized in the serum to 5-HMT 7–9 h	Non-selective anticholinergic action	1 × 4–8 mg	A
Darifenacin	12 h	M3	7.5 or 15 mg/day	A
Solifenacin	45–68 h	M2, M3	1 × 5–10 mg	A
β3-adrenoceptor agonist				
Mirabegron	50 h	β3-adrenoceptor agonist	50 mg/day	A
Other				
Estrogens				C
Botulinum toxin			100 u. 200 u.	A
Resiniferatoxin, Capsaicin			Intravesical	C
Antidiuretic Desmopressin			Indicated in nocturnal polyuria	A
α-adrenergic receptor blocker			–	C

5-HMT — 5-hydroxymethyl tolterodine metabolite

leads to fewer dose-related side effects, increasing therapy continuation rates.

The drug penetrates the blood-brain barrier and may cause cognitive disorders so it should not be used in older patients (LE2b) [3].

Trospium chloride

Trospium chloride has an anticholinergic non-selective effect on the muscarinic receptors. It does not penetrate the blood-brain barrier, so it does not negatively affect the cognitive functions of the patient. Trospium chloride has a documented effect in the reduction of smooth muscle tension, among others in the urogenital and gastrointestinal tract, allowing for the relaxation of the detrusor muscle and reduction of the uncontrolled detrusor contractions [20]. Trospium efficacy has been demonstrated, both compared to the placebo and other anticholinergics. After 12 weeks of therapy (20 mg twice daily) with trospium, mean voided volume increased by 36 mL, whereas mean number of micturitions decreased by three per day and urgency leakage episodes by two per day [20, 21]. In a long-term (52 weeks) study, the efficacy of trospium was like oxybutynin, but with better overall tolerance [22].

Tolterodine

The parent drug, tolterodine, and its active metabolite, 5-hydroxymethyl tolterodine (5-HMT), are responsible for the effect. Tolterodine has low lipophilicity, which is the reason for its very limited penetration into the central nervous system and no adverse effects on the cognitive functions. It exhibits non-selective activity against the M receptor subtypes and has a higher affinity for the bladder than for the salivary glands [19]. The use of tolterodine resulted in a significantly reduced number of micturitions and urgency incontinence episodes (LE1a) in various randomized trials. After 12 weeks of therapy, symptom reduction was as follows: UUI — 80%, urgency — 78%, nocturnal frequency — 40%, and daytime frequency — 30% [23].

Fesoterodine

Fesoterodine, a non-selective anticholinergic, is a pro-drug which is hydrolyzed to 5-hydroxymethyl tolterodine

after oral administration. Fesoterodine is a specific, but non-selective, oral antimuscarinic which acts as a competitive antagonist of muscarinic receptors. 5-HMT is an active metabolite, same as the metabolite formed from tolterodine. Part of 5-HMT is metabolized in the liver, but > 15% of the administered dose is eliminated unchanged with the urine. The dose-dependent clinical effect of fesoterodine has been confirmed but it was associated with increased adverse effects [24]. After 12 weeks of therapy with fesoterodine, mean daily number of micturitions decreased by 2.2, urgency episodes by 3.5, and urgency urinary incontinence episodes by almost 2, whereas mean voided volume increased by 33 mL. No statistically significant reduction in the number of nocturia episodes was observed. In comparison to tolterodine ER, fesoterodine was statistically significantly more effective in reducing the number of urgency incontinence episodes and increasing the voided volume [25]. Fesoterodine does not prolong the QT/QTc interval, either at therapeutic or higher doses [19].

Darifenacin

Darifenacin has an 11-fold higher affinity for M3 than for M2 receptor subtypes. Its inhibitory activity of bladder contraction is comparable to that of atropine, at the same time demonstrating a 5-fold lower affinity for the muscarinic receptors in the salivary glands. Darifenacin was developed as a controlled-release preparation to address the inconvenience of multiple dosing per day. It is metabolized in the liver by the P450 cytochrome, is moderately lipophilic, and has no negative impact on the cognitive functions. Darifenacin is an M3-selective receptor antagonist, however, its role in developing constipation symptoms has been increasingly reported. After a two-year follow-up, 20.9% of the patients reported constipation as compared to 7.9% in the placebo group, and 5.6% were required to use fiber supplements, stool softeners or laxatives [26]. Darifenacin does not prolong the QT/QTc interval [18]. Significant improvement in OAB symptom intensity was observed already after 6–8 days of therapy [27]. After 12 weeks of therapy with the dose of 7.5 mg and 15 mg, mean daily number of micturitions decreased by 1.6 and 1.7, urgency episodes by 2, and urgency incontinence episodes by 4.0 and 4.7, respectively. Darifenacin did not significantly impact the number of nocturia episodes [28].

Solifenacin

Solifenacin is a competitive inhibitor of the muscarinic M3 receptor and has low affinity for other M receptors (M2 and M1). Solifenacin has higher affinity for the urinary bladder than for the salivary glands. It has a long half-life, and its slow pharmacokinetics is associated with steady efficacy and reduced side effects. Solifenacin is metabolized in the liver via the cytochrome P450 system. First significant therapeutic effects may be observed as early as on day 7 of therapy, with the maximum effect after 28 days. Randomized controlled trials demonstrated the efficacy of solifenacin to be higher as compared to placebo or tolterodine. In the STAR study, after 12 weeks of therapy with 5 mg of solifenacin/day, mean daily number of micturitions decreased by 2.5, urgency episodes by 3.1, and urgency incontinence episodes by 1.5. Solifenacin at the dose of 5 mg was more effective in reducing the number of urgency and urgency incontinence episodes and was associated with lower pad use as compared to 4 mg of tolterodine ER. At the endpoint of the study, 59% of solifenacin and 49% of tolterodine ER users did not experience UUI episodes, and the difference was statistically significant [24, 29].

In the group of patients with multiple sclerosis and after spinal injuries, 10 mg of solifenacin improved the urodynamic parameters, including an increase in the maximum cystometric capacity of the bladder (by 134 mL) as compared to the placebo group (by 5 mL) [30].

Mirabegron

Mirabegron is a β3-adrenoceptor agonist. The sympathetic nervous system regulates the urine storage phase, and the β-adrenergic receptors present in the bladder mediate the relaxation of the detrusor and foster urine accumulation. There are three β receptor subtypes: β1, β2, β3. Approximately 97% of the β-adrenergic receptors in the urinary bladder are β3 receptors [31]. Stimulation of β3-adrenergic receptors increases bladder capacity without changing the micturition pressure or residual volume. In consequence, β3-adrenoceptor agonist increases bladder capacity without affecting the contraction amplitude during micturition [32]. The recommended daily dose is 50 mg, with 25 mg for patients with severe renal impairment (creatinine clearance 15–29 mL/min) or moderate liver impairment.

Four large, randomized trials demonstrated mirabegron efficacy in reducing OAB symptoms as compared to placebo. In a study by Khullar et al. [33], after 12 weeks of therapy with 50 mg of mirabegron, mean daily number of micturitions decreased by 1.9, episodes of urinary incontinence by 1.6, and of urgency by 2.3, while mean voided volume increased by 24 mL. The incidence of treatment-related adverse events (hypertension, urinary tract infection, headache, nasopharyngitis) was similar in the mirabegron and the placebo groups. Additional analysis revealed a similar efficacy of mirabegron as far as the number of incontinence episodes and micturitions was concerned, both in OAB patients with no history of antimuscarinic therapy (treatment naïve) and those who had discontinued prior antimuscarinic therapy [34]. The SYNERGY I and II studies confirmed higher efficacy of the combination therapy (solifenacin and mirabegron) as

compared to the monotherapy. The combination therapy additionally decreased mean daily number of micturitions by 0.1–0.5 and of incontinence episodes by 0.4–0.5, and increased mean voided volume by another 13–16 mL per micturition [35].

Antidepressants

Imipramine is an antidepressant used in the treatment of OAB but is currently unavailable in Poland [36]. It exerts a complex pharmacological impact through its antimuscarinic activity as well as serotonin and noradrenaline reuptake blocking properties. Imipramine has an indirect α-adrenergic effect, thus promoting detrusor relaxation and causing an increase in the intraurethral pressure [37].

Duloxetine is a norepinephrine and serotonin reuptake inhibitor, and weakly inhibits dopamine reuptake. Duloxetine increases the activity of the urethral sphincters in the urine storage phase [19]. The Onuf nucleus is a distinct group of motor neurons, located in anterior horns of the spinal cord in the sacral segment, and is the origin of the pudendal nerve. Through the pudendal nerve, the Onuf nucleus innervates the urethral striated muscles. Noradrenaline and serotonin potentiate the glutaminergic stimulation of the motor neurons, increasing striated muscle contraction [19].

Most research so far has focused on the use of duloxetine to treat stress urinary incontinence, but few reports concerned its beneficial effect in OAB therapy. Duloxetine reduces the daily number of micturitions and urgency episodes and improves the quality of patient life, while mean voided volume remains unchanged (LE4). The efficacy of duloxetine therapy has been confirmed in patients with detrusor overactivity and mixed urinary incontinence. In light of its efficacy in treating depression, duloxetine may present a therapeutic option for patients with depression and concomitant OAB symptoms (off-label use, the drug is not registered for urinary incontinence in Poland) [36].

Management of nocturia with concurrent overactive bladder

Desmopressin (DDAVP, deamino-D-arginine vasopressin) is a synthetic analogue of vasopressin and exhibits antidiuretic activity through vasopressin V2 receptors, affecting water reabsorption in the renal tubules. Desmopressin is used in the treatment of nocturia caused by nocturnal polyuria [3]. The recommended daily dose is 25 µg for women (50 µg for men) of desmopressin lyophilizate, administered sublingually, one hour before bedtime. Food may reduce drug strength and effect duration. Some studies support the efficacy of desmopressin for treating nocturia in patients with OAB. A randomized trial compared the use of combination therapy (25 µg of desmopressin and 4 mg of tolterodine ER) versus tolterodine monotherapy. After 12 weeks of therapy, a significant difference in the nocturnal

urine volume and prolonged time between the initial sleep point and the first episode of nocturia were observed in the desmopressin group of patients treated for OAB and nocturnal polyuria.

Administration of desmopressin may be considered in patients affected by nocturia with concurrent OAB to reduce the number and volume of nocturnal micturitions [38].

Therapy continuation

Numerous studies demonstrated low continuation rates of antimuscarinic therapy, mainly due to patient-reported lack of results and adverse effects. Wagg et al. [39], reported the following results for therapy continuation after 12 months: 35% — solifenacin, 28% — tolterodine ER, 26% — trospium, 24% — tolterodine IR, 22% — oxybutynin IR, and 17% — darifenacin [39]. However, after 24 months, the rates of therapy continuation ranged from 6 to 12% [40]. According to the literature, mirabegron has a significantly longer time to therapy discontinuation as compared to antimuscarinics. After 12 months of therapy, 38% of the patients continued mirabegron. Mean time to mirabegron and tolterodine ER discontinuation was 169 and 56 days, respectively. Factors promoting therapy discontinuation in OAB patients included: younger age (< 60 years), insufficient information about the purpose of treatment, exceedingly high expectations about the therapy effects, reluctance to use chronic pharmacotherapy, or significant alleviation of OAB symptoms [19].

Cardiovascular effects

Drug selection for OAB therapy needs to include the possible effect of chronic pharmacotherapy on the cardiovascular system [41]. The safety profile of antimuscarinics has been confirmed by numerous studies. Unfortunately, the risk for developing drug-induced cardiac events and symptoms such as increased heart rate (HR), prolonged QT interval, and polymorphic ventricular tachycardia is a cause for some concern [42]. The M2 receptors are predominant muscarinic receptor subtypes expressed in the heart and they play an important role in the maintenance of the heart rate and cardiac output. M2 receptor blockade in the sinus node, the heart's natural pacemaker, increases the pulse and decreases other parameters of the vagal tone, *e.g.*, return to resting heart rate after exertion and baroreceptor reflex response [42].

Darifenacin selectivity for M3 receptors is suggestive of a minor effect on the cardiovascular system. Olshansky et al., evaluated the effects of a seven-day treatment regimen with 15 mg/day of darifenacin, 4 mg/day of tolterodine and placebo in healthy participants. Tolterodine was found to significantly increase the heart rate as compared to darifenacin and placebo, while darifenacin did not affect the heart rate as compared to placebo. The maximum increase in HR for tolter-

odine occurred at times of maximum plasma concentration and was approximately 4 bpm [43]. Fesoterodine was also found to cause a dose-related increase in HR. Mean change in HR for 4 and 8 mg of fesoterodine and placebo was 3, 4 and 1 bpm, respectively [44]. As for oxybutynin, no increase in HR as compared to placebo was observed [45].

Solifenacin did not cause an increase in mean HR or mean blood pressure [46]. Trospium therapy may be associated with dose-related increase in HR. Mean increase in HR after trospium was 9 bpm for the 20 mg dose and 18 bpm for the 100 mg dose. The increase in HR was noted after 4-8 hours and disappeared 12 hours after administration. No significant effect on the blood pressure was detected, regardless of the dose [19]. In conclusion, darifenacin, solifenacin, and oxybutynin show no significant effect on HR [47].

In a study with placebo, mirabegron increased HR by 1–2 bpm [48]. A pooled analysis of clinical trial data found no proof of increased risk for cardiovascular adverse events for mirabegron or antimuscarinic therapy as compared to placebo. Cardiovascular adverse events were related to the pre-existing conditions of the patients, not the OAB pharmacotherapy. **No correlation between OAB treatment and increased risk for adverse cardiac events was demonstrated** [49]. In the SYNERGY study, which analyzed combination therapy with mirabegron and solifenacin, no statistically significant increase in resting blood pressure was observed [50]. The analysis of the safety profile for the combination therapy with mirabegron and solifenacin revealed comparable rates of adverse cardiovascular events for both, combination and monotherapy [50].

QT-interval prolongation and its consequences result from inhibition of the cardiac hERG potassium channel [42]. Among antimuscarinics, darifenacin, fesoterodine and trospium chloride do not affect the QT/QTc interval [19, 42, 51]. Solifenacin may prolong the QT interval but not to a clinically relevant degree (10 mg — by 2 milliseconds, 30 mg — three times the maximum therapeutic dose — by 8 milliseconds) [19]. The effect of tolterodine on the QT interval correlates with its plasma concentration. Tolterodine blocks hERG channels with high affinity but produces little QT prolongation clinically [42]. Data on the possible QT effects in patients using oxybutynin are limited [19, 42, 52]. Studies on mirabegron monotherapy found no effect on the QT/QTc interval, either in the study group or in the combination therapy with solifenacin or placebo [50]. Imipramine has a negative effect on the cardiovascular system; it prolongs the QTc interval and has a potent antiarrhythmic action [19].

Polypharmacy and metabolism

Polypharmacy (> 5 drugs) is a common phenomenon in the older populations. Drug interactions frequently involve the P450 cytochrome hepatic isoenzymes. Tolterodine, darifena-

cin, solifenacin, oxybutynin, and mirabegron are metabolized by the P450 cytochrome system. Consequently, susceptibility to altered drug metabolism in case of drug interactions of medications based on hepatic metabolism is increased. Trospium is eliminated unchanged through the kidneys [19].

Anticholinergic burden

Anticholinergic burden should be considered when treating patients who use polypharmacy. Numerous drugs from other groups have an additional anticholinergic activity (antimuscarinics together with antidepressants and antihistamines constitute > 90% of medications with anticholinergic properties prescribed to patients). The additive effect of the drugs can be expressed as higher number of adverse effects (dry mouth, constipation, blurred vision, cognitive impairment) and lower effectiveness. The anticholinergic effect of the drugs is dose-dependent [53]. Various scales are used to assess the overall anticholinergic effect of the drugs [54]. The list of selected drugs with high and low anticholinergic potential is presented in Table 4 [55].

Pharmacotherapy in older patients

Mirabegron is effective and safe in older populations (LE1b). Antimuscarinics are equally effective in older patients and other age groups (LE1b). Over time, the impact of anticholinergic drugs on the cognitive functions increases with drug accumulation (LE2b). Oxybutynin may worsen cognitive functions in older patients, so it is not recommended for people over the age of 65 years (LE2b). In short-term studies, solifenacin, darifenacin, fesoterodine, and trospium were not found to cause cognitive dysfunction in older patients. Long-term antimuscarinic therapy should be used with caution in older patients, especially those at risk for developing cognitive impairment [2, 3].

2. Vaginal estrogens

The role of estrogens in OAB therapy remains ambiguous and they are not included in most international guidelines. Patients with estrogen deficiency have been confirmed to be at an increased risk for OAB [56]. In rat models after ovariectomy, a significant reduction in voided volume and an increase in micturition frequency were observed, and the administration of exogenous estrogen reversed these changes [57].

A systematic review of 11 randomized trials demonstrated the efficacy of estrogens versus placebo in reducing the number of frequency, nocturia, urgency, and incontinence episodes, and increasing bladder volume and bladder volume at the first sensation. These results pertained to local therapy (vaginal and intravesical). Systemic therapy was effective only in reducing the number of incontinence episodes and increasing the bladder volume at the first sensation, while at the same time intensifying the symptoms of nocturia [58].

Table 4. Anticholinergic drugs and their anticholinergic potential [54, 55]

Drug	anticholinergic potential: 1 — low 2 — high
Psychotropic drugs (N)	
Amitriptyline	2
Carbamazepine	1
Citalopram	1
Diazepam	1
Fentanyl	1
Fluoxetine	1
Clozapine	2
Quetiapine	1
Lithium	1
Mirtazapine	1
Olanzapine	1
Paroxetine	1
Promazine	1
Risperidone	1
Trazodone	1
Drugs which affect the digestive and metabolic system (A)	
Domperidone	1
Hyoscine	2
Loperamide	1
Ranitidine	1
Drugs which affect the respiratory system and antiallergic drugs (R)	
Cetirizine	1
Fexofenadine	1
Codeine	1
Loratadine	1
Theophylline	1
Drugs which affect the musculoskeletal system (M)	
Baclofen	1
Tizanidine	2
Drugs which affect the urogenital system (G)	
Darifenacin	2
Oxybutynin	2
Tolterodine	2
Drugs which affect the cardiovascular system (C)	
Digoxin	1

The results of studies which compared the use of antimuscarinic drugs in combination with intravaginal estrogen versus antimuscarinic monotherapy remain conflicting. Tseng et al., demonstrated significant improvement in frequency, voided volume, and quality of life among women who received tolterodine and vaginal conjugated equine estrogen treatment as compared to tolterodine monotherapy. Symptoms of nocturia, urgency and UUI after treatment improved as compared to baseline, but the combination therapy was not superior [59]. Serati et al. [60], analyzed a group of women with detrusor overactivity confirmed by urodynamic tests and showed no synergistic effect of 4 mg of tolterodine ER and estriol cream in OAB therapy. Jiang et al., showed that solifenacin efficacy in reducing OAB symptoms was identical in combination with vaginal estradiol and without estrogens. However, the addition of estradiol significantly improved patient-reported subjective impressions and quality of life [61].

THIRD-LINE TREATMENT: BOTULINUM TOXIN AND NEUROMODULATION (POSTERIOR TIBIAL NERVE STIMULATION AND SACRAL NERVE STIMULATION)

Botulinum toxin

1. Patients with OAB resistant to first- and second-line therapy may be offered onabotulinumtoxin A (100 U) bladder wall injections [3].
2. Patients should be informed about the limited duration of action of the drug, the risk of urinary tract infection and the possibility of self-catheterization (make sure the patient will be cooperative). The patient is required to return for post-void residual evaluation [3].
3. The next injection should not be performed within three months. In clinical trials, the median duration of the effect was 166 days (approx. 24 weeks) [3, 62].

Onabotulinumtoxin A belongs to the A group of toxins. It is a neurotoxin which binds permanently to the neuromuscular junction, paralyzes neuromuscular conduction by fragmenting the synaptosomal-associated protein 25 (SNAP-25) and inhibiting the release of acetylcholine from the presynaptic terminal.

Onabotulinumtoxin A is used in idiopathic detrusor overactivity (IDO) at the dose of 100 U dissolved in 10 mL of saline and injected into 20 points of the bladder wall above the bladder trigone (0.5 mL per injection site). Different types of type A botulinum toxin are currently available on the market, including those not registered for OAB treatment (abobotulinumtoxin A and incobotulinumtoxin A). Considerable attention should be paid to the registered indications of the drugs, especially in the absence of dose equivalence for these preparations [3].

In a randomized trial after 12 weeks of follow-up, onabotulinum significantly reduced all OAB symptoms as compared to the placebo group, decreased the daily number of UUI episodes (–2.95 vs –1.03; p < 0.001), and positively affected the quality of patient life (positive response to treatment was reported by 62.8% of the patients as compared to 26.8% in the placebo group) [63]. UUI episodes were not

reported by 22.9% of the patients in the onabotulinum group and 6.5% in the placebo group [62].

In a study comparing onabotulinum with antimuscarinics after 6 months of follow-up, both methods proved to be associated with a similar reduction in the frequency of UUI episodes (3.3 vs 3.4, respectively). However, complete resolution of UUI symptoms occurred in 27% of the patients in the onabotulinum group and only 13% in the antimuscarinic group (p = 0.003). The onabotulinum group had significantly lower probability of dry mouth (31% vs 46%, respectively), but higher probability of urine retention (5% vs 0%, respectively in the first 2 months of therapy) and urinary tract infections (33% vs 13%, respectively). The treatment effect was maintained in 38% of the patients after 12 months of onabotulinum therapy (LE1b) [3, 64].

In case of neurogenic detrusor overactivity (NDO), the recommended dose of onabotulinum is 200 U (30 intra-detrusor muscle injections at the dose of 1 mL per site), in which case median duration of the drug effect is 256–295 days according to phase III studies [65].

Other bladder injection protocols

The concept of preventing vesicoureteral reflux is the main reason behind injecting the area above the trigone. However, several studies investigated other locations for bladder onabotulinum injections [19].

The studies which compared various sites of bladder injections did not demonstrate any increase either in post-void urine retention, or the rates of patients requiring self-catheterization, or the vesicoureteral reflux in cases when the injections were performed into the trigone [19]. In one study among patients with idiopathic detrusor overactivity (IDO), three types of injection sites were compared: body of the bladder (100U); body of the bladder (75U) and the trigone (25U); as well as the fundus (50U) and the trigone (50U). The success rate at three months of follow-up was 70% for the body of the bladder, 74% for the body and trigone, and 73% for the fundus and trigone. No statistically significant differences were found in success rates, number of urgency and UUI episodes, or long-term measures among the three subgroups. The incidence of adverse events was similar in the three groups. No vesicoureteral reflux was detected in any of the patients [66].

In contrast, a meta-analysis of eight studies and 419 patients with NDO and IDO revealed that trigone injections were more effective and were not associated with higher complication rate as compared to trigone-sparing injections. Injection depth did not affect the efficacy or safety of onabotulinumtoxin A [67].

The most common side effects of onabotulinumtoxin are related to the urinary tract. At 12 weeks of follow-up,

uncomplicated UTI were found in 15.5% of the patients in the onabotulinumtoxin group and in 5.9% in the placebo group. Additionally, symptoms of dysuria (12.2%), bacteriuria (5%) and urinary retention (5.4%) were reported. An increase in post-void residual (PVR) of ≥ 200 mL as compared to baseline was observed in 8.7% of the patients. No significant increase in PVR was observed in the placebo group. The rate of patients who required self-catheterization at any time during the first treatment cycle was 6.1% as compared to 0% in the placebo group [68].

Posterior tibial nerve stimulation (PTNS)

Percutaneous tibial nerve stimulation (PTNS) may be used as third-line treatment in some patients [3].

The tibial nerve is a peripheral nerve, with sensory and motor fibers. It originates from the L4–S3 spinal nerve roots, which are also responsible for the sensory and motor innervation of the urinary bladder and the pelvic floor. The PTNS effect is believed to be related to the retrograde stimulation of the sacral nerve plexus. The treatment typically consists in 12 weekly sessions, 30 min each, after which maintenance therapy sessions are recommended. The stimulation is performed percutaneously using a slim 34-Gauge needle inserted just above the medial condyle of the ankle (P-PTNS) [3].

PTNS is effective in treating therapy resistant OAB. It demonstrates significantly higher efficacy as compared to placebo, without serious side effects, and comparable efficacy to antimuscarinic therapy (LE1b). According to various meta-analyses, PTNS shows 37–100% effectiveness and decreases the number of frequency, urgency, UUI and nocturia episodes [69]. Stimulation with transcutaneous electrodes (T-PTNS), whose effectiveness in reducing daytime frequency is comparable to P-PTNS, is also an available treatment modality (LE1b) [70].

P-PTNS maintenance therapy, performed approximately once a month, proved to be effective in maintaining the treatment effect for up to three years of follow-up (LE1b) [3]. It can also be conducted with adhesive skin surface electrodes (T-PTNS) in a weekly three-session regimen (30 min//session), (LE1b) [71].

In OAB patients, a physiotherapist may use vaginal, transrectal and transcutaneous electrostimulation (paraspinal electrostimulation of the micturition centers, non-invasive electrostimulation of the tibial or peroneal nerves). Based on the available sources, it is challenging to determine the sufficient number of sessions. Also, there is no consensus on the duration of one series of the electrostimulation. The authors of the present study recommend that the electrostimulation parameters be adjusted individually, taking into consideration the condition of the patient and symptom severity [72, 73].

Sacral nerve stimulation (SNS)

SNS may be suggested as the third-line treatment to carefully selected populations of patients with severe therapy resistant OAB or those not eligible for second-line treatment and willing to undergo surgery [2]. In Poland, only a handful of procedures have been performed so far so the experience is limited. The efficacy of SNS is higher if juxtaposed with the option of continuing unsuccessful conservative treatment to treat UUI (LE1b) [3].

The efficacy of SNS was demonstrated in patients with therapy resistant UUI. At six months of follow-up, 50% of the patients after SNS implantation showed over 90% improvement as far as UUI symptoms were concerned as compared to 1.6% in the group with continuous pharmacotherapy (LE1b) [74].

In a prospective randomized study in patients resistant to therapy with at least one antimuscarinic drug, at six months of follow-up 86% of the patients in the SNS group reported improved or very much improved OAB symptoms as compared to 44% in the antimuscarinic group (p < 0.001). The therapeutic success rate for SNS was 85% at 12 months and 82% at five years of follow-up. Therapeutic success was defined as at least 50% improvement in UUI episodes or at least 50% improvement in the daily number of micturitions, or a return to the normal daily number of micturitions (< 8 per day). At five years of follow-up, mean daily number of UI episodes decreased by 2.0 ± 2.2 as compared to baseline (p < 0.0001), and complete continence was achieved in 45% of the patients. Mean daily reduction in the number of micturitions was 5.4 ± 4.3 (p < 0.0001). At 12 months of follow-up, the most common device-related adverse events included 'undesirable' change in stimulation in 12%, implant site pain in 7%, and implant site infection in 3% of the patients. The cumulative five-year rate of lead-related adverse events which required reoperation after complete implantation was 22.4%. Ineffectiveness of the therapeutic product was observed in 13% of the patients. At five years of follow-up, the rate of patients with device removal was 19.1% (LE1b) [75].

In a ROSETTA study, which compared SNS with injections of 200 U of onabotulinum at six months of follow-up, patients in the onabotulinum group had higher reduction in the mean daily number of UUI episodes as compared to the SNS group (–3.9 vs –3.3 episodes/day; p = 0.01). They also reported significantly greater improvement in the Overactive Bladder Questionnaire SF, which evaluates symptom bother, and a higher level of satisfaction with the treatment. Urinary tract infections were significantly more frequent in patients from the onabotulinum group (35% vs 11%, p < 0.001) as well as the need for self-catheterization (8% at 1 month, 4% at 3 months, and 2% at 6 months of follow-up). The need for device revisions and removals was found in 3% of the patients. The small but significant difference in subjective and objective indices of therapy efficacy reported in that study gave rise to a heated debate about the clinical significance of the obtained results [76]. Based on that, the consensus in the European recommendations is that SNS efficacy is not superior to injection therapy with 200 units of onabotulinum at six months of follow-up (LE1b) [3].

Although SNS constitutes the third-line treatment, along with PTNS and onabotulinum, it should be treated as a higher-risk and more invasive method. Therefore, it is recommended to patients who are resistant to other methods of treatment [4].

In addition to OAB therapy, SNS is also effective in treating painful bladder syndrome, interstitial cystitis, urine retention not induced by bladder outlet obstruction, and fecal incontinence [69].

SNS and magnetic resonance imaging

SNS is a relative contraindication for magnetic resonance imaging (MRI). The magnetic field generates electric currents in the neuroelectrodes, which heats the electrodes *in vivo* and *in vitro*, and may cause nerve damage. Device removal is recommended if elective MRI is required. In newer devices, it is possible to perform a head examination under highly specified conditions [69].

SUMMARY

Before treatment commencement, it is necessary to conduct an adequate and thorough diagnostic process. If the therapy proves ineffective, the patient needs to be referred to a specialist. In selected situations, a multidisciplinary team consultation may be recommended.

Pharmacotherapy remains the gold standard in OAB treatment and should not be delayed. However, the limitations and side effects of pharmacotherapy are the reasons why the search for new solutions continues. Animal studies are conducted to find new drugs to treat the OAB syndrome [19, 36, 77–80]. Preclinical studies lead to the development of new drugs, which may in time find applications in clinical practice [16, 77].

Conflict of interest

None.

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