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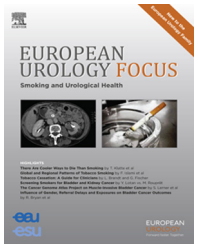

Review – Female Urology - Incontinence

Management of Idiopathic Overactive Bladder Syndrome: What Is the Optimal Strategy After Failure of Conservative Treatment?

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Abstract

Context: A considerable number of patients affected by the overactive bladder syndrome (OAB) do not respond to pharmacotherapy and bladder training due to unsatisfactory response or intolerability.
Objective: To review the available literature assessing therapeutic effect of the available third-line treatment modalities for OAB.
Evidence acquisition: PubMed, Medline, and Cochrane databases were searched for all studies comparing outcomes of the available third-line treatment modalities for OAB.
Evidence synthesis: Several minimally invasive surgical procedures are available for patients with refractory OAB. These therapies include intravesical botulinum toxin type A, posterior tibial nerve stimulation, and sacral neuromodulation.
Conclusions: None of the mentioned therapeutic modalities shows strong superiority over another. If the results of one therapy are not satisfactory, switching to another third-line treatment can be attempted. The treatment algorithm is dependent on several factors, including age, comorbidity, patient preference, surgical expertise, and financial concerns. All these factors should be taken into consideration before initiation of treatment.
Patient summary: In the management of drug-resistant overactive bladder syndrome, the different minimally invasive treatments that are available are equal. If the results of one therapy are not satisfactory, switching to another treatment can be attempted. The treatment algorithm is dependent on several factors, including age, comorbidity, patient preference, surgical expertise, and financial concerns.

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1. Introduction

Overactive bladder syndrome (OAB) is a prevalent disorder with a major impact on quality of life. It is estimated that OAB affects approximately 11–16% of the adult population, and its prevalence increases with age [1,2]. The aetiology of OAB is probably multifactorial, including changes in anatomy and body composition, lifestyle factors, and comorbidities. Initial management consists of behavioural therapy. This includes bladder training, pelvic floor muscle training,

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and fluid management. Next, treatment for OAB consists of pharmacologic therapy. Antimuscarinics are widely used, although they are frequently discontinued due to low efficacy and bothersome side effects. A review of the literature demonstrated that 43–83% of women withdraw their treatment by 1 mo and that <35% of women continue their medication after the 1st year [3]. In 2012, the beta-3 agonist mirabegron was introduced as a new drug for OAB. Although some studies have shown similar midterm results to antimuscarinics, long-term efficacy and tolerability (>5 yr) of this drug still need to be evaluated.

A considerable number of patients do not respond to conservative treatment due to unsatisfactory response or intolerability. When conservative therapies are insufficient, specialised management can be considered. Traditionally, augmentation cystoplasty and urinary diversion were the only surgical options for refractory urgency urinary incontinence (UUI) seen in patients affected by OAB; however, several minimally invasive surgical procedures are now available for refractory OAB. These therapies include intravesical botulinum toxin type A (BoNT-A), posterior tibial nerve stimulation (PTNS), and sacral neuromodulation (SNM). In addition, with the introduction of mirabegron, combination therapy with antimuscarinics may be considered.

The optimal algorithm for using these third-line treatments is still unclear. Various guidelines recommend the use of all three modalities, without mentioning a preferred sequence. The choice is dependent on multiple factors including patient preference, surgical expertise, available resources, and financial considerations. In this review, we evaluate the current evidence of third-line therapies in the management of refractory OAB. Furthermore, various factors that influence the treatment algorithm are discussed.

2. Evidence acquisition

PubMed, Medline, and Cochrane databases were searched for all studies comparing outcomes of the available third-line treatment modalities for OAB.

3. Evidence synthesis

3.1. Treatment evidence

3.1.1. Sacral neuromodulation

In SNM, the sacral root S3 is stimulated with an implantable pulse generator. The exact working mechanism of SNM is complex and not fully understood. It probably involves different modes of action on various levels of the nervous system, including sacral, spinal, supraspinal, and cortical areas. SNM has been approved by the U.S. Food and Drug Administration (FDA) in 1997 for urgency incontinence as well as urgency-frequency syndrome. There is convincing evidence for the success of SNM with positive long-term results regarding efficacy and safety [4,5]. Eight randomised studies and many long-term observational studies have been published, with a reported clinical response between 64% and 88% [6–10]. In 2002, the tined procedure was introduced, which allowed percutaneous placement of the lead. Marcelissen et al [11] showed that this technique was safe and effective in the long term, with a reported success rate of 64% after a mean follow-up of 53 mo.

In a recent randomised controlled trial, Siegel et al [12] compared the results of SNM with standard medical therapy (SMT). All individuals had overactive bladder symptoms refractory to maximum one antimuscarinic treatment and were randomised to SNM ($n = 70$) or SMT ($n = 77$). Of all patients, 93% were female and mean age was 58 yr. Intention-to-treat analysis showed that the success rate at 6 mo was significantly greater in the SNM group (61%) than in the SMT group (42%, $p = 0.02$). The device-related adverse event rate was 30.5% and the medication-related adverse event rate was 27.3%.

Although SNM is an effective minimally invasive treatment, adverse events can occur after implantation. The most common device-related adverse events are undesirable change in stimulation, implant site pain, and lead migration. Furthermore, many patients require reprogramming of the device during follow-up due to decrease in therapeutic effect. Other possible disadvantages include battery replacement after 5–8 yr and incompatibility with magnetic resonance imaging (MRI).

3.1.2. Percutaneous tibial nerve stimulation

PTNS is a peripheral neuromodulation technique, in which the posterior tibial nerve is stimulated above the medial malleolus. The possible working mechanism is neuromodulation at the spinal level [13]. PTNS requires repeated sessions of stimulation, varying from 6 to 12 weekly. There is evidence of significant improvement in overactive bladder symptoms using PTNS, which is comparable with the effect of antimuscarinics but with a better side-effect profile. The SUmiT trial, a multicentre, double-blind, randomised controlled trial, compared the efficacy of PTNS with sham therapy through 12 wk of therapy [14]. A total of 220 adults with overactive bladder symptoms were randomised to 12 wk of treatment with weekly PTNS or sham therapy. The PTNS group had statistically significant improvement in frequency, night-time voids, and UUI episodes compared with sham therapy. No serious device-related adverse events were reported. In the OrBIT trial, 100 adults were randomised to treatment with PTNS to extended-release tolterodine [15]. Assessment of their overactive bladder symptoms compared with baseline was statistically significant in the PTNS group (79.5%) compared with the tolterodine group (54.8%, $p = 0.01$).

A review by Biemans and van Balken [16] reported improvement by 60–80% of OAB patients in incontinence episodes, frequency, and urgency. Peters et al [17] showed that PTNS has sustained safety and efficacy over 36 mo with initial success after 12 weekly treatments. The average number of treatments was 1.1 per month. Although PTNS is considered a safe and effective treatment, long-term results (>5 yr) are still lacking. The current NICE guidelines do not recommend PTNS as first-line therapy for the treatment of refractory OAB because of lack of clinical evidence.

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However, the European Association of Urology (EAU) guidelines clearly state that "offer, if available, PTNS as an option for improvement of urgency urinary incontinence in women who have not benefitted from antimuscarinic medication".

3.1.3. *Onabotulinum toxin A*

Botulinum toxin causes a neuromuscular blockade of vesicular acetylcholine release at somatic and autonomic presynaptic nerve terminals. Initially, BoNT-A has been used in the treatment of patients with neurogenic bladder dysfunction. In 2014, BoNT-A received FDA approval for the treatment of idiopathic OAB. Cui et al [18] conducted a systematic review and meta-analysis comprising a total of 1020 participants from 12 randomised controlled trials. BoNT-A was associated with lower urinary frequency, fewer incontinence episodes, and improvement in quality of life. Higher doses (up to 300 U) did not equate to greater improvement in quality of life or voiding diary parameters. The most common adverse effects were high postvoid residuals (necessitating clean intermittent catheterisation) and an increase in urinary tract infections. No statistically significant difference was seen between bladder injections into the bladder body, base, or trigone regarding the risk of urinary retention and urinary tract infection.

In a recent placebo controlled randomised trial, 100 U of BoNT-A showed significant and clinically relevant improvement in all overactive bladder symptoms and health-related quality of life in patients inadequately treated with anticholinergics [19].

As the effect of botulinum toxin wears off after 6–12 mo, repeated injections after this period are necessary to maintain control of symptoms. Although long-term results are still sparse, the efficacy seems to be durable after repeated injections [20,21].

Makovey et al [22] evaluated a group of 85 patients with refractory OAB who received BoNT-A. They found that patients with intolerance to side effects of antimuscarinic therapy were more likely to respond to BoNT-A than those who experienced insufficient effect. Patients with intolerance had a 86% success rate as opposed to 60% in patients with antimuscarinic inefficacy. This finding might indicate that patients who respond to antimuscarinics are more suitable candidates for BoNT-A. The small sample size and retrospective nature of this study demand further investigation in a larger cohort.

In the ABC trial, the effect of anticholinergic therapy was compared with that of BoNT-A [23]. For a period of 6 mo, patients with urgency incontinence were randomised to receiving 100 U of BoNT-A plus placebo drug or solifenacin 5 mg (with possible upgrade to 10 mg) plus placebo intravesical saline injection. Both groups showed similar reductions in the frequency of daily episodes of UUI. The BoNT-A group was less likely to have dry mouth and more likely to have complete resolution of UUI, but had higher rates of transient urinary retention and urinary tract infections.

3.1.4. *Augmentation cystoplasty and urinary diversion*

After the introduction of BoNT-A, the question arises whether there is still a role for surgery and, in particular, bladder augmentation in OAB treatment [24].

The preferable procedure, the ideal candidate, and the appropriate time in the course of OAB treatment remain unclear. As with most surgical procedures, randomised studies comparing surgical procedures such as augmentation, cystoplasty, or urinary diversion with BoNT-A or SNM are not available.

Both bladder autoaugmentation via detrusor myectomy and the classical augmentation cystoplasty with the use of bowel have been applied in predominantly younger neurogenic OAB patients, with reported success rates of 33–94% [25–27].

EAU guidelines denote detrusor myectomy and clam cystoplasty as valid options to decrease detrusor pressure and increase bladder capacity, whenever more conservative approaches have failed [24] (grade B recommendation). American Urological Association guidelines consider augmentation cystoplasty or urinary diversion only as an additional treatment option in rare cases, for severe, refractory, complicated OAB patients on the level of expert opinion [28]. Further research to classify the role of surgery in OAB is mandatory and should include cost effectiveness and long-term outcome data.

3.2. *Comparing treatments*

Table 1 presents an overview of the possible treatments for refractory OAB. Few studies have directly compared

Table 1 – Overview of possible treatments for refractory OAB.

	SNM	PTNS	BoNT-A
FDA/EC approval	Yes	Yes	Yes
Long-term results	Yes	No	Limited
Advantages	• Minimally invasive • Works for both urinary and bowel disorders	Noninvasive, simple	• Minimally invasive • Direct effect
Disadvantages	• Permanent implant • Battery replacement every 5–8 yr	• Repeat after 8–12 wk • Inferior efficacy	• Repeat after 6–12 mo • Need for CISC
Reversibility	Removal of implant	Instantly	After 6 mo
Adverse events	• Wound infection • Device-related pain • Device malfunction	None	• Urinary retention • Urinary tract infection • Haematuria

BoNT-A = botulinum toxin type A; CISC = clean intermittent self-catheterisation; EC = European Commission; FDA = Food and Drug Administration; OAB = overactive bladder syndrome; PTNS = posterior tibial nerve stimulation; SNM = sacral neuromodulation.

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treatment strategies for OAB. In 2012, the ROSETTA trial was started. In this randomised, open-label trial, the results of 200 U BoNT-A were compared with SNM in patients with refractory urge incontinence [29]. A total of 386 patients were randomly assigned, and the duration of follow-up was 6 mo. Compared with SNM, intradetrusor injections with 200 U BoNT-A resulted in greater reduction in mean daily episodes of UUI and higher satisfaction, albeit with an increased risk of urinary tract infections and need for transient catheterisation.

One should take into account that in the ROSETTA trial, 200 U of BoNT-A was used instead of the recommended 100 U of BoNT-A for idiopathic OAB. Furthermore, key information of this trial was that after 6 mo, 20% of the patients in the BoNT-A group had complete resolution of their urgency incontinence compared with 2% in the SNM group [29].

Furthermore, a recent study comparing BoNT-A and other pharmacotherapy showed that, after 12 wk, 100 U of BoNT-A provided greater relief of overactive bladder symptoms compared with most other licensed doses of other pharmacotherapies available [30].

Sherif et al [31] randomised 60 patients with refractory idiopathic OAB to receive intradetrusor injections with BoNT-A 100 U or PTNS. Patients in the BoNT-A group showed significant improvements in all voiding diary parameters compared with baseline. Patients in the PTNS group initially had significant improvements in all parameters, but by 9 mo, this effect diminished. Overall, the improvements were higher in the BoNT-A group, especially at 9 mo.

Some studies evaluated sequential use of treatments for OAB. Smits et al [32] reported the results of SNM in 20 patients who were initially treated with BoNT-A. Most of these patients had discontinued BoNT-A due to lack of efficacy ($n = 17$), and some patients requested a more permanent solution despite good results ($n = 3$). The mean interval between the BoNT-A and the SNM test stimulation was 23 mo. In 14 patients (70%) the test stimulation was successful, and they were implanted with a device. Hoag et al also evaluated the efficacy of SNM in patients with prior BoNT-A treatment in 36 patients with refractory OAB. Twenty-three patients (64%) had successful first-stage SNM and underwent implantation. After a mean follow-up of 29 mo, 74% of patients were satisfied and using the device at the last follow-up.

3.3. Which factors determine treatment selection?

3.3.1. Age and comorbidity

When considering third-line treatment in elderly patients, multiple factors have to be taken into account. Complications of surgical procedures increase with higher age and advanced comorbidity. In addition, impaired cognitive functioning and reduced mobility can have a negative impact on treatment efficacy and compliance. Peters et al [33] evaluated the impact of age on treatment response in SNM. The authors found significant improvement in all age groups regarding urinary frequency and incontinence episodes, with no loss of the treatment efficacy in older patients. They concluded that SNM is equally effective and safe for treating OAB patients in various age ranges. However, patients should be able to correctly operate the programmer or a dedicated nurse should be available for adequate supervision. In BoNT-A, the potential risks of urinary retention may limit the feasibility of therapy in elderly patients who might not be able to perform intermittent catheterisation. In addition, the need for repeated injections might limit its use in the frail elderly. In a subanalysis of the ROSETTA trial, baseline participant characteristics and clinical variables were associated with treatment success. They found that older women with multiple comorbidities and impaired quality of life had decreased treatment response and satisfaction with BoNT-A compared with SNM.

3.3.2. Concomitant symptoms

Functional disorders of the lower urinary tract often coexist with defaecation disorders, pelvic pain, or sexual dysfunction. Anatomically, the bladder, anorectum, and reproductive organs are closely related. Different factors can be involved, such as neurogenic, mechanical, or systemic disease. Depending on the exact changes in these factors, both evacuation disorders (urinary retention and obstipation) as well as storage disorders (urinary and faecal incontinence) can occur. Compared with BoNT-A, SNM has the advantage that both micturition and defaecation can improve with the same therapy. Long-term success with SNM for faecal incontinence and constipation ranges from 54% to 63% [34]. In addition, SNM has been proved to be effective in certain patients with chronic pelvic pain [35]. Some studies evaluated the results of SNM in patients with combined urinary and faecal symptoms [36,37]. El-Gazzaz et al [37] reported that 40% of all treated patients had significant improvement at a mean follow-up of 24 mo. Caremel et al [38] conducted a survey among patients with double incontinence. They interviewed 37 patients who were treated with SNM (average 30 mo since implantation) about their urinary and faecal complaints. In total, 49% reported improvement in both complaints.

Although the mechanism of action of PTNS is essentially the same as in SNM, the evidence of PTNS in the treatment of functional bowel disorders is less convincing. Recently, a large randomised controlled trial showed no significant clinical benefit of PTNS over sham electrical stimulation in the treatment of adults with faecal incontinence [39]. Thin et al [34] conducted a randomised clinical trial of SNM versus PTNS for faecal incontinence. Although both treatments showed a clinical effect, patients in the SNM group experienced fewer incontinence episodes compared with the PTNS group. Therefore, in patients with combined symptoms, SNM might be the preferred treatment. Yet, the degree of bother from each symptom must be taken into consideration, and the focus of treatment should initially be on the most debilitating symptom.

3.3.3. Patient preference

Although patient satisfaction with OAB treatments has been studied, little research has been done to ascertain patient preference and factors influencing their decision making. In

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studies focusing on SNM, temporary loss of efficacy, discomfort at the implant site, battery replacement procedure, medical need for MRI, and concerns about passing through metal detectors were found to be associated with patient satisfaction [40]. With respect to BoNT-A, the need for repeated injections, potential need for self-catheterisation, and side effects were found to be associated with patient satisfaction [41]. Hashim et al [42] conducted a survey among patients with refractory OAB and asked about their preference for third-line treatment, scaling via best-worst, focusing on treatment characteristics. Among these patients, 57% chose PTNS, 34% chose SNM, and 9.4% chose BoNT-A as their most preferred option. Nevertheless, over 80% of the patients reported that they would be willing to try each of the options. In contrast, Balchandra and Rogerson [43], who compared preferences for BoNT-A versus SNM among 50 women in the UK, found that 74% preferred BoNT-A and 26% preferred SNM. Based on these conflicting results, it seems that the way physicians counsel their patients has an impact on the treatment preference. Since PTNS is the least invasive procedure of the three, most patients would probably choose this treatment as a first option. Nevertheless, patient preference is an important factor in the decision-making process and should always be taken into account when commencing a third-line treatment for OAB.

3.3.4. Cost effectiveness

The main goal in dealing with refractory OAB is to provide the best quality of life to each patient at the lowest possible cost. The preferred methodology for an economic evaluation is cost-utility analysis, and the calculation of the incremental cost per additional quality adjusted life year (QALY) gained. Various studies have previously evaluated the cost effectiveness of third-line treatments in both Europe [44,45] and North America [46,47]. Most studies suggested that SNM is cost effective in the medium and long term compared with BoNT-A. Two recent studies also evaluated the cost effectiveness of SNM compared with other therapies. Bertapelle et al [48] conducted a cost-utility analysis of the Italian healthcare system. They showed that initiating treatment with SNM versus BoNT-A appears to be cost effective from year 3 onwards and becomes dominant (ie, more effective and less costly) at year 10: cumulative costs were €32 975 for early SNM and €33 309 for early BoNT-A, while cumulative QALYs were 7.52 and 6.93, respectively. Autiero et al [49] compared SNM with optimal medical therapy, BoNT-A, and PTNS in the UK. At 5 yr, SNM (with use of percutaneous nerve evaluation [PNE] or tined lead) was more effective and less costly than PTNS. Compared with ongoing medical therapy at 10 yr, SNM was more costly and more effective, and compared with BoNT-A, SNM with PNE was less costly and more effective, and SNM with tined lead was more costly and more effective.

In conclusion, SNM seems to be either cost saving and more effective, or acceptably cost effective compared with ongoing medical therapy, PTNS, or BoNT-A. The costs for SNM mainly involve device acquisition and implantation. All other treatments involve ongoing drug costs and physician visits for treatment maintenance. However, it has to be noted that most study groups received financial support from a manufacturer of SNM devices, which possibly introduces a bias. Furthermore, all studies used a simulation model (Markov) that does not fully represent clinical practice.

3.4. Treatment algorithm

In order to select the best treatment after failure of conservative management of OAB such as bladder training and pharmacotherapy, several factors should be taken into account, which are depicted in Figure 1. Since there is no strong evidence for superiority in efficacy between treatments, the selection should be focussed on patient preference, which translates into a shared decision approach. Good counselling is important, and the pros and cons of each treatment must be thoroughly discussed. However, other factors can also influence the decision making, such as concomitant bowel symptoms (eg, constipation and faecal incontinence) or pain (eg, interstitial cystitis and genital pain). Patients with these accompanying symptoms might be more suitable candidates for SNM, since this treatment has shown to be effective for both urinary and bowel symptoms as well as chronic pelvic pain. In patients with recurrent urinary tract infections, BoNT-A might not be the first-choice treatment since the postvoid residual can increase after detrusor injections. Patients who need to undergo frequent MRI investigations in the future (eg, neurogenic disease and vertebral disc herniation) are

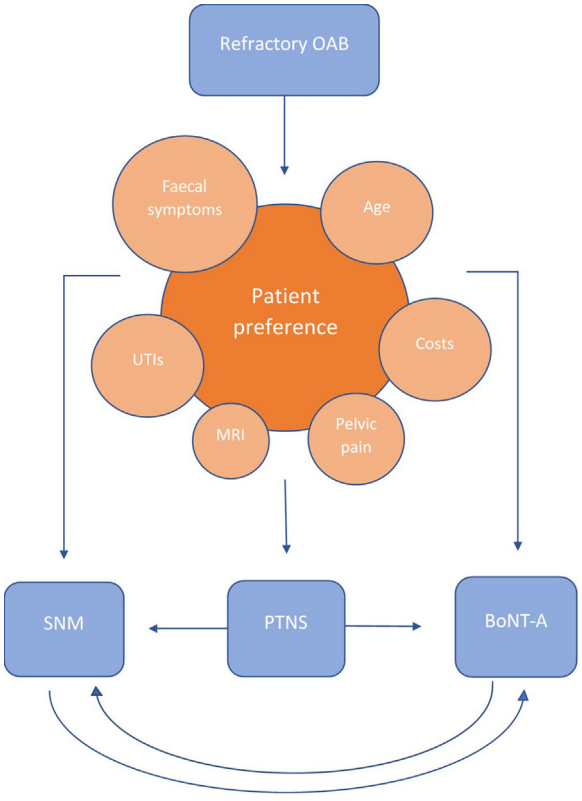

Fig. 1 – Treatment options in patients with OAB. BoNT-A = botulinum toxin type A; MRI = magnetic resonance imaging; OAB = overactive bladder syndrome; PTNS = posterior tibial nerve stimulation; SNM = sacral neuromodulation; UTI = urinary tract infection.

perhaps less suitable candidates for SNM, since the device is not MRI compatible.

In elderly patients or patients with cognitive impairment, several factors are involved that can make decision making challenging. For example, patients who undergo SNM need to be able to cope with the remote control and programming of the device, whereas patients who undergo BoNT-A injections need to be able to self-catheterise. In PTNS, frequent visits for stimulation can also be stressful for elderly patients, especially those who have limited mobility or autonomy. Hence, the treatment choice has to be tailored to the individual needs and abilities of these patients. Finally, treatment costs or availability can affect treatment choice. Although the cost effectiveness of the treatments seems to be comparable, not all treatment modalities are available or reimbursed in all countries or institutions. Furthermore, financial incentives could also influence the choice of treatment.

If one of the treatment modalities gives insufficient symptom relief, combination with medication (anticholinergics or mirabegron) might increase treatment efficacy [50]. Although there is currently limited evidence, both therapies might have a synergistic effect on bladder function. If the surgical treatment fails or is not tolerated, switching to another approach can be attempted (Fig. 1). Simultaneous utilisation of BoNT-A with PTNS or SNM might also be attempted, although the clinical results have yet to be reported in the literature. In a preclinical trial assessing the potential interactions between BoNT-A and SNM in rats, BoNT-A did not alter the ability of SNM to inhibit bladder contractions following intradetrusor injection for 2 d, 2 wk, or 1 mo [51]. Since most patients with refractory OAB who receive treatment are not completely cured (dry), a multimodal approach could be attempted in order to optimise efficacy. Perhaps this could be investigated in future trials.

4. Conclusions

In the management of refractory OAB, multiple minimally invasive treatments are available, with none showing strong superiority over another at this time. If the results of one therapy are not satisfactory, switching to another third-line treatment can be attempted. The treatment algorithm is dependent on several factors, including age, comorbidity, patient preference, surgical expertise, and financial concerns. All these factors should be taken into consideration before initiation of treatment.

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Study concept and design: Marcelissen, Cornu.
Acquisition of data: Marcelissen, Cornu, Rashid, Geavlete.
Analysis and interpretation of data: Marcelissen, Cornu, Rashid, Geavlete, Antunes-Lopes.
Drafting of the manuscript: Marcelissen, Cornu, Rashid, Geavlete, Antunes-Lopes, Rahnama'i, Delongchamps.
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References

[1] Link CL, Steers WD, Kusek JW, McKinlay JB. The association of adiposity and overactive bladder appears to differ by gender: results from the Boston Area Community Health survey. J Urol 2011;185:955–63.
[2] Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int 2011;108:1132–8.
[3] Sexton CC, Notte SM, Maroulis C, et al. Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy: a systematic review of the literature. Int J Clin Pract 2011;65:567–85.
[4] Bartley J, Gilleran J, Peters K. Neuromodulation for overactive bladder. Nat Rev Urol 2013;10:513–21.
[5] Herbison GP, Arnold EP. Sacral neuromodulation with implanted devices for urinary storage and voiding dysfunction in adults. Cochrane Database Syst Rev 2009;2:CD004202.
[6] Sutherland SE, Lavers A, Carlson A, Holtz C, Kesha J, Siegel SW. Sacral nerve stimulation for voiding dysfunction: one institution's 11-year experience. Neurourol Urodyn 2007;26:19–28, discussion 36.
[7] van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol 2007;178:2029–34.
[8] Hassouna MM, Siegel SW, Nÿeholt AA, et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety. J Urol 2000;163:1849–54.
[9] Bosch JL, Groen J. Sacral nerve neuromodulation in the treatment of patients with refractory motor urge incontinence: long-term results of a prospective longitudinal study. J Urol 2000;163:1219–22.
[10] Siegel SW, Catanzaro F, Dijkema HE, et al. Long-term results of a multicenter study on sacral nerve stimulation for treatment of urinary urge incontinence, urgency-frequency, and retention. Urology 2000;56(6 Suppl 1):87–91.
[11] Marcelissen TA, Leong RK, de Bie RA, van Kerrebroeck PE, de Wachter SG. Long-term results of sacral neuromodulation with the tined lead procedure. J Urol 2010;184:1997–2000.
[12] Siegel S, Noblett K, Mangel J, et al. Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. Neurourol Urodyn 2015;34:224–30.
[13] Pal F, Heesakkers JP, Bemelmans LH. Current opinion on the working mechanisms of neuromodulation in the treatment of lower urinary tract dysfunction. Curr Opin Urol 2006;16:261–7.

Please cite this article in press as: Marcelissen T, et al. Management of Idiopathic Overactive Bladder Syndrome: What Is the Optimal Strategy After Failure of Conservative Treatment?. Eur Urol Focus (2018), https://doi.org/10.1016/j.euf.2018.05.004

[14] Peters KM, Carrico DJ, Perez-Marrero RA, et al. Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial. J Urol 2010;183:1438–43.
[15] Peters KM, Macdiarmid SA, Wooldridge LS, et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy trial. J Urol 2009;182:1055–61.
[16] Biemans JM, van Balken MR. Efficacy and effectiveness of percutaneous tibial nerve stimulation in the treatment of pelvic organ disorders: a systematic review. Neuromodulation 2013;16:25–33, discussion 33.
[17] Peters KM, Carrico DJ, Wooldridge LS, Miller CJ, MacDiarmid SA. Percutaneous tibial nerve stimulation for the long-term treatment of overactive bladder: 3-year results of the STEP study. J Urol 2013;189:2194–201.
[18] Cui Y, Wang L, Liu L, et al. Botulinum toxin-A injections for idiopathic overactive bladder: a systematic review and meta-analysis. Urol Int 2013;91:429–38.
[19] Nitti VW, Dmochowski R, Herschorn S, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol 2017;197(2S):S216–23.
[20] Mohee A, Khan A, Harris N, Eardley I. Long-term outcome of the use of intravesical botulinum toxin for the treatment of overactive bladder (OAB). BJU Int 2013;111:106–13.
[21] Veeratterapillay R, Harding C, Teo L, et al. Discontinuation rates and inter-injection interval for repeated intravesical botulinum toxin type A injections for detrusor overactivity. Int J Urol 2014;21:175–8.
[22] Makovey I, Davis T, Guralnick ML, O'Connor RC. Botulinum toxin outcomes for idiopathic overactive bladder stratified by indication: lack of anticholinergic efficacy versus intolerability. Neurourol Urodyn 2011;30:1538–40.
[23] Visco AG, Brubaker L, Richter HE, et al. Anticholinergic therapy vs. onabotulinumtoxinA for urgency urinary incontinence. N Engl J Med 2012;367:1803–13.
[24] Apostolidis A, Averbeck MA, Sahai A, et al. Can we create a valid treatment algorithm for patients with drug resistant overactive bladder (OAB) syndrome or detrusor overactivity (DO)? Results from a think tank (ICI-RS 2015) Neurourol Urodyn 2017;36:882–93.
[25] Westney OL, Lee JT, McGuire EJ, Palmer JL, Cespedes RD, Amundsen CL. Long-term results of Ingelman-Sundberg denervation procedure for urge incontinence refractory to medical therapy. J Urol 2002;168:1044–7.
[26] Westney OL, McGuire EJ. Surgical procedures for the treatment of urge incontinence. Tech Urol 2001;7:126–32.
[27] Leng WW, Blalock HJ, Fredriksson WH, English SF, McGuire EJ. Enterocystoplasty or detrusor myectomy? Comparison of indications and outcomes for bladder augmentation. J Urol 1999;161:758–63.
[28] Gormley EA, Lightner DJ, Faraday M, Vasavada SP. American Urological Association; Society of Urodynamics, Female Pelvic Medicine. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol 2015;193:1572–80.
[29] Amundsen CL, Richter HE, Menefee SA, et al. OnabotulinumtoxinA vs sacral neuromodulation on refractory urgency urinary incontinence in women: a randomized clinical trial. JAMA 2016;316:1366–74.
[30] Drake MJ, Nitti VW, Ginsberg DA, et al. Comparative assessment of the efficacy of onabotulinumtoxinA and oral therapies (anticholinergics and mirabegron) for overactive bladder: a systematic review and network meta-analysis. BJU Int 2017;120:611–22.
[31] Sherif H, Khalil M, Omar R. Management of refractory idiopathic overactive bladder: intradetrusor injection of botulinum toxin type A versus posterior tibial nerve stimulation. Can J Urol 2017;24:8838–46.
[32] Smits MA, Oerlemans D, Marcelissen TA, Van Kerrebroeck PE, De Wachter SG. Sacral neuromodulation in patients with idiopathic overactive bladder after initial botulinum toxin therapy. J Urol 2013;190:2148–52.
[33] Peters KM, Killinger KA, Gilleran J, Boura JA. Does patient age impact outcomes of neuromodulation? Neurourol Urodyn 2013;32:30–6.
[34] Thin NN, Horrocks EJ, Hotouras A, et al. Systematic review of the clinical effectiveness of neuromodulation in the treatment of faecal incontinence. Br J Surg 2013;100:1430–47.
[35] Marcelissen T, Jacobs R, van Kerrebroeck P, de Wachter S. Sacral neuromodulation as a treatment for chronic pelvic pain. J Urol 2011;186:387–93.
[36] Uludag O, Melenhorst J, Koch SM, van Gemert WG, Dejong CH, Baeten CG. Sacral neuromodulation: long-term outcome and quality of life in patients with faecal incontinence. Colorectal Dis 2011;13:1162–6.
[37] El-Gazzaz G, Zutshi M, Salcedo L, Hammel J, Rackley R, Hull T. Sacral neuromodulation for the treatment of fecal incontinence and urinary incontinence in female patients: long-term follow-up. Int J Colorectal Dis 2009;24:1377–81.
[38] Caremel R, Damon H, Ruffion A, et al. Can sacral neuromodulation improve minor incontinence symptoms in doubly incontinent patients successfully treated for major incontinence symptoms? Urology 2012;79:80–5.
[39] Knowles CH, Horrocks EJ, Bremner SA, et al. Percutaneous tibial nerve stimulation versus sham electrical stimulation for the treatment of faecal incontinence in adults (CONFIDeNT): a double-blind, multicentre, pragmatic, parallel-group, randomised controlled trial. Lancet 2015;386:1640–8.
[40] Leong RK, Marcelissen TA, Nieman FH, De Bie RA, Van Kerrebroeck PE, De Wachter SG. Satisfaction and patient experience with sacral neuromodulation: results of a single center sample survey. J Urol 2011;185:588–92.
[41] Imam SZ, Syed KS, Ali SA, et al. Patients' satisfaction and opinions of their experiences during admission in a tertiary care hospital in Pakistan—a cross sectional study. BMC Health Serv Res 2007;7:161.
[42] Hashim H, Beusterien K, Bridges JF, Amos K, Cardozo L. Patient preferences for treating refractory overactive bladder in the UK. Int Urol Nephrol 2015;47:1619–27.
[43] Balchandra P, Rogerson L. Women's perspective: intra-detrusor botox versus sacral neuromodulation for overactive bladder symptoms after unsuccessful anticholinergic treatment. Int Urogynecol J 2014;25:1059–64.
[44] Arlandis S, Castro D, Errando C, et al. Cost-effectiveness of sacral neuromodulation compared to botulinum neurotoxin a or continued medical management in refractory overactive bladder. Value Health 2011;14:219–28.
[45] Leong RK, de Wachter SG, Joore MA, van Kerrebroeck PE. Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder. BJU Int 2011;108:558–64.
[46] Hassouna MM, Sadri H. Economic evaluation of sacral neuromodulation in overactive bladder: a Canadian perspective. Can Urol Assoc J 2015;9:242–7.
[47] Siddiqui NY, Amundsen CL, Visco AG, Myers ER, Wu JM. Cost-effectiveness of sacral neuromodulation versus intravesical botulinum A toxin for treatment of refractory urge incontinence. J Urol 2009;182:2799–804.
[48] Bertapelle MP, Vottero M, Popolo GD, et al. Sacral neuromodulation and Botulinum toxin A for refractory idiopathic overactive bladder:

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a cost-utility analysis in the perspective of Italian healthcare system. World J Urol 2015;33:1109–17.

[49] Autiero SW, Hallas N, Betts CD, Ockrim JL. The cost-effectiveness of sacral nerve stimulation (SNS) for the treatment of idiopathic medically refractory overactive bladder (wet) in the UK. BJU Int 2015;116:945–54.

[50] George E, Lane F, Noblett K. Use of combined anticholinergic medication and sacral neuromodulation in the treatment of refractory overactive bladder. Female Pelvic Med Reconstr Surg 2011;17:97–9.

[51] Su X, Nickles A, Nelson DE. Preclinical assessment of potential interactions between botulinum toxin and neuromodulation for bladder micturition reflex. BMC Urol 2015;15:50.

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