The management of overactive bladder: percutaneous tibial nerve stimulation, sacral nerve stimulation, or botulinum toxin?

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Purpose of review
We have reviewed the evidence published on botulinum toxin A (BoNT/A), percutaneous tibial nerve stimulation (PTNS), and sacral nerve stimulation (SNS) in the management of overactive bladder (OAB).

Recent findings
BoNT/A is effective irrespectively of the number of previous anticholinergic treatments and of the reason for failure. Doses up to 360U 3-monthly are well tolerated. BoNT/A is well tolerated and effective also in the pediatric population. Bladder instillation of liposome encapsulated BoNT/A is a new approach, deserving further research. When using PTNS, motor response from the electrical stimulus is not required, a sensory response suffices. PTNS has a lasting effect compared to oxybutynin alone. SNS is superior to standard medical treatment but the combination of SNS and anticholinergics is more effective than anticholinergic alone.

Summary
The evidence published in the last 18 months has increased the level of evidence on safety and effectiveness of BoNT/A, PTNS, and SNS in the management of OAB. BoNT/A is now recommended as standard third-line treatment for OAB (in the USA) and urgency incontinence (in the USA and in Europe) in selected patients refractory to pharmacological therapy. All available third-line treatment options for OAB/urgency urinary incontinence should be offered before surgery is contemplated.

Video abstract
http://links.lww.com/COU/A7.

Keywords
botulinum toxin A, overactive bladder, percutaneous tibial nerve stimulation, sacral nerve stimulation, urgency urinary incontinence

INTRODUCTION

Overactive bladder (OAB) syndrome is defined by the presence of urgency, with or without urgency urinary incontinence (UUI), usually with frequency and nocturia [1]. Symptoms may or may not be associated with detrusor overactivity (DO) [2–4]. First-line treatments include conservative strategies such as adjustment of fluid and food habits, review of drug treatment, timed voiding, bladder retraining, and pelvic floor muscle training. Second-line treatments include pharmacological therapy for a minimum of 3 months with either anticholinergic/antimuscarinic agents or β3 agonists, as recommended by the International Consultation on Incontinence [5]. Notwithstanding the proven effectiveness of the pharmacological treatment of OAB and UUI, response to it is difficult to forecast in the individual patient and adherence to the prescribed regimen is known to be low with only 31–36% of patients remaining on treatment at 52 weeks [6▪,7].

Different third-line treatments of OAB/detrusor overactivity are available and may be offered to patients who do not respond or do not tolerate pharmacological treatment. The aim of this article

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KEY POINTS

- Third-line treatment of OAB/DO includes intravesical injection of botulinum toxin A, PTNS, and SNS.
- The available evidence confirms that all three treatment approaches are well tolerated and effective, although only BoNT/A and SNS can achieve cure of UUI.
- In case of OAB/DO refractory to pharmacological treatment, the choice among the different second-line treatment relies on patient preference, availability, and local expertise.
- Further research is needed to identify ideal candidates for the different third-line treatments of OAB/IDO.

was to review the evidence published over the last calendar year on intravesical injection of botulinum toxin A (BoNT/A), neuromodulation techniques [i.e., percutaneous tibial nerve stimulation (PTNS), and sacral nerve stimulation (SNS)].

TEXT OF REVIEW

MEDLINE database was searched for papers published over the last 18 months (September 2013–February 2015), using the following PICOs: overactive bladder, BoNT/A, PTNS, SNS, no treatment, placebo, comparator, antimuscarinics, anticholinergics, improvement, cure. Two hundred and nine references were retrieved, 112 were obtained full-text, four additional references were obtained from full-text papers, and a total of 39 were found to be relevant to the current review.

Botulinum toxin A

The mechanism of action of BoNT/A in the urinary bladder has already been extensively described [8▪]. BoNT/A has been studied as a local therapy for the treatment of detrusor overactivity since the year 2000 [9]. Two different preparations of BoNT/A exist (Botox, onaBoNT/A and Dysport, aboBoNT/A) and they differ because of the isolation, manufacturing, and stabilization processes, their units are not interchangeable and results from studies with one product cannot be transferred to the other product [10▪▪,11].

Following the two pivotal trials that led to the registration of onaBoNT/A, phase IV studies addressing different issues of OAB/DO treatment with botulinum toxin have been published and reviews of randomized trials have been produced. Recently, two systematic reviews and meta-analyses have been published by Mangera *et al.* [10▪▪] and Cui *et al.* [12▪▪], raising the level of evidence on this subject. A number of narrative reviews have also been published recently, providing a useful summary of the available evidence for the use of BoNT/A in the management of OAB and UUI [13,11]. High-level evidence on the effectiveness of BoNT/A continues to accumulate. A randomized trial on BoNT/A versus placebo in male patients with refractory OAB persisting after benign prostatic hyperplasia (BPH) surgery showed improvement of daily frequency, which did not reach statistical significance [14▪▪].

Interesting evidence was also published from nonrandomized studies. Nuanthaisong *et al.* [15▪] investigated the safety of onaBoNT/A for multiple indications, suggesting that a dose more than 360 units every 3 months was well tolerated in a small cohort of 13 patients with no life-threatening adverse events.

An interesting study from Sievert *et al.* [16] investigated the effect of 100 U of BoNT/A in patients with idiopathic UUI and found the clinical response to be independent from the number of anticholinergic agents that patients received and from the reason of pharmacological treatment failure.

Sager *et al.* [17▪] reported on the use of BoNT/A in the management of children with neurogenic bladder, although a continence rate of 50–77% was achieved, urodynamic improvement was considered to be insufficient and five patients underwent augmentation cystoplasty. In a different study, 14 of 17 children avoided surgical reconstruction of the bladder following BoNT/A treatment, suggesting a significant role for such treatment approach in the pediatric population [18]. Amundsen *et al.* [19▪] published the design of the ROSETTA (The Refractory Overactive Bladder: Sacral Neuromodulation vs. Botulinum Toxin Assessment) trial aiming at randomizing patients with refractory UUI between BoNT/A and SNS, the study will provide further evidence on the subject.

A totally new approach to reduce the invasiveness on BoNT/A was proposed by Chuang using liposome encapsulated BoNT/A. The intravesical instillation clearly represents an interesting step to reduce the invasiveness associated with the endoscopic injection. The preliminary data suggest a significant improvement of daytime frequency and urgency severity score, although no significant change in urgency and UUI was observed. More research into this interesting concept is required [20▪].

Schurch and Carda reviewed the evidence on BoNT/A injection in the management of UUI in patients with multiple sclerosis. According to the Swiss authors, the clinical response in patients with

multiple sclerosis is no different from the one observed in the spinal cord injury, one with a 75–90% efficacy; training for clean intermittent self catheterization is mandatory prior to initiate treatment [3].

Although the mechanisms of action of botulinum toxin are rather well known, new information becomes available every year. Hegele *et al.* [21▪] published an interesting paper showing that BoNT/A is also effective in decreasing prostaglandin E2 blood levels in patients with OAB/IDO (overactive bladder (idiopathic detrusor overactivity) responding to treatment, suggesting prostaglandin E2 may be used as a biomarker during follow-up. A pharmacoeconomic analysis by Hamid *et al.* [22▪▪] confirms the cost-effectiveness of Botox + best supportive care versus best supportive care alone with a 100% probability of being cost-effective [22▪▪]. Effectiveness of BoNT/A administration has also been investigated using patient reported outcome. Malde and coworkers reported OAB/IDO patients experienced and found high satisfaction rate with the service offered, especially in those who repeated treatments [4].

Based on the available evidence on BoNT/A, the AUA (American Urological Association) guidelines recently stated: clinicians may offer intradetrusor onaBoNT/A (100 U) as third-line treatment in the carefully selected and thoroughly counseled patient who has been refractory to first and second-line OAB treatments [23▪▪]. The patient must be able and willing to return for frequent postvoid residual evaluation and to perform self-catheterization if necessary.

Percutaneous posterior tibial nerve stimulation

PTNS is a peripheral neuromodulation technique first described by Stroller in the 1990s for the treatment of OAB [24]. Mechanism of action is not yet fully understood, but it is likely to exert both motor and sensory neuromodulatory effects, such as increasing inhibitory tone, decreasing awareness of abnormal stimuli, and reorganization of the neuronal system, resulting in restoration of normal reflexes [25,26▪].

The evidence published in 2014 on PTNS in the treatment of OAB is rather scarce. The last systematic review on PTNS in the management of lower urinary tract dysfunctions was published in 2013 by Graziev *et al.* PTNS was found to be effective in reducing urinary frequency, urinary incontinence episodes, and involuntary detrusor contractions in 37–100% of patients with OAB [27]. A less-invasive approach to PTNS by transcutaneous stimulation seems to be effective in short term and long term, as after daily session for 30 days, 53% of patients showed symptoms of improvement and after a mean follow-up of 11 months, 49% of patients still used it [28].

The combined use of PTNS and anticholinergic has been explored. A randomized study by Souto *et al.* showed a comparable efficacy among oxybutynin ER (extended release) 10 mg/day and PTNS ± oxybutynin ER 10 mg/day at 12 weeks. However, 12 weeks after treatment cessation, the oxybutynin group had lower QoL (quality of life) measures compared to 12 weeks, but this was not true for both PTNS groups [29▪▪].

A recent update of the AUA/SUFU (American Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction) guidelines for the management of OAB (non-neurogenic) in adults states that clinicians may offer PTNS as third-line treatment in a carefully selected patients [23▪▪].

Sacral nerve stimulation

SNS works by delivering mild electrical impulses to the sacral nerve roots, thanks to an electrode implanted adjacent to the third sacral nerve root and connected to a neurostimulator placed in a subcutaneous pocket over the buttocks, thus controlling either bladder, detrusor sphincter, or bowel [30]. Effectiveness of SNS has been investigated but results should always be stratified for the different indications. Long-term follow-up of SNS treatment, in a single center cohort of 216 patients (86% of which were female), has been recently published by Peeters *et al.* [31▪]. Success and cure rates of ≈70 and 20% for urgency incontinence and of 68 and 33% for urgency frequency syndrome were reported after a mean follow-up of 46.9 months (actually on 27.2 for UUI and 31.6 for those usually with frequency patients). Forty-one percent of patients needed surgical reintervention and an average of 1.7 reinterventions were needed [31▪].

Analysis of a large sample of the Medicare population (1474 patients) by Chungtai *et al.* [32] showed how 17.3% of devices were removed and 11.3 replaced over 5 years whereas 73.9% of patients maintained the original device. Bowel (constipation and diarrhea) and neurological (numbness and extreme pain) complaints were consistent with those observed in the year prior to implantation.

The effectiveness of the combined treatment with tolterodine and SNS versus tolterodine alone was explored by Tang *et al.* in a randomized trial. The results of the study show a significant advantage of the combination treatment in terms of urinary

frequency, mean voided volume, bladder volume at first desire to void, and maximum cystometric capacity. The observed clinical improvement was associated with a significant improvement in anxiety and depression [33▪▪].

Investigating mechanisms of action of SNS, Shalom *et al.* reported a significant decrease of uNGF (urinary Nerve Growth Factor) in patients receiving PNE (percutaneous nerve evaluation) test for SNS. Patients with detrusor overactivity have a higher baseline level of uNGF (19.82 vs. 7.88 pg/mg, $P < 0.002$) compared to controls. Patients with detrusor overactivity had a significant improvement in quality-of-life, using the urinary distress inventory and the incontinence quality-of-life scale; uNGF levels significantly decreased from 17.23 to 9.24 pg/mg ($P < 0.02$) [34]. Using a Markov model and a 10-year horizon, Walleser Autiero *et al.* were able to show that SNS with percutaneous needle evaluation is the most effective strategy, from a cost-utility analysis, for managing patients with idiopathic wet OAB [35▪▪].

Referral for SNS treatment of IDO is still considered to be limited. Kessler *et al.* investigated the urologist referral's attitude in the UK and identified three major factors preventing referral including absolute contraindications (low bladder compliance, progressive neurological disease, urinary tumors, etc.) and relative ones such as cardiac pacemaker and diabetes mellitus. Analysis of a neurourologists subgroup revealed that noncritical contraindications did not prevent referral, suggesting that proper information on SNS is of importance in improving management of OAB. The use of decision tools such as TIPS (Tool for InterStim Patient Selection) (www.tips-snm.org) is proposed to improve referral [36▪].

SNS is currently used in the management of voiding dysfunction including urinary frequency and urgency urinary incontinence, but a recent report suggests that beyond improving disease-specific quality of life, SNS ameliorates female sexual function. Benakhar *et al.* observed a significant improvement in female sexual function index total score ($P = 0.011$) and in the domains regarding desire ($P = 0.014$) and orgasm ($P = 0.035$) following implantation, even if no correlation was found between QoL domains and improvement of the female sexual function index score [37▪].

The recent update of the AUA/SUFU guidelines on the diagnosis and treatment of OAB suggests that clinicians may offer SNS, a third-line treatment, in a carefully selected patient population characterized by refractory OAB symptoms or patients who are not candidates for second-line therapy and are willing to undergo surgical procedure [23▪▪].

Open question: which third-line strategy is better?

As third-line treatments BoNT/A, PTNS, and SNS have proven to be well tolerated and effective and it is time to compare their cost and cost-effectiveness, as follow-up of up to 5–10 years are now available.

Using a Markov model, Walleser Autiero *et al.* evaluated cost-effectiveness of PTNS, SNS [both percutaneous nerve evaluation (PNE) and tined lead evaluation (TLE)], BoNT/A, and optimal medical therapy (OMT) for OAB wet/IDO in a 5 and 10-year time frame in the UK. QALYs (Quality Adjusted Life Years) were calculated and they included device and drug acquisition costs, preprocedure and postprocedure costs, and adverse events management costs. They found that at 5 years, SNS and BoNT/A were more effective and less costly than PTNS; at 10 years, SNS compared to OMT was more costly and more effective; at 10 years, SNS/PNE was less costly and more effective than BoNT/A; and at 10 years, SNS/TLE was more costly and more effective than BoNT/A. Authors concluded that SNS (PNE and TLE) is either cost saving and more effective compared to OMT, PTNS, and BoNT/A for idiopathic refractory wet OAB [35▪▪].

Cost-effectiveness is often related to the local health system. Bertapelle *et al.* performed a cost-effectiveness analysis of SNS versus BoNT/A for OAB/IDO in the Italian Healthcare system, similar to those already performed in Spanish, Dutch, and UK healthcare contexts. The same Markov model over a 10-year time horizon has been applied and QALYs gained, showing that SNS is cost-effective from year 3 onward and becomes cost saving at year 10 [38▪].

The decision to go for a third-line treatment of OAB and the choice of the treatment modality is certainly influenced by the consulting urologist, but it is ultimately taken by the patient. The decision relies on several factors. A cohort of 50 women with refractory OAB were counseled, regarding SNS and BoNT/A and the reasons associated with the individual choice were analyzed. Thirty-seven of 50 patients (74%) were elected to receive BoNT/A because of quicker improvement, easy access to treatment, easier treatment modality, being unease with the thought of a foreign body implanted, and management of battery and device in case of SNS. On the contrary, 14 of 50 patients (26%) chose SNS because it is more a permanent therapy, with long intervals between battery replacements (6 years) instead of more frequent reinjections, does not affect postvoid residual, and may also treat coexisting bowel symptoms [39▪].

CONCLUSION

The evidence on third-line treatment of OAB with PTNS, BoNT/A, and SNS continue to evolve allowing guidelines to provide more solid recommendations. All treatments proved to be well tolerated and patients' expectations can be properly set based on the available evidence. Health technology assessment of the different treatment suggests that what appears to be the more expensive treatment can be the more cost-effective in the long term. Evaluation of the peer-reviewed literature confirms the need for multiple treatment options being available for our patients and that PTNS, BoNT/A, and SNS must remain in our armamentarium. Clinical research on the management of OAB has often tried to understand which is the more effective treatment for the condition, but maybe it should better look into what is the best treatment option for the individual patient. Ultimately, patients do not necessarily choose the more effective treatment, but the one that best fits their needs, and this remains one of their fundamental rights.

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Conflicts of interest

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