

Expanding the Role of Neuromodulation for Overactive Bladder: New Indications and Alternatives to Delivery

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Abstract From the time that it was granted US Food and Drug Administration approval, neuromodulation has secured a firm position in the treatment algorithm for overactive bladder. With neuromodulation, physicians were able to bridge the gap between the two ends of the treatment spectrum (medical therapy and open surgery). Sacral nerve stimulation has been the most widely used form of neuromodulation. Recent modifications to its design, namely the development of the tined lead and the launching of the refined InterStim II (Medtronic, Minneapolis, MN), have made sacral nerve stimulation even less invasive and more effective. While InterStim is maintaining a level of success with these advancements, peripheral means of neuromodulation are being explored. The current literature takes a closer look at posterior tibial and pudendal nerve stimulation as alternatives to sacral nerve stimulation. The field of neuromodulation is also expanding in terms of the target patient population, as it is being used to treat children, patients with neurological disease, and others. As the role of neuromodulation increases, we must continue to assess its efficacy, safety, and cost-effectiveness in comparison to other therapeutic options.

Keywords Overactive bladder · Sacral neuromodulation · Urinary incontinence · Neurostimulation · Sacral nerve stimulation · InterStim · Posterior tibial nerve stimulation ·

Peripheral nerve stimulation · Efficacy · Cost-effectiveness · Safety · Pudendal nerve stimulation · Neurogenic bladder · Cardiac pacemaker

Introduction

Overactive bladder (OAB) is defined as urgency with or without urgency incontinence, usually with frequency (>8 micturitions/24 h) and nocturia [1]. Conservative management of OAB usually includes pelvic floor physical therapy and/or use of pharmacotherapy such as antimuscarinic medications. However, a significant number of patients are refractory to pharmacotherapy, and long-term compliance is poor, so much so that only 30% of individuals with OAB syndrome still take their medication 1 year after initiation [2]. Traditionally, patients who failed conservative measures were left with highly invasive treatment options, such as myomectomy, augmentation cystoplasty, and various urinary diversions [3]. In 1997, the US Food and Drug Administration approved neuromodulation for urgency incontinence, and subsequently for urgency-frequency syndrome and non-obstructive chronic urinary retention. Although its mode of action is still not completely understood, recent research indicates that this therapy involves not just electrostimulation of sacral nerves but also neuromodulation due to somatosensory bladder afferents projecting into the pontine micturition center in the brainstem [4]. The objective of this article is to review the current literature and discuss the latest advances, significant trends, and current debates in the treatment of OAB with neuromodulation. Of particular interest are the articles focusing on peripheral nerve stimulation (PNS), cost-effectiveness, and nontraditional patient populations.

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Cost-Effectiveness, Adverse Effects, and Safety

During the past year, several articles examined the efficacy and cost-effectiveness of neuromodulation, as well as the adverse effects and safety profile of this procedure. In one such article, Siddiqui et al. [5•] systematically reviewed the literature regarding the efficacy of sacral nerve stimulation (SNS) using the InterStim (Medtronic, Minneapolis, MN) for women with refractory OAB. The highest-quality data were found in three independent studies of efficacy. In these studies, incontinent episodes per day and pad usage significantly decreased after SNS therapy. After SNS, there was a significant decrease in mean incontinent episodes per day (2–3) and mean daily pad use (1–3). About 45% of patients reported “cure,” or lack of daily incontinence episodes, up to 3 years after implant. Moreover, 54% of patients maintained improvements in daily incontinence episodes after implant. Subjective outcomes were also assessed and shown to be beneficial. Amundsen et al. [6] reported a 65- to 67-point decrease in Incontinence Impact Questionnaire (IIQ) scores 2 years after SNS implant.

In a separate article, Siddiqui et al. [7••] compared the cost-effectiveness of SNS versus that of intravesical botulinum A toxin (BoNT-A) for treatment of refractory urge incontinence. Using the Markov decision model to compare cost (2008 US dollars) and effectiveness (quality-adjusted life-years [QALYs]), they calculated the incremental cost-effectiveness ratio (ICER), which compares the difference in cost with the difference in effectiveness (ie, QALYs). In the best-case scenario, SNS was more expensive (\$15,743 vs \$4,392) and more effective (1.73 vs 1.63 QALYs) than BoNT-A during a 2-year period. During a 2-year period, the ICER was \$116,427 per QALY, indicating that although SNS was more effective, BoNT-A was the more cost-effective option. One could argue that the cost-effectiveness comparison could change dramatically if it were recalculated beyond the 2-year period. However, the authors were limited to a 2-year period because long-term data regarding BoNT-A injections are limited.

In addition to demonstrating that this procedure is effective, the literature also suggests that neuromodulation is relatively safe. Six good studies were available regarding adverse events associated with SNS [5•]. Adverse events mainly encompassed pain, infection, and change in clinical effect, often due to lead migration. The surgical revision rates when using tined leads ranged from 3% to 16%, as most complications were managed conservatively. Six percent of patients were explanted due to lack of efficacy, and 5% to 11% were explanted due to infection.

Another safety issue regarding sacral neuromodulation is the potential for cross-talk between the InterStim device and cardiac pacemakers. Roth [8] recently pre-

sented a series of three patients with cardiac pacemakers who subsequently underwent staged SNS implantation, and two patients who had successful internal pulse generator (IPG) implantation who later required cardiac pacemaker implantation. Patients had continuous cardiac monitoring by anesthesia, and there were no observed changes in rhythm perioperatively. This case series includes the two patients who did not have their IPGs turned off at the time of cardiac pacemaker implantation. At the time of 2-week follow-up, interrogation of the IPGs revealed that the settings had remained the same on both devices. The IPGs were all programmed for continuous bipolar stimulation. They were implanted on the contralateral side of the cardiac pacemakers in the three patients who had previously undergone cardiac pacemaker placement. Of note, none of the pacemakers had cardioversion or defibrillator capabilities. Based on this study, SNS can be safely used in patients with cardiac pacemakers.

Alternatives to Sacral Nerve Stimulation

Posterior Tibial Nerve Stimulation

During the past year, the bulk of the literature regarding advancements in neuromodulation for OAB has focused on alternatives to SNS. The literature suggests that PNS via the posterior tibial nerve or the pudendal nerve may be viable options. Posterior tibial nerve stimulation (PTNS) was first introduced by McGuire and colleagues in 1983, and more recent studies have confirmed a 60% to 80% positive response rate after 10 to 12 weekly treatments [9]. PTNS is performed by inserting a 34-gauge needle about 3 to 4 cm cephalad to the medial malleolus, between the posterior margin of the tibia and soleus muscle. Once connected, an adjustable voltage pulse intensity of 0 to 10 mA, a fixed pulse width of 200, and a frequency of 20 Hz were delivered during weekly 30-min sessions. Correct position is confirmed by flexion of the great toe or fanning of the toes and a tingling sensation. Adverse events associated with PTNS are minimal, mostly minor hematomas at the site of needle insertion.

Peters et al. [10•] published a randomized, multicenter study that compared the efficacy of PTNS with that of extended-release tolterodine, also known as the OrBIT (Overactive Bladder Innovative Therapy) trial. A total of 100 adults with urinary frequency were randomly assigned to 12 weeks of treatment with PTNS or 4 mg/d of extended-release tolterodine. After 12 weeks of therapy, the PTNS arm reported a 79.5% cure or improvement rate, compared with 54.8% of those on tolterodine ($P=0.01$) on the global response assessments. The two groups had similar improvements on objective measures, including reductions in

urinary frequency, urge urinary incontinence episodes, urge severity, and nighttime voids, and increased voided volume. The authors concluded that PTNS was safe and efficacious, with statistically significant subjective and objective improvements comparable to that of pharmacotherapy.

Peters et al. [11•] also compared the efficacy of PTNS to that of sham in a multicenter, double-blind, randomized trial known as SUmIT (Study of Urgent PC Versus Sham Effectiveness in Treatment of Overactive Bladder Symptoms). After 12 weeks, 54.5% of the PTNS patients reported moderate or markedly improved response from baseline, compared with 20.9% of sham patients ($P < 0.001$). PTNS also increased voided volume when compared with baseline from 83 to 169.5 mL ($P = 0.01$). Patients were not able to correctly identify if they were part of the sham or PTNS group, as both groups had leads placed. The results from this study suggest that the therapeutic effect of PTNS is a result of stimulation of the posterior tibial nerve and not a placebo effect.

Following the encouraging results from the SUmIT and OrBIT studies demonstrating true therapeutic effects comparable to those of tolterodine, other authors focused on various treatment courses and durability. The traditional PTNS treatment course runs for 12 weeks, with weekly 30-min sessions. Yoong et al. [12] reported initial outcome data following a shortened 6-week treatment protocol with PTNS. Forty-three women underwent this shortened treatment course and were evaluated with bladder symptom diaries and the Incontinence Impact Questionnaire (IIQ-7), which is a health-related quality-of-life questionnaire. A positive response to therapy was defined as 1) OAB symptoms no longer being bothersome, 2) reduction by half in frequency episodes, and 3) reduction by 25% in IIQ-7 outcomes. The positive response rate was 69.7%, with an almost 50% decrease in the median daytime and nocturnal frequency (11.8 vs 6.9 and 3.5 vs 1.8; $P < 0.05$). Patients reported fewer urge incontinence episodes per 24 h, from a median of 3.5 to 2.4 ($P < 0.05$). The median IIQ-7 scores decreased by 25% (30.4 vs 24.3; $P < 0.05$), and the median number of pads used in 24 hours decreased by 34% (3.8 vs 2.5; $P < 0.05$). However, the participants reported return of symptoms 3 weeks after the treatment, and no predictors of duration of symptomatic relief could be identified. These early data suggest that the PTNS treatment course can be halved, but more conclusive studies are needed to determine the optimal duration of initial treatment and maintenance program.

The question of durability of PTNS treatment was addressed by MacDiarmid et al. [13•] in the second phase of the OrBIT study. Thirty-three of the 35 responders from the initial 12-week treatment course elected for maintenance therapy. Participants selected treatment intervals allowing them to control OAB symptoms at an acceptable level. A

total of 32 completed 6 months of maintenance, and 25 completed 12 months. The participants received a mean of 12.1 ± 4.9 treatments over an average of 263 days, with a mean of 21 days (median, 17) between treatments. However, the participants had longer time intervals during the second 6 months than during the first 6 months of the evaluation (14 vs 24 days). Subjective global assessments showed a sustained improvement of symptoms from 12 weeks at the 6-month and 12-month evaluations (94% and 96%, respectively). There were also objective improvements from baseline, with decreases of 2.8 voids per day ($P < 0.001$), 1.6 urge incontinence episodes per day ($P < 0.001$), 0.8 nocturnal voids ($P < 0.05$), and an increase of 39 mL in voided volume ($P < 0.01$). The authors concluded that PTNS can be a viable long-term therapeutic option for OAB patients.

A global evaluation of PTNS as a treatment option for OAB was performed by Ridout and Yoong [9] with a review of the published literature. Six articles were identified that assessed the efficacy of PTNS as therapy for OAB. These studies used various criteria for “positive response,” such as objective reduction in symptoms and the request for maintenance therapy following completion of the 12-week course. Using these varying definitions of success, PTNS has been reported to have a 60% to 81% response rate. Most authors agree that PTNS requires indefinite maintenance therapy, but the specifics of the maintenance program have not yet been defined. Van der Pal et al. [14] showed that 64% of patients reported greater than 50% worsening in frequency and incontinence episodes after a 6-week pause in treatment. Overall, PTNS seems to offer symptomatic relief for OAB patients who are refractory to conservative therapy, but standard guidelines for initial therapy and maintenance regimens are lacking.

Pudendal Neuromodulation

In addition to the sacral and the posterior tibial nerves, physicians can target the pudendal nerves for neuromodulation. The sacral nerve sensory afferent fibers originate in the pudendal nerve, which innervates the pelvic floor muscles, external urethral and anal sphincters, and pelvic organs. Peters et al. [15] performed a retrospective review of patients undergoing tined lead placement at the pudendal nerve via the ischial-rectal approach for chronic pudendal neuromodulation. There were 84 patients with various primary urologic diagnoses, including interstitial cystitis/painful bladder syndrome, urgency/frequency or urge incontinence, nonobstructive urinary retention, and pelvic/bladder pain without interstitial cystitis. Almost all individuals with a history of failed sacral neuromodulation responded to the pudendal lead stimulation (93.2% [41 of 44]). Overall, positive pudendal response ($\geq 50\%$ improvement on the

puddendal lead) was achieved in 60 of 84 participants (71.4%). These are encouraging results that warrant further investigation and suggest that pudendal nerve–targeted neuromodulation may be a viable alternative to SNS.

Technological Development

Since its introduction, Medtronic has made some advancement in the design of the SNS device. The introduction of the tined lead 5 years ago changed sacral neuromodulation from a single-stage open surgery requiring general anesthesia to a two-stage, minimally invasive, percutaneous procedure with local anesthesia. Because there is less lead migration, the permanent tined lead allows for a longer trial period, during which the physician and patient can reprogram the device until they achieve optimal settings. As a result of this extended test period, the technical failure rate has decreased, and the response rate has almost doubled to approximately 80% [3].

The most recent technological development in the InterStim apparatus has been the InterStim II device. The InterStim II received its regulatory approval in 2006. Like its prototype, the InterStim II is an implantable neurostimulator but is 50% lighter and smaller. This change purportedly increases patient comfort and makes the implant procedure easier and quicker for the surgeon [3]. A postmarket, Web-based survey among 11 European experts in urology, gynecology, and gastroenterology evaluated their initial experience with the new InterStim II therapy in 55 patients [16]. The less bulky InterStim II implantable neurostimulator allowed for a tinier incision and shallower pocket (3.5 cm less), which made implantation more tolerable, especially for thinner patients. Moreover, the new device does not require an extension cable, which reduced operative time. The new small iCon patient programmer also offers the patient more flexibility, with four preset programs to optimize the response rate.

Novel Applications

During the past year, several authors reported their experience with sacral neuromodulation in nontraditional patient populations, including patients with neurogenic detrusor overactivity, failed augmentation cystoplasty, and children. A recent article from Italy looked at PTNS as a treatment option for children with lower urinary tract dysfunction [17]. Forty-four children with a variety of urologic diagnoses (including idiopathic OAB, dysfunctional voiding, underactive bladder, underactive valve bladder, and neurogenic bladder) were enrolled in a prospective clinical trial of PTNS efficacy. A total of 25 were female and 18 were male (average age, 10.7±4.8 years). They underwent the conventional 12-week course of PTNS with

weekly 30-min sessions. Follow-up assessment was performed every 6 months for 2 years after treatment. Symptomatic improvement was greater in non-neurogenic than in neurogenic cases (78% vs 14%; $P<0.002$). At 1-year follow-up, the cure rate was greater in dysfunctional voiding than in OAB cases (71% vs 41%), and it remained the same at 2 years. Chronic neuromodulation was required to maintain results in 29% of patients with dysfunctional voiding and 50% of patients with OAB. Thus, PTNS appears to be a viable option for treating pediatric lower urinary tract dysfunction, especially in non-neurogenic cases.

As in the pediatric population, lower urinary tract dysfunction is also common in adults with neurological disease. However, apart from spinal cord injury patients, neuromodulation is not commonly offered to this group of patients. Van Rey and Heesakkers [18•] wrote a review article on the applications of neurostimulation for urinary storage and voiding dysfunction in neurological patients. This article reviewed the use and results of pudendal nerve stimulation, SNS, and lower limb stimulation in patients with neurogenic detrusor overactivity. Some evidence has demonstrated SNS efficacy in treating neurogenic bladder disorders in multiple sclerosis patients, but this population has a chance of negative test stimulation that is four times higher [18•]. Pudendal nerve stimulation via dorsal penile/clitoral nerve stimulation has been shown to benefit spinal cord injury patients by increasing cystometric capacity and inhibiting neurogenic bladder overactivity [19]. The current use of pudendal nerve stimulation is limited by a lack of reliable stimulation technique, as pudendal nerve stimulation via tined leads and surface electrodes is still in the preliminary stages. As a third alternative to sacral and pudendal nerve stimulation, PTNS also has been reported to be effective for a patient population of individuals with multiple sclerosis, myelitis, incomplete spinal cord injury, stroke, and Parkinson's disease [20, 21]. These studies suggest there is significant benefit to neuromodulation among this special patient population that warrants further study.

Part of the advantage of SNS is that it provides treatment for refractory OAB patients without requiring extensive surgery (eg, augmentation cystoplasty). However, some patients have already undergone augmentation cystoplasty and continue to suffer with OAB symptoms. Rasmussen et al. [21] reported on their case series of two such patients who were treated with sacral neuromodulation. One patient continued to void every 30 to 60 min despite medical therapy, intravesical treatment with BoNT-A, and augmentation cystoplasty. This patient ultimately underwent staged sacral approach implantation and was able to wait 3 h between voids during the trial period. She had durable improvement at 14 months of follow-up after the second-stage implantation. The second patient had undergone a supratrigonal ileocystoplasty but still voided every 1.5 h

with volumes ranging from 50 to 220 mL. After her staged sacral neuromodulator implantation, she was able to wait 3 to 4 h, and her voided volume ranged from 300 to 500 mL. Her improvements have persisted with a follow-up of 17 months. Both patients had videourodynamics as part of their preoperative assessment, which demonstrated good compliance and capacity. This case series indicates that SNS may be an important adjunctive therapy for patients with truly refractory OAB despite bladder augmentation.

Conclusions

During the past year, the literature regarding neuromodulation for treating OAB has focused heavily on validating PTNS and pudendal nerve stimulation as reasonable alternatives to SNS. Other significant articles re-examined SNS in terms of safety, efficacy, and cost-effectiveness. The general conclusion is that neuromodulation is an efficacious and safe treatment option for patients with medically refractory OAB. The inclusion criteria for SNS treatment have expanded to embrace the neurogenic and pediatric populations, as well as those who have undergone augmentation cystoplasty. Future efforts should focus on defining optimal treatment and maintenance schedules for less invasive PTNS and reporting the preliminary experience with the new InterStim II device. The current developments in technology and clinical applicability will continue to broaden the field of neuromodulation for urologic patients.

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