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LOWER URINARY TRACT SYMPTOMS & VOIDING DYSFUNCTION (J SANDHU, SECTION EDITOR)

What Is New in Neuromodulation?

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Abstract
Neuromodulation encompassing sacral and peripheral modalities is an established, effective, and safe higher-order treatment option approved in the USA for managing refractory overactive bladder, non-obstructive urinary retention, and fecal incontinence. This review highlights the most recent literature, indications, treatment durability, and the latest innovations in this field. Regarding sacral neuromodulation (SNM), recent work suggests improved parameters for optimal lead placement, increased data to support the lasting effects of treatment, and novel applications of this technology to other pelvic disorders. In addition, there are emerging technologies with smaller MRI compatible devices. Newer data on percutaneous tibial nerve stimulation (PTNS) suggests it may be more beneficial for certain patients. With new technology, implantable tibial nerve stimulators are ushering in a new frontier of nerve stimulation in the comfort of the patient's home.

Keywords Neuromodulation · Sacral neuromodulation · LUTS · PTNS · Tibial nerve stimulators

Introduction

Rooted in evidence-based practices, consensus-driven recommendations on the management of OAB algorithmically progress from the least to most invasive treatment options. Per American Urological Association (AUA) recommendations, third-line therapy includes neuromodulation (sacral or peripheral) and intradetrusor botulinum toxin injection [1]. Neuromodulation is based on the theory that constant low amplitude stimulation directly or indirectly through the sacral nerve roots results in ascending signals to the micturition centers that modulate efferent signals to both the bladder and bowel [2]. The S3 nerve root is a primary target for SNM therapy in that it contains afferent sensory nerve fibers to the pelvic floor and parasympathetic fibers of the detrusor [3]. Contrastingly, posterior tibial nerve stimulation (PTNS) acts via indirect stimulation of these same neural pathways [4]. Stimulation of the tibial nerve can be delivered either percutaneously with a needle or transcutaneously, referred to as transcutaneous posterior tibial nerve stimulation (TTNS). Here we discuss recent developments in the realm of neuromodulation, touching on topics including treatment response durability, new indications for use, and novel technology as it relates to these treatments.

This article is part of the Topical Collection on *Lower Urinary Tract Symptoms & Voiding Dysfunction*

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Sacral Neuromodulation

Since sacral neuromodulation (SNM) was approved by the Food and Drug Administration (FDA), the therapy continues to be a frequent topic among urologic publications regarding long-term efficacy, application to off-label conditions, and ongoing innovations. At the moment, the InterStim™ device (Medtronic; Fridley, MN) is the only FDA-approved implantable SNM device for treatment of refractory urgency urinary incontinence, urgency-frequency, non-obstructive urinary retention, and fecal incontinence. However, newer rechargeable

SNM devices (Axonics SNM system™; Irvine, Ca) may be available soon.

Surgical Technique

The surgical technique of SNM involves placement of a quadripolar lead at the superior medial location of the S3 foramen with a standard transcutaneous image-guided approach, using a tined lead and a stylet. The curved stylet is an innovation from the straight stylet, allowing closer association with the S3 nerve and ultimately a higher percentage of therapeutic success [5]. For lead placement, the goal is to achieve motor responses at low amplitudes (< 2 mA) on all four electrodes. The optimal motor response needed for a successful lead placement continues to be an area of ongoing research. Gilleran et al. argued that obtaining motor responses in less than 4 electrodes does not negatively affect the rates of progressing to full implant or short-term revision rates [6]. Meanwhile, Pizarro et al. indicated that a higher number of electrodes that produced a toe motor response was associated with a lower likelihood of future lead revision while the higher number of bellows responses did not have the same association [7]. Thus, optimization of SNM lead placement is ongoing; however, the high rates of progression to full implant and efficacy for FDA-approved indications have been well established.

Long-term Efficacy of FDA-Approved Indications for Sacral Neuromodulation

The efficacy of sacral neuromodulation has been substantiated by grade A evidence for the treatment of urgency incontinence and urgency-frequency [3]. The InSite trial, a prospective multicenter trial, evaluated InterStim therapy in subjects with overactive bladder (InSite trial) [8•]. Of the 272 patients who underwent full InterStim implant for urgency incontinence, 67% had continued success with an average reduction of 2 leaks a day, and 38% reporting complete continence at 5 years. Of those with urgency frequency, 57% reported therapeutic success, with an average reduction of 4 voids per day. Additional statistically significant sustained benefits were reported in quality of life scores, sexual function in females, depression, and pelvic pain scores.

For patients with non-obstructive urinary retention (NOUR), SNM can be an effective option in restoring spontaneous voiding and decreasing post void residuals [9]. In regard to long-term efficacy, Datta et al. reported sustained efficacy with spontaneous voiding in 72% of 63 patients at 4 years with 50% of patients no longer requiring self-catheterization [10]. Interestingly, Fowler's syndrome as a cause for NOUR has been shown as a positive predictive factor for success with SNM therapy. In 30 patients with Fowler's syndrome, Ridder et al. found that 72% compared with 46% idiopathic NOUR were voiding normally at 5 years [11].

Use of SNM in fecal incontinence (FI) has also been evaluated with long-term studies. Janssen et al. followed 325 patients with FI treated with SNM, of which 197 (52%) had persistent efficacy at 15-year follow-up [12]. A durable response was demonstrated in these patients with average FI episodes per 3-week period decreasing from 16 at baseline to 3 after stage 1, and 1.6 at 15-year follow-up. Patients also more than doubled the amount of time they were able to delay defecation from 2–3 min to 7–10 min.

Expanding Indications for Sacral Neuromodulation

Application of SNM therapy to populations outside the current FDA-approved indications is an area of ongoing research. Included in this is application to off-label conditions such as pelvic pain, constipation, pregnant women, children, and patients with neurogenic bladder.

SNM has been evaluated as a fourth-line treatment option for refractory interstitial cystitis/bladder pain syndrome (IC/BPS) [13]. Gajewski and Al-Zahrani performed a retrospective review of 78 patients with refractory BPS, who underwent trial of SNM at a single institution [14]. The full implantation rate was 59%, with a long-term success of 72% at an average follow-up of 61 months. Application to non-specific pelvic pain has also been described with lead placement varying from bilateral leads through the sacral hiatus to leads placed at the pudendal nerve, S3, S4, or hypogastric nerve roots. In a review of 64 patients who underwent SNM for pelvic pain, 32 who had the device implanted reported improved pain control and quality of life [14, 15].

Constipation is another area where off-label use of SNM has been trialed. A Cochrane systematic review from 2015 noted limited studies on this population and reported no significant improvement to fecal frequency in the one crossover trial comparing SNM with sham stimulation in 59 patients with refractory constipation [16]. This experience was not reproduced in several studies that applied this therapy to children and adolescents. Van der Wilt et al. reviewed their cohort of 30 children and adolescents (mean age 16) with functional constipation who underwent treatment with SNM [17]. A full implant was pursued in 27, and the mean defecation frequency in this cohort significantly increased from 2 per week to 6, which was sustained in 43% of patients at up to 22-month follow-up. Failure of SNM alone occurred in 15 patients, with 9 requiring SNM combined with medical management, and 6 requiring total colectomy. In a systematic review of 7 studies of SNM use for FI and constipation in children, all studies suggested an improvement in constipation refractory to medical management with persistent improvement seen at the longest interval of 2 years. However, the rate of complications was between 17 and 50% in all studies [18].

Currently, SNM is not approved for children with urinary or fecal incontinence; however, given the morbidity of a surgery for these conditions in children, many have been interested in a trial of SNM prior to surgery. Haddad et al. performed a prospective randomized open-label crossover study in 41 children with UI or FI secondary to neurogenic causes which ranged from spina bifida, sacral agenesis, miscellaneous neurologic anomalies, or congenital malformations [19]. A positive response, of greater than 50% improvement, neared 80% for both UI and FI. Sharifiaghdas et al. also attempted sacral neuromodulation in a similar population of 25 children with neurogenic bladder who underwent peripheral nerve evaluation (PNE) followed by a full implant for responders. Of those tested with PNE, 8 went on to full implant with an 85% persistent positive response at 14.5-month follow-up [20].

Adults with neurogenic causes of urinary or fecal incontinence have also been taboo population to trial SNM therapy. However, this may not always be the case. For instance, one barrier to use in neurogenic patients is the restriction related to the compatibility of magnetic resonance imaging (MRI) with InterStim. The current InterStim model II 3058 is approved for head only 1.5 Tesla MRI; thus, current recommendations dictate need for SNM explants for those patients requiring MRI for a non-cranial indication. This is cited as the reason for removal in up to 23% of InterStim removal surgeries with a staggering low number of those patients, 10%, choosing to have their devices replaced at a later date [21]. Several studies have been conducted to indicate that use of MRI with the SNM is safe. An ex vivo phantom model study indicated that the intact system undergoes no significant heating [22]. A pilot study by the same institution had 11 patients receive lumbar MRI with an intact system and no significant adverse events seen [23••]. Thus, perhaps this is one area that will change. Nevertheless, this limitation has led to development of new devices in the industry that are MRI conditional, most notably the Axonics SNM system™. A prospective multicenter post market clinical study of 51 patients with OAB treated with Axonics SNM system™ reported that 32 (71%) were responders at 1 month, and continued with therapy [24••]. Of those patients, 94% continued to be responders at 1 year, with average decrease in urinary frequency from 14 to 8, and incontinence episodes from 2.5 daily to 0.4 daily. Total continence was achieved in 23%. These short-term results are comparable with short-term results with the InterStim™ SNM device. Additional notable differences of the Axonics SNM system™ are a decreased size of the implantable pulse generator and the 1 step surgery with no trial phase through PNE or lead only implant.

Innovative use of SNM therapy in patients with spinal cord injury may also be in the near future. Sievert et al. published a series of 4 patients who had SNM therapy early after their complete spinal cord injury and went on to have no detrusor overactivity or incontinence [25]. The Neurogenic Bladder Research Group plans to replicate this data in a multicenter prospective trial of patients with spinal cord injury [26••]. This is one potential application of SNM that could change our practice in neurogenic bladder patients.

Posterior Tibial Nerve Stimulation

Introduced in 1999, PTNS was approved by the FDA in 2000 and the National Institute for Health and Clinical Excellence (NICE) in 2009 as an office procedure to treat OAB. These recommendations are based on grade A evidence that PNS is effective and safe for treating idiopathic and neurogenic OAB [27, 28].

Treatment Durability

Despite evidence of PTNS's success in managing OAB, questions remain as to its practicality, the duration of response, and predictors of success. Rostaminia et al. retrospectively evaluated their series of 162 patients undergoing PTNS and aimed to identify prognostic factors to predict successful treatment [29]. On multivariate analysis, patients responded better to PTNS if they had a history of depression or anxiety and worse if they had a history of hypertension, prior intradetrusor botulinum toxin injection, or SNM. Predictors of treatment success ($\geq$ 50% symptom improvement) included moderate to severe urgency incontinence at baseline or a history of depression or anxiety. Predictors of PTNS failure were severe nocturia ($\geq$ 3 episodes) and higher maximal detrusor pressure (cutoff not identified). Despite limitations, lack of voiding diary data and the requirement that participants complete, not just attempt, a 12-week PTNS trial, we are provided some evidence that PTNS treatment may be more successful in certain patients.

In the setting of a successful PTNS trial, maintenance treatment approximately once every month is required to sustain results [30, 31]. That being said, a large portion of patients discontinue therapy over time. In the OrBIT trial, 28% of participants withdrew after 1 year [27]. In the STEP trial, attrition was even greater (42%) at 3 years [32]. Salatzki et al. aimed to characterize patient factors contributing to return for PTNS maintenance therapy after completion of a successful 12-week course [33••]. Enthusiasm for PTNS waned on follow-up among patients who technically responded but did not pursue maintenance therapy, 64% of whom reported an inadequate durability, poor quality of life (QOL), and social continence improvement. Comparatively, patients seeking maintenance were much more likely to perceive a benefit to treatment and objectively had more improvement in their

nocturia symptoms. Factors related to obtaining treatment (i.e., transportation, distance traveled, time commitment) did not contribute to pursuing maintenance therapy.

These data were echoed by Sirls et al. who have also reported that the most common factor for non-compliance with maintenance therapy is a lack of perceived efficacy [34•]. In their series of 105 patients, they also noted that factors like copay, employment status, and distance traveled to the clinic did not predict progression to maintenance therapy. Both studies reaffirm that the logistical and financial resources needed to participate in PTNS do not affect compliance.

Transcutaneous Tibial Nerve Stimulation

Given the above-mentioned challenges of PTNS, TTNS provides an alternative approach to the same treatment that may be more manageable and comfortable for many patients. Ramirez-Garcia et al. sought to compare PTNS and TTNS by performing the first prospective, randomized comparison in patients with OAB [35]. All patients were assigned to undergo 30-min sessions with either modality weekly for 12 weeks. In 68 consecutive patients, TTNS was found not only to be non-inferior but outperformed PTNS (− 1.2 vs. − 0.4 voids/day, $p = 0.06$). While 24-h frequency and urgency episodes and daytime frequency improved in both groups, the results were only statistically significant in the TTNS cohort. These results favoring TTNS were particularly promising given the regimen tested was used for direct comparison with PTNS without capitalizing on the main advantage of TTNS, namely that it can be performed at home by the patient with much more flexibility in frequency and duration of therapy. Given these findings, it can be suggested that the difference in response would be greater in the setting of more typical daily TTNS regimens. Indeed, it has also been suggested that daily PTNS may be more effective than weekly therapy [36].

Booth et al. further highlighted the state of the literature on TTNS in a recently published meta-analysis of 13 studies (10 randomized controlled trials and 3 cohort studies) assessing its use in both idiopathic and neurogenic OAB [37]. The overall efficacy of TTNS was difficult to assess. All of the studies varied regarding their procedures, metrics, and outcomes, limiting the investigators' ability to pool data. Resultantly, Booth et al. do not draw conclusions or make any definitive recommendations based on the data at hand, citing a "limited quality of evidence". In most of the studies, the risk of bias was either unclear or high, and the heterogeneity in numerous aspects of the studies, particularly in how TTNS was administered, makes direct comparisons a challenge. The current data infers efficacy, but at this time, TTNS cannot be recommended for incorporation into standardized guidelines.

Non-urinary Applications

Given the breath of the innervated region affected by neuromodulation, the benefits of PTNS treatment are not specific to alleviating voiding dysfunction alone. The therapy has been evaluated for application of other pelvic ailments. Recent literature has expanded on its use for treating fecal incontinence (FI), postoperative ileus, and sexual dysfunction.

The application of PTNS in treating FI was first proposed in 2003 and listed as an effective treatment by NICE in 2011 [38]. Hidalgo-Pujol evaluated the use of PTNS in treating FI prospectively between 2012 and 2014 in 56 patients with symptoms mainly from an obstetric injury or colorectal surgery [39]. Patients were followed for 2 years after undergoing 16 sessions: weekly 30-min treatments × 12, then biweekly treatments × 4. No maintenance therapy was offered. After the treatment course, 41% of the patients noted a positive response, defined as > 50% symptom improvement. The treatment was most effective in patients with mild incontinence (46% vs. intermediate, 31.2% and severe, 25%) and urge incontinence; it was least effective in those with mixed and passive FI. Success was independent of age, gender, or FI etiology.

Simillis et al. compared SNM with PTNS in treating FI. In a systematic literature review of approximately 300 patients, each study individually noted improvement in both treatment modalities without any significant difference in efficacy [40]. However, SNM was superior to PTNS in Wexner score reduction and improvement in weekly FI episodes (mean difference, 2.3 and 8.1 episodes, respectively; $p < 0.01$). In addition, SNM showed greater improvement in Fecal Incontinence Quality of Life (FIQL) domains of coping and depression as compared with PTNS. No differences in safety or adverse events were noted. The authors rightfully note that despite these findings, the results should be interpreted with caution. The meta-analysis was not appropriately powered to definitively compare SNM with PTNS for FI. Additional research difficulties that plague many PTNS studies include variability in protocol, follow-up time, metrics, and FI etiology, making data pooling a challenge.

In a pilot study, Venara et al. investigated the use of TTNS on the return of GI function following a colectomy or high anterior resection [41]. Interest in this application stemmed from previous literature that suggests SNM can reduce inflammation in cases of proctitis [42]. No differences were noted in GI motility recovery, incidence of postoperative ileus, first passage of flatus, or hospital length of stay. The treatment was well tolerated, and no adverse events were documented. Moving forward, the expectation is to design an appropriately powered study to further assess this indication for TTNS use.

Some studies have noted that women undergoing PTNS for the treatment of urinary symptoms also report improvement in

sexual function, specifically with sexual arousal, desire, lubrication, and orgasm [43]. Zimmerman et al. further evaluated these anecdotal findings in a rat model. Using vaginal blood flow as a surrogate for female sexual dysfunction (FSD), tibial nerve stimulation with a bipolar nerve cuff revealed that a majority of stimulation sessions (76%) led to a 500% increase in vaginal blood flow [44]. This increase was within 30 min of stimulation. When applied to human subjects, another study sought to assess the effect of TTNS and dorsal genital nerve stimulation in women suffering from female sexual dysfunction (FSD) without any urinary complaints [45]. These data noted a Female Sexual Functioning Index (FSFI) score peak increases (6.7 points) at 12 weeks of treatment. This level of improvement exceeds that of the FDA-approved filbaserin—5.3 points compared with placebo [46]. A marginal decrease in efficacy was noted 6 weeks after treatment was discontinued, suggesting necessary maintenance therapy to sustain results. All in all, however, these findings suggest a possible future role of PTNS in treating FSD.

Implantable Tibial Nerve Stimulators

Attempting to improve the efficacy and success of PTNS, implantable tibial nerve stimulators have been developed. Like TTNS devices, implantable stimulators reduce the level of in-office commitment PTNS requires, while conceptually improving treatment compliance and long-term use. Short-term data has suggested that implantable tibial nerve stimulators may reach maximal efficacy on the order of weeks as compared with months with PTNS and are equally well tolerated.

The first device in this category to provide outcomes data was the RENOVA iStim™ system (BlueWind Medical Ltd.; Herzliya, Israel) [47]. This device is composed of 3 parts: the implant—consisting of an electrical power receiver and two bipolar electrodes; the external control unit (ECU)—a band worn around the ankle during treatment to control and adjust therapy; and the Physician Programmer (PP)—a remote to communicate and transfer data to the ECU. The device may be placed in the office under local anesthesia 5 cm above the medial malleolus and rests superficial to the fascia to which it is sutured. Treatment begins 1 month after implantation. The regimen involved one 30-min treatment session six times a week for 3 months followed by 3 treatments a week for another 3 months. After 6 months of treatment, 70.6% of patients reported > 50% improvement in objective study endpoints (urgent voids or leaks), with another 17.6% reporting 30–50% improvement. This is a value comparable with literature detailing the success of traditional PTNS. Furthermore, about 28% of patients were completely dry following treatment. Quality of life metrics (coping, concern, social, and sleeping domains) all showed significant improvement after treatment. Additionally, the device had a low safety risk profile—only 8.3% reported any wound complications. A subgroup that was followed for 3 years demonstrated a stable, durable response. In an Intention to treat (ITT) analysis, 75% maintained > 50% improvement in OAB symptoms, and 50% had > 50% improvement in urge incontinence episodes [48••].

Similar short-term success has also been reported with the competing eCOIN™ (Valencia Technologies Corp.; Valencia, CA) [49••]. Unlike the RENOVA iStim™, this device has a power source that does not require an external apparatus to be applied to the ankle during stimulation and therefore would need to be exchanged periodically. Contrastingly, the device provides an automatic 30-min treatment session for 12 weeks and subsequently every 15 days afterwards. Seventy-one percent of participants reported a significant reduction in urge incontinence episodes with concomitant improvements in QOL metrics and mild adverse events. The most notable difference between these two devices was the procedure time. The eCOIN™ was implanted in an average of 17 min in the office, half the time it took to implant the RENOVA iStim™ (35 min) which in some cases was also implanted intraoperatively.

Taken together, the results of implantable tibial nerve stimulators suggest an effective, safe, and lasting treatment option. In-office implantation and patient engagement with programming and maintenance therapy are major advantages over current approved neuromodulation offerings. However, with the economics of healthcare to consider in today's medical climate, the long-term cost of these novel device platforms will additionally need to be evaluated in order for providers and patients to make educated decisions over which treatment path to take.

Conclusion

In conclusion, SNM is an effective long-term therapy with proven efficacy and safety. Modifications in surgical technique have led to lasting, positive impacts on a patient's conditions and quality of life. Moreover, the treatment success achieved with neuromodulation has stemmed interest in finding new applications for this technology in other pelvic conditions. Moving forward, our current evidence suggests that PTNS may be better suited for some patients rather than others—who exactly remain to be determined, but finances and access to PTNS maintenance therapy have not been shown to adversely affect treatment adherence. Looking forward, implantable tibial nerve stimulators provide a more convenient patient-friendly approach to implementing neuromodulation and have the potential to significantly change the landscape of this discipline.

Compliance with Ethical Standards

Conflict of Interest Courtenay K. Moore, Jessica J. Rueb, and Samir Derisavifard each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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