Chapter

Neuromodulation in Urology: Current Trends and Future Applications

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Abstract

Urological applications of neuromodulation and neurostimulation are among the most evolving fields for these technologies. First approved for management of refractory urge incontinence, different modalities of neuromodulation and stimulation have been tested, applied and verified for a vast spectrum of voiding and pelvic floor dysfunction disorders. The modalities of delivering this treatment have also evolved in the last three decades, with a focus on sacral neuromodulation. The experimental and established "off-label" applications of neuromodulation have also encompassed chronic pelvic pain disorders, including chronic prostatitis and bladder pain syndrome, among others. In this chapter, we discuss all the hypothesized theories suggested on how this technology provides therapeutic potential for a number of chronic and debilitating urological conditions, the modes of delivery be it anterior, sacral, and posterior tibial to name a few, and the evolving and future applications.

Keywords: neuromodulation, sacral neuromodulation, posterior tibial nerve stimulation, lower urinary tract dysfunction

1. Introduction

Neuromodulation in urological practice is not a novel concept, but certainly one that has lagged in dissemination. The first reports of the use of neuromodulation to stimulate bladder emptying date back to as early as the 1970s, although the results back then were disappointing [1]. It was not until 1988 that Schmidt and Tanagho restarted the discussion on applications of neuromodulation and electrical stimulation of the sacral nerve in urology, and since then reports on different novel techniques and applications ensued [2, 3]. The term "neurostimulation" was recoined later to "neuromodulation," as experts in the neuro-urology field argued that electrical currents do not only stimulate but rather modulate the messages carried by different nerves involved in the micturition reflex and the lower urinary tract [4].

1.1 Review of lower urinary tract innervation and processes of storage and micturition

The urinary bladder has both afferent and efferent innervation. Efferent innervation is both sympathetic and parasympathetic. The hypogastric nerve carries postganglionic sympathetic fibers innervated at the inferior mesenteric ganglion

by preganglionic fibers arising from T11-L2. Their main function is inhibition of bladder wall contraction and excitation of the internal urethral sphincter, both necessary to maintain continence and facilitate urinary storage. Parasympathetic efferents which originate preganglionically from the sacral spinal cord through the S2 to S4 spinal nerve roots reach postganglionic fibers in the pelvic plexus and bladder wall and through stimulation of release of acetylcholine act on muscarinic receptors to produce bladder wall contraction.

Afferent innervation from the bladder consists of small myelinated Aδ fibers, which relay information via the pelvic and pudendal nerves to the sacral spinal cord at S2 to S4 about the properties of a bladder contraction, and synapse with spinal interneurons and autonomic fibers constituting what is known as the micturition reflex arc. The interneurons also relay information to higher centers, namely the periaqueductal gray and pontine micturition centers, as well as the hypothalamus, thalamus, prefrontal cortex and angulate gyrus in the cerebrum, among other areas. These centers have a modulatory voluntary control over bladder function and what is perceived by us from somatic sensation in the bladder and pelvic floor, such as sensation of bladder fullness. Bladder afferents also consist of unmyelinated C-fibers which are inactive in normal circumstances but are responsible for transmission of noxious stimuli such as bladder pain and are involved in the development of neurologic lower urinary tract dysfunction [1].

During the phase of urinary storage, information about increasing bladder volume and pressure is carried by afferent discharges that stimulate both the sympathetic and parasympathetic preganglionic fibers. While the stimulated parasympathetic fibers would elicit a bladder contraction, their activity is inhibited by sympathetic discharges at the postganglionic level, which also maintain contraction of the internal urethral sphincter at the level of the bladder neck and contraction of the pelvic floor in response to bladder filling. This coordination of afferent and efferent pathways ensures stable bladder filling and urinary storage and subsequently continence. Beyond a certain threshold of bladder filling, afferent discharges trigger the micturition reflex at the pontine level. This reflex results in inhibition of sympathetic and efferent continence signals and allowance of parasympathetic mediated bladder contractions to facilitate bladder emptying, preceded by relaxation of the urinary sphincters and pelvic floor.

Any interruption at the gross or microcellular level of these neural circuits would result in voiding dysfunction, be it by increased bladder sensation resulting in urinary frequency as is the case in overactive bladder and urgency-frequency disorders, loss of continence as in urgency urinary incontinence, loss of bladder sensation or inability to generate a voiding pressure as in non-obstructive urinary retention, or formation or upregulation of pathological neural circuits for reflex bladder activity or transmission of noxious stimuli such as is neurogenic bladder or pelvic pain disorders.

1.2 Mechanisms of action of neuromodulation of lower urinary tract

Neuromodulation of the lower urinary tract aims to restore lost or dysfunctional neural functions to fulfill the two main functions of the bladder, storage and voiding. Artificial stimulators directly or indirectly apply electrical stimulation that achieves this purpose. Through continuous or intermittent electrical stimuli at different nerves and sites, neuromodulation treats both bladder over- and under-activity, as well as pelvic and bladder pain [5].

The modes by which these electrical stimulations achieve such restoration differ from one type of neuromodulation to the other, and this will be further discussed in each section.

1.3 General indications

Neuromodulation in urology is aimed at control of uninhibited bladder contractions to eliminate sensation of urgency and provide appropriate urinary continence. This is the scenario for overactive bladder disease and neurogenic bladder overactivity. Inability to void resulting in urinary retention is also corrected by neuromodulation, though the literature has been less evident for neurogenic causes of retention versus the established restorative effects on voiding in idiopathic non-obstructive urinary retention (NOUR). Other effects through action on shared nerves between the lower urinary tract and the pelvic floor musculature are less reported on and are yet to be approved, but results have shown consistent alleviation of pelvic pain and sexual dysfunction parameters.

2. Neuromodulation modalities in urology

The spectrum of neuromodulation modalities in urology has evolved yet focuses around two manners that correspond to our understanding of the innervation of the lower urinary tract and pelvic floor muscles: sacral neuromodulation, by sacral anterior root stimulation, sacral nerve modulation and recently pudendal nerve stimulation (PNS) and its derivatives, and less invasive neuromodulators and peripheral nerve stimulators, the most studied of which is posterior tibial nerve stimulation.

2.1 Sacral anterior root stimulation

Though this mode of urological neuromodulation is almost of historical interest in the face of current advances in the field and the dominance of sacral neuromodulation, it yet deserves honorable mention as it paved the way to utilize the sacral region for restoration of bladder function. Through stimulation of the anterior sacral nerve, both bladder parasympathetic efferents and somatic motor fibers to the external urethral sphincter are activated. This ventral activation facilitates intermittent bladder emptying [1].

Brindley in 1976 implanted intradurally and bilaterally on the ventral roots from S2 to S5 subcutaneous cables that were externally powered and would provide on-demand electromagnetic stimulation to facilitate voiding [5–7]. He later modified his procedure by performing posterior rhizotomy at the S2–S3 level during implantation of the stimulator to improve the continence outcome by eliminating the effect C-fiber bladder afferents had on amplifying the micturition reflex. This is what was later named the Brindley procedure, and its popularity phased out years later as more studies and reports demonstrated debilitating and unacceptable complications such as sacral dermatome hyperalgesia, cerebrospinal fluid leak, and damage to the anterior nerve root. The procedure, however, remains indicated for patients with complete spinal cord injury (SCI) with maintained bladder reflexes [1, 7–9].

2.2 Sacral neuromodulation

The first reports describing the application of sacral neuromodulation were by Schmidt and Tanagho, the latter concentrating on its application in neurogenic lower urinary tract dysfunction [2, 3]. Since then, both experimental and approved applications and research aiming to understand the mechanism of action by which sacral neurostimulation, or more appropriately now termed sacral neuromodulation (SNM), affects and rehabilitates the functions of the lower urinary tract, both in facilitating bladder storage and voiding, has expanded. Researchers also embarked

on assessing its efficacy, particularly cost-effectiveness, when compared to other modes of treatment for its indications. SNM is, perhaps, the best studied mode of neuromodulation in urology [5].

Compared to the Brindley procedure, SNM posed numerous advantages and technical differences. The SNM procedure involves extradural electrode implantation usually in one of the paired S3 foramens. It does not require posterior rhizotomy either. This minimized the risks of nerve root injury or cerebrospinal fluid leakage. It provides continuous electrical stimulation to the nerves in its proximity and is controlled remotely without the need for subcutaneous cables as it has a built in-battery and antenna. It also modulates for restoration of normal micturition and suppresses bladder overactivity, which made it applicable to non-neurogenic voiding dysfunctions as well [1, 3].

The first SNM device made commercially available was the Interstim® (Medtronic Neuromodulation, Minneapolis USA). It was first approved in 1997 by the US Food & Drug Administration (FDA) for use in refractory urge incontinence, and later in 1999 its approval was expanded to include significant urgency, frequency, and idiopathic urinary retention. The US market was the most enthusiastic to adopt it, and back then and by the year 2004 15,000 units were implanted, the majority of which were in the USA [10, 11]. Since then, the rates of SNM implantations increased by at least 10 to 20-folds [12, 13].

Sacral neuromodulation is dedicated to the S3 foramen, targeting the S3 nerve root which is identified as the most relevant home for impulses, containing sensory fibers from the pelvic floor and parasympathetic neural fibers affecting the detrusor muscle of the bladder. This differs from the target of other neuromodulation modalities, and provides a distinct pattern of identification during implantation, which will be discussed later [14, 15].

2.2.1 Mechanism of action

The goal of SNM is to modulate abnormal bladder sensations the patient may have, as well as involuntary uncontrollable reflexes in the lower urinary tract to restore the patient's voluntary control and facilitate normal function [16]. The theories on how it actually achieves these goals are vast, and expanding to date, and remain complex. This is perhaps in part due to the sophisticated interaction of higher central voiding centers in the brain and spinal cord and the peripheral nervous system in facilitating the functions of the lower urinary tract.

Investigators have assessed a multitude of concepts, from the molecular neurophysiological level to broader neurocirculatory behaviors in the brain and spine, in both animal models and human studies. Yet to date, no single theorem has been solely agreed upon. Some studies have even shown dual or multiple mechanisms through different channels by which SNM exerts its modulatory effect on the lower urinary tract, partly by studying its different effects in many neuro-urological conditions ranging from bladder overactivity to chronic pelvic pain.

SNM therapeutic effects are speculated to arise through electric stimulation of both afferent and efferent neural circuits in the pelvic viscera and connections with spinal interneurons. The stimulator produces an electrical charge in close proximity to the sacral root nerves, regenerating propagational axonal action potentials in the region. This in turn stimulates somatic afferents which modulate higher center control of micturition including the prefrontal cortex and insula, by restoring normal bladder function and perhaps suppressing reflex bladder activity such as that seen in overactive bladder (OAB). This indirect effect both on the bladder and the urinary sphincter is achieved through adaptive neural plasticity, and thus, an intact neural system, at least distally, is a neural requirement for SNM to successfully restore

bladder function [15–21]. The SNM device can provide different levels of stimulation, which may further modulate efferents to the bladder-sphincter complex; however, it does not have any direct effect on urethral resistance [16, 22].

Several studies have proved that SNM has modulatory effects in the brain. Earlier work has demonstrated stimulatory and inhibitory effects in specific brain regions including those responsible for alertness, sensation of bladder filling, and timing of micturition [23, 24]. Utilizing positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) of the brain, researchers were able to identify decreased function after SNM in areas like the orbitofrontal cortex, angulate gyrus, and thalamus, while stimulating the dorsolateral prefrontal cortex, and the therapeutic effect of SNM corresponded to pre-implantation increased activity in the angulate and inferior frontal gyri, insula and thalamus. Such patterns of activity in the brain were shown to predict response to SNM treatment in females with OAB. Furthermore, investigators were able to show that different SNM stimulus intensities had varied brain responses, which may have differential therapeutic implications [23–27].

On the neurophysiological level, much has been investigated to understand which neural receptors and neurotransmitters may be affected by neuromodulation, SNM in particular. Opiod receptors are shown to be inhibited by SNM, and this inhibitory effect is augmented by tramadol and other opiod receptor agonists [28]. From animal models, blockade of opiod receptors with naloxone significantly reduced bladder capacity during sacral neuromodulation for reflex bladder activity. Blockade of beta-2 receptors, however, showed the opposite response during SNM [29]. Also mediated by opiod receptors are the SNM inhibitory effects of bladder overactivity mediated by supraspinal $GABA_A$ receptors [30].

2.2.2 Indications and contraindications

2.2.2.1 FDA approved indications

The US Food and Drug Administration has approved four main indications for SNM application, three of which are urological: refractory urinary urgency and frequency, urge urinary incontinence (UUI), non-obstructive urinary retention (NOUR), and lastly, fecal incontinence. This has been agreed upon and resounded by multiple authorities including the International Continence Society in their best practice statements, among other bodies [4]. However, FDA approval does not indicate level of recommendation, and authoritarians and experts in the field have built on this approval to debate and set the grade and the line of therapy at which SNM serves for a number of conditions, as well as argue for and against other indications or applications the FDA has not seen the benefit of SNM for eye-to-eye with available literature and results. There are, moreover, conditions that must be met prior to justifying an implantation regardless of the aforementioned indications and contraindications that must be observed.

The International Continence Society (ICS) assessed the evidence available for SNM in different pathological genitourinary conditions and published its recommendations based on available literature. In summary, the ICS panel found grade A evidence to support the efficacy of SNM in overactive bladder and non-obstructive urinary retention including Fowler's syndrome and voiding dysfunction; however, this high level evidence did not change their recommendation of maintaining SNM as a second or third-line mode of therapy in these disorders. For other conditions including interstitial cystitis/bladder pain syndrome (IC/BPS) and neurogenic lower urinary tract symptoms, SNM remained an option based on lower levels of evidence (grade C evidence/level III recommendations) [4, 31].

2.2.2.2 Off-label uses

Although the FDA has not recognized or approved these applications of SNM, there is a growing body of evidence that demonstrates its effectiveness in other genitourinary pathological conditions. In particular are chronic pelvic pain disorders including both IC/BPS and non-IC chronic pelvic pain syndrome (CPPS). Despite lack of availability of high-level evidence, the off-label application of SNM in these conditions continues with variable results in improving associated urinary symptoms and quality of life parameters.

Other non-approved applications of SNM include its use in special populations such as those with neurogenic lower urinary tract symptoms, pediatrics and adolescents, and even in contraindicated situations including continued SNM in pregnancy for women with urological conditions. Most of these applications carry hypothetical risks, a spectrum of which have been refuted in small case series and reports in literature, but bigger studies are needed to elucidate and clarify the role of SNM in these situations.

2.2.2.3 Contraindications

Authorities have agreed on certain absolute and relative contraindications for SNM [4], with exceptions and points up for debate to date in the literature.

Absolute contraindications of SNM are:

1. An inadequate clinical response—this is dictated by the universally accepted cut-off of more than 50% improvement during the test phase of SNM.

2. The patient's inability to operate the SNM device, or lack of caregiver support thereof who could assist in doing so.

3. Pregnancy, and this remains a point of debate across literature, as will be discussed further next.

The *relative contraindications* for SNM therapy, as outlined by many guidelines including the ICS best practice statements, do not preclude use of SNM, but must be vigilantly observed and discussed with the patient prior to embarking on treatment. These include:

1. Severe and/or rapidly progressive neurologic disease with urinary symptoms—in such a state, the patient's foreseeable benefit from treatment, even based on a successful test phase, would be challenged by the changing neurological status or development and progression of the disease.

2. Complete SCI, which would hinder the modulatory effect of SNM in higher nervous centers as discussed earlier.

3. The ongoing recognized or observed need for magnetic resonance imaging (MRI) examination, particularly in patients with established neurological disorders like multiple sclerosis (MS) that may need continued MRI assessment or patients undergoing work-up for other conditions that may need it, particularly non-head MRI examination, which will be discussed further in a separate segment as growing reports continue to argue MRI safety with implanted SNM devices.

4. Abnormal sacral anatomy is a sensible contraindication in which such deformities would hinder the identification of the correct sacral foramens required for optimum effect and implantation.

2.2.2.4 Magnetic resonance imaging

With the exception of head MRI examination, the ongoing or anticipated need for MRI examination for patients is a relative contraindication for SNM implantation [4, 32]. The potential effect of non-head MRI examinations on an implantable metallic device such as SNM have debilitated practitioners and potential patients alike with one series reporting that 23% of device explantations at their center were due to the need of the patient to undergo this examination. This has absurd financial and clinical implications in the face of an effective implantation [33].

In the same series, two thirds of the explanted patients required a change in management post-explantation, including intradetrusor botulinum injections, or to resort to self-intermittent urinary catheterization or even require in one case cystectomy and urinary diversion. Thus, explantation has dire consequences that must be outweighed against the potential need and risks of undergoing MRI especially when over 20% of the patients that were explanted prior to MRI examination ended up not undergoing the imaging test and just over 50% of those MRI results influenced non-genitourinary treatment decision making [33]. Additionally, one cannot help but wonder the number of patients who may have benefitted from SNM therapy had they not been excluded due to prospective need for MRI with better and alternative planning.

2.2.2.5 Pregnancy

It is difficult to design trials to test for the effects of SNM, or any form of neuromodulation or therapy for that matter, when there is a hypothesis of potential teratogenic effect on the fetus, or risk of abortion or premature delivery. Apart from the overridden potential for damage to the SNM system when it was historically being implanted in the anterior abdominal wall, completely posterior SNM implants or their predecessors have not been shown in a number of series and reviews to be associated with any fetal malformations or early deliveries or a higher rate of cesarean sections. These reports are based on pregnant women who against recommendation and electively opted to maintain their SNM devices on during their pregnancies fully or at certain periods and trimesters [34, 35].

Thus, the decision to continue neuromodulation, or to proceed with implantation for a woman who has not completed her family or is actively trying to conceive, remains a debatable and individualized decision, but in accordance with manufacturer recommendations and societal guidelines and until more compelling evidence arises, pregnancy will remain a contraindication for SNM, though more relatedly relevant than absolute [34].

2.2.2.6 Other considerations

Potential interference of SNM devices with other implantable electrostimulators such as cardiac pacemakers has long been speculated. A series of three patients who have cardiac pacemakers and underwent SNM implantation has reported that no interference was observed on the part of either of the implanted devices by the other [36].

2.2.3 Predictors of effect

One of the hallmarks of diagnosis of urinary and voiding dysfunction disorders is the utility of urodynamic testing (UDS). Of different types and modes, this diagnostic test aims at reproducing patient symptoms and correlating them to net intradetrusor pressure, among other parameters, in simulated bladder filling and voiding phases. Much has been disputed about the need for UDS testing to diagnose straightforward and clinically apparent conditions such as overactive bladder, and whether UDS findings could help predict outcomes of therapy including SNM prior to its implantation. However, evidence suggests that no single UDS parameter or finding can predict SNM success [37].

In its best practice statement, the ICS did not find sufficient evidence to support that urodynamic studies can predict outcomes of treatment for SNM, while it supported based on higher level of evidence a stronger recommendation for performing SNM trial phases as the "single most valuable tool" to predict outcome of SNM [4].

Attention has been given to difference in SNM effects between certain patient populations. Gender differences have been long hypothesized, with attention focusing on SNM effects on pelvic floor rehabilitation and its close relatedness to urinary and chronic pelvic disorders in females as a potential modality of effect. In a matched pair analysis, a group of researchers reported on 80 patients who received SNM implants for urge urinary incontinence and found that more women tended to receive implants than men. While urinary frequency and symptom scores improved in both groups, over 3 years, the number of urge incontinence episodes per day improved in men more than women, while the severity of the incontinence improved in women more than men [38]. This gender discrepancy may be explained in part by SNM effect, but perhaps is also due to anatomical difference of the distal urinary tract in men and women.

Another patient population suspected to be at a lesser advantage from SNM efficacy are older patients and those with certain comorbidities such as obesity. Interestingly, one study did not only find no difference in response among older patients but further identified that age correlated with a lower rate of surgical revisions of the implantation—3% lower odds per year. In the same study, BMI did not influence explantation rates [39].

It is undeniable that there are identifiable structural changes in the bladder muscle and wall that incur from long standing overactive bladder and non-obstructive urinary retention, and hypotheses suggest this may affect the therapeutic outcomes of SNM as the symptom duration increases. However, even symptoms extending for more than 10 years have not been shown to have any significant effect on the success of SNM [40].

2.2.4 Results of SNM and its efficacy

SNM has proven an efficacious modality of treatment of different genitourinary disorders, with durable success rates between 70 to 80% in certain conditions such as refractory OAB [11, 31, 41, 42]. In one survey of SNM patients, satisfaction rates were reported to be over 95% with SNM therapy and were not affected by patient age or any complications or program type, a testament to the efficacy of this treatment [43]. The multitude of data in the literature also attests to the general safety of SNM [44].

History of prior back surgery may be deemed a challenging patient condition for SNM implantation, but a review of 500 patients has shown that such a history did not negatively affect SNM outcomes [45]. Even in patients with prior anti-incontinence

surgery and history of pelvic organ prolapse surgery, the efficacy of SNM has been established. Surgeries of the bladder and pelvic floor may slightly affect the outcomes of SNM, however, these remain generally good and acceptable [46].

2.2.5 Cost-effectiveness

The debate continues on what is the cost-effectiveness of SNM compared to other available treatments for refractory voiding conditions be it OAB or UUI or others. These include in general combination medication, intradetrusor botulinum injections (repeated as the effect of one injection wears out necessitating periodic repeat injections), and more definite bladder or anti-incontinence surgeries.

The long term outcomes of SNM compared to the need for maximal medical therapy or repeated botulinum injections poses a cost-effective benefit superior to the aforementioned counterparts, with some authors even arguing that from a patient's perspective it may well be considered an appropriate primary therapy rather than a second or third line alternative [47]. Compared to botulinum injections in particular, SNM was shown in one study to be cost-effective from the third year of application onwards, with a clear dominance should treatment be continued for 10 years [48]. However, results from the ROSETTA randomized trial which compared SNM and botulinum bladder injections for refractory UUI showed SNM as a less cost-effective alternative [49].

Perhaps the arguments for and against the cost-effectiveness of SNM versus other treatments lay not just in the treatments it is being compared to but in terms of what condition these treatments are being utilized for. In a focus article on safety and cost of SNM compared to botulinum injections for OAB, although SNM was costlier, it was safer than intradetrusor botulinum injections. The latter carries a substantial side effect profile including urinary tract infections, hematuria, urinary retention, and more frequent emergency room visits, all not common occurrences, but may tip the scale in favor of SNM [50].

2.2.6 Preoperative assessment and counseling

As with any surgical procedure, preoperative assessment and counseling are of paramount importance. It has been identified that such counseling should include discussions on possible expected side effects and adverse events of SNM therapy, such as implant site pain, infection, paresthesia, and leg and buttock pain. Moreover, the patient must understand that within the spectrum of approved devices in clinical practice, currently the Interstim® device in its two generations, there may arise a need for surgical revision of the implant or ongoing reprogramming atop an eminent and eventual need for replacement of the implantable pulse generator (IPG) once the battery wears out should treatment extend beyond an expected life-expectancy of 3 to 5 years on average. Additionally, and based on ICS recommendations, urodynamic testing is not mandatory, but phase testing is highly recommended prior to embarking on surgical implantation of the SNM IPG [4, 51].

One side effect profile that has been raised in the literature has been the psychological aspects of SNM therapy, though some authors have argued that a reverse pathology is possible with patients with chronic genitourinary and pelvic pain disorders who are potential candidates for SNM are pre-operatively burdened or have pre-existing psychological ailments. As is the limited evidence from some case reports and series, some patients encounter behavioral changes or exacerbation of preexisting psychological conditions such as depression, which has led to the argument of need for psychological assessment of certain traits that may affect SNM outcomes [52]. However, this has yet to be reflected in the guidelines and societal recommendations

and a causality has not been established. On the other hand, other researchers have shown no influence of psychological and psychiatric factors on SNM outcomes [53].

2.2.6.1 General considerations

SNM implantation requires, most commonly, fluoroscopic guidance in the lead placement stage of the procedure to correctly identify the S3 foramen and the depth of lead placement and direction and correlate it with the reflex responses of the patient. Though of ongoing concern, studies have shown that radiation during SNM implantation, be it staged or office-based percutaneous nerve evaluation (PNE), is safe and within the recommended limits set by the International Commission on Radiological Protection [54]. That, however, did not alter an ongoing debate on whether "fluoro-guidance" can be replaced by a less radioactive imaging modality, the ultrasound. Apart from having a far lower radiation exposure profile, if any, ultrasound-guided lead placement was found in one study to lower the number of needle punctures needed to identify the most suitable S3 foramen for patient response; however, that had minimal effects on total operative time [55].

Preoperative antibiotic administration is also advocated in both stages of implantation. The recommended antibiotic regimens should target common skin flora pathogens. Guidelines published by the French Association of Urology suggest the use of amoxycillin or broad-spectrum cephalosporins, and in case of hypersensitivity to these antibiotics, an alternative combination of vancomycin and clindamycin is suitable [56].

2.2.7 Technical aspects and techniques

2.2.7.1 The device: lead and implantable pulse generator

The SNM device consists of a tinned lead, connected to a stimulator, the implantable pulse generator (IPG), by insulated cords. Improvements have been made between the initial and current Interstim II device available on the market, including the tinned lead technology, deflected lead tip, and increased capacity of storage of programming and patient data, among others.

The tines allow for anchorage of the lead and prevent displacement. The quadripolar lead contains four electrical stimulation contact regions or electrodes, which are used to designate four different programmable charges on each region to provide an endless number of possible combinations of modulatory programs for patients for a variety of symptoms and effects. These are under the control of an external programming remote that allows the surgeon or programmer to store certain programs to the system of the patient. The patient can then use their own remote to initiate or shutdown certain programs at different times, or switch off the device all together, as well as control the intensity of the stimulation. An illustration of the quadripolar tinned lead can be seen in **Figure 1**.

The IPG is a battery-dependent neuromodulator that delivers electrical stimulation transmitted via the lead. It has an embedded antenna that receives signals from the operator remote controllers [42].

2.2.7.2 Office-based percutaneous nerve evaluation

This modality of lead testing or screening for possible responses is done in the office setting under local anesthesia and allows assessment of both sensory and motor responses of the patient to stimulation. It can be done under fluoroscopy or ultrasound guidance. It is deemed a less invasive and less resource-intensive testing phase prior to implantation. However, it is more uncomfortable to the patient since

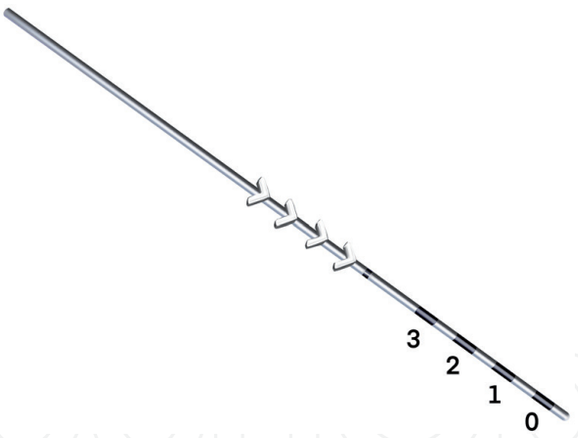

Figure 1.
Quadripolar tinned lead utilized in SNM. Labeled are the electrode positions, "0" being most distal and "3" most proximal. An optimum insertion is eliciting a response on all electrodes at low voltage.

only local anesthesia is being used [57]. As a matter of fact, single-staged implantation after PNE could save US $1500–5000 depending on how high the success rate of the implantation is, an argument well utilized on part of advocates at both ends of the debate of whether to stage or not [58].

Local anesthesia is applied subcutaneously to the mid-sacral region where testing will be performed. In the prone position, a needle harboring a single-electrode lead is advanced to correctly identify the S3 foramen. The S3 foramen can be identified fluoroscopically, or approximated anatomically as evident from cadaveric studies that showed the mean distance of the superior aspect of the S3 foramen is approximately 9 cm from the coccyx, and laterally it is 2 cm from the middle of the sacral back region, while vertical interforamenal spaces are around 1.5 cm in length [59].

The patient is asked to report any sensations felt in the perineal region or the foot, and motor responses are also examined in the buttock region and the ipsilateral foot. Stimulation is then performed at different voltages and the area is marked. Successful office-based PNE is followed by one-stage surgical tinned 4-electrode lead placement and IPG implantation. Motor responses are rechecked during implantation, and location and laterality may be modified to obtain the most appropriate response. This is probably one of the most important disadvantages and arguments against PNE in favor of staged implantation: bypassing a longer assessment or testing period that would reveal more information about the prospective efficacy of the chosen S3 foramen and SNM implant.

The ideal patient for PNE is a cooperative and apprehensive one who can remain relaxed during the procedure. Patients who cannot lay prone for any reason or medical condition, and those who may need more deeper stimulation such as those morbidly obese or anyone with anatomical variations or previous sacral scars may preclude office-based PNE [57]. However, in one study by Gonssen and colleagues, the need for general anesthesia was substituted by a complete permanent SNM implantation under local anesthesia, and was reported to be both safe and tolerable with successful outcomes [60].

Focus has been given in current research and modifications of leads to replace current PNE leads with more functional multipolar leads that would allow a more idealistic response and minimal manipulation of the lead [57].

2.2.7.3 Stage I testing of two-stage implantation

Under sedation or general anesthesia should the patient require it if they cannot maintain an airway in the prone position, staged SNM implantation depends

on a primary stage I of testing done in the operative theater where the tinned lead is eventually implanted after eliciting the best motor response and insulated cord cables are tracked to the contralateral side and eventually out of the skin to be connected to a temporary pulse generator for the testing phase. These cables are later re-tunneled back the ipsilateral side where the tinned leads have been implanted and are connected to the implantable IPG.

This is the method utilized at our center, where we deem it and it has been proven to be more comfortable for the patient in a controlled setting where even sedation can be switched to anesthesia should the patient become restless. Nevertheless, muscle relaxation is not administered to maintain the ability to assess motor response on lead placement and testing. One particular population of patients which are ideal candidates for this mode of testing are morbidly obese patients where local anesthesia administered subcutaneously may not be sufficient for the deep layer manipulation necessary to deliver the lead to the sacral foramens [57].

Some researchers have continuously advocated staged testing and implantation despite PNE being a more resourceful alternative. Arguments included the increased comfort of the patient allows for better identification of ideal patients for therapy and less likely to result in a misleading positive screening but unsuccessful subsequent implantation. It also allows the employment of a longer testing trial period and has the added potential of fine-tuning stimulation parameters. It has been advocated as the ideal modality of screening for responses in patients with NOUR, sensory urgency and CPPS [57].

The two-stage implantation technique depends on a 2–4 weeks arbitrary period of testing for improved responses in patients planned for implantation. This period has been contested in literature, as are the arguments in favor of office-based PNE. The range of reported successful test phases is around 60% [61]. However, the length of this period has been also up for debate. One group of researchers studied a group of patients who underwent stage I SNM implantation test phase and found that the mean time needed to identify potential successful outcomes of the test was 3 days, ranging from 1 to 9 days in total. This was not different between patients implanted for OAB and those for NOUR, and thus they concluded that a test stage I period of two or more weeks may not be necessary [61].

The importance of such an argument lays in the potential morbidities of a prolonged test period, with partially exposed external leads liable for displacement and a possible route for infection, though the literature does not report on either. The length of stage I has been suspected to be a risk factor for SNM implant infections, but the evidence is lacking, and the identifiable association if any may be the result of improper antibiotic regimens or assessment of small sample sizes of patients [62].

Disadvantages of staged screening and implantation include that only motor responses are assessed during lead placement. Sensory responses cannot be assessed in the presence of even light sedation. However, two formal studies have found that motor responses more importantly surpass sensory responses in predicting SNM successful outcomes [57]. These are in addition to the logical added financial and time requirements for testing in the operation theater and the need for anesthesia.

2.2.7.4 Lead placement

In SNM, the lead is placed in the S3 foramen, either on the right or left side, and rarely bilateral lead placement is undertaken. The S3 foramen has been identified to be relevant to the target nerve fibers required to achieve the effect of SNM [15]. Patients exhibit and experience typical motor and sensory responses to lead placement in the S3 foramen, depending on the setting of lead placement under local or general anesthesia. This is further summarized in **Table 1**, along with responses

Foramen	Sensory response	Motor response
S2	Buttock sensation Leg sensation	Foot: plantar flexion, foot rotation Anal sphincter "clamp movement"
S3	Perineal paresthesia or pulling sensation in rectum, scrotum or vagina	Anal bellows "winking" Great toe dorsiflexion
S4	Pulling sensation in rectum only	Anal bellows only without leg or foot movement

Hubsher et al. [63] and Thompson et al. [64].

Table 1.
Expected responses from SNM at different sacral levels.

of adjacent S2 and S4 foramens, which surgeons utilize to correctly identify the S3 foramen and avoid the formers [63, 64].

The placement of the actual tinned lead is preceded by testing or screening using a conductive long needle that is introduced first in the correct foramen, and a conductor is used to elicit the best response possible on the most number of electrodes (optimum being four-out-of-four positive electrodes at the lowest stimulatory voltage possible). Once finalized, a small skin incision around the needle facilitates for the introduction of the tinned lead in the chosen foramen. This tracking is aided by an introducer stylet [42, 63, 65, 66]. **Figures 2–5** show an illustration of the steps on the introduction of the tinned lead and implantation of the IPG, while **Figure 6** shows how the inserted tinned lead looks like and is confirmed to be correctly placed on fluoroscopy.

There is no agreed upon definition of optimal lead placement, and many factors have been speculated to alter placement and SNM outcomes, including position and depth of lead, angle, and deflection (straight, lateral or medial related to the foramen), but none shown to have any relation to SNM outcome. Lateral deflection is the only factor found to be associated with identifying more active electrodes, although the number of active electrodes itself has not been shown to correlate with a better motor response. Thus, the concentration during lead placement especially under general anesthesia should be on identifying the best motor response rather than on anatomical details [67].

In the quest for optimal lead positioning and how to facilitate this process, some researchers have advocated for the use of a curved stylet during the introduction of

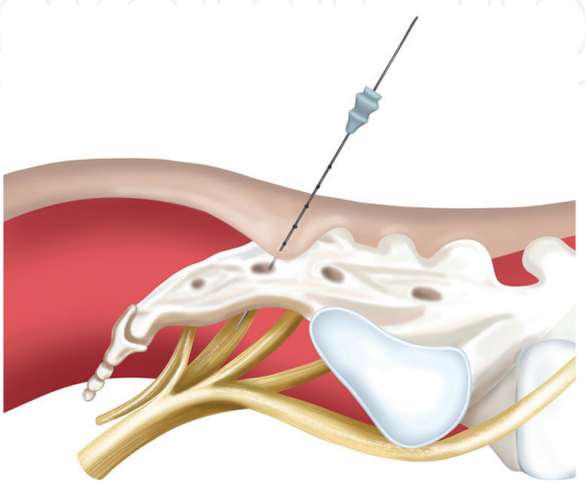

Figure 2.
Test needle insertion into the S3 foramen. The needle position is confirmed fluoroscopically or by ultrasound. An electrostimulation probe is then used in contact with the distal end of the needle to test for appropriate motor responses.

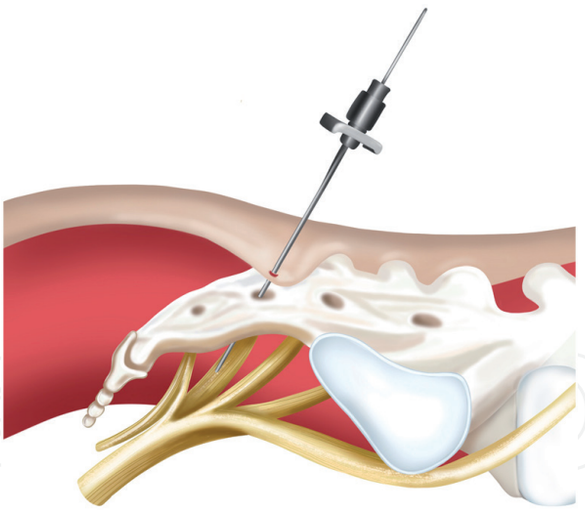

Figure 3.
Introductory stylet inserted in chosen S3 foramen. The stylet guides enclosed lead. Once removed, tines allow for anchorage of lead in proper position.

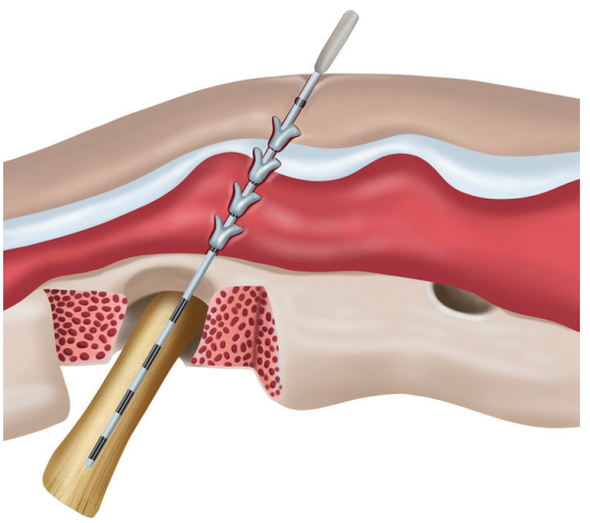

Figure 4.
Tined lead position after removing of stylet and introductory sheath. Note position of electrodes deep to foramen and in proximity to nerve root.

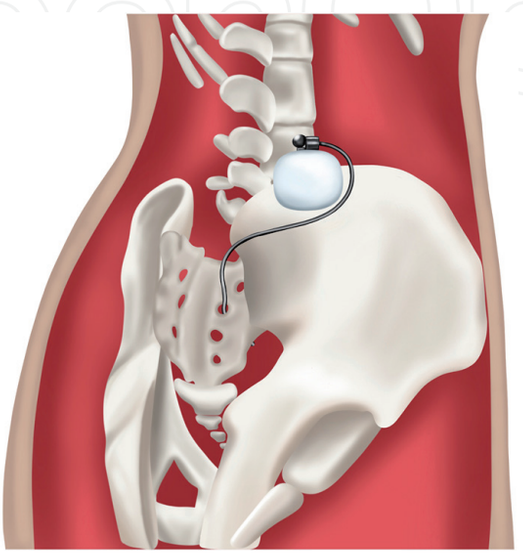

Figure 5.
Final position of implanted pulse generator (IPG) and connections.

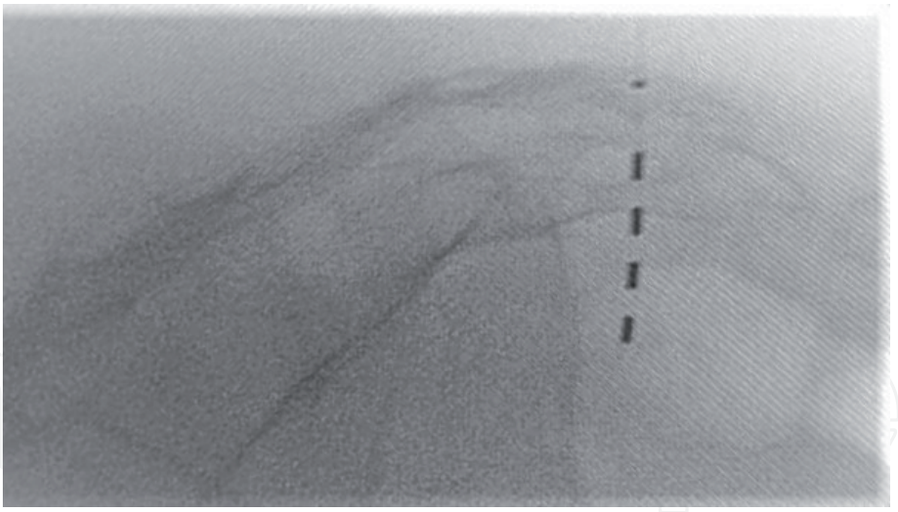

Figure 6.
Fluoroscopic confirmation of position of lead and electrodes in relation to sacral spine.

the tinned lead into the foramen. The tip of this stylet has an 18° bend that allows it to follow the natural pathway of the sacral root nerve. This is thought to allow for identification of an ideal response on all 4 electrodes at low voltage, subsequently providing greater flexibility with programming [68].

During lead placement and testing, the requirement is not only limited to correct identification of the S3 foramen, but also to eliciting the best response from the patient on stimulation at the lowest voltage possible. Researchers have argued for years for unilateral or bilateral lead testing. What is evident from studies to date is that the side that tests with the best motor response (or sensory response if patient can relay it) does not necessarily translate into the best outcome for therapy on the long-term. However, bilateral testing has the advantage of allowing patients to choose the side that they find more beneficial or comfortable [57].

2.2.7.5 Implantation of internal pulse generator/stage II procedure

Implantation of the internal or implantable pulse generator (IPG) can be in the setting of a single-stage along with lead placement following successful PNE testing, or the second stage of a staged implantation after a successful trial period following stage I lead implantation. Regardless of the staging, the IPG is implanted in a subcutaneous pocket on the same side the tinned lead has been placed in the S3 foramen. Sterility of the IPG device must be maintained to avoid acute or chronic infections.

After skin preparation and administration of necessary local anesthesia, a subcutaneous pocket is created under the skin in the patient's buttock. This pocket should be high enough away from the seating area of the patient, and deep enough to avoid superficial sensation of the IPG by the patient as well. Preoperative marking is helpful in such scenarios, keeping in mind distance from the employed S3 foramen as well to avoid tension on the connection between the tinned lead and the IPG. The cord is tunneled from the lead to the IPG subcutaneously and the connections are made. Before wound closure, wash with a sterile water-based antibiotic solution has been described by some authors. It is important to avoid saline-based solutions that may cause electronic malfunction of the device [41, 42, 63, 65, 69].

2.2.8 Post-implantation programming and troubleshooting

Programming is done after IPG implantation when the patient is fully awake and conscious to provide feedback on different modes and programs as they are being

tested and tried out and allows them to choose their preferred settings. At our center this is done on the next day postoperatively and ensues removal of the urinary catheter placed during the procedure to allow for trials of voiding [41, 70]. Patient follow-up is periodic thereafter, during which voiding and stimulation parameters are checked and patient compliance is evaluated [42].

Good communication between the patient, surgeon and the programmer are necessary to obtain the optimum results and efficacy of SNM. In cases where any unforeseeable event occurs, such as sudden loss of efficacy or any of the adverse events that will be discussed as follows, proper testing of the programs and circuit impedance, as well as efforts at reprogramming operational electrodes should be utilized extensively before reaching the morbid decision of revision or explantation [42, 71, 72].

2.2.9 Adverse events and complications

Adverse events associated with SNM are numerous and well-documented. The majority of such events are anticipated and even counseled for preoperatively, with a documented range of 16–30% between the test and final implantation stages. Unanticipated or unexpected adverse events and complications are rare and are limited to isolated case reports and limited series [73].

2.2.9.1 Pain

Implant site pain is pain perceived at the site of the IPG. This could be the result of many reasons. A too-superficial implant may be cutaneously felt and pose a source of discomfort especially if implanted at a lower gluteal point and as such would be "sat on" by the patient. In one review, the most commonly cited reason for explantation was site pain [74]. Another series reported this to occur in 7% of implants, with the majority presenting beyond 30 days of implantation and some associated with trauma.

Another cause of pain could be stimulation program related. Turning off the IPG can differentiate between IPG-related and program-related pain, the latter usually requiring changes in stimulator settings by the programmer [42]. In the most debilitating cases, and often, this complaint would require surgical revision of the pocket or implant [73].

Pain could also be felt at the site where the stimulatory sensation is perceived, and this too, could often be differentiated by turning off the stimulator, and subsequently altering the settings [42].

2.2.9.2 Undesirable change in stimulation

Perhaps one of the most unfortunate adverse events is an undesirable change in stimulation that leads to loss of a successful SNM effect or subjective dissatisfaction with an objectively successful implant. In one series, researchers reported this to occur in 12% of their surveyed adverse events in SNM implants for OAB. The majority of such incidences can be corrected with simple or sometimes more complex reprogramming of the neuromodulator, and rarely requires revision or explantation [73]. However, decrease in efficacy of stimulation is a major reason for reoperation and explantation should reprogramming in absence of lead migration fail to correct the deficiency [42, 75].

Checking the impedance can be useful to assess for any possible lead breakage or dislodgement which would show high impedance, but if the impedance is less than 50 ohms, this may indicate a short circuit that could be due to a wet connection.

Reprogramming electrodes with acceptable impedances could provide a temporary or alternative solution, but lead revision is often necessary [71].

2.2.9.3 Implant infection

In a multicenter retrospective case–control assessment of risk factors for explantation of the SNM device due to infection, researchers reported on an almost 2–3% incidence of infection and identified that hematoma formation and IPG pocket depth of greater than 3 cm were independently associated with development of infection, while implant infection was the leading cause of device explantation at 1 year follow-up in another large trial [68, 73, 76]. The most common pathogen reported on cultures obtained from these explants was the skin flora resident *S. aureus*. Infection is probable both early in the postoperative period within 30 days of implantation, or later beyond 30 days and sometimes up to 10 months post-implantation [73, 76].

Risk factors associated with SNM implantation infection have been studied, and some have been refuted. The choice of preoperative antibiotic regimen is of importance in both stage I and final IPG implant, and the antibiotic administered should target potential and common skin organisms such as *S. aureus* [62].

Prevention of such infections has also been reviewed. One group of researchers reported on the use of an antibiotic-coated collagen layer placed over the IPG before wound closure with noticeable results. Skin preparation is also important, particularly with chlorhexidine-based solutions per international recommendations [62, 68]. And although many surgeons still do administer certain courses of post-implantation antibiotics, this is not supported by any clinical evidence of benefit, though further research may better define its role as is the case with other prosthetic or implantable devices [62].

2.2.9.4 Lead fracture and displacement

Lead fracture, migration or dislodgement are a rare occurrence reported at around 1% of adverse events and eminent needs for device and lead replacements. The introduction of the tinned leads has aided in lowering the incidence of lead migration [41].

Patients may have, against better judgment and counseling, engaged electively in physically demanding exercises, or it may be the result of sudden acute movements or trauma. The result is a sudden loss of or major change in stimulation. On testing, high impedance (>4000 ohms) is found on all 4 electrodes [73]. Additionally, sacral x-ray imaging can help determine if any lead displacement or dislodgement is present. If evident, especially in the presence of complete loss of efficacy and all other alternative reprogramming efforts have been extorted, replacement of the lead is necessary, and sometimes contralateral placement or even bilateral stimulation may be needed, though the latter may not always prove successful [42, 71, 77].

2.2.9.5 Unanticipated adverse events and complications

It is important to understand that although rare, complications are an important predictor of SNM reoperation and may result in severe morbidity [75, 78]. Rare complications of lead placement and implantation have been reported in separate case reports and limited series, including one case of retroperitoneal hemorrhage after SNM implanted for urge incontinence [79]. Another case of lead migration into the sigmoid colon during implantation was complicated by and presented as a colocutaneous fistula [80].

2.3 Direct PNS

As our understanding grew of the neurological contribution and circuits from the sacral nerve roots, new-found focus has been on stimulation of the whole pudendal nerve as it originates from its S2, S3 and S4 nerve roots, and not just the S3 nerve root as with SNM. Theoretically, this should provide a more inclusive sacral nerve stimulation than targeting S3 alone, resulting in inhibition of the micturition reflex and controlling uninhibited detrusor contractions while increasing bladder capacity [14]. This was the hypothesis of the early work on PNS, proposing it would particularly benefit neurogenic bladder patients who fared less successfully with SNM [5].

By placement of both a sacral and pudendal tinned leads in Alcock's canal either tranperineally or through a posterior approach, continuous electrical stimulation similar to SNM is delivered to both nerves [5]. One group of researchers demonstrated comparable improvements in voiding parameters between the PNS and SNM groups, but subjective superiority for PNS reported by patients [81]. PNS was not only found to improve continence but increase bladder capacity in neurogenic bladder patients [5]. Another variation of pudendal PNS is dorsal genital nerve stimulation (DGN), the pudendal nerve's most anterior branch, and this may be the next therapeutic alternative [5, 82].

2.4 Peripheral, cutaneous and minimally invasive neuromodulation modalities

Bypassing the need for formal implantation of any device, these varied modalities of neuromodulation employ concepts on transmitted electrical stimulatory signals from the skin to the nerve vicinity or from peripheral nerves to more central sacral nerve roots and in turn, resulting in a modulatory effect and control on reflex bladder activity particularly bladder hyperactivity, neurogenic or non.

2.4.1 Posterior tibial nerve stimulation

2.4.1.1 Mode of effect

Posterior tibial nerve stimulation (PTNS) provides indirect and retrograde electrical stimulation to the posterior tibial nerve as it passes posteriorly to the medial malleolus of the ankle; the posterior tibial nerve is a mixed nerve with roots from L4 to S3, and as such, provides its modulatory effects on sacral complex roots involved in the lower urinary tract through activation of somatic fibers and inhibiting bladder contractions [1, 15, 83].

PTNS is performed by placement of a needle superoposteriorly to the medial malleolus and a grounding pad placed on the sole of the foot laterally (**Figure 7**). The needle is connected to the stimulator device, and low-voltage stimulation is applied: correct placement is confirmed when flexion of the greater toe is observed and the patient reports sensations from the sole of the foot [84]. Treatment sessions are repeated weekly for a period of 12 weeks and in 30-minute sessions. Repeat session cycles are possible [85].

One of the advantages of PTNS is a "carryover" effect. This has been described as continued symptomatic improvement not necessarily just during the nerve stimulation sessions, which is in contrast to the loss of efficacy when the SNM device is switched off. Many studies have examined the carryover effect and what implications it may have in devising PTNS regimens and schedules, with variable success [84, 86, 87].

Another advantage of PTNS is the fact it can be administered by any healthcare provider or the patient themselves after appropriate training. As a matter of fact,

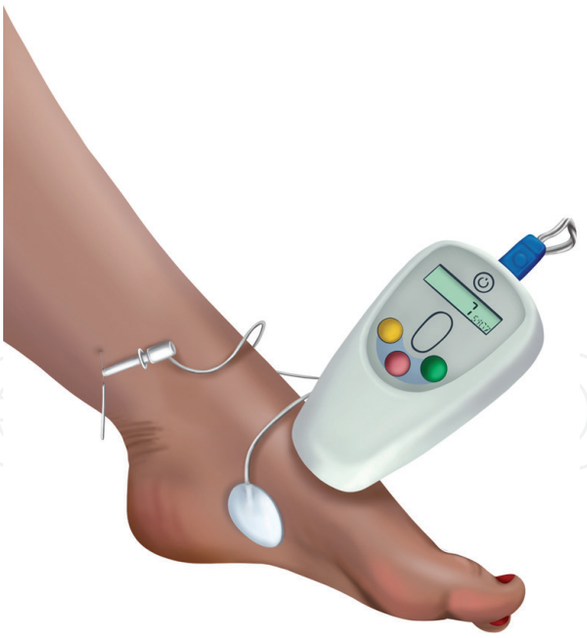

Figure 7.
Posterior tibial nerve stimulation.

home administration systems and micro implants are being developed for that sole purpose [84, 88]. PTNS, too, is less costly than SNM, on average [89, 90].

2.4.1.2 Predictors of PTNS success

In an effort to identify ideal candidates for PTNS treatment in OAB, a number of investigators identified that history of prior SNM therapy correlated negatively with PTNS outcomes. On the other hand, more severe complaints of urge urinary incontinence and urinary bladder volume at first sensation (a UDS parameter) were predictors of PTNS success [90].

2.4.1.3 Efficacy of PTNS

Efficacy of PTNS as evident from review of 4 randomized controlled trials, none of which pinned comparison against SNM, showed a majority of patients were able to achieve at least 50% improvement from baseline complaint; these studies ruled out the possibility of a hypothesized placebo effect, according to the reviewers. A substantial complaint from PTNS treatment was temporary foot pain [74].

Several trials have also compared PTNS to medical treatment of OAB, including the OrBIT trial, and reported comparable if not somewhat superior results with a lower side effect profile, particularly dry mouth and constipation among other side effects associated with anticholinergic medication [85, 91, 92].

2.4.2 Transcutaneous tibial nerve stimulation

Utilizing needles applied transcutaneously to stimulate the posterior tibial nerve, this modality of treatment has been investigated for MS and OAB patients [9]. There are limited studies that demonstrate variable improvements for OAB patients with transcutaneous tibial nerve stimulation (TTNS). Perhaps its advantages stem from its safety and fairly minimal adverse events profile, and its low costs [93].

2.4.3 Transcutaneous electrical nerve stimulation

As the name suggests, this modality is applied to areas in close proximity to target internal nerves. These include the pudendal nerve, be it through transcutaneous stimulation in the vagina in a female or in the perineal region in the male, or both the pudendal and sacral nerves when applied to the sacral skin. DGN is also a form of transcutaneous electrical nerve stimulation (TENS). It is advocated as a less invasive and low-cost neuromodulation system that can also be taught to patients for self-application [5].

Multiple small-sized trials have demonstrated improvements in symptom scores and efficacy in patients with refractory OAB or MS with bladder hyperactivity. However, although it is safe, the durability of its effect has been called into question [9, 94].

3. Neuromodulation applications for urological conditions

3.1 Overactive bladder, urgency urinary incontinence and urgency-frequency syndromes

Bladder overactivity manifests in a number of urinary conditions, depending on the pathophysiology and associated conditions and symptoms. Overactive bladder (OAB), defined by a compelling frequent urge to void, is not a precession of urgency urinary incontinence (UUI), nor is it a more defined form urgency-frequency syndromes: these are all an overlapping number of conditions where evidence of overactivity of the detrusor muscle may or may not be demonstrable, but is subjectively reported by patients and often objectively measurable.

The treatment for these conditions is mainly conservative and medical, be it targeting the bladder muscle or the other offending factors that lead to the overactivity, followed by intradetrusor botulinum injections, which has attained a more defined role in the OAB treatment scheme. SNM is an established mode of treatment for cases of OAB, UUI and urgency-frequency syndromes that are refractory to medical treatment, and despite arguments and established results and testaments, is yet to be designated a more primary or first line place in the treatment of these conditions [95].

3.1.1 Mode of effect in OAB

It has been shown that SNM has an established modulatory effect both on micturition reflexes and higher brain centers. The SNM electrical charging of sacral roots alters neural activity, stimulating somatic afferents that signal to higher brain centers and in part restore normal control over the bladder while also inhibiting certain sensory pathways to suppress reflex bladder hyperactivity. From animal models, evidence suggests this effect is achieved through SNM's inhibition of abnormal sensory input from the pudendal nerve and neuropathological C-fibers, affecting release of μ-opiods and glutamate and suppressing bladder reflexes [16].

3.1.2 SNM efficacy in OAB

Efficacy of SNM is perhaps most studied and evidently reported in refractory OAB [96]. Analysis of five trials have analytically shown significantly higher success rates for SNM in treatment of OAB compared to standard medical treatment, and equally as efficacious as intradetrusor botulinum injections with less side effects

associated with the latter including risk of post-injection urinary retention and urinary tract infections [41, 74].

In one prospectively conducted multicenter trial on OAB patients, the 5-year success rate of SNM was 67%, with the most common adverse event or reason for failure demonstrated to be an undesirable change in stimulation, followed by site pain and ineffectiveness of treatment [97]. The InSite trial reported on one of the longest prospective follow-ups for SNM implants for refractory OAB. At 36-months follow-up, 83% of implants were found to have sustained efficacy [68].

3.2 Non-obstructive urinary retention and Fowler's syndrome

Non-obstructive urinary retention (NOUR) is one of the main indications for SNM therapy. It denotes an unidentifiable mechanical cause that may obstruct urinary outflow from the urinary bladder, resulting in urinary retention. It may be the result of an established neurological disease, as is the case in the acute phase of spinal shock after spinal cord trauma, or in a minority of MS patients. Neither of these conditions are indicated for SNM treatment. However, chronic or recurrent urinary retention in a "neurologically-intact" patient is.

One form of NOUR is termed Fowler's syndrome after the neurophysiologist Professor Clare J. Fowler who first described it in 1985. It is a cluster of symptoms and findings identified in a typically young woman with unexplained urinary retention, increased electromyographic activity of the external urinary sphincter and its failure to relax, and some associations to other female syndromes have been described including polycystic ovaries. Application of SNM in these patients has been shown to restore normal voiding activity [98].

3.2.1 Mode of effect

Researchers have used a number of animal models to establish the mode of effect SNM exerts in NOUR and Fowler's. Basic science evidence suggests that by blocking the inhibitory effect that abnormal afferent activity from the external urethral and anal sphincters has on micturition, restoration of the ability of the patient to void occurs. This stimulation is through blockade of the pudendal nerve's stimulatory effect of the micturition reflex [99].

3.3 Neurogenic lower urinary tract dysfunction

Lower urinary tract symptoms resulting from neurological disease are varied, and thus, determination of these symptoms and assessment is necessary before consideration for neuromodulation as not all symptoms would be ideally treated using this modality. Neurological diseases that have documented voiding dysfunction elements include SCI, MS, Parkinson's disease, cerebrovascular accidents, and diabetic neuropathy. Congenital neurologic disorders such myelomeningoceles are becoming apparent causes of voiding dysfunction in adults and SNM candidates, as management of these pediatric disorders improves, and these patients grow into the adult population [9].

Previously thought to lack efficacy in neurogenic LUTD because of lack of an intact nervous system, SNM is emerging as an efficacious therapeutic modality for this population of patients especially in reducing incontinence episodes [9, 100–104]. The concept of neural remodeling as a hypothesized effect of SNM has also been visited as a potential role in neurogenic LUTD, particularly in acute spinal shock phases [9, 104].

The ICS recommends SNM as an option for control of urinary symptoms in patients with stable neurological conditions who are at a low risk of developing

upper tract deterioration from controlled voiding [4]. It is thus important to stress the need for proper assessment and continued evaluation of these patients as urinary retention, acute or chronic, could have consequences including urinary tract infection and renal failure [9].

3.3.1 Spinal cord injury

SCI, especially complete transection, has long been accepted as a contraindication for sacral neuromodulation on the basis of a disturbed neural circuit. However, numerous reports have been reviewed that show promising results for SNM in the management of neurologically-stable SCI patients, even those with complete disruption [105]. In the acute phase of spinal shock where the bladder is atonic, SNM has been found to facilitate neurogenic remodeling as researchers theorize and demonstrate sustained SNM effects and remodeling in the brain [9, 104].

In a review of eight studies where SNM was employed in the management of lower urinary tract dysfunction in SCI patients, the success rate of the test phase was a shy 45%, but that later translated into a 75% success rate once the screened patients proceeded with IPG implantation. The treatment was well-tolerated and safe without any unexpected adverse events [106].

3.3.2 Multiple sclerosis

MS is of special interest to neuro-urologists as the disease manifests with a spectrum of urinary symptoms and progresses with different patterns in this spectrum along the course of the disorder as well. Demyelination, the pathological hallmark of MS, eventually affects lower urinary tract nerves, resulting in dysfunction. Up to 80% of patients show neuro-urological symptoms within 10 years of diagnosis, most frequently bladder overactivity. As a matter of fact, voiding dysfunction is the first sign of the disease in up to 10% of patients [107].

Though not FDA approved, neuromodulation has been applied in MS patients for years, and its efficacy has been repeatedly demonstrated. SNM and PTNS have been shown in a number of series to decrease urinary symptoms and improve the quality of life of MS patients who demonstrate bladder overactivity; however, although SNM is approved for NOUR, it has not shown any benefit for MS patients demonstrating "hypoactive" urinary bladders with retention [107, 108].

What remains an important issue for MS patients being considered for SNM is appropriate patient counseling and communication with their treating physician or neurologist to assess the need for MRI examination in the future as well as stability of the disease, as disease progression and relapse would negatively affect the SNM outcomes [9, 105, 107].

3.3.3 Diabetic cystopathy

Diabetic cystopathy is a condition that describes the neuromuscular effect long-standing diabetes has on the urinary bladder. Part of the condition stems from diabetic neuropathy, while another part may stem from vasculopathy affecting the detrusor muscle itself. In the application of neuromodulation to the control of overactivity symptoms resulting from diabetic cystopathy, promising results from series were overshadowed by a substantially higher than average rate of infections (17%) compared to the accepted average, as would be expected from any foreign body implantation in diabetic patients especially those with poor glycemic control [105].

3.4 Special populations and effects

3.4.1 CPPS and IC/BPS

Chronic pelvic pain syndrome in males and its predominantly female counterpart interstitial cystitis/bladder pain syndrome are chronic conditions of pelvic pain and voiding dysfunction with a poorly understood etiology [109]. Off-label use of SNM in the treatment of these disorders is established with significant results, and similar to its unknown etiology, the way SNM provides subjective and objective improvements in bladder pain syndrome for example is yet to be clearly defined, with obvious differences in outcomes between IC/BPS and non-IC/BPS CPPS [110].

Many theories have been suggested for this mode of effect, from restoration of balance between excitatory and inhibitory signals in the pelvic plexus at different spinal levels as well as SNM's modulatory effect on bladder function and in turn pain. Another issue for consideration is the bilateral or multiple sacral root involvement in bladder and pelvic pain disorders, thus S3 stimulation may be insufficient to providing symptomatic relief, and some researchers have demonstrated efficacy of bilateral stimulation [14].

A multitude of studies and researchers are reporting on promising results for SNM in symptomatic management of CPP disorders, demonstrating improvements in pain indices and quality of life measures particularly relating to improvements in sleep, social life and sexual activity [110, 111]. With 10% of patients of IC/BPS reaching a severe stage refractory to conservative and other modes of management, SNM has found an emerging role in the therapeutic void for this condition. Success rates of SNM in IC/BPS have been reported to be high, north of 80% in some series, with apparent and significant objective improvements in pelvic pain and specific interstitial cystitis symptom scores as well as improvements in daytime frequency, nocturia, urinary urgency, and average voided volume [112].

The ICS based on grade C evidence released a level III recommendation that designates SNM as an option for patients who are deemed non-responsive to conservative treatment measures of IC/BPS and non-IC CPPS [4]. However, large randomized controlled trials are lacking, perhaps in part due to the mixed spectrum of CPP disorders, both pathologically and symptomatically, heterogenous patient population, and unclear etiologies, and poorly understood differences in outcomes between the disorders [109, 110, 113].

3.4.2 Sexual function

The effects of neuromodulation, particularly SNM, on improving sexual function among female patients, and male patients to an extent, are becoming more evident in the literature [114]. Dysfunction of the pudendal nerve, an important nerve in sexual stimulation, has been demonstrated in both refractory OAB and NOUR [115].

In a cohort of female patients who received SNM implants for OAB, urgency-frequency syndrome or NOUR, improvements in both female sexual function index and quality of life indices were reported, though they were not correlated [116]. In another study on SCI female patients who had sexual dysfunction, there was a demonstratable improvement in the female sexual distress scale after neuromodulation therapy [117].

The argument is whether the improvements SNM provides with regards to urinary symptoms allows for a better sexual experience and confidence among patients or does SNM's effect on the pelvic floor musculature rejuvenise sexual function.

This argument is important in current applications and future considerations of neuromodulation for the treatment of sexual dysfunction. This was demonstrated in reviews of studies where sacral neuromodulation was employed in the treatment of neurogenic lower urinary tract symptoms and had demonstratable and maintainable improvements in erectile function indices to almost normal levels in a majority of patients after up to 3 years of follow-up [118].

On the contrary, another study assessing for pudendal nerve dysfunction in female patients who received SNM for refractory OAB or NOUR showed nonsignificant improvement in sexual dysfunction indices, and the authors found that these improvements as well as others in quality of life measures were in part due to improvements in urinary function; this finding was supported by a recent review [115, 119].

3.4.3 Neuromodulation in children and adolescents

Scarce data, changing anatomy and somatic growth, physical activity, high reoperation rates, and neurologic instability and disease progression: all are valid arguments against application of SNM in children and adolescents. However, data is emerging on its off-label use, with modest responses. In a single center experience on eight children and adolescents with congenital lumbosacral and traumatic spinal cord defects and lower urinary tract dysfunction, the initial response rate to SNM application was 85%. This translated into a sustained efficacy in 50% of patients on 14-month follow-up, and three patients were able to abandon self-catheterization completely. These results, although on a heterogenous and small cohort of young patients, are promising and could defy the current status quo [120, 121].

Nevertheless, based on lack of evidence and limited studies, the ICS best practice statement stressed that the safety of SNM in this population cannot be established, highlighting the technical challenges associated with anatomical variations and difference in children and effects of somatic growth [4].

4. Future directions and research

4.1 Further evaluation of effects of neuromodulation in urology

Basic science research is still ongoing and perhaps still early in deciphering the exact mechanism of action of neuromodulation in restoring and normalizing bladder function. The different levels of speculated effect, in higher brain and spinal centers and in the more distal micturition pathways and reflex arcs make for a vast field of investigation, as well as the interplay of different neural and cellular messengers.

A better and clearer understanding of all factors involved would definitely allow for the optimization of patient outcomes, including most suitable candidates, duration of symptoms, and required concomitant medication, if any, that would maximize the benefit from different neuromodulation modalities. This is of particular importance when conflicting data on different effects on receptor pathways and modulated areas in the brain continue to emerge, and the definition and descriptions of the mechanisms of action are updated.

4.2 Rechargeable and MRI-compatible systems

SNM, like any battery system, faces depletion. Thus, a rechargeable system is one of special appeal. Perhaps one of the most appealing arguments for upcoming

rechargeable systems is the fact it may potentially eliminate replacement surgery. The Relax-OAB study investigated the Axonics r-SNM system, a rechargeable SNM system granted post-marketing permission in Europe in 2016 and is under FDA assessment. Designed to last 15 years with charging requirements for 2 hours every 1–3 weeks, it has shown comparable objective improvements of up to 91% [83, 122, 123]. The Axonics system and the next generation InterStim Micro could revolutionize sacral neuromodulation durability.

The growing need for MR-compatible systems is not a wishful thought, but in the face of evolving biomechanical technology and a growing population that needs both SNM and regular MRI assessment, it seems sensible that the development of such devices is just a matter of time [14].

4.3 Closed-loop neuromodulation

Casually described as a system that "listens to the patient" closed-loop or functional stimulation is a mode of conditional electrical stimulation that is being investigated as a potential neuro-prosthesis that senses bladder fullness, detects bladder contractions, and eventually modulates an electrical response "blindly" without the patient having to actively control their micturition habits. To date there are a number of animal and limited human trials on a set of intelligent electrodes specifically designed to fulfill this purpose. The advantages of such a system are numerous, mainly bypassing chronic stimulation and subsequent bladder muscle fatigue through improvements in warning time for impending bladder contractions, as well as a more natural control on voiding and improved SNM battery life [83]. Many investigators have also looked into improved neurological and bladder pressure sensors as a modality for functional stimulation.

4.4 Expanding indications and revisiting limited applications

Thirty years into its first reintroduction, it is still surprising how limited the indications for SNM in particular remain in the face of accumulating evidence, albeit from small trials restricted by a small pool of patients and candidates. Off-label use of SNM in chronic pelvic pain syndromes, pregnant women, children and neurogenic bladder patients should be the priority of authoritarian bodies to promote research and insight especially when treatment of such conditions could have remarkable effects on the quality of life of those affected [124].

4.5 Dorsal genital nerve stimulation

Though an existing technology, this direct PNS variation has further potential to modulate the combined sacral nerve roots that the former effects without the need of a sacral lead. Utilizing a percutaneous prepubic electrode placed on the clitoris to temporarily deliver electric stimulation and subsequently modulate the dorsal genital nerve, the anterior terminal branch of the pudendal nerve, this technology has been tested in small scale trials with promising results.

Hypothesized to exert its effect through inhibition of bladder efferents, particularly parasympathetic pathways via vesical ganglia and detrusor smooth muscle, the dorsal genital nerve is stimulated using an external pulse generator, and has been shown to reduce urgency incontinence episodes in a number of patient cohorts. However, the device is still not appealing due to lead migration and difficult controls, improvements on which would surely stir further interest among physicians and patients alike [82].

5. Conclusion

Urological applications of neuromodulation are both established and evolving and are among the most dynamic fields for this modality of electrical stimulation. The safety and efficacy of sacral neuromodulation and posterior tibial nerve stimulation in refractory overactive bladder syndrome are high. Other indications of sacral neuromodulation include non-obstructive urinary retention including Fowler's syndrome and urgency incontinence as well as frequency-urgency syndromes. Minimally invasive and broader neuromodulation targets provide an opportunity for improving neuromodulation outcomes, as well as potential advances in the device itself.

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