# Current advances in neuromodulation techniques in urology practices: A review of literature

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## ABSTRACT

Neuromodulation has become a valid therapeutic option for patients with various lower urinary tract disorders. In clinical practice, the most used and recommended neuromodulation techniques are sacral neuromodulation (SNM), pudendal neuromodulation (PN), and percutaneous tibial nerve stimulation (PTNS). There are many theories concerning the mechanism of action of neuromodulation. Although SNM, PN, and PTNS show their activities through different nerve roots, all provide central and peripheral nervous system modulations. SNM has been approved for the treatment of overactive bladder (OAB), nonobstructive urinary retention, and fecal incontinence, while PTNS has been approved for OAB treatment. However, they are also used off-label in other urinary and nonurinary pelvic floor disorders, such as neurogenic lower urinary system disorder, interstitial cystitis, chronic pelvic pain, and sexual dysfunction. Minor and nonsurgical reversible complications are usually seen after neuromodulation techniques. In addition, in the last few years, there have been various developments in neuromodulation technology. Some of the examples of these developments are rechargeable batteries with wireless charging, improvements in programing, less invasive single-stage implantation in outpatient settings, and lower-cost new devices. We performed a literature search using Medline (PubMed), Cochrane Library, EMBASE, and Google scholar databases in the English language from January 2010 to February 2021. We included reviews, meta-analyses, randomized controlled trials, and prospective and retrospective studies to evaluate the activities and reliability of SNM, PN, and PTNS and the developments in this area in the last decade based on the current literature.

**Keywords:** Cystitis; implantable neurostimulators; interstitial urinary bladder; overactive; sexual dysfunctions; urinary bladder.

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## Introduction

The most commonly utilized neuromodulation techniques are percutaneous tibial nerve stimulation (PTNS), pudendal neuromodulation (PN), and sacral neuromodulation (SNM).[1,2] The Food and Drug Administration (FDA) has approved the use of SNM in the treatment of pharmacotherapy-resistant overactive bladder (OAB), chronic nonobstructive urinary retention (NOR), and fecal incontinence, while the use of PTNS is only allowed in the treatment of OAB.[3,4] PN (S2-S4 nerve roots) is not approved by the FDA for the treatment of lower urinary tract dysfunction.[3] However, the off-label use of these techniques is also currently adopted as a therapeutic modality in other urinary and nonurinary pelvic floor disorders, such as neurogenic lower urinary system disorder, interstitial cystitis (IC)/bladder pain syndrome (BPS), chronic pelvic pain (CPP), pudendal neuralgia, and sexual dysfunction (SD).[5] Neuromodulation is one of the fastest growing multidisciplinary fields of medicine, covering various specialties and applied to thousands of people with various disorders worldwide.[6] The International Neuromodulation Society defines neuromodulation as a field that includes the processes of inhibition, stimulation, modification, regulation, or therapeutic alteration of activity, either electrically or chemically, in central,

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peripheral, or autonomic nervous systems and addresses science, medicine, and engineering together.[7] Various neuroprosthetics are used in clinical practice, but in order to be able to call a treatment method for neuromodulation, it should be dynamic and allow for interventions, the efficiency of certain neural networks should be affected by electrical or neuropharmacological stimulations, and the clinical effect should be able to meet the patient's expectation and should be manageable in order to modify one or more stimulation parameters.[7]

Nerve stimulation can be induced by surface electrodes, transcutaneous needles, or needles implanted into the nerves, or through the alternating external magnetic field applied proximal to the nerves.[8] Electrical stimulation can be performed at home or in the clinic with intermittent or continuously implanted devices and electrodes. SNM refers to the electrical stimulation of the sacral nerve root, which provides continuous electrical stimulation through a surgically implanted device and to modulate the neural pathway in the presence of various indications.[9] PTNS is an alternative effective neuromodulation method for the treatment of neurogenic and non-neurogenic lower urinary tract dysfunction resistant to medical treatment and has the advantage of not requiring a permanent implant.[3,10] PN stimulation can be successful for pelvic pain when the pain is identified as being perineal in nature, and if the pain is associated with features of pudendal neuralgia.[2] This review will highlight recent developments in SNM, PTNS, and PN, which have been used in the treatment of various lower urinary tract dysfunction for many years.

## Methods

We performed a literature search using Medline (PubMed), Cochrane Library, EMBASE, and Google scholar databases in the English language from January 2010 to February 2021. We used the search string of "sacral neuromodulation" AND "pudendal neuromodulation" AND "tibial neuromodulation" AND "lower urinary tract dysfunction" AND "overactive bladder" AND "urinary retention" AND "chronic pelvic pain" AND "bladder pain syndrome" AND "sexual dysfunction". We included reviews, meta-analyses, randomized controlled trials (RCTs), and prospective and retrospective studies. After removing duplicates, 34 papers were excluded (language other than English and abstract-only studies), while 117 papers were screened. We limited our search to studies assessing the effectiveness and safety of neuromodulation in various pelvic floor disorders with a good sample size and acceptable follow-up period. After applying these criteria, a total of 51 eligible papers were included in the final review.

**Main Points**

- Neuromodulation is an effective and up-to-date technique in the treatment of a variety of pelvic disorders in both genders.
- The most commonly utilized neuromodulation techniques are percutaneous tibial nerve stimulation, pudendal neuromodulation, and sacral neuromodulation.
- Neuromodulation is still recommended only for patients who do not respond to standard treatments before more invasive surgery.
- Minor and reversible complications that do not require surgery are seen after neuromodulation techniques.
- Better lead placement techniques, developments in programing, rechargeable batteries, and body- and MRI-compliant leads make sacral neuromodulation more cost-effective day by day.

## Neuromodulation for OAB

The American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) recommends SNM and PTNS as the third-line treatments in selected patients with non-neurogenic refractory OAB resistant to behavioral therapy and medical treatment.[11–13] The International Continence Society states that it is not necessary to perform a urodynamic study (UDS) before neuromodulation for the treatment of OAB, but 54.2% of these patients are observed to have detrusor overactivity (DO) in UDS.[9,14] In the acute phase of SNM, a significant improvement cannot be achieved in relation to the standard UDS parameters of OAB. In these patients, an improvement in DO seen in the filling and emptying phase of UDS, increased bladder capacity, increased bladder volume at first sensation, and decreased maximum detrusor pressure during filling may occur after the 6th month of SNM treatment.[14] This is considered to be due to the decrease in regional cerebral blood flow in areas related to sensorimotor control after the chronic stimulation of SNM, while an increase in this blood flow is observed in the same areas of the brain during the acute period of SNM.[15]

In patients with OAB, both SNM and PTNS are reliable and effective methods that can achieve 61-90% and 60-70% success, respectively. This wide range of success rates is due to the limited number of studies in the literature with a small number of patients and short follow-up periods.[16,17] In RCTs, comparing patients who have undergone immediate SNM implantation and those who have undergone delayed SNM implantation after receiving medical or conservative treatment, it was determined that the reduction in daily incontinence episodes, incontinence severity, number of pads, and rate of

remaining completely dry were higher in the former.[5] While conservative treatment is recommended for patients with OAB, there is no reliable predictor of which patient will respond better; therefore, although conservative treatment options are primarily recommended for this patient group, they should also be informed about the neuromodulation option.[9] In an RCT in the literature (SUmiT), PTNS and sham stimulation were compared, and the rate of improvement in OAB symptoms was reported to be 54.5% in PTNS and 20.9% in the sham group. A significant improvement was observed in voiding parameters obtained from diaries (frequency, nighttime void, and urinary urgency incontinence episode) in the PTNS group compared to the sham group. There was also a significant improvement in the quality of life (QoL) scores, the Overactive Bladder Questionnaire symptom severity score, and Short Form-36 scores in the PTNS group compared to the sham group. In the same study including 220 patients, six had mild or moderate PTNS-related adverse events.[3,10,18] In another RCT, it was proven that PTNS improved DO and voided volume compared to placebo in OAB-wet patients.[4,10] In a prospective trial (InSite), comparing SNM and standard medical therapy in patients with mild and moderate OAB symptoms, the improvement rate was 76% in patients with SNM and 49% in those treated with medical therapy. According to the 3-year long-term results of the same study, complete continence was observed in 43% of the patients in the OAB-wet group, while a significant reduction in the number of daily voids and return to normal voiding patterns were achieved in 66% of those in the OAB-dry group. The improvement in the QoL of patients with SNM lasted throughout the 36 month study.[19] SNM reduces the use of medical treatments for OAB and can be preferred in elderly patients with complaints related to the side effects of anticholinergics or those with changes in mental status.[20] In the OrBIT trial, PTNS and tolterodine ER (4 mg $day^{-1}$) were compared, and improvement was achieved in 79.5% of the patients in the PTNS group and in 54.8% of those in the tolterodine group. In addition, subjective improvement in PTNS was greater for general health-related QoL compared to tolterodine.[4] Furthermore, the efficacy of PTNS was reported to be 94% and 96% at the 6th and 12th months, respectively.[10]

In a prospective randomized study (Rosetta trial), published in recent years, the success of SNM and onabotulinumtoxinA (BoNT-A) was compared in 386 patients with OAB. It was determined that there was a greater decrease in urgency incontinence episodes in the BoNT-A group compared to the SNM group, but likely not clinically significant. After 6 months, the Overactive Bladder Short Form symptom-bother score and the Overactive Bladder Satisfaction for treatment and endorsement scores were higher in the BoNT-A group compared to the SNM group. However, both treatment methods were found to be similar in terms of QoL and the subscales of treatment preference, convenience, and adverse effects. Clean intermittent catheterization (CIC) was required in 8% of the patients in the BoNT-A group, while device revision was required in 3% of those in the SNM group. In addition, it was observed that there was a higher rate of urinary tract infections in the BoNT-A group compared to the SNM group (35% vs. 11%). However, in this study, unlike routine use, 200 IU BoNT-A was administered to all patients as the first injection. This would cause difficulties in applying the results of the study to clinical practice.[21] Limited information is available on the efficacy of SNM in patients with refractory OAB who previously received BoNT-A treatment. Hoag et al.,[22] who included a total of 83 patients, determined that SNM had higher efficacy in patients with refractory OAB that had received BoNT-A compared to the BoNT-A naive group (70.2% vs. 63.9%). During a mean follow-up of 29 months, there was no difference between the two groups in terms of SNM success (73.9% vs. 75.8%).

In a prospective study evaluating the efficacy of SNM in refractory OAB cases, the authors observed a significant reduction in urgency incontinence episodes, severity of urgency episodes, daily urgency episodes, daytime micturition, and nighttime micturition during the 1-year follow-up of the SNM application. When the first-year UDS parameters were evaluated, there was an increase in the bladder volumes at first unstable contraction, first desire to void and urgency sensation, and maximal cystometric capacity.[23] The bladder capacity of the patients before SNM treatment had no effect on improvement in clinical symptoms, but those with low baseline bladder capacity had increased bladder capacity after SNM.[24] In another study evaluating the long-term follow-up of PTNS, the efficacy of treatment was reported to continue for an average of 188 (0-1,360) days in 47 of 113 patients.[25]

Neuromodulation has promising results in patients with OAB not accompanied by a neurogenic disease, as well as in those with multiple sclerosis (MS) presenting with bladder overactivity symptoms. Studies have shown that SNM provides significant improvement in QoL, bladder symptoms, and number of CICs in this patient group.[26] In addition, UDSs have shown that PTNS suppresses DO in this patient group. In a multicentric randomized study, patients with MS unresponsive to anticholinergic treatment achieved a significant reduction in nocturia, daytime frequency, and mean postmicturition residual volume after 12 sessions of PTNS treatment. In addition, there was a significant improvement in the mean voided volume and QoL scores in these patients.[26]

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SNM restores normal function of the bladder by modulating nerve signals to the spinal cord and the brain and can have a secondary gain on bowels and pelvic pain. Conversely, BoNT-A inhibits or disrupts normal bladder function by paralyzing the detrusor muscle, and hoping that the degree of inhibition of the detrusor will result in reduced OAB symptoms without creating urinary retention. While BoNT-A treatment is frequently preferred in patients with urge incontinence, SNM is applied in both wet and dry cases of OAB. BoNT-A can be immediately applied in the case of SNM failure, but SNM cannot be immediately applied to reduce false negativity in the case of BoNT-A failure. According to the European Association of Urology (EAU) guideline, in patients with treatment-resistant OAB, the cure rate for BoNT-A is 22.9% and the cure rate for SNM is 15%. In addition, the 6th-month results of SNM treatment indicate that it is not more effective than BoNT-A. In addition, unlike BoNT-A, SNM does not cause urinary tract infection or urinary retention. SNM, which has a long-term and reversible efficacy in patients with OAB, can be safely preferred in these patients as a third-line therapy.[27]

## Neuromodulation for Chronic Nonobstructive Urinary Retention

The normal lower urinary system includes the phases of low-pressure storage of urine and voluntary coordinated micturition. The neurogenic voiding pattern is evaluated on a wide scale from bladder atony to hyperreflexia together with detrusor sphincter dyssynergia (DSD) or synergy.[17] In these patients, anticholinergics, alpha blockers, or CIC can be used to minimize the effects of high storage pressures or uncoordinated voiding. However, even if the efficacy of these treatments has been proven, they have the possibility of causing urethral stricture, urinary tract infection, and upper urinary tract disorders.[11,17]

It has been suggested that the brain's response to the bladder afferent effect is weakened in patients with neurogenic lower urinary system disorders.[11] Imaging performed in patients with Fowler's syndrome showed that the response in the brain was reduced after bladder filling. In addition, it has been shown that deactivation occurs in the regions responsible for bladder control (the periaqueductal gray and thalamus), and activation takes place after neuromodulation.[28] The impulses reaching the periaqueductal gray prevent the urethral inhibition of afferent information flow from the bladder, thus providing voiding ability.[11] In addition, neuromodulation can cure voiding dysfunction and sphincter dyssynergia by changing the afferent signals to the spinal cord that affect the basal tone and activity of the pelvic floor.[17] It is assumed that neuromodulation can also be used in patients with incomplete spinal cord injury (SCI) to provide voiding and restore many other functions of the body. Through low-frequency stimulation, large, myelinated afferents, particularly proprioceptive primary afferents in the spinal roots are stimulated. Studies have shown that the activation of proprioceptive sensory fibers can support both short-term and long-term improvements in the modulation of spinal motor reflexes.[29]

Studies showing the effectiveness of PTNS in this patient group are limited. In a study including 39 patients with NOR, 59% of the patients wanted to continue the treatment, and a significant improvement was achieved in 41% according to the parameters recorded in the voiding diary.[10] In a recent article that investigated the efficacy of PTNS in children with voiding dysfunction, patients with non-neurogenic bladder were observed to have more improvement in relation to lower urinary tract symptoms than those with neurogenic bladder (78% vs. 14%).[17]

When SNM was applied to 32 patients with voiding dysfunction after spinal cord surgery, improvement in urinary retention was achieved at a rate of 61.5%.[30] When SNM was applied to 62 patients with chronic urinary retention due to various neurological diseases, there was a significant increase in the mean maximum urinary flow rates and a significant decrease in mean postvoid residual volumes of patients. The voiding diaries of the patients revealed a significant reduction in the mean number of micturition, incontinence episodes, urinary urgency episodes, and nocturia. UDS showed that the maximum cystometric capacity increased, and the maximum intravesical pressure decreased. The authors determined that the efficacy of SNM continued in 75.7% of the patients during an average follow-up of 4.3 years.[31] While SNM produces favorable results in NOR with DO and DSD in MS cases, it has low success rates in those with NOR with acontractile or hypocontractile bladder.[9] In addition, the effect of SNM may decrease over time in progressive diseases such as MS. Peeters et al.[32] reported the rates of success (>50% improvement in at least one voiding diary parameter) to be 73%, 62.5%, and 53% for the patients with idiopathic retention, Fowler's syndrome, and non-Fowler idiopathic retention, respectively, over a mean follow-up of 46.8 months.

In patients with incomplete SCI and neurogenic lower urinary tract symptoms, 69% success was achieved with the SNM application. It was determined that there was a significant decrease in the number of catheterizations and a significant increase in the void frequency and void volume in these patients.[17]

In patients with detrusor underactivity, increasing age and detrusor acontractility are factors that predict the success of the stage 1 trial of SNM. Detrusor acontractility is a marker for end-stage bladder dysfunction and responds less to central and peripheral afferent stimulation created by neuromodulation. For SNM to be effective in the treatment of lower urinary system disorders, there is a need for intact and functioning afferent pathways.[33] In complex cases with neurogenic lower urinary tract dysfunction or NOR, longer test periods are more appropriate than in idiopathic patients.[9] In these patients, the combined use of traditional urodynamics and ambulatory monitoring before the test period can provide additional predictive value compared to conventional methods.[9]

We consider that SNM, which is currently applied off-label in patients with NOR, will find more place in urology practice as future studies prove its efficacy.

## Neuromodulation for Chronic Pelvic Pain

CPP, which refers to pelvic pain lasting for at least 6 months and is localized to the bladder, genitals, perineum, or anorectum, may be a direct result of nerve injury and inflammation or may occur due to a secondary nerve component that contributes to the escalation or persistence of pain.[2,34] CPP has a multifactorial nature with many etiological reasons. These factors may be of musculoskeletal, psychological, urological, gynecological, infectious, or hormonal origin.[35] The proper functioning of the pelvic floor muscles is important for bladder, intestine, and sexual function, and neuromodulation is an off-label treatment option for refractory CPP.[36] It is assumed that the therapeutic effect of SNM in CPP is mostly related to the triggering of brainstem autoregulation, which helps reset the functions of the pelvic floor and related muscle structures.[35] As another view, the gate control theory of pain has been presented. Neuromodulation can activate large myelinated afferent nerve fibers in the dorsal horn to block conduction in primary afferent nociceptive fibers. Accordingly, it stops abnormal sensory input from entering the spinal cord and the brain. In addition, SNM inhibits abnormal C-fiber activity and decreases substance P in target organs.[34,37]

In a study by Martellucci et al.[38] evaluating 27 patients with medication-resistant pelvic pain, the implantation rate was reported to be 59%, and a significant decrease was achieved in the visual analog scale (VAS) scores (from 8.1 vs. to 2.1) over a mean follow-up of 37 months. In a systematic review, SNM provided an average of 35-52% decrease in the pain scores of patients with CPP, but it was reported that patients without IC/BPS had a greater decrease in pain scores than those with IC/BPS. This was attributed to the pathogenesis of IC/BPS being more complex and involving factors associated with voiding dysfunction.[35]

Improvements have been shown in urinary frequency, urgency, nocturia, and voided volume in patients with IC/BPS who have undergone SNM.[35] After a multidisciplinary evaluation, SNM or PTNS treatment can be considered in IC/BPS cases, in which first-, second-, and third-line treatments have failed.[34] The AUA/SUFU guidelines define SNM as a fourth-line therapy option for patients with IC/BPS.[9] SNM provides objective and subjective improvements in the symptoms of IC/BPS in the long term. In this patient group, SNM treatment results in a decrease in perception of pain, pelvic pain, urinary frequency, urgency, and nocturia, and an increase in the average voided volume and QoL.[2,5] With this treatment, patients require less use of narcotics or quit them completely.[5] In a study including 21 patients with IC/BPS, the significant improvement in urgency, frequency, average voided volume, nocturia, and VAS scores was observed to continue during the 62-84 month follow-up.[37]

The EAU guidelines recommended that pudendal nerve stimulation is superior to SNM for the treatment of IC/BPS.[27] When the Pudendal nerve is stimulate the afferent signals transmit to the spinal cord and brain and may inhibit bladder function through hypogastric nerve activation, inhibition of parasympathetic ganglionic transmission, direct smooth muscle relaxation, or other central reflex mechanisms. Sympathetic efferent pathways have a role in sensory pudendal nerve inhibition of nociceptive reflex activity.[39] In cohorts of patients with IC/BPS, PN has been shown in several studies and case reports to be effective in alleviating pain, especially in patients who have failed management with SNM. Peters et al.[40] conducted a retrospective review in which 19 patients who had undergone PN for pudendal neuralgia were sent questionnaires to evaluate outcome. All patients had some improvement in pain at the time of implantation. Only 10 out of 19 patients returned the questionnaires; of these, seven reported some improvement. However, pain medications received more favorable assessments, with six out of 10 patients describing a marked improvement. Studies have shown that PN provides significant greater reduction than SNM in IC/BPS symptoms.[41] Gonzalez and Grill[39] reported that electrical stimulation to the sensory branch of the pudendal nerve increased bladder capacity by up to 51% in cyclophosphamide-induced cystitis rats. This result suggests that PN may be an alternative approach to manage bladder capacity in IC/BPS.

In another study, a significant increase was achieved with PTNS in VAS and National Institutes of Health Chronic

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Prostatitis Symptom Index scores. The authors concluded that PTNS was an effective treatment method in patients with category IIIB prostatitis or CPP.[10] Other studies included in the review reported that the increase in QoL caused by PTNS in patients with CPP continued for 6 months, and there were minor adverse events in a small number of patients.[42] However, further research on combination therapies (intravesical instillation + PTNS) is needed to better demonstrate the efficacy of PTNS in this patient group.[2]

Large RCTs evaluating the efficacy of SNM in patients with CPP are lacking. While studies in the literature generally evaluate female patients, long-term follow-up results remain insufficient.[2] Current guidelines suggest that SNM should be tried in medication refractory patients with IC/BPS who are considered for major surgical treatments, such as augmentation procedures, urinary diversion, and cystectomy.[43]

## Neuromodulation for Sexual Dysfunction

Urinary dysfunction can be associated with SD, and both have a negative effect on QoL. There is a complex interaction of symptoms such as urinary incontinence or pain during sexual intercourse, which leads to psychological distress, physical discomfort, and embarrassment.[1,44] SD can be seen in various forms in both genders, including inadequate lubrication, pain, and erectile dysfunction.[45] In the prevalence evaluation of a review, the rate of lubrication and arousal disorder was determined to be 8-28%, orgasmic dysfunction 16-25%, and orgasmic dysfunction 16-25% in female gender. In addition, 26% of women between the ages of 20 and 39 years and 39% of those over 50 were reported to suffer from SD.[1] In a study conducted on 350 women with urinary incontinence, it was determined that 60% of the patients had incontinence during sexual intercourse, and this negatively affected their sex life.[1] Correcting organic disorders such as voiding dysfunction improves sexual function directly or indirectly.[46] For example, less urinary incontinence during intercourse leads to more frequent and satisfying sexual activity, while decreased concentration disturbance caused by urinary incontinence increases the ability to achieve an orgasm. On the other hand, sexual function can also be directly improved through the stimulation of the nerves with neuromodulation.[46]

The mechanism of action of SNM on SD has been attempted to be explained with many theories. SNM functions by stimulating afferent nerves and inhibiting or stimulating impulses to or from pelvic organs at the sacral and supraspinal level or by inhibiting afferent somatic pathways.[47] In addition, sexual and urinary functions can share the same stimulated neural pathways. Erection consists of the stimulation of the pudendal somatic afferent neurons by tactile stimuli and parasympathetic efferent innervation phases. In addition, the stimulation of the pudendal nerve causes an arousal response. In women, the pudendal nerve branches inferiorly into the perineal nerve, posterior labial nerve, and dorsal nerve of the clitoris. All these pathways can be stimulated with SNM, providing improvement in the sexual functions of both genders.[47]

In a study including 34 male and female patients with urinary dysfunction, de Oliveira et al.[47] showed a significant increase in the median International Index of Erectile Dysfunction (IIEF) and Female Sexual Function Index (FSFI) scores after SNM treatment. Better results were obtained in younger patients under 40 years, and it was determined that the highest improvement was in orgasm and lubrication. Improvement in lubrication reduces pain, thus improving orgasm disorders and sexual function.[47] In a meta-analysis, significant improvement was achieved in desire, arousal, pain, and satisfaction in patients who underwent SNM due to urinary indications and fecal incontinence, while there was no improvement in lubrication and orgasm. However, in these patients, even reducing incontinence and keeping the vagina and vulva cleaner and dry can improve sexual functions without any other intervention.[45] It has been determined that in patients with improved FSFI scores after SNM, this improvement continued for 1-3 years of follow-up.[48]

Signorello et al.[44] reported that SNM resulted in a greater improvement in the total FSFI scores of patients with neurogenic lower urinary dysfunction than those without neurogenic lower urinary dysfunction (52% vs. 13.4%). Furthermore, it was shown that the improved results continued in patients with neurogenic lower urinary dysfunction during the follow-up of 19-49 months (46% vs. 12.5%). The absence of a hysterectomy history, being sexually active at baseline, and improvement in urinary symptoms are factors that predict the development of sexual function.[1]

SNM can have an effect on young patients recovering from SD, which has a complex pathology and an important place in the QoL of sexual function in this patient group. In addition to SNM, cavernous nerve stimulation, which has been proven to be effective in penile rehabilitation with experimental studies, can also offer an alternative neuromodulation option for patients with ED. Angiogenesis, activation of intracellular signaling mediators, and inhibition of tissue fibrosis have been shown to occur in cavernous tissue after cavernous nerve stimulation.[49,50] However, current studies in the literature are still in the preclinical phase or contain a low number of patients

evaluated over a limited follow-up period. Therefore, large, multicentric, and prospective studies are needed to obtain further data concerning the effects of neuromodulation on sexual function (Table 1).[47,48]

## Safety of Neuromodulation

Generally, minor and reversible complications that do not require surgery are seen after neuromodulation techniques. With the increase in experience and development in techniques and technologies, device-related adverse events and surgical intervention requirements now show a tendency to decrease compared to previous years.[11] General complication rates reported in the literature range from 12% to 53%. The most frequently reported side effect and the most common cause of surgical revision are pain in the implant area (15-42%), with the remaining common side effects being lack of efficacy, lead migration, and trauma.[16,17] The revision surgery rate is 9-33%, and lack of efficacy, worsening of symptoms, device removal, migration, lead breakage, infection, and battery depletion are among the reasons that require revision surgery other than pain.[6,10]

Peeters et al.[32] applied lead repositioning in 32% of patients due to weak activity, suspicion of migration, or pain. Device repositioning was performed in 7.3% of patients due to pain in implant site, and battery exchange was undertaken in 15% due to battery depletion (within 5-7 years). In a prospective study, the researchers determined that a history of trauma, a decrease in body mass index, previous referral to a pain clinic, and a history of adverse events were predictive factors for revision surgery.[3] Other predictive factors included IC/BPS and receiving hormonal replacement during the implantation period among female patients.[6] One of the common adverse events is implant site infection seen at a rate of 0-11%.[5] However, the reoperation rates due to infection are lower than for other reasons.[6] No major complications have been related to PTNS, which is a method that does not require permanent implantation, and minor complications of this treatment are reported as mild bleeding and temporary pain sensation at a rate of 1-2%.[4,10] The major concern about SNM is the high revision rates, but the measures to be taken considering the factors described above and developing technologies can reduce these rates.[16]

## Neuromodulation in the Future

In the last few years, there have been new developments in neuromodulation technologies, including longer lasting rechargeable batteries, wireless charging, improvements in programing, less invasive single stage implantation in outpatient settings, and lower-cost new devices.[11] The first rechargeable system on the market was the Axonics® SNM that is 60% smaller than the Medtronic InterStim® II device and has a battery life of 15 years. The system requires 2 hours of wireless and transcutaneous charging every 1-3 weeks.[51] In a study testing the Axonics system in 48 patients, it was determined that 83% of the patients were completely satisfied with the treatment, but it was noted that this system was currently approved for use only in Europe and Canada.[45] Not to be outdone, Medtronic has brought to market a new rechargeable device called the Interstim Micro. The IPG is 50% smaller than Axonics, requires weekly charging for 20 minutes, and has at least a 15 year battery life. Having rechargeable options allows for a smaller IPG for the patient and a prolonged battery life. However, not all patients are candidates for a rechargeable system.[49]

PTNS has been shown to be effective in the treatment of OAB, but the technique involves weekly office visits to place a needle electrode at the tibial nerve and is likely underdosed. There is evidence that daily stimulation of the tibial nerve may be more effective than weekly stimulation. To that end, several implantable devices at the tibial nerve are in clinical trials for OAB. These include e-Coin (Valencia), Renova (BlueWind), StimRouter (Bioness), and Protect-PNS (Micron Medical). These devices have the potential to move neuromodulation from the operating rooms to the office and may provide outcomes similar to SNM.[52]

Today, the S3 sacral nerve is the only nerve root approved by the FDA for the treatment of bladder and bowel dysfunctions. Neuromodulation that reaches the central nervous system and stimulates afferent fibers, as well as motor fibers can be applied for the further improvement of symptoms. Therefore, the pudendal nerve (S2-S4) and tibial nerve (L4-S3) can be considered as other alternative implantation targets.

In order to increase clinical efficacy, one of the new developments is to apply high-amplitude energy when the patient's urge symptoms or incontinence episode approaches based on real-time monitoring through a modified system that can be controlled by the patient.[52] This system is considered to be able to control urge incontinence and OAB symptoms with a prepubic electrode that can placed through a quick outpatient procedure in the future.[52] Another development is body-responsive neuroprosthesis, in which electrical stimulus response occurs in bladder filling and detection of bladder contractions. Conditional feedback reduces muscle fatigue caused by continuous stimulation and increases the battery capacity of the implanted device.[52]

**Table 1. Main Characteristics of Included Studies for Efficacy in Patients Treated with Various Neuromodulation Techniques**

| Study | Study Design | Indications | Treatment Experimental Control | Sample Size Experimental Control | Age (year) Experimental Control | Questionnaire Forms | Follow-Up Times | Success (%) Experimental Control | Complication (%) Experimental Control |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Overactive Bladder Questionnaire SF | | | |
| | | | | | | Urogenital Distress Inventory | | | |
| Amundsen et al.[21] | Multicenter open-label randomized (ROSETTA trial) | OAB | SNM BoNT-A | 174<br>190 | 63.1 ± 11.8<br>62.9 ± 11.5 | Incontinence Impact Questionnaire | 6 months | 2<br>20 | 30 (UTI)<br>9 (UTI) |
| | | | | | | The Health Utility Index Mark | | | 0 (CIC requirement)<br>2 (CIC requirement) |
| Peters et al.[18] | RCT | OAB | PTNS sham | 86<br>88 | 62.5<br>60.2 | OAB-q Symptom Severity Score | 13 weeks | 58.3<br>21.9 | 0.6 (discomfort, bleeding, tinglin)/0 |
| | | | | | | Incontinence Modular Questionnaire-OABqol | | | |
| | | | | | | Beck Depression Inventory | | | |
| Siegel et al.[19] | Multicenter prospective (InSite trial) | OAB | SNM | 340 | 57 | Male/Female Lower Urinary Track Symptoms | 36 months | 79 | 16 (device related, implant site infection, skin infection, and respiratory arrest during surgery) |
| | | | | | | Visual Analog Scale | | | |
| Arlen et al.[30] | Retrospective | NOR | SNM with spinal surgery history/ SNM without spinal surgery history | 32<br>136 | 56 (30-77) | | 2.3 years | 52.9<br>80.3 | 30<br>26.5 |
| Chaabane et al.[31] | Retrospective | NOR | SNM | 62 | 50.5 ± 14.8 | | 4.3 ± 3.7 | 75.7 | 1.2 |
| Ghazwani et al.[37] | Retrospective | BPS | SNM | 21 | 44.3 ± 8.9 | Urinary Distress Inventory Short Form (UDI-6) | 71.5 ± 9.3 months | 52 | 14.2 |
| | | | | | | Visual Analog Scale | | | |

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**Table 1. Main Characteristics of Included Studies for Efficacy in Patients Treated with Various Neuromodulation Techniques (continued)**

| Study | Study Design | Indications | Treatment Experimental Control | Sample Size Experimental Control | Age (year) Experimental Control | Questionnaire Forms | Follow-Up Times | Success (%) Experimental Control | Complication (%) Experimental Control |
|---|---|---|---|---|---|---|---|---|---|
| Martellucci et al.[38] | Prospective | CPP | SNM | 27 | 53 (29-75) | Visual Analog Scale | 37 months | 59 | 0 |
| | | | | | | Short Form-36 | | | |
| de Oliveira et al.[47] | Retrospective | SD | SNM | 49 | 41 (26-72) | International Index of Erectile Function (IIEF) | 20.7 months | 69.3 | 37.5 |
| | | | | | | Female Sexual Function Index (FSFI) | | | |
| Signorello et al.[44] | Prospective | SD | SNM | 30 | 53 (35-79) | Female Sexual Function Index (FSFI) | 36.3 months | 25 | |
| | | | | | | Status of Health Questionnaire (SF-36) | | | |
| | | | | | | Incontinence Quality of Life Index (IQoL) | | | |

OAB, overactive bladder; NOR, nonobstructive urinary retention; BPS, bladder pain syndrome; CPP, chronic pelvic pain; SD, sexual dysfunction; BoNT-A, onabotulinumtoxinA; SNM, sacral neuromodulation; PTNS, percutaneous tibial nerve stimulation; UTI, urinary tract infection; CIC, clean intermittent self-catheterization.

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Better lead placement techniques, developments in programing, rechargeable batteries, and body- and MRI-compliant leads make SNM more cost-effective day by day. As technological advances continue, many researchers around the world continue to work on devices that will accurately record bladder-related effects obtained with newly developed devices and promptly prevent unwanted contractions.

## Conclusion

Neuromodulation is an effective and up-to-date technique in the treatment of a variety of pelvic disorders in both genders. However, currently, patients suitable for this treatment are selected based on their symptoms, with no biochemical and functional testing being performed in the preimplantation period. Pelvic floor, urinary, and bowel tests are still not reliable in selecting appropriate cases for neuromodulation. Today, neuromodulation is still recommended only for patients who do not respond to standard treatments before more invasive surgery. However, the lack of high-level comparative studies comparing the efficacy of third- and fourth-line treatments with SNM, PN, and PTNS limits the degree of the recommendations by relevant guidelines. Further innovations and future research will provide a better understanding of neurophysiology and develop new stimulation targets, new programing techniques, and prolonged battery life, allowing for neuromodulation to take place as a first-line treatment algorithm in patients with complex pelvic disorders in future.

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