TOPIC PAPER

# Sacral neuromodulation for lower urinary tract dysfunction

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## Abstract

*Objectives* To review the technique, indications, results and working mechanisms of sacral neuromodulation (SNM) for lower urinary tract dysfunction.

*Methods* The available literature on SNM for lower urinary tract dysfunction was searched. Based on the information available in the literature and also based on personal experience, the urological indications, technique, mechanisms of action and results of SNM are presented and discussed.

*Results* SNM for lower urinary tract dysfunction involves stimulation of the 3rd sacral nerve with an electrode implanted in the sacral foramen and connected to a pulse generator. The technique is accepted by the FDA since 1997. Currently, SNM for lower urinary tract dysfunction has been successfully used in about 26,000 patients with various forms of lower urinary tract dysfunction, including urgency, frequency and urgency incontinence as well as non-obstructive urinary retention. The actual procedure of SNM consists of a minimal invasive technique and is effective in about 70% of the patients who have been implanted with a permanent system. Also, in pelvic pain, interesting results have been described. SNM modulates the micturition reflexes at different levels in the central nervous system.

*Conclusions* Sacral neuromodulation is a safe and effective therapy for various forms of lower urinary tract dysfunction, including urgency, frequency and urgency incontinence as well as non-obstructive urinary retention. It should be the first choice after failure of maximal conservative therapy.

**Keywords** Sacral neuromodulation · Lower urinary tract dysfunction · Pulse generator · Sacral nerve

## Introduction

Chronic types of lower urinary tract dysfunction (urgency, frequency, urgency incontinence as well as non-obstructive urinary retention) still present a therapeutic challenge. Most patients are initially treated with conservative therapies (bladder retraining, pelvic floor exercises, biofeedback and intermittent catheterization) often supported with pharmacological therapy. However, a significant proportion of patients do not achieve an acceptable level of therapeutic benefit. Several surgical procedures (bladder transsection, transvesical phenol injection, augmentation cystoplasty and urinary diversion) have been advocated with variable efficacy and significant morbidity. Sacral neuromodulation (SNM) offers an alternative treatment for these patients [1]. SNM was developed in the early 1980 s by Tanagho and Schmidt. They demonstrated that continuous stimulation of the sacral root S3 with an electrode connected to an implanted pulse generator (Fig. 1) could modulate detrusor and sphincter activity and stabilize micturition reflexes [2].

S3 sacral neuromodulation received approval by the US Food and Drug Administration (FDA) for the treatment of urge incontinence in 1997 and for urgency/frequency and non-obstructive urinary retention in 1999 [3]. Currently, SNM for lower urinary tract dysfunction has been successfully used in about 26,000 patients.

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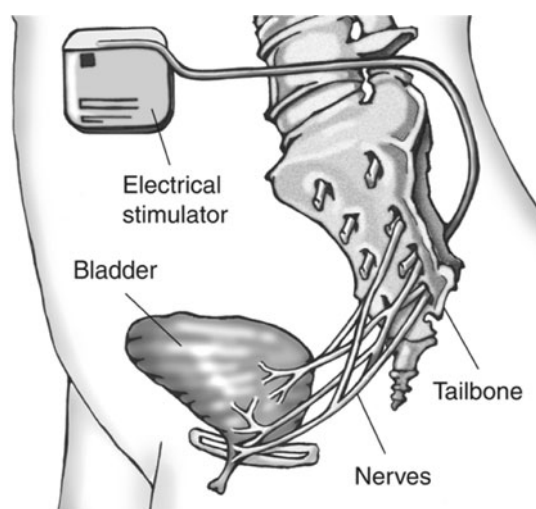
Fig. 1 Stimulation of the S3 nerve root with an electrode in the sacral foramen and connected to an implanted stimulator

## Indications

Sacral neuromodulation is a potential treatment for patients with various forms of bladder dysfunction. Although SNM currently only has FDA approval for overactive bladder and urinary retention, clinical benefit has been observed for various other chronic pelvic floor disorders, including faecal incontinence, chronic pelvic pain and interstitial cystitis.

### Overactive bladder

Overactive bladder (OAB) syndrome involves a group of symptoms including urgency and frequency with or without urgency incontinence (OAB wet and OAB dry). Before considering treatment, a proper clinical evaluation should be performed in order to rule out underlying causes, such as infections, malignancies and anatomical abnormalities. Conservative management is always advocated as an initial intervention. However, often, these conservative treatments do not result in sufficient symptom relief, and many patients cannot tolerate the side effects of drugs. When conservative treatments fail after 8–12 weeks, alternative therapies can be considered [4]. At present, several minimally invasive techniques are available including SNM, posterior tibial nerve stimulation (PTNS) and intravesical injections with botulinum toxin (BTX). PTNS can be seen as an alternative option to SNM but needs to be repeated at regular intervals in order to have persistent results. No comparative trial between PTNS and SNM is available yet. BTX is currently not approved by the FDA for the indication OAB, but the initial results are promising. The most common adverse events are high post-void residual requiring clean intermittent self-catheterization, and

urinary tract infection. BTX treatment also needs to be repeated at regular intervals. At this moment, there are no comparative trials between BTX and SNM available, and hence, the decision to offer SNM or BTX will be the result of an informed consent between the doctor and the patient.

Scheepens et al. identified several predictive factors in SNM in a retrospective study evaluating 211 patients [5]. They found that a history of intervertebral disc prolapse surgery and the duration of complaints are factors that may affect the chance of a successful test stimulation. Everaert et al. reported that patients with a history of surgery for stress incontinence had a significantly better long-term outcome with SNM, whatever their symptoms were [6]. In a group of 100 patients undergoing test stimulation, Koldewijn et al. did not show any predictors of success, although it appeared that patients with detrusor overactivity and urethral instability responded best to SNM [7].

Amundsen et al. demonstrated that age greater than 55 was associated with a lower response to SNM [8]. For the time being, a trial stimulation remains the only reliable factor in predicting success with permanent treatment.

### Urinary retention

Voiding can be impaired by either bladder outlet obstruction or insufficient contractility of the detrusor. In turn, bladder outlet obstruction can be of anatomical or functional origin. Anatomical obstruction is often caused by prostate enlargement, urinary tract tumours, bladder neck stenosis or urethral stricture. Although poorly understood, functional aetiologies include detrusor external sphincter dyssynergia or detrusor bladder neck dyssynergia. In addition, pelvic floor dysfunction can cause inhibition of detrusor function, resulting in difficult bladder emptying and varying degrees of urinary retention. Fowler et al. described overactivity of the urethral sphincter as a cause of urinary retention, especially in young women (Fowler's syndrome) [9].

Also, neurological disorders (e.g., spinal cord disease, spinal disc hernation, multiple sclerosis, small fibre neuropathy) should be considered as a possible basis for non-obstructive urinary retention. Patients with 'idiopathic' urinary retention often have a history of a triggering event such as pelvic surgery or even emotional stress. They also frequently have a history of dysfunctional disorders in their childhood, such as lifelong constipation or urinary tract infections [10].

Previously, there was no effective treatment for functional urinary retention except clean intermittent self-catheterization. More invasive treatments, such as urethral dilatation and bladder neck incisions, have been associated with inconsistent results, a high relapse rate and complications. SNM has been recognized as an effective treatment

for patients with functional urinary retention. A large multicentre clinical trial in 1999 resulted in FDA approval of SNM for treating idiopathic non-obstructive chronic urinary retention and now has become a well-established treatment modality for patients with non-obstructive urinary retention [3, 11]. No predictors of success have currently been identified. It is important to note that an elevated cystometric capacity or absence of detrusor contractility does not predict failure of SNM. However, Bertapelle et al. demonstrated that patients who showed a lack of detrusor response to acute stimulation of the sacral nerve roots might have a lower chance of treatment success [12]. Patients with pelvic floor hypertonicity, such as in Fowler's syndrome, appear to have a higher success rate [13].

Pelvic pain

Although SNM is not an FDA-approved treatment for patients with urological pain syndromes, various authors have reported on the 'off-label' treatment and the results seem promising with a success rate of 72–77% [14, 15].

## Mechanism of action

Although the exact mechanism of SNM is not well understood, it seems to involve modulation of the spinal cord reflexes and brain networks by peripheral afferents, rather than direct stimulation of the motor response of the detrusor or urethral sphincter. In patients with overactive bladder, SNM is thought to inhibit detrusor activity without affecting urethral resistance or the strength of detrusor contractions during voiding [16]. The observation that early, bilateral SNM initiated during spinal shock could prevent the development of detrusor overactivity in complete spinal cord injury might indicate modulation at the level of the spinal cord itself [17]. PET studies indicated that at the level of the brain, the activity of centres involved in activation or inhibition of the micturition reflex can be enhanced or reduced with SNM [18]. This results in activation or inhibition of lower urinary tract activity. Blok et al. compared the effect of acute and chronic SNM on brain activity by evaluating the regional cerebral blood flow with PET [19]. Their findings suggested that acute SNM predominantly modulates areas involved in sensorimotor learning, whereas chronic SNM influences areas related to awareness of bladder filling, the urge to void and the timing of micturition.

For urinary retention, SNM has been postulated to suppress the guarding reflex, resulting in decreased urethral sphincter tone and thereby facilitating voiding. Animal studies indicated that the guarding reflexes can be modulated by afferent nerve activation and inhibit bladder

activity by spinal or supraspinal pathways [20]. In contrast, the results of a study of 30 women with Fowler's syndrome showed that the maximum urethral closure pressure did not change significantly. Instead, the return of voiding ability seemed to be attributable to a slight increase in detrusor contractility [21]. In a recent study, functional MRI was used to evaluate brain responses to bladder filling in patients with Fowler's syndrome [22]. The data showed abnormal brain responses in these patients, which are most likely caused by abnormally strong inhibition of the bladder afferents by overactivity of the urethral sphincter. The authors suggested that SNM acts at a sacral level, by blocking the urethral inhibition of afferent information from the bladder. Because the transmission of afferent information to the brain is restored, bladder sensations return as well as the ability to void.

## Technique of sacral neuromodulation

For SNM, one of the sacral nerves (usually S3) is stimulated with a quadripolar lead (Model 3889, Medtronic Inc.), which is positioned in the sacral foramen. The lead is connected to an implantable, reprogrammable pulse generator (Interstim I or II, Medtronic Inc.) The pulse generator can be implanted by creating a subcutaneous pocket in the lower abdomen or buttock. Patients are selected for SNM treatment based on their response to test stimulation with a temporary electrode. During the test procedure, a needle is inserted into the third sacral foramen. Next, it is connected to an external stimulator, and current is applied. Correct placement is confirmed by evaluating the sensory and motor responses to stimulation. Typical responses are sensation in the anal, vaginal or perineal area, contraction of the levator ani muscle, and flexion of the great toe on the ipsilateral side of stimulation. In addition, correct position of the needle can be confirmed by fluoroscopy. When adequate responses have been obtained, the electrode is inserted through the needle, and the needle is removed. In turn, the electrode is connected to an external stimulator. During the trial stimulation, which lasts for a minimum of 3 days, the response to subchronic stimulation can be evaluated.

Initially, test stimulation was performed with the percutaneous nerve evaluation (PNE), in which a basic wire electrode is connected to an external stimulator. However, due to the high risk of lead migration, the test duration is rather limited, and the reported success rate is between 40 and 50% [3]. Later, the two-stage implantation procedure was introduced, which enables screening with the permanent electrode during the first stage [23]. If the patient is considered eligible for definitive SNM, the implantable neurostimulator (INS) is inserted in a second stage. This

procedure enables prolonged screening for up to 1 month, resulting in a success rate of approximately 80%, which is significantly higher than with PNE testing [23]. Before the introduction of the tined lead, the permanent lead was implanted under direct vision and in turn secured to the sacral periosteum during an open surgical technique. Spinelli et al. introduced a self-anchoring 'tined' lead in 2002, allowing percutaneous placement of the lead under radiological guidance (Fig. 2) [24]. Potential advantages of the tined lead include a shorter operation time, reduced risk of infection, less pain and shorter post-operative recovery time. In addition, the lead can be inserted under local anaesthesia, enabling evaluation of the sensory responses to acute stimulation.

## Clinical results

If more than 50% improvement in voiding symptoms is observed based on the comparison of the results of the voiding diary that is kept before and during the test stimulation, patients are considered eligible candidates for SNM treatment. Depending on the type of complaint, different primary voiding parameters are used to evaluate the clinical effect. In patients with OAB wet, improvement in incontinence parameters is considered most important (number of leakages per day and the number of pads per day). In patients with OAB dry, the voiding frequency and voided volume per void are evaluated, and in patients with chronic urinary retention, reduction in the volume per catheterization and increase in voided volume are assessed.

Numerous reports on the clinical efficacy of SNM have been published. In early studies by Tanagho et al. SNM resulted in restoration of continence in patients with detrusor overactivity due to suprasacral spinal cord injury [2]. In 1995, Bosch et al. evaluated 18 implanted patients with urgency incontinence [25]. The voiding diaries of these patients showed a highly significant drop in leakage episodes and frequency, with a significant increase in the average voided volume. The number of pads used per day dropped significantly as well. The effect was durable, as 13 patients who were followed for more than 2 years maintained the same initial improvement. In addition, early studies reported on the use of SNM for the restoration of voiding in patients with non-obstructive urinary retention. Gajewski et al. reported long-lasting improvement in 70%
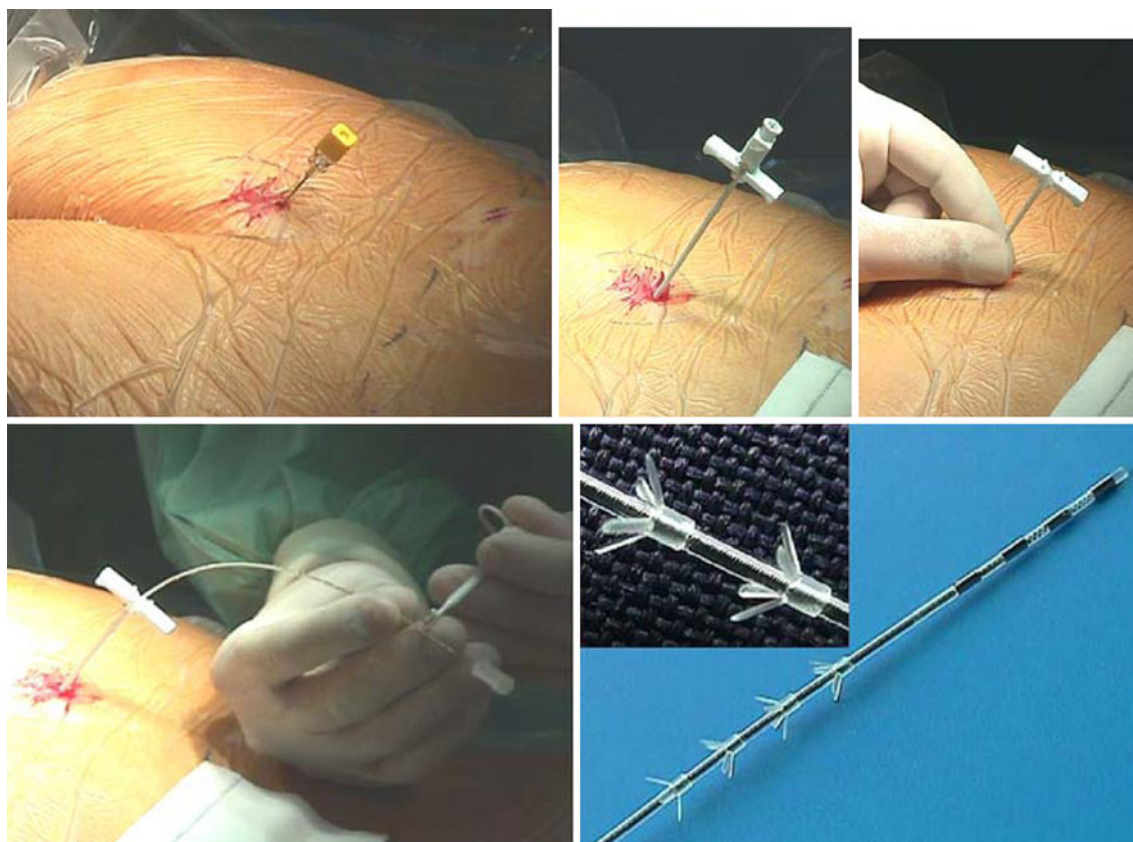


**Fig. 2** Percutaneous technique of lead implantation. After correct positioning of the patient, a test needle is used to probe and localize the third sacral foramen. Next, the test lead is inserted near the nerve through the needle and connected to an external stimulator. Due to silicone barbs ('tines'), the lead is self-anchored in the sacral foramen

**Table 1** Long-term results of SNM treatment

Success of treatment was defined as the percentage of patients who had a successful outcome at last follow-up visit (more than 50% improvement in key voiding diary variables)

| Study | Year | No of patients | Success of treatment % | Follow-up (months) |
|---|---|---|---|---|
| Siegel et al. [27] | 2000 | 112 | 62 | 26 |
| Bosch et al. [28] | 2000 | 45 | 60 | 47 |
| Dasgupta et al. [29] | 2004 | 26 | 77 | 37 |
| van Kerrebroeck et al. [3] | 2007 | 105 | 70 | 49 |
| Sutherland et al. [30] | 2007 | 104 | 69 | 22 |

of the implanted patients [26]. Jonas et al. also reported a high success rate in these patients [11].

Long-term outcome of SNM for lower urinary tract dysfunction has been assessed in several clinical trials. Table 1 presents an overview of a number of studies that evaluated the long-term efficacy. All studies showed that SNM treatment is safe and effective for patients with OAB as well as patients with urinary retention, and most studies showed a higher success rate in the retention group. The largest prospective study, including 17 centres worldwide, reported a long-term success rate of approximately 70% [3, 6].

### Follow-up and adverse events

Directly after implantation, the implantable neurostimulator (INS) is activated, and optimal stimulation settings are chosen by evaluating the sensory response to different combinations. The tip of the implanted lead contains 4 stimulation points, and each one can be used as a cathode or anode. Also, the case of the stimulator can be used as an anode, which results in unipolar type of stimulation. When the lead itself is used for both the cathode and anode, bipolar stimulation is the result. The stimulation setting (uni- or bipolar) that gives the best sensory response (anal, vaginal or perineal) at the lowest amplitude is considered optimal. The amplitude of stimulation is normally set just above sensory threshold. Not much is known about the optimal pulse rate with chronic stimulation. Although it is generally advised to set the pulse rate between 10 and 16 Hz, the effect of different pulse rates on treatment efficacy have never been evaluated in clinical studies. This also applies for the pulse width, which is advised to set at 210 ms. Patients receive a 'patient programmer', which they can use to turn the INS on or off when necessary. Also, the programmer grants the ability to make small alterations in the stimulation amplitude. Patients are advised to keep the INS on during the day and night.

Patient follow-up after implantation of the neurostimulator is scheduled after 6 weeks, 6 months and yearly thereafter. During each follow-up visit, the stimulation parameters are checked in order to evaluate patient compliance and correct use of the patient programmer. Also, the impedance can be measured. If the impedance is less than 50 Ohms or more than 4,000 Ohms, there may be a short cut or an open circuit as a result of damage to the lead. In case of decreased efficacy without signs of lead damage, parameter settings can be adjusted. In case of permanent loss of efficacy, an X-ray will be considered to rule out lead migration. If all these changes do not lead to any improvement and all parameters and sensory responses are correct, it is often challenging to find a satisfactory solution. First of all, the symptoms of the patients have to be re-evaluated to rule out other causes of therapy failure (e.g., stress incontinence, neurological disease), especially in patients who have been treated with SNM for several years. Next, replacement of the lead or contralateral placement of a new lead can be considered. Eventually, bilateral stimulation could be attempted.

Pain can occur in 24–34% with long-term follow-up and can be located at the site of the INS or at the site where the stimulation sensation is perceived. This can often be differentiated by turning the stimulator off. If pain symptoms persist, they are often a result of mechanical discomfort of the INS. If pain symptoms decrease, they are often stimulation-related. The physician can attempt to relieve pain symptoms by altering the stimulation settings. If no pain relief occurs, repositioning of the INS or lead can be necessary.

### Conclusions

Sacral neuromodulation is well-established treatment option for patients with lower urinary tract dysfunction. The exact mechanism of action most likely involves a combination of different modes of action, involving the neuroaxis at different levels. The efficacy has been proven in several clinical trials, with reported 5-year efficacy of approximately 70%. Due to technological advancements, the technique has become minimally invasive and is easy to apply even on an out-patient basis.

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