Sacral Neuromodulation

Marco Torella, Antonio Schiattarella, Nicola Colacurci, and A. Di Gesu

Sacral nerve modulation (SNM) is a procedure used to treat patients with bladder and/or bowels conditions. Neuromodulation is based on the theory that a constant low amplitude stimulation directly or indirectly through the sacral nerve roots results in ascending signals to the micturition centers that modulate efferent signals to both the bladder and bowel. This treatment is usually offered as a third-line therapy after conservative treatments, lifestyle modification, and oral drugs have failed. The first neuromodulation procedure was performed in 1954 as deep brain stimulation (DBS) for the treatment of chronic pain. In 1988, Tanagho and Schmidt introduced SNM for lower urinary tract dysfunction (LUTD) therapy, including OAB treatment [1]. The Food and Drug Administration (FDA) approved SNM for the treatment of refractory OAB, frequency, and non-obstructive post-void residual urinary retention in 1997 and 1999. Recently, rechargeable and conditional magnetic resonance imaging (MRI)-safe devices (Axonics r-SNM SystemTM, Irvine, CA) have been introduced in both Europe and USA. The clinical effectiveness of this system appears to be similar to that of the current recharge-free InterStimTM II device (Medtronic, Minneapolis, MN). However, newer InterStim devices have been submitted for CE mark and FDA approval in order to improve patient preference and provide full-body MRI safety for both 1.5 and 3 Tesla with the latter field strength having become the clinical standard. Rechargeable batteries result in smaller volume implantable pulse generators (IPGs). These may result in more comfort for patients with low body mass index (BMI), and the much smaller size will be more attractive to the patient than the current InterStim II IPG.

M. Torella (✉) · A. Schiattarella · N. Colacurci
Department of Woman, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy

A. Di Gesu
St. Mary's Hospital. Imperial College, Paddington, London, UK

D. Veneziano, E. Huri (eds.), *Urologic Surgery in the Digital Era*,
https://doi.org/10.1007/978-3-030-63948-8_6

1 Mechanism of Action

The mechanism of action of SNM is still unclear. However, the electrical stimulation modulates nerves that supply the bladder, bowels, urinary and anal sphincters, and pelvic floor muscles. The intensity and frequency of the pulses can be modified by both the physician and the patient through an external programmer. The S3 nerve root is a primary target for SNM therapy in that it contains afferent sensory nerve fibers to the pelvic floor and parasympathetic fibers of the detrusor. The effect of SNM appears to be modulated by the activation of somatic afferents that in turn inhibit bladder sensory pathways and reflex bladder hyperactivity [2]. A possible mechanism of action on pain relies on the gate control theory. The stimulation of bigger Aβ fibers, such as with pressure or tactile stimuli, may activate inhibiting interneurons that in turn reduce the activity of smaller nociceptive Aδ and C fibers. A lower urinary tract neural control is showed in Fig. 1.

Cats models suggest that the inhibition of bladder activity occurs primarily in the central nervous system (CNS) by inhibition of the ascending or descending pathways of the spino-bulbo-spinal micturition reflex [3]. A recent work applying functional magnetic resonance on women treated with SNM for overactive bladder evidenced that SNM may directly influence brain activity [4]. The increasing of stimulation amplitude determined a progressive overall brain activation. A subsensory stimulation determined the deactivation of the pons and periaqueductal gray matter, with stable activation of the right inferior frontal gyrus. A sensory stimulation determined the activation of the insula and the deactivation of the medial and

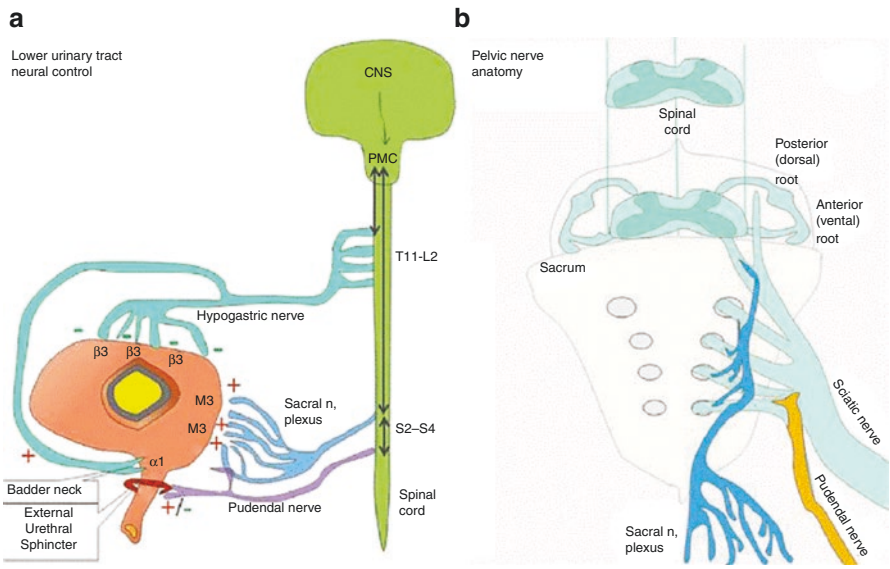

Fig. 1 Lower urinary tract neural control. *CNS* Central Nervous System, *PMC* Pontine micturition center

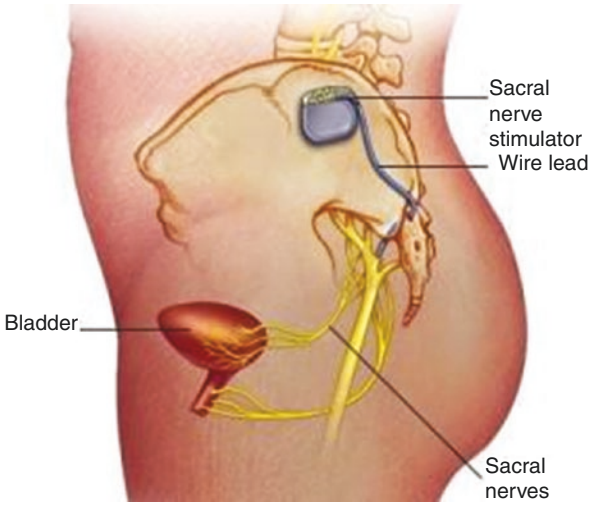

Fig. 2 Apposition of the sacral nerve stimulator

superior parietal lobes. A suprasensory stimulation determined the activation of multiple structures and the expected S3 somatosensory region. The device is inserted into the lower part of your back and is made up of a wire and a battery.

SNM comes in two stages: a basic evaluation (test phase) and a full system implant (permanent implant) (Fig. 2).

2 Indications

SNM is indicated for the treatment of urinary retention and symptoms of overactive bladder, including urinary incontinence and significant symptoms of urinary frequency, alone or in combination, in patients in whom more conservative therapies have failed or were not tolerated.

At the moment, the InterStim device (Medtronic, Fridley, MN) is the only FDA approved implantable SNM device for treatment of refractory urgency urinary incontinence, urgency-frequency, non-obstructive urinary retention and fecal incontinence (Fig. 3). It is also indicated for the treatment of chronic fecal incontinence (FI) in patients who have failed or are not candidates for more conservative treatments.

A Cochrane Review by Thaha et al. reported that SNM could improve continence in patients with fecal incontinence [5]. However, the study added that SNM did not improve symptoms in patients with constipation. SMN has also been evaluated as a fourth line treatment option for refractory interstitial cystitis/bladder pain syndrome (IC/BPS) [6]. Chronic pelvic pain and constipation is another area where off-label use of SNM has been trialed [7, 8]. Fowler's Syndrome or a primary disorder of external urethral sphinter relaxation, has been studied as a target for SNM [9].

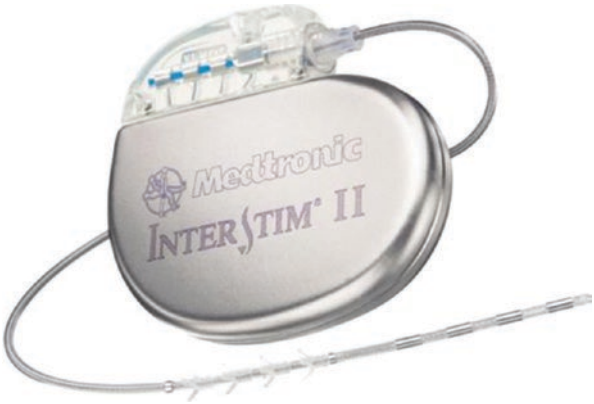

Fig. 3 InterStim II Device

A study by Schober et al. proposed that sacral nerve stimulation is a valid adjunctive therapy for refractory pediatric lower urinary tract dysfunction [10]. SNM can constitute a safe therapeutic alternative for such patients who have undergone multiple failed treatments in their medical history. A meta-analysis performed by Kessler et al., which included patients with multiple sclerosis, Parkinson's disease, cerebrovascular accidents, spinal cord injuries, and other neurogenic LUTDs, revealed a success rate of 68% for the test phase and 92% for permanent neuromodulation [11].

3 Contraindications

SNM presents several contraindications such as:

- Mechanical outlet obstruction
- Diathermy use (shortwave, microwave, ultrasound)
- Inadequate response to test stimulation or inability to operate the device
- Magnetic resonance represents a relative contraindication for non-cranial indication.

However, safety and efficacy have not been determined for other conditions such as:

- Bilateral stimulation
- Pregnancy
- Unborn fetus and delivery
- Age younger than 16 years
- Patients with neurologic conditions such as multiple sclerosis

4 Precautions

The SNM system could adversely affect cardiac devices, electrocautery, defibrillators, ultrasonic equipment, radiation therapy, magnetic resonance imaging, theft detectors, and screening devices.

Individuals with very low perception thresholds may perceive fluctuations in the stimulation intensity as the battery nears depletion and may have to increase or decrease the amplitude to maintain symptom control. Patients should carry a control device at all times to be able to adjust and/or turn off the device.

The control device may affect other implanted devices and should not be placed over other implanted devices. The patient programmer should not be immersed in liquid or cleaned with bleach, nail polish remover, mineral oil, or other similar substances. When the programmer is in use, flammable or explosive atmospheres should be avoided.

5 Warnings

Sources of strong electromagnetic interference can result in dangerous injuries from heating of the implanted Interstim components and damage to surrounding tissue, damage to the Interstim requiring replacement, operational changes causing it to turn on or off or to reset to power-on-reset (POR) settings, and unexpected changes in stimulation causing an increase in stimulation or intermittent stimulation.

Damage to the case may result in leakage of battery chemicals, which can cause severe burns. The Interstim may affect the function of other implanted devices such as cardiac devices, other neurostimulators, and implantable drug pumps. To minimize interactions with cardiac devices, the Interstim should be programmed to bipolar configuration and a minimum rate of 60 Hertz and the cardiac device programmed to bipolar sensing. Defibrillators, when active, may damage the Interstim device. Activities that involve sudden, excessive, or repetitive bending, twisting, bouncing, or stretching (eg, gymnastics, mountain biking) can cause fracture or dislodgement.

Manipulation or rubbing of the system through the skin may result in damage to the system, lead dislodgement, skin erosion, or uncomfortable stimulation at the implant site.

Patients should not scuba dive below 10 meters (33 feet) or enter hyperbaric chambers of more than 2.0 atmospheres absolute (ATA). High altitudes do not affect the neurostimulator. However, skydiving or hiking may cause stress on the system, causing lead dislodgement or fractures.

6 Basic Evaluation Phase

Prior to the test phase, the patient is asked to complete a voiding diary, which will serve as a baseline. The initial test phase may be performed in the office or the operating room.

The test stimulator has 3 components.

- White verifier which is connected to the patient via a white cable and this delivers the stimulation.
- Handheld controller which is a touch screen and used to alter the intensity of the stimulation or to turn the device on/off.
- Thin wire which is inserted into the bottom of patient's back/spine in the sacrum.

The patient is placed in a prone position, and his or her lower back and gluteal region are prepared and draped. Socks are removed so that the physician can visualize the feet.

A portable c-arm and fluoroscopy are used to identify the midline of the spine and level of the S3 foramen. The skin is marked, and the area infiltrated with local anesthetic. A 20-gauge, 3.5-inch insulated foramen needle is then inserted into the S3 foramen on each side at a 60° angle relative to the skin under fluoroscopic guidance. A lateral image can be used to confirm the location and depth in the foramen.

The needles are then stimulated to confirm appropriate positioning. If the needles are in the correct position, there will be bellows contraction of the pelvic floor due to contraction of the levator muscles and plantar flexion of the great toe. The patient, if awake, will be able to confirm correct positioning with contraction or tingling of the pelvic floor muscles. If the needles are in the S2 foramen, plantar flexion of the whole foot with lateral rotation will occur with stimulation. If the needles are in the S4 foramen, there will be no lower extremity movement despite bellows response (Fig. 4).

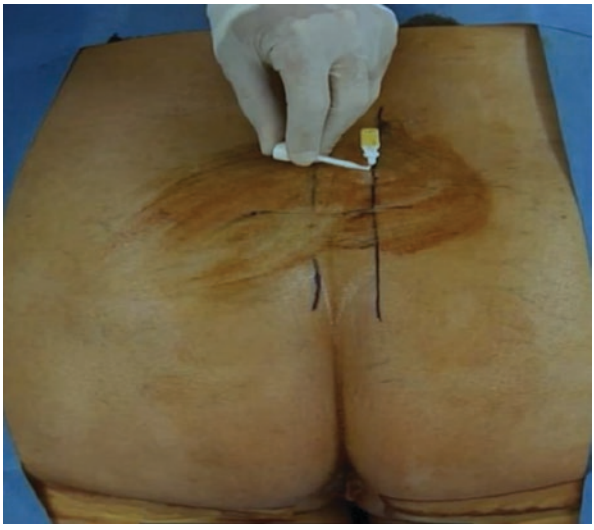

Fig. 4 Needles apposition in sacral region

Once correct positioning of the needles has been confirmed, temporary lead wires are passed through the foramen needles, and the needles are removed carefully to prevent dislodgement of the leads. The temporary leads with unipolar electrodes are steri-stripped to the patient's back and a dressing placed.

The patient then goes home with an external stimulator after instruction regarding its use. Prophylactic antibiotics are often given while the temporary leads are in place. The temporary leads are typically left in place for 5–7 days while the patient completes treatment voiding diaries.

The patient should be instructed to avoid bending, stretching, or lifting heavy objects during the initial trial period to decrease the risk of wire dislodgment. The patient's response to treatment is compared to the baseline voiding diary. If the change in symptoms is 50% or greater, he or she is a candidate for placement of the permanent stimulator.

7 Advanced Evaluation (Tined Lead Test)

In some cases, with a not optimal test phase, maybe because the wire moved out of position early in the trial, an advanced evaluation with a tined lead could be performed. An advanced evaluation involves having the permanent tined lead/wire inserted in theatre with you asleep, but once again connected up to an external battery pack as described in the basic evaluation section. The benefit of this is that the permanent wire has small fixation points on it, called tines, which make it less likely to migrate out of position during the trial phase. The disadvantage of an advanced evaluation is that the wire needs to be put in in the operating room/theatre initially and you will then require a second surgical appointment 2–4 weeks after the insertion to either remove the wire if it has not worked, or attach the neurostimulator (battery) to the wire if you have had a significant improvement in symptoms. The process of lead insertion and subsequent neurostimulator attachment are outlined in the full system implant section below.

8 Permanent Implant Implant Phase

The second phase involves implantation of the permanent device. The InterStim device consists of:

- An implantable nerve stimulator (inside which is the battery) is inserted under the skin (just larger than a £2 coin). Usually in the buttock area.
- An electrode or thin wire with barbs/tines that carries the electrical pulses to the bladder nerves.
- A hand-held patient programmer that enables you to adjust the level of the stimulation and allows you to turn your implant on or off.

This is performed in the operating room under anesthesia. The patient is placed in a prone position and prepared and draped in a sterile fashion. Perioperative antibiotics are administered. The next step depends on whether a permanent quadripolar lead was placed during the first phase (often the case if the first phase is performed in the operating room) or temporary leads were placed (office based first phase). If the permanent quadripolar was placed during the first phase, the second phase is quick and does not require fluoroscopy. The incision where the temporary connector was placed in the buttock is opened and the permanent implantable pulse generator (IPG) is connected to the lead and buried in a deep subcutaneous pocket in the right buttock. It is important to ensure the IPG is functioning properly prior to closure of the incision. If the first phase was performed in the office and temporary leads are in place, fluoroscopy will be needed, and the quadripolar lead is placed on the side on which the patient had the best in-office test response. The lead is tunneled deeply through the subcutaneous fat to an incision in the buttock region, where the IPG will be placed. The lead is connected to the IPG and buried in the deep subcutaneous pocket.

9 Surgical Technique

The surgical technique involves placement of a quadripolar lead at the superior medial location of the S3 foramen with a standard transcutaneous image-guided approach, using a tined lead and a stylet. The curved stylet is an innovation from the straight stylet, allowing closer association with the S3 nerve and ultimately a higher percentage of therapeutic success. For lead placement, the goal is to achieve motor responses at low amplitudes (<2 mA) on all four electrodes. The optimal motor response needed for a successful lead placement continues to be an area of ongoing research. Gilleran et al. argued that obtaining motor responses in less than 4 electrodes does not negatively affect the rates of progressing to full implant or short-term revision rates [12].

Meanwhile, Pizarro et al. indicated that a higher number of electrodes that produced a toe motor response was associated with a lower likelihood of future lead revision while the higher number of bellows responses did not have the same association [13]. Thus, optimization of SNM lead placement is ongoing; however, the high rates of progression to full implant and efficacy for FDA-approved indications have been well established.

10 Monitoring & Follow-up

Once implanted, the neurostimulator is activated. The physician initially programs the device and adjusts the stimulator to optimize the therapy for each patient. The patient will also need instructions to adjust the intensity of the stimulation. Once an

optimal strength and intensity of pulse stimulation has been determined, the patient can modulate the stimulator for maximal response. Periodic follow-up, usually every 6–12 months, is recommended to monitor the therapy's effectiveness.

11 Adverse Events

Several adverse events have been reported such as:

- Infections in lead site
- Migration of device
- Malfunctioning
- Pain at implantation site
- Spontaneous resolved seroma
- Surgical revision

Rare:

- urinary tract infections
- electrical shock sensation
- foreign-body sensation
- lower-limb numbness.

12 Outcomes

SNM has shown to achieve good long-term success in many patients, better than previous treatment methods. A review of neuromodulation devices showed at the long-term (>1 year) clinical response rates of SNM for urge incontinence and urgency frequency ranging around 50% or higher [14].

A study reported that 30% of patients had adverse effects with the most common being undesirable change in stimulation, 12% long-term complications of the SNM device showed that within the first 5 years about 30–40% of the devices had to be removed or replaced [15]. The main adverse events were pain at stimulator site, lead migration, infection or malfunctioning. However, if compared to drug therapies in OAB patients, SNS is considered more expensive, but more effective in a two-year period [16]. Carone et al. proved that SNM is effective and safe third-line treatments for OAB, non-obstructive urinary retention, and chronic pelvic pain/IC. The overall success rate of SNM ranges from 43% to 85%. The technique has demonstrated to be safe, with a low rate of complications and need of reintervention [17].

The InSite study trial showed a reduction of >50% of urinary leaks with a success rate of 76%, compared to standard medical therapy (SMT) that assessed at 49% ($p = 0.002$) [18]. A 3-years prospective evaluation of efficacy of the SNM arm was performed: the group of patients suffering of urgency incontinence, 43% returned to

complete continence ($p < 0.001$), and there was a significant reduction of leaks episodes (from 3.1 ± 2.7 to 2.1 ± 2.3/24 h, $p < 0.001$). In the group of patients suffering of urgency without incontinence episodes, 66% of patients returned to a normal voiding frequency, with a significant reduction in number of voids/day (from 12.6 ± 4.5 to 4.8 ± 4.1) [19].

The ROSETTA trial (Refractory Overactive Bladder: Sacral Neuromodulation vs Botulinum Toxin Assessment), enrolled women suffering of OAB and randomized to two arms, SNM, and botulinum toxin injection. After a follow-up of 6 months, the results showed that both techniques lead to a significant decline in the main number of daily urgency incontinence events, which was greater for the botulinum toxin arm (−3.89 (−4.26/−3.52) vs −3.25 (−3.64/−2.87)). However, the Botulinum toxin arm was afflicted by a greater incidence of urinary tract infections (UTI), perhaps due to the higher need of self-intermittent catheterization [20]. Weil et al. in a smaller RCT, compared the results of SNM versus SMT with a follow-up of 18 months. It showed an increase in pad use in 85% of patients, with a significant reduction in leakage severity and mean number of leakage episodes [21]. Two smaller RCT by Hassouna et al. and Schmidt et al., compared the results of SNM to SMT with 6 months follow-up. The first study showed a significant reduction of daily number of voids in 56% of patients (vs 4% in the SMT group) and degree of urgency and a significant increase of voided volume per void (226 ± 124 vs 123 ± 75, $p < 0.0001$) [22]. The second study demonstrated a significant reduction in the daily number of urinary leakage (2.6 ± 5.1 vs 11.3 ± 5.9, $p < 0.001$) and leakage severity (0.03 ± 0.9 vs 3.9 ± 3.8, $p < 0.0001$) [23]. After the turn off of the stimulation, the results were comparable to baseline, pointing out that an active stimulation may be needed to achieve the curative effect of SNM.

Nobrega et al. demonstrated that a cohort of 99 consecutive patients with 47% response after first stage tined lead placement, that there was no significant difference in any urodynamic parameter between first stage success and failure groups. There was a tendency of having a lower compliance in the failure group, but it did not reach statistical significance [24]. Another study of Jadav et al., showed that female patients with pelvic floor dysfunction, demonstrated after a median 6.8 months follow-up a reduction on OAB symptoms from baseline with the use of ePAQ-PF score (20.9 ± 19.7 vs 28.5 ± 21.5, $p < 0.05$) with clinical benefit also in other domains such as bowel and sexual function [25]. Sutherland et al. in retrospective series of 83 patients treated with SNM with a mean follow-up of 22 months evidenced a decrease in daily mean number of voids (8.5 ± 5.0 vs 12.4 ± 5.1, $p < 0.0001$), mean night voids (1.6 ± 2.2 vs 2.3 ± 1.8, $p = 0.0091$), mean daily leakage episodes (1.0 ± 1.4 vs 5.0 ± 4.7, $p < 0.0001$), and number of daily pads (0.3 ± 0.7 vs 2.3 ± 2.6, $p < 0.0001$) [26]. In another retrospective study, Peeters et al. evidenced in a cohort of 104 patients, with a mean follow-up of 46.8 months, a significant decrease in urinary incontinence (70%) and urgency/frequency symptoms (68%). A smaller group of 94 patients suffered of idiopathic retention (32 patients with a diagnosis of Fowler's syndrome) and showed good results even in this peculiar subgroup with a success rate (symptom reduction >50%) of 73% in idiopathic retention and a cure rate of 62.5% in the Fowler's syndrome group and 53% in the

remainder patients [27]. Another prospective study on 31 patients with non-obstructive urinary retention with a longer follow-up of 49.3 months showed a success rate of 58% with regard to the average number of daily catheters (1.9 ± 2.8 vs 5.3 ± 2.8, $p < 0.001$) and of 71% with regard to the average volume per catheter (109.2 ± 184.3 vs 379.9 ± 183.8, $p < 0.001$) [28]. There is a lower number of good quality studies on the treatment of IC/BPS with SNM. In a small retrospective study on 44 patients with IC/BPS with a long follow-up of 61.5 months, Gajewski and Al-Zahrani reported an 80% improvement of the global response assessment (GRA) and a 43% clinical success. They reported the need of surgical revision in 50% of patients, with an explant rate of 28%, in four cases due to painful stimulation [29]. A multicenter cross-sectional observational study evaluated the impact of pregnancy in SNM treatment. Roulette et al. enrolled a group of 21 women with SNM implant carrying 27 pregnancies. In all, 18.5% of women turned off the device while trying to conceive, all the remainder in the first trimester and during all pregnancy. Before pregnancy, SNM was effective in 76.19% of patients; during pregnancy, urinary symptoms were recurrent in all but one patient. In all, 74% of patients reactivated the SNM after pregnancy and 20% reported a reduction in efficacy, in two of four cases due to a displacement of the electrode. Three of four patients with chronic retention resumed self-catheterization and 25.9% of patients had complications, mainly UTI and one case of pelvic pain [30].

SNM is an effective therapy for CPP in both IC/BSP and non-IC/BSP patients, with better results in non-IC/BSP patients. Outcomes of the antegrade caudal approach were comparable with the standard retrograde approach [7]. SNM in women with pelvic floor disorders, especially bladder dysfunction, seems to have a positive effect on sexual function. Studies reported a positive effect of SNM on sexual function. Pooled analysis of data from 11 studies involving 573 patients before SNM and 438 patients after SNM showed significant improvement in sexual function [31]. SNM was superior to PTNS in Wexner score reduction and improvement in weekly FI episodes. SNM showed greater improvement in Fecal Incontinence Quality of Life (FIQL) domains of coping and depression as compared with PTNS [32].

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