Sacral Nerve Stimulation/ Neuromodulation

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DESCRIPTION

Sacral nerve stimulation (SNS), also known as sacral nerve neuromodulation (SNM), involves the implantation of a permanent device that modulates the neural pathways controlling bladder or rectal function.

Treatment using sacral nerve stimulation (SNS)/sacral nerve neuromodulation (SNM), is one of several alternative modalities for individuals with fecal incontinence or urinary incontinence (urge incontinence, urgency-frequency syndrome, non-obstructive urinary retention or overactive bladder) who have a documented failure or intolerance to conventional conservative therapies (behavior training such as bladder training, promoted voiding, pelvic muscle exercise training; dietary modification; and pharmacologic therapies).

Urinary and Fecal Incontinence
Urinary voiding dysfunction is usually defined as the inability to control urination and are divided into different types:

- **Urinary urge incontinence:** Is defined as the involuntary leakage of urine when there is a strong urge to void due to bladder spasms or contractions with enough force to override the sphincter muscles of the urethra.
- **Urinary urgency-frequency incontinence**: Is defined as strong and abnormal urge to urinate, resulting in frequent urination without a loss of the feeling of the fullness of the bladder.
- **Non-obstructed urinary retention:** Is usually caused by weak pelvic floor muscles or dysfunction in the neural pathway between the brain and bladder and results in the inability to completely empty the bladder of urine.
- **Overactive bladder (OAB, Urgency) Syndrome**: Defined as urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence (OAB-wet) or without (OAB-dry), in the absence of urinary tract infection or other detectable disease.

Treatment options for urinary voiding disorders may include behavioral strategies, pharmacological interventions, electrical stimulation, or reconstructive surgery.

Fecal incontinence is the inability to control bowl movements leading to feces leaking from the rectum. Fecal incontinence may be caused by several factors including muscle damage, such as that experienced by childbirth, or after rectal surgery, or from damage to the nerves that control the anal muscle or regulate rectal sensation. Additionally, it may be caused by a reduction in the elasticity of the rectum, which shortens the time between the sensation of the stool and the urgent need to have a bowel movement. Surgery or radiation injury can scar and stiffen the rectum. Inflammatory bowel disease can also make the rectum less elastic.

Treatment depends on the cause of the fecal incontinence and may include dietary changes, drug therapy, bowel training, sacral nerve stimulation or surgery.

The mechanism of action of sacral nerve stimulation/sacral neuromodulation is not completely understood regarding the effects on the lower urinary tract. However, the therapy seems to modulate spinal cord reflexes and brain involvement via afferent signaling rather than direct motor stimulation of the detrusor or urethral sphincter. The most widely accepted therapy suggests that sacral nerve modulation blocks or otherwise interferes with the afferent input to the sacral spinal code, inhibiting detrusor overactivity resulting in clinical relief of urinary frequency and urgency.

The precise mechanisms explaining how sacral modulation helps control fecal incontinence are poorly understood. Most research suggests that placement of the sacral nerve modulation lead in the S3 region will cause stimulation of afferent fibers from the anal sphincter, rectum, and pelvic floor. Stimulation of these afferents reduces activation of C fibers during rectal filling, blocking inputs from the rectum to pontine center. It is

also suggested that sacral nerve modulation can active somatic afferent fibers to inhibit colonic activity and promote internal anal sphincter tone in a somato-visceral reflex mechanism.

Sacral Nerve Stimulation/Neuromodulation Temporary and Permanent Placement
Before implantation of the permanent device, individuals undergo an initial trial testing phase to estimate potential response to treatment. The first type of testing developed was percutaneous nerve evaluation (PNE). This procedure is done under local anesthesia, using a test needle to identify the appropriate sacral nerve(s). Once identified, a temporary lead wire is inserted through the test needle and the wire is attached to an external stimulator, which is carried in the pocket or on a belt loop for a trial period of 7 to 14 days. The individual records voiding patterns during the trial period and for one week after the wire is removed. Data from the voiding diaries are used to compare the symptoms that are experienced at baseline, during the test phase, and after removal of the wire. The results of this test phase are used to determine whether individuals are appropriate candidates for the permanent device. If the trial stimulation demonstrates the individual had 50% or greater reduction in symptom frequency, they are deemed eligible for the permanent device.

A second type of testing is a 2-stage surgical procedure. In the first stage, a quadripolar-tined lead is implanted (stage 1). The testing phase can last as long as several weeks, and if individual show a 50% or greater reduction in symptom frequency, they can proceed to stage 2 of the surgery, which is permanent implantation of the stimulation/neuromodulation device. The 2-stage surgical procedure has been used in various ways. They include its use instead of PNE (percutaneous nerve evaluation), for individuals who fail PNE, for individuals with an inconclusive PNE, or for individual who had a successful PNE to refine individual selection further.

The permanent device is implanted with the individual under general anesthesia. The electrical leads are placed in contact with the sacral nerve root(s) via an incision in the lower back, and the wire leads are extended through a second incision underneath the skin, across the flank to the lower abdomen where the pulse generator is inserted and connected to the wire leads. Following implantation, the physician programs the pulse generator to the optimal settings for the individual. The individual can switch the pulse generator on and off by placing the control magnet over the area of the pulse generator for 1 to 2 seconds.

Urinary Incontinence

Clinical Context and Therapy Purpose
Urge incontinence is defined as leakage of urine when there is a strong urge to void. Urgency-frequency is an uncontrollable urge to urinate, resulting in very frequent, small volumes and is a prominent symptom of interstitial cystitis (also called bladder pain syndrome). Urinary retention is the inability to empty the bladder of urine completely.

The purpose of sacral nerve neuromodulation in individuals with urinary incontinence is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Population
The relevant population of interest is individuals with urinary incontinence.

Interventions
The treatment being considered is sacral nerve neuromodulation.

Comparators
The comparator of interest is pharmacologic treatment.

Outcomes
The outcomes of interest are symptoms, morbid events, and treatment-related morbidity.

Positive outcomes include reduction or elimination of episodes of incontinence without complications from the device or implantation procedure.

Negative outcomes would be infection, bleeding, pain, and lead breakages, and lack of improvement in incontinence.

Although no set standard for length of follow-up has been established, the existing literature evaluating sacral nerve neuromodulation for urinary incontinence has lengths of follow-up ranging from 6 months to 5 years. Follow-up of at least 1 year would be preferred.

Review of Evidence

Randomized Controlled Trials (RCTs)
Several RCTs on sacral nerve stimulation/neuromodulation (SNS/SNM) for urinary incontinence have been conducted. One was sponsored by Medtronic and submitted to the U.S. Food and Drug Administration as part of the device approval process. Findings have not otherwise been published. Based on this RCT, the authors concluded that SNS reduced urge incontinence compared with control patients. The trial was well-designed, using standardized clinical and functional status outcomes measurements, and enrolled patients with severe urge incontinence who had failed extensive prior treatments. The magnitude of effect (approximately one-half of patients became dry, three-quarters experienced at least 50% reduction in incontinence) was fairly large, probably at least as great as with surgical procedures, and larger than expected from a placebo effect or conservative measures such as behavioral therapy or drugs. The therapy evaluation test, in which the device was turned off (i.e., sham treatment was provided) and patients thus served as their controls, provided further evidence that the effect on incontinence was due to electrical stimulation and demonstrated that the effect of SNS is reversible. The cohort analysis of the clinical trial provided some evidence that the effect of SNS could be maintained for up to 2 years. There was a high rate of adverse events reported in this trial.

Most were minor and reversible; however, approximately one-third of patients required surgical revision for pain at the operative sites or migration of the leads.

In this RCT, 177 of 581 patients had urinary retention. Patients with urinary retention reported significant improvements regarding volume per catheterization, a decrease in the number of catheterizations per day, and increased total voided volume per day. At 12 months post-implant, 61% of patients had ceased use of catheterization. At baseline, 220 (38%) of 581 had significant urgency-frequency symptoms. After 6 months, 83% of patients with urgency-frequency symptoms reported increased voiding volumes with the same or reduced degree of frequency. At 12 months, 81% of patients had reached normal voiding frequency. Compared with a control group, patients with implants reported significant improvements in quality of life (QOL), as evaluated by the Short-Form 36-Item Health Survey.

An additional prospective RCT of 44 patients with urge incontinence was published by Weil et. al., at 6 months, the implant group showed significantly greater improvements in standardized clinical outcomes, compared with those receiving conservative therapy. The magnitude of effect was substantial.

Siegel et. al. (2015) published results of an industry-sponsored, Food and Drug Administration mandated a post-approval study known as the Insite trial. This RCT compared sacral nerve neuromodulation (SNM) using a 2-stage surgical procedure with standard medical therapy. Study inclusion criteria were a diagnosis of overactive bladder (at least 8 voids per day and/or at least 2 involuntary leaking episodes in 72 hours) and a failed trial of at least 1 anticholinergic or antimuscarinic medication. Also, there needed to be at least 1 such medication that had not yet been prescribed. Patients with neurologic diseases and with primary stress incontinence were excluded. Seventy patients were allocated to SNM and 77 to standard medical therapy. Of the 70 patients in the SNM group, 11 elected not to receive test stimulation with the tined lead and 8 received the lead but did not receive a full system implant due to lack of response to a 14-day test stimulation period (response was defined as ≥50% reduction in average leaks and/or voids). Patients in the medical treatment group tried the next recommended medication or restarted a discontinued medication. Therapeutic success was defined as at least a 50% improvement in average leaks per day or at least a 50% improvement in the number of voids per day or a return to fewer than 8 voids per day. In intention-to-treat (ITT) analysis, the therapeutic success rate at 6 months was 61% in the SNM group and 42% in the standard treatment group; the difference between groups was statistically significant ($p=0.02$). QOL at 6 months was a secondary outcome. Several validated QOL scales were used, and all favored the SNM group compared with the standard treatment group ($p<0.002$ for all comparisons).

Twelve-month follow-up of the Insite trial was published by Noblett et. al. (2016). They analyzed patients from in the sacral nerve stimulation (SNS) group of initial RCT plus additional patients enrolled and implanted in the interim. A total of 340 patients underwent test stimulation, 272 underwent implantation, and 255 completed 12 months

of follow-up. In a modified completers' analysis, the therapeutic success rate was 82%. This modified completers' analysis included patients who were implanted and had either a baseline or 12-month evaluation or withdrew from the trial due to a device-related adverse event or lack of efficacy. In an analysis limited to study completers, the therapeutic response rate was 85%. The Noblett analysis did not include data from the control group of patients receiving only standard medical therapy.

Amundsen et. al. (2016) reported on an RCT comparing intradetrusor injection of onabotulinumtoxinA (n=192) with SNM (n=189) in women with refractory urgency urinary incontinence, defined as at least 1 supervised behavioral or physical therapy intervention and the use of a minimum of 2 anticholinergics (or inability to tolerate or contraindications to the medication). In ITT analysis, patients in the onabotulinumtoxinA-treated group had greater reductions in urge incontinence per day (3.9 per day) than in the SNM-treated group (3.3 per day; mean difference, 0.63; 95% confidence interval [CI], 0.13 to 1.14; p=0.01). OnabotulinumtoxinA-treated patients had greater reductions in some overactive bladder-related QOL questionnaire-related measures, although the clinical meaningfulness of the changes was uncertain. Patients in the onabotulinumtoxinA-treated group were more likely to have urinary tract infections (35% vs 11%; risk difference, -23%; 95% CI, -33% to -13%; p<0.001).

Case Series

Case series have provided longer follow-up data than the RCTs. For example, a series by Groen et. al. (2011) in the Netherlands reported the longest follow-up. Sixty patients had at least 5 years of follow-up after SNM for refractory idiopathic urge urinary incontinence. Success was defined as at least a 50% decrease in the number of incontinent episodes or pads used per day. The success rate was 52 (87%) of 60 at 1 month and gradually decreased to 37 (62%) at 5 years. The number of women who were completely continent was 15 (25%) at 1 month and 9 (15%) at 5 years. At the 5-year follow-up, SNM was still used by 48 (80%) of 60 women. Fifty-seven adverse events were reported in 32 (53%) of 60 patients. The most frequent were hardware-related or pain or discomfort. There were 23 reoperations in 15 patients. In most cases, the pain was managed conservatively.

Findings from a large prospective series were reported by White et. al. (2009). The series focused on complications associated with SNM in 202 patients with urge incontinence, urinary urgency, or urinary retention. At a mean follow-up of 37 months (range, 7-84 months), 67 (30%) patients had experienced adverse events that required either lead or implantable pulse generator revisions. Complications included pain (3%), device malfunction secondary to trauma (9%), infection (4%), postoperative hematoma (2%), and lead migration (6%). Also, 5% of patients underwent elective removal, 4% had device removal due to lack of efficacy, and 2% required removal due to battery expiration. At the last follow-up, 172 (85%) patients had functional implanted units.

Section Summary
Data from randomized controlled trials (RCTs) and case series with long-term follow-up have suggested that sacral nerve stimulation/neuromodulation (SNS/SNM) reduces symptoms of urge incontinence, urgency-frequency syndrome, non-obstructive urinary retention, and overactive bladder in selected individuals.

Fecal Incontinence

Clinical Context and Therapy Purpose

Fecal incontinence can arise from a variety of mechanisms, including rectal wall compliance, efferent and afferent neural pathways, central and peripheral nervous systems, and voluntary and involuntary muscles. Fecal incontinence is more common in women, due mainly to muscular and neural damage that may occur during vaginal delivery.

The purpose of sacral nerve neuromodulation in individuals with fecal incontinence is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Population
The relevant population of interest is individuals with fecal incontinence.

Interventions
The treatment being considered is sacral nerve neuromodulation.

Comparators
The comparator of interest is continued conservative therapy, such as dietary modification, bulking, or pharmacologic treatment.

Outcomes
The outcomes of interest are symptoms, morbid events, and treatment-related morbidity.

Positive outcomes include reduction or elimination of episodes of incontinence without complications from the device or implantation procedure.

Negative outcomes would be infection, bleeding, pain, and lead breakages, and lack of improvement in incontinence.

Although no set standard for length of follow-up has been established, the existing literature evaluating sacral nerve neuromodulation for fecal incontinence has lengths of follow-up ranging from 2 weeks to 84 months. Follow-up of at least 1 year would be preferred.

Review of Evidence

Systematic Reviews

Tan et. al. (2011) published a meta-analysis of studies sacral nerve neuromodulation (SNM) for treating fecal incontinence. They identified 34 studies that reported on at least 1 of their outcomes of interest and documented how many patients underwent temporary and permanent SNM. Only 1 study was an RCT (Tjandra et al [2008]). In the 34 studies, 944 patients underwent temporary SNS, and 665 subsequently underwent permanent SNS implantation. There were 279 patients who did not receive permanent implantation, and 154 of them were lost to follow-up. Follow-up in the studies ranged from 2 to 35 weeks. In a pooled analysis of findings of 28 studies, there was a statistically significant decrease in the number of incontinence episodes per week with SNM compared with maximal conservative therapy (weighted mean difference, -6.83; 95% CI, -8.05 to -5.60; $p<0.001$). Fourteen studies reported incontinence scores, and when these results were pooled, there was also a significantly greater improvement in scores with SNS than with conservative therapy (weighted mean difference, -10.57; 95% CI, -11.89 to -9.24; $p<0.001$).

Maeda et. al. (2011) published a systematic review of studies on complications following permanent implantation of a sacral nerve stimulation (SNS) device for fecal incontinence and constipation. Reviewers identified 94 articles. Most addressed fecal incontinence. A combined analysis of data from 31 studies on SNS for fecal incontinence reported a 12% suboptimal response to therapy (149/1232 patients). A review of complications reported in the studies found that the most commonly reported complication was pain around the site of implantation, with a pooled rate of 13% (81/621 patients). The most common response to this complication was repositioning the stimulator, followed by device explantation and reprogramming. The second most common adverse event was an infection, with a pooled rate of 4% (40/1025 patients). Twenty-five (63%) of the 40 infections led to device explantation.

Thin et. al. (2013) published a systematic review of randomized trials and observational studies evaluating sacral nerve neuromodulation (SNM) for treating fecal incontinence. Sixty-one studies met the following eligibility criteria: assessed at least 10 patients, had a clear follow-up interval, and reported the success rate of therapy based on a 50% or greater reduction in fecal incontinence episodes. Only 2 studies were RCTs (Tjandra et al [2008], Leroi et al [2005]; described next) and 50 were prospective case series. Data from 2 studies with long-term follow-up were pooled to calculate median success rates using ITT analysis. These median success rates were 63% in the short term (≤12 months of follow-up), 58% in the medium term (12-36 months), and 54% in the long-term (>36 months). The per-protocol short-, medium-, and long-term success rates were 79%, 80%, and 84%, respectively.

Thaha et. al. (2015) conducted a Cochrane review assessing sacral nerve stimulation (SNS) for fecal incontinence and constipation in adults, which included randomized, quasi-randomized, and crossover trials. For fecal incontinence, reviewers included 6 trials of SNM (n=219 patients), 2 of which used parallel-group designs (Thin et al [2015],

Tjandra et al [2008]; the latter described below); the others used crossover designs. The primary methodologic quality issue noted was a lack of clarity involving randomization techniques and allocation concealment. Reviewers concluded: "The limited evidence from the included trials suggests that SNS can improve continence in a proportion of patients with fecal incontinence."

Randomized Controlled Trials (RCTs)

Tjandra et. al. (2008) published an RCT assessing 120 patients with severe fecal incontinence. Patients were randomized to sacral nerve stimulation (SNS) or best supportive therapy, consisting of pelvic floor exercises with biofeedback, bulking agents, and dietary management with a team of dieticians. Exclusion criteria included neurologic disorders and external anal sphincter defects of more than 120° of the circumferences, although a "high proportion" of the patients had pudendal neuropathy. The trial was not blinded. Of the 60 patients randomized to SNS, 54 (90%) had successful test stimulation and 53 proceeded with the implant of the pulse generator. At baseline, the SNS group had an average of 9.5 incontinent episodes per week, and the controls had 9.2. Both groups had an average of 3.3 days per week with incontinence. At 12-month follow-up, episodes had decreased to 1 day per week, with 3.1 episodes in the SNS group, but no change in the control group (mean, 3.1 d/wk), with 9.4 episodes. Complete continence was achieved in 22 (42%) of the 53 SNS patients and 13 (24%) patients improved by 75% to 99%. None of the patients had worsening of fecal continence. Adverse events included pain at implant site (6%), seroma (2%), and excessive tingling in the vaginal region (9%).

Prospective Noncomparative Studies

A key multicenter prospective trial is the 16-site multicenter Food and Drug Administration investigational device exemption study of SNS in 120 patients with fecal incontinence. Findings were initially reported by Wexner et. al. (2010). To be included, patients had to have chronic fecal incontinence for more than 6 months or more than 12 months after vaginal childbirth, defined as more than 2 incontinent episodes on average per week. All patients had failed or were not candidates for more conservative treatments. Exclusion criteria included congenital anorectal malformation; previous rectal surgery, if performed within the last 12 months (or 24 months in case of cancer); defects of the external anal sphincter over 60°; chronic inflammatory bowel disease; visible sequelae of pelvic radiotherapy; active anal abscesses and fistulae; neurologic diseases such as clinically significant peripheral neuropathy or complete spinal cord injury; and anatomic limitations preventing the successful placement of an electrode. A total of 285 patients were screened; 133 were enrolled and underwent acute test stimulation, and 120 showed at least 50% improvement during the test phase and received a permanent stimulator. Thirty-four of the 120 patients exited the study for various reasons both related (ie, lack of efficacy in 6, implant site infection or skin irritation in 5) and unrelated to the implant (i.e., the death of a local principal investigator). Analysis based on the initial 133 patients showed a 66% success rate (≥50% improvement), while analysis based on 106 patients considered completed cases at 12 months showed an 83% success rate. The success rate based on the 120 patients who received a permanently implanted stimulator would fall between these 2 rates. Of 106 cases included in the 12-month results, perfect continence

(100% improvement) was reported in approximately 40%, while an additional 30% of patients achieved 75% or greater reduction in incontinent episodes. Success was lower in patients with an internal anal sphincter defect (65% [n=20]) than in patients without a defect (87% [n=86]).

Three- and 5-year findings were subsequently published. Mellgren et. al. (2011) reported on the 120 patients who received a permanently implanted stimulator. Mean length of follow-up was 3.1 years, and 83 (69%) completed at least part of the 3-year follow-up assessment. In ITT analysis using the last observation carried forward, 79% of patients experienced at least a 50% reduction in the number of incontinent episodes per week compared with baseline, and 74% experienced at least a 50% reduction in the number of incontinent days per week. In a per-protocol analysis at 3 years, 86% of patients experienced at least a 50% reduction in the number of incontinent episodes per week, and 78% experienced at least a 50% reduction in the number of incontinent days per week. By the 3-year follow-up, 334 adverse events considered potentially device-related had been reported in 99 patients; 67% of these occurred within the first year. The most frequently reported adverse events among the 120 patients were implant site pain (28%), paresthesia (15%), implant site infection (10%), diarrhea (6%), and extremity pain (6%). Six infections required surgical intervention (5 device removals, 1 device replacement). Hull et al (2013) reported on outcomes in 72 patients (60% of the 120 implanted patients) who had completed a 5-year follow-up visit.18 Sixty-four (89%) of the patients who contributed bowel diary data at 5 years had at least a 50% improvement from baseline in weekly incontinent episodes, and 26 36%) of the 72 patients had achieved total continence. It is uncertain whether outcomes differed in the 40% of patients missing from the 5-year analysis.

A study by Altomare et. al. (2015) also reported on long-term outcome (minimum, 60-month follow-up; median, 84-month follow-up) in patients implanted with a sacral nerve stimulator for fecal incontinence. Patients were identified from a European registry and surveyed. Long-term success was defined as maintaining the temporary stimulation success criteria, i.e., at least 50% reduction in the number of fecal incontinence episodes (or fecal incontinence symptom score) at last follow-up, compared with baseline. A total of 272 patients underwent permanent implantation of an SNS device, and 228 were available for follow-up. A total of 194 (71.3%) of the 272 patients with implants, maintained improvement in the long-term.

In 2020, Leo et.al., prospectively evaluated long-term function with sacral nerve stimulation for fecal incontinence (N=256).[18,] The median incontinence score improved from 19/24 at baseline to 7/24 at the 6-month follow-up. Of the total cohort, 235 patients were followed for a median of 110 months (range 12 to 270) with a median continence score of 10/24; this score was confirmed at longer-term follow-up (132 months, range 60 to 276) of 185 patients.

Desprez et. al. (2020) retrospectively analyzed prospectively collected data found that long-term efficacy with sacral nerve stimulation was maintained for at least 10 years

post-implantation in approximately half of the patients treated for fecal incontinence. A similarly designed study by De Meyere et. al. (2020) in a single center in Belgium demonstrated that the efficacy of sacral nerve stimulation in patients with fecal incontinence or low anterior resection syndrome was maintained for at least 5 years. A study by Picciariello et. al. (2022) identified patients who had a sacral nerve modulation implantation procedure more than 10 years earlier for fecal incontinence to assess long-term functional outcomes and quality of life. They found that only 17 (27%) of 58 patients originally identified are still experiencing efficacy with sacral nerve modulation, after a median follow-up of 13 years.

Section Summary
The evidence consists of randomized controlled trials (RCTs), observational studies, systematic reviews of RTCs and uncontrolled studies. Collectively, findings from these studies have suggested that sacral nerve stimulation (SNS)/sacral nerve neuromodulation (SNM) improve outcomes when used to treat chronic fecal incontinence in well-selected individuals s who have failed conservative therapy.

Constipation

Clinical Context and Therapy Purpose
The purpose of sacral nerve neuromodulation in individuals with constipation who have failed conservative treatment is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Population
The relevant population of interest is individuals with constipation who have failed conservative treatment.

Interventions
The treatment being considered is sacral nerve neuromodulation.

Comparators
The comparator of interest is continued conservative therapy, such as dietary modification or pharmacologic treatment.

Outcomes
The outcomes of interest are symptoms, morbid events, and treatment-related morbidity.

Positive outcomes include regular bowel movements without complications from the device or implantation procedure.

Negative outcomes would be infection, bleeding, pain, and lead breakages, and lack of improvement in constipation.

Although no set standard for length of follow-up has been established, the existing literature evaluating sacral nerve neuromodulation for constipation has lengths of follow-up ranging from 3 weeks to 55 months.

Review of Evidence

Systematic Reviews
A systematic review by Pauwels et. al. (2021) assessed the role of neuromodulation for treatment in chronic constipation. Seventeen studies on sacral nerve modulation were included. Although multiple uncontrolled retrospective and prospective studies included in the analysis demonstrated positive results on the effect of sacral nerve modulation in constipation, the 3 RCTs that were identified (Dinning et. al. [2015] and Zerbib et. al. [2017], described below, and Thomas et al [2015]) demonstrated no significant improvements in outcomes. The RCT by Thomas et al (2015) only included 11 patients.

In 2017, The Pelvic Floor Society, an affiliate of Association of Coloproctology of Great Britain and Ireland, conducted a systemic review as the basis for practice recommendations on the use of sacral nerve stimulation for the treatment of constipation. The systematic review assessed 7 observational studies, all generally of poor quality due to inadequate description of methods. Due to inconsistent reporting on harms and treatment success, and heterogeneity in the patient populations, the Society could not recommend sacral nerve stimulation.

The Cochrane review by Thaha et. al. (2015) assessed sacral nerve stimulation (SNS) for constipation and fecal incontinence in adults. Two trials on SNM for constipation were included (Dinning et al [2015], and a crossover trial). In 1 trial, the time with abdominal pain and bloating decreased during the "on" period from 79% to 33%. However, in the larger Dinning trial (discussed below), there was no improvement with SNM during the "on" period. Reviewers concluded: "SNS did not improve symptoms in patients with constipation."

Thomas et. al. (2013) published a systematic review of controlled and uncontrolled studies evaluating sacral nerve stimulation (SNS) for treatment of chronic constipation. Reviewers identified 11 case series and 2 blinded crossover studies. Sample sizes for the case series ranged from 4 to 68 patients implanted with a permanent SNS device; in 7 of the 11 studies, fewer than 25 patients underwent SNS implantation. Among the 2 crossover studies, one included 2 patients implanted with an SNS device. The other, a study by Knowles et al (2012),21 evaluated temporary stimulation in only 14 patients (see below). Patients were included if they were diagnosed with evacuatory dysfunction and rectal hyposensitivity and had failed maximal conservative treatment. They were randomized to 2 weeks of stimulation with the SNS device turned on and 2 weeks with the SNS device turned off, in random order. There was no wash-out period between treatments. The primary efficacy outcome was change in rectal sensitivity, which was assessed using 3 measures of rectal sensory thresholds. The trial found a statistically significantly greater increase in rectal sensitivity with the device turned on for 2 of the 3

measures. Among the secondary outcome measures, there was a significantly greater benefit of active treatment on the percentage of successful bowel movements per week and the percentage of episodes with a sense of complete evacuation. In addition to its small sample size, the trial lacked a washout period between treatments (ie, there could have been a carryover effect when the device was used first in the on position). Moreover, the patients were highly selected; only 14 of the approximately 1800 patients approached met the eligibility criteria and agreed to participate in the study.

In 2017, Pilkington et. al. assessed the outcomes of sacral nerve stimulation in adults with chronic constipation. Seven articles were identified, providing data on outcomes in 375 patients. Length of procedures and length of stay was not reported. Data on harms were inconsistently reported and heterogeneous, making estimates of harm tentative and imprecise. Morbidity rates ranged between 13 and 34%, with overall device removal rate between 8 and 23%. Although inconsistently reported, pooled treatment success was typically 57-87% for patients receiving permanent implants, although there was significant variation between studies. Patient selection was inconsistently documented. No conclusions could be drawn regarding particular phenotypes that responded favorably or unfavorably to sacral nerve stimulation. The authors concluded, evidence supporting sacral nerve stimulation is derived from poor quality studies. Three methodologically robust trials have reported since this review and all have all urged greater caution.

Randomized Controlled Trials (RCTs)
A larger randomized crossover trial was published by Dinning et. al. (2015). The trial included patients (age range, 18-75 years) with slow transit constipation. Potentially eligible patients completed a 3-week stool diary and, in order to continue participating, they had to indicate in the diary that they had complete bowel movements less than 3 days per week for at least 2 of the 3 weeks. Patients with metabolic, neurogenic, or endocrine disorders known to cause constipation were excluded. Fifty-seven met eligibility criteria and had temporary (percutaneous nerve evaluation) PNE, and 55 underwent permanent implantation. In random order, patients received active stimulation (subsensory in phase 1, suprasensory in phase 2) or sham stimulation (device was on, but pulse width and frequency were set to 0). The primary outcome measure, determined by stool diaries, was a bowel movement with feelings of complete evacuation more than 2 days per week for at least 2 of 3 weeks; it was only assessed in phase 2. Compared with sham stimulation, 16 (29.6%) of 54 patients met the primary outcome during suprasensory stimulation, and 11 (20.8%) of 53 patients met it during sham stimulation; the difference was not statistically significant (p=0.23). Other outcomes did not differ significantly with suprastimulation vs sham stimulation and outcomes did not differ in the phase 1 comparison of subsensory vs sham stimulation.

Zerbib et. al. (2017) reported on a double-blind crossover RCT of (sacral nerve stimulation) SNS in 36 women with refractory constipation. Subjects were eligible if they had chronic constipation (>1 year), with 2 or fewer bowel movements per week, straining to evacuate with more than 25% of attempts, or sensation of incomplete evacuation with more than 25% of attempts, with lack of response to standard therapies. Thirty-six

subjects meeting inclusion criteria underwent an initial peripheral nerve evaluation (PNE); those who had adequate symptom improvement to a predefined level were offered permanent SNS implant. After a 2-week washout, subjects were randomized to "on" or "off" for 8 weeks, followed by a 2-week washout, when the groups crossed over. Of the 36 patients enrolled, 20 responded and underwent randomization. Four were excluded (2 due to wound infection, 1 each due to the withdrawal of consent and lack of compliance). At 1-year follow-up, a positive response was observed in 12 of 20 and 11 of 20 patients after active and sham stimulation periods, respectively (p=0.746).

Case Series

One of the larger case series was published by Kamm et. al. (2010). This prospective study was conducted at multiple sites in Europe. It included 62 patients who had idiopathic chronic constipation lasting at least 1 year and who had failed medical and behavioral treatments. Constipation was defined as at least one of the following: fewer than 2 bowel movements per week, straining to evacuate in at least 25% of attempts, or a sensation of incomplete evacuation on at least 25% of occasions. Forty-five (73%) of the 62 met criteria for permanent implantation during the 3-week trial period. Criteria included an increase in evacuation frequency to at least 3 per week or a 50% reduction in either frequency of straining during evacuation or in episodes with the sensation of incomplete evacuation. After a median follow-up of 28 months (range, 1-55 months) after permanent implantation, 39 (87%) of 45 patients were classified as treatment successes (ie, met the same improvement criteria as used to evaluate temporary stimulation). There was a significant increase in the frequency of bowel movements from a median of 2.3 per week at baseline to 6.6 per week at latest follow-up ($p<0.001$). The frequency of spontaneous bowel movements (i.e., without laxatives or other stimulation) increased from a median of 1.7 per week at baseline to 4.3 per week at last follow-up (p=0.001). A total of 101 adverse events were reported; 40 (40%) of these were attributed to underlying constipation or an unrelated diagnosis. Eleven serious adverse events related to treatment were reported (the authors did not specify whether any patients experienced >1 serious event). The serious adverse events included a deep postoperative infection (n=2), superficial erosion of lead through the skin (n=1), persistent postoperative pain at the site of implantation (n=2), conditions leading to lead revision (n=4), and device failure (n=2). The study was criticized for including a large number of patients who had more than 2 bowel movements per week at study entry.

Another study, published by Maeda et al (2010), focused on adverse events. This chart review included 38 patients with constipation who received permanent sacral nerve stimulation (SNS) after a successful trial period. When charts were reviewed, a mean of 25.7 months had elapsed since implantation. A total of 58 reportable events were identified in 22 (58%) of the 38 patients. A median of 2 (range, 1-9) events per patient was reported; 26 (45%) of 58 events were reported in the first 6 months after device implantation. The most common reportable events were lack or loss of efficacy (26/58 [45%] events) and pain (16 [28%] events). Twenty-eight (48%) of the events were resolved by reprogramming. Surgical interventions were required for 19 (33%) of the

events, most commonly permanent electrode replacement (14 events). Three (8%) of 38 patients discontinued device use due to reportable events.

Section Summary
Systemic reviews that include 3 randomized crossover studies along with other studies are available; 1 of the 3 RCTs had a sample size of 2, and the other 2 RCTs reported mixed outcomes when active sacral nerve stimulation was compared with sham stimulation. Results of an additional RCT did not support permanent implantation of a sacral nerve stimulator in individuals with refractory constipation who initially responded to temporary stimulation. There are also several, mainly small, case series, some of which were included as part of the systematic reviews. Collectively, available data are insufficient to permit scientific conclusions about the effect of sacral nerve neuromodulation or sacral nerve stimulation on health outcomes in individuals with constipation.

Chronic Pelvic Pain

Clinical Context and Therapy Purpose
The purpose of sacral nerve neuromodulation in individuals with chronic pelvic pain is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Population
The relevant population of interest is individuals with chronic pelvic pain.

Interventions
The treatment being considered is sacral nerve neuromodulation.

Comparators
The comparator of interest is continued conservative therapy, such as cognitive behavioral therapy or pharmacologic treatment.

Outcomes

The outcomes of interest are symptoms, morbid events, and treatment-related morbidity.

Positive outcomes include relief from chronic pelvic pain without complications from the device or implantation procedure.

Negative outcomes would be infection, bleeding, pain, and lead breakages, and lack of improvement in constipation.

Although no set standard for length of follow-up has been established, the existing literature evaluating sacral nerve neuromodulation for chronic pelvic pain has a length of follow-up of 1 year.

Review Evidence
A systematic review by Tirlapur et. al. (2013), evaluating studies on nerve stimulation for chronic pelvic pain, did not identify any RCTs on sacral nerve stimulation (SNS) for treatment of chronic pelvic pain or bladder pain. The published evidence was limited to case series. For example, Martellucci et. al. (2012) reported on 27 patients with chronic pelvic pain (at least 6 months) who underwent testing for sacral nerve neuromodulation (SNM) implantation. After a 4-week temporary stimulation phase, 16 (59%) of 27 patients underwent implantation of an InterStim device. In the 16 implanted patients, mean pain on a visual analog scale was 8.1 before implantation and 2.1 at the 6- and 12-month follow-ups. An earlier study by Siegel et al (2001) reported on 10 patients and reported that 9 of them experienced a decrease in pain with SNS stimulation.

Section Summary
Data from several small case series with heterogenous individuals samples represent insufficient evidence on the effect of sacral nerve neuromodulation (SNM) and sacral nerve stimulation (SNS) on net health outcomes in individuals with chronic pelvic pain. Randomized controlled trials (RCTs) are needed, especially with sham controls, reporting pain as the primary outcome.

Neurogenic Bladder and Neurogenic Bowel Dysfunction

Neurogenic Bladder Dysfunction
The normal function of the urinary bladder is to store and expel urine in a coordinated, controlled fashion. This coordinated activity is regulated by the central and peripheral nervous systems. Neurogenic bladder is a term applied to urinary bladder malfunction due to neurologic dysfunction emanating from internal or external trauma, disease, or injury.

Symptoms of neurogenic bladder range from detrusor underactivity to overactivity, depending on the site of neurologic insult. The urinary sphincter also may be affected, resulting in sphincter underactivity or overactivity and loss of sphincter coordination with bladder function. The appropriate therapy for neurogenic bladder and a successful treatment outcome are predicated upon an accurate diagnosis through a careful medical and voiding history, together with a variety of clinical examinations, including urodynamics and selective radiographic imaging studies.

Types of Neurogenic Bladders:

- Supraspinal lesions involve the central nervous system above the pons. They include stroke, brain tumor, Parkinson disease, and Shy-Drager syndrome.
- Spinal cord lesions, neurogenic bladder from spinal cord lesions may take various forms, depending on the mechanism and site of injury.
    - Spinal cord trauma: when an individual sustains a spinal cord injury.
    - Multiple sclerosis (MS): MS is caused by demyelinating lesions for the central nervous system. It most commonly involves the posterior and lateral columns of the cervical spinal cord.

- Peripheral Nerve Lesions resulting in detrusor areflexia may be due to any of the following:
    - Diabetes mellitus
    - Tabes dorsalis (neurosyphilis)
    - Herpes zoster
    - Herniated lumbar disc disease
    - Radical pelvic surgery

Treatment of neurogenic bladder depends on the type of incontinence, conservative therapy includes absorbent products, catheters (suprapubic or intermittent catheterization), fluid intake, pelvic floor exercises and pharmacologic therapy. Electrical stimulation, such as sacral nerve stimulation (SNS) is an area of active research in the treatment of neurogenic bladder.

Engler et. al. (2015), prospectively evaluated the efficacy and safety of sacral neuromodulation in patients with multiple sclerosis (MS). Seventeen patients (13 women, 4 men) treated with sacral neuromodulation for refractory neurogenic lower urinary tract dysfunction caused by multiple sclerosis were prospectively enrolled (2007-2011). Patients had to have stable disease and confirmed neurogenic lower urinary tract dysfunction (LUTD). Voiding variables, adverse events, and subjective satisfaction were assessed. Sixteen (94 %) patients had a positive test phase with a >70 % improvement. After implantation of the pulse generator (InterStim II), the improvement in voiding variables persisted. At 3 years, the median voided volume had improved significantly from 125 (range 0 to 350) to 265 ml (range 200 to 350) ($p < 0.001$), the post void residual from 170 (range 0 to 730) to 25 ml (range 0 to 300) ($p = 0.01$), micturition frequency from 12 (range 6 to 20) to 7 (range 4 to 12) ($p = 0.003$), and number of incontinence episodes from 3 (range 0 to 10) to 0 (range 0 to 1) ($p = 0.006$). The median subjective degree of satisfaction was 80 %. Only two patients developed lack of benefit. No major complications occurred. The authors concluded, our own mid-term experience and work from others suggest that sacral nerve modulation (SNM) for refractory neurogenic LUTD due to MS is a good option in carefully selected patients with a high probability of objective and subjective success, including improvement of quality of life. Confirmation in a randomized controlled trial is needed.

In 2017, Barboglio et. al. reviewed the current literature regarding urinary and bowel outcomes in patients with neurogenic lower urinary tract dysfunction (NLUTD), there has been interest in the efficacy of using sacral and peripheral neuromodulation. Contemporary data suggest promising outcomes for urinary and bowel symptoms in carefully selected patients with spinal cord injury and/or multiple sclerosis. Small case studies suggest that treatment during particular stages of neurologic injury may prevent long-term urinary sequelae. Randomized controlled trials are needed to confirm what the data suggests.

Section Summary
Sacral nerve stimulation (SNS)/sacral neuromodulation (SNM) is an established treatment of refractory, non-neurogenic lower urinary tract dysfunction, but its efficacy and safety in individuals with lower urinary tract dysfunction of neurologic origin is unclear. Only a few case series have been reported regarding sacral nerve stimulation for the treatment of neurogenic lower urinary tract dysfunction (NLUTD) primarily in indviduals with multiple sclerosis and spinal cord injuries. While these case series may show promise, randomized controlled trials are needed to determine the safety and efficacy for the use of sacral nerve stimulation in the treatment of neurogenic lower urinary tract dysfunction (NLUTD) for any indication. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Neurogenic Bowel Dysfunction
Individuals with central nervous system (CNS) disease or injury often have fecal incontinence and constipation, also referred to as neurogenic bowel dysfunction (NBD). Common causes of NBD include spinal cord injury (SCI), amyotrophic lateral sclerosis (ALS), spina bifida, myelomeningocele (MMC), multiple sclerosis (MS), Parkinson disease (PD), stroke and diabetes mellitus.

Neurogenic bowel dysfunction results from loss of normal sensory or motor control and may encompass both the upper and lower gastrointestinal (GI) tract. Quality of life is greatly affected; individuals often find their symptoms to be socially disabling. Although bowel dysfunction is a common event, to date there have been relatively few studies addressing bowel management.

Treatment of neurogenic bowel dysfunction (NBD) is initially conservative. Conservative measures include a bowel management program, pharmacologic options (colonic stimulation, hyperosmolar agents, bulking agents, and stool softeners), and transanal irrigation. Sacral nerve stimulation (SNS) has been proposed as a surgical treatment option for the treatment of NBD.

Krassioukov et. al. (2011) systematically reviewed the evidence for the management of neurogenic bowel in individuals with spinal cord injuries (SCI). Randomized controlled trials, prospective cohort, case-control, and pre-post studies, and case reports that assessed pharmacological and non-pharmacological intervention of the management of the neurogenic bowel in SCI were included. Fifty-two studies met the inclusion criteria. The authors concluded, multi-faceted bowel management programs are the first approach to neurogenic bowel programs and are supported by lower levels of evidence (pre-post studies). Often, more than one procedure is necessary for individuals that are unable to develop an effective bowel routine. Digital rectal stimulation is often incorporated within these multi-faceted programs and increases motility in the left colon in individuals with SCI. Diet and fluid intake are important components of multi-faceted bowel management programs, although there is a need for further research to examine the optimal level of dietary intake in spinal cord injured patients. Transanal irrigation is a promising technique to reduce constipation and fecal incontinence. When conservative management

is not effective, prokinetic agents such as cisapride, prucalopride, metoclopramide, neostigmine, and fampridine are supported by strong evidence for the treatment of chronic constipation in persons with SCI. Surgical interventions such as colostomy, MACE (Malone Antegrade Continence Enema) and implanted stimulation are not routinely used, lower levels of evidence (pre-post studies) in reducing bowel-related complications and improving quality of life.

In 2011, Awad reviewed neurogenic bowel dysfunction in patients with spinal cord injury (SCI), myelomenigocele, multiple sclerosis (MS) and Parkinson's disease. Recent approaches include sacral neuromodulation for neurogenic bowel dysfunction (NBD) treatment. Good quality research data is needed to evaluate the effects of this treatment for these conditions. The author concluded, this article reviews the current knowledge in all the fields of neurological diseases with neurogenic bowel dysfunction (NBD) and the common issues in need of clarification. The hope is that the full perspective of the situation, researchers can generate new ideas that can be useful for prevention, cure, or at a better of quality of life for the patient.

Coggrave et. al. (2014) performed a review to determine the effects of management strategies for fecal incontinence and constipation in people with a neurological disease or injury affecting the central nervous system. This is an updated Cochrane review, and this review is relevant to individuals with any disease directly and chronically affecting the central nervous system (post-traumatic, degenerative, ischemic, or neoplastic) such as multiple sclerosis (MS), spinal cord injury, cerebrovascular disease, Parkinson's disease and Alzheimer's disease. Randomized and quasi-randomized trials evaluating any type of conservative or surgical intervention for the management of fecal incontinence and constipation in people with central neurological disease or injury were selected. Specific therapies for the treatment of neurological diseases that indirectly affect bowel dysfunction were also considered. At least two review authors independently assessed the risk of bias of eligible trials and independently extracted data from the included trials using a range of pre-specified outcome measures. Twenty trials involving 902 people were included. Oral medications: There was evidence from individual small trials that people with Parkinson's disease had a statistically significant improvement in the number of bowel motions or successful bowel care routines per week when fiber (psyllium) (mean difference (MD) -2.2 bowel motions, 95% confidence interval (CI) -3.3 to -1.4) or oral laxative (isosmotic macrogol electrolyte solution) (MD 2.9 bowel motions per week, 95% CI 1.48 to 4.32) are used compared with placebo. One trial in people with spinal cord injury showed statistically significant improvement in total bowel care time comparing intramuscular neostigmine-glycopyrrolate (anticholinesterase plus an anticholinergic drug) with placebo (MD 23.3 minutes, 95% CI 4.68 to 41.92). Five studies reported the use of cisapride and tegaserod in people with spinal cord injuries or Parkinson's disease. These drugs have since been withdrawn from the market due to adverse effects as they are no longer available, they have been removed from this review. Rectal stimulants: One small trial in people with spinal cord injuries compared two bisacodyl suppositories, one polyethylene glycol-based (PGB) and one hydrogenated vegetable oil-based (HVB). The trial found that the PGB bisacodyl suppository

significantly reduced the mean defecation period (PGB 20 minutes versus HVB 36 minutes, P < 0.03) and mean total time for bowel care (PGB 43 minutes versus HVB 74.5 minutes, P < 0.01) compared with the HVB bisacodyl suppository. Physical interventions: There was evidence from one small trial with 31 participants that abdominal massage statistically improved the number of bowel motions in people who had a stroke compared with no massage (MD 1.7 bowel motions per week, 95% CI 2.22 to 1.18). A small feasibility trial including 30 individuals with multiple sclerosis also found evidence to support the use of abdominal massage. Constipation scores were statistically better with the abdominal massage during treatment although this was not supported by a change in outcome measures (for example the neurogenic bowel dysfunction score). One small trial in people with spinal cord injury showed statistically significant improvement in total bowel care time using electrical stimulation of abdominal muscles compared with no electrical stimulation (MD 29.3 minutes, 95% CI 7.35 to 51.25). There was evidence from one trial with a low risk of bias that for people with spinal cord injury transanal irrigation, compared against conservative bowel care, statistically improved constipation scores, neurogenic bowel dysfunction score, faecal incontinence score and total time for bowel care (MD 27.4 minutes, 95% CI 7.96 to 46.84). Patients were also more satisfied with this method. Other interventions: In one trial in stroke patients, there appeared to be a short-term benefit (less than six months) to patients in terms of the number of bowel motions per week with a one-off educational intervention from nurses (a structured nurse assessment leading to targeted education versus routine care), but this did not persist at 12 months. A trial in individuals with spinal cord injury found that a stepwise protocol did not reduce the need for oral laxatives and manual evacuation of stool. Finally, one further trial reported in abstract form showed that oral carbonated water (rather than tap water) improved constipation scores in people who had had a stroke. The authors concluded, there is still remarkably little research on this common and, to patients, very significant issue of bowel management. The available evidence is almost uniformly of low methodological quality. The clinical significance of some of the research findings presented here is difficult to interpret, not least because each intervention has only been addressed in individual trials, against control rather than compared against each other, and the interventions are very different from each other. There was very limited evidence from individual trials in favor of a bulk-forming laxative (psyllium), an isosmotic macrogol laxative, abdominal massage, electrical stimulation, and an anticholinesterase-anticholinergic drug combination (neostigmine-glycopyrrolate) compared to no treatment or controls. There was also evidence in favor of transanal irrigation (compared to conservative management), oral carbonated (rather than tap) water and abdominal massage with lifestyle advice (compared to lifestyle advice alone). However, these findings need to be confirmed by larger well-designed controlled trials which should include evaluation of the acceptability of the intervention to patients and the effect on their quality of life.

In 2017, Barboglio et. al. reviewed the current literature regarding urinary and bowel outcomes in patients with neurogenic lower urinary tract dysfunction (NLUTD), there has been interest in the efficacy of using sacral and peripheral neuromodulation. Contemporary data suggest promising outcomes for urinary and bowel symptoms in carefully selected patients with spinal cord injury and/or multiple sclerosis. Small case

studies suggest that treatment during particular stages of neurologic injury may prevent long-term urinary sequelae. Randomized controlled trials are needed to confirm what the data suggests.

Deng et. al. 2018, performed a systematic literature review of the clinical trial evidence on electrical stimulation for the treatment of neurogenic bowel dysfunction (NBD) after spinal cord injury (SCI). Systematic searches were carried out in PubMED/Medline, EMBASE and Cochrane Central Register of Controlled Trials. Eleven studies were included in this systematic review, comprising transcutaneous electrical stimulation, transrectal bowel stimulation, sacral nerve stimulation and intravesical electrical stimulation. Of the 11 studies, 3 were randomized controlled trials, and 8 were controlled before-and-after trials. The authors concluded, in the 11 clinical studies with 298 participants have evaluated the efficacy of electrical stimulation for NDB after SCI. Although some studies showed electrical stimulation was a benefit for the patient with NBD after SCI, there was currently not enough evidence to support the use of electrical stimulation improves the clinical symptoms of these patients. Thus, well-designed randomized controlled trials with larger patient population are warranted to establish its benefit in clinical practice in the future.

In 2018, Preziosi et. al. reviewed the pathophysiology of multiple sclerosis (MS) – related bowel dysfunction, reviewing the essential anatomy and physiology of defecation, the psychosocial and financial impact and management strategies. The authors conducted a search on PubMed/MeSH and Medline databases. Given the paucity of studies, particularly on treatment, a systematic review was not possible, and this is a narrative review. The use of sacral nerve stimulation (SNS) in MS for neurogenic bowel dysfunction (NBD) is only anecdotal and should be reserved to selected patients with stable relapsing remitting disease who had no relapses for at least 2 years. A crucial issue is not only the progression of disease and consequent loss of efficacy, but also the need for MRI scans which might require explantation of the stimulator. The authors concluded, neuromodulation has very little scope for the treatment of NBD.

Section Summary
Sacral nerve stimulation (SNS)/sacral neuromodulation (SNM) is an established treatment of refractory, non-neurogenic lower urinary tract dysfunction, but its efficacy and safety in individuals with neurologic bowel dysfunction of neurologic origin is unclear. Based on review of the peer reviewed medical literature, although some studies may have shown sacral nerve stimulation (SNS) was a benefit in certain individuals with neurogenic bowel dysfunction (NBD) after spinal cord injury (SCI) and in multiple sclerosis (MS), however, there is currently not enough evidence to support the use of sacral nerve stimulation (SNS) in improving the clinical symptoms of these individuals. Well-designed randomized controlled trials with larger individual population are warranted to establish its benefit in clinical practice in the treatment of neurogenic bowel dysfunction with neurologic origin. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Summary of Evidence
For individuals with urinary incontinence who have failed conservative treatment who receive sacral nerve stimulation (SNS)/sacral nerve neuromodulation (SNM), the evidence includes randomized controlled trials (RCTs) and case series with long-term follow-up have suggested that sacral nerve stimulation/neuromodulation (SNS/SNM) reduces symptoms of urge incontinence, urgency-frequency syndrome, non-obstructive urinary retention, and overactive bladder in selected individuals. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.

For individuals with fecal incontinence who have failed conservative treatment who receive sacral nerve stimulation (SNS)/sacral nerve neuromodulation (SNM), the evidence consists of randomized controlled trials (RCTs), observational studies, systematic reviews of RTCs and uncontrolled studies. Collectively, findings from these studies have suggested that sacral nerve stimulation (SNS)/sacral nerve neuromodulation (SNM) improve outcomes when used to treat chronic fecal incontinence in well-selected individuals who have failed conservative therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.

For individuals with constipation who have failed conservative treatment who receive sacral nerve stimulation (SNS)/sacral nerve neuromodulation (SNM), the evidence includes randomized controlled trials (RCTs),systematic reviews, and case series including several with long-term follow-up. The available trials have not consistently reported improvements in outcomes with SNS/SNM. Additional studies are needed to demonstrate the health benefits of this technology. The evidence is insufficient to determine the effects of the technology on net health outcomes.

For individuals with chronic pelvic pain who receive sacral nerve stimulation (SNS)/sacral nerve neuromodulation (SNM), the evidence is limited to case series. The evidence is insufficient to determine the effects of this technology on net health outcomes.

For individuals with neurogenic bladder dysfunction and/or neurological bowel dysfunction due to central neurological disease or injury (spinal cord injury (SCI), multiple sclerosis (MS), diabetes mellitus, amyotrophic lateral sclerosis (ALS), spinal bifida, Parkinson’s disease and stroke) who receive sacral nerve stimulation (SNS)/sacral nerve neuromodulation (SNM), the evidence is limited. While some studies may show promise in spinal cord injury (SCI) and multiple sclerosis (MS), efficacy and safety in individuals with urinary and bowel dysfunction of neurologic origin is unclear. There’s currently not enough evidence to support the use of sacral nerve stimulation (SNS) in improving the clinical symptoms of these individuals. Well-designed randomized controlled trials with larger individual population are warranted to establish its benefit in clinical practice for neurogenic bladder dysfunction and neurogenic bowel dysfunction with neurologic origin. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Practice Guidelines and Position Statements

Fecal Disorders

American College of Gastroenterology (ACG)
In 2021, the American College of Gastroenterology (ACG) issued an updated clinical guideline on the management of benign anorectal disorders which includes fecal incontinence. The treatment recommendations included the following:

- We recommend sacral nerve stimulation (SNS) for patients with moderate to severe fecal incontinence (FI) who have failed conservative measures, biofeedback, and other low-cost, low-risk techniques (strong recommendation: quality of evidence: low)

American College of Obstetricians and Gynecologists (ACOG)
In 2019, the American College of Obstetricians and Gynecologists (ACOG) issued a practice bulletin on fecal incontinence that stated: "sacral nerve stimulation can be considered as a surgical treatment option for women with fecal incontinence with or without anal sphincter disruption who have failed conservative treatment."

American Society of Colon and Rectal Surgeons (ASCRS)
In the 2015 practice parameter, the American Society of Colon and Rectal Surgeons (ASCRS) clinical practice guideline for the treatment of fecal incontinence states sacral neuromodulation may be considered as first line surgical option for incontinent patients with and without sphincter defects. Grade of Recommendation: Strong recommendation based on moderate quality of evidence, 1B.

Urinary Disorders

American College of Obstetricians and Gynecologists (ACOG)
In 2015, practice bulletin on urinary incontinence (replaced practice bulletin number 63, 2005; reaffirmed in 2018) for the American College of Obstetricians and Gynecologists (ACOG) stated, sacral neuromodulation may be considered for patients with recalcitrant urinary urge incontinence who have failed other conservative measures, including bladder training, pelvic floor physical therapy with biofeedback, and pharmacologic treatment.

American Urological Association (AUA)
In 2019, the American Urological Association (AUA) issued an updated guideline on diagnosis and treatment of non-neurogenic overactive bladder (OAB). The guideline states that sacral neuromodulation may be offered as a third-line treatment in a carefully selected patient population characterized by severe refractory OAB symptoms or patients who are not candidates for second line therapy (e.g., oral anti-muscarinic, oral B_3 – adrenoceptor agonists or transdermal oxybutynin) and are willing to undergo a surgical procedure. (Recommendation. Evidence Strength Grade C)

In 2017, the American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) issued a guideline on surgical treatment of female stress urinary incontinence (SIU) which does not include or indicate the use of sacral neuromodulation in the treatment of stress urinary incontinence (SUI).

Regulatory Status

Device	Description and FDA Approval Information
Axonics Rechargeable Sacral Neuromodulation (r-SNM) System®	• FDA granted premarket approval application (PMA) to Axonics Rechargeable Sacral Neuromodulation (r-SNM) System® to treat fecal incontinence in September 2019. The indication for use reads: "This device is indicated for the treatment of chronic fecal incontinence in patients who have failed or are not candidates for more conservative treatments." • FDA granted premarket approval application (PMA) to Axonics Rechargeable Sacral Neuromodulation (r-SNM) System® to treat urinary incontinence in November 2019. The indication for use reads: "The device is indicated for the treatment of urinary retention and the symptoms of overactive bladder, including urinary urge incontinence and significant symptoms of urgency-frequency alone or in combination, in patients who have failed or could not tolerate more conservative treatments."
Medtronic® InterStim® Therapy System	• In 1997, the Medtronic® InterStim® Therapy System received FDA approval for marketing for the indication of

	urinary incontinence in patients who have failed or could not tolerate more conservative treatments. In 1999, the device received FDA approval for the additional indications of urgency-frequency and urinary retention in patients without mechanical obstruction. In 2006, the Medtronic InterStim II System received FDA approval for treatment of intractable cases of overactive bladder and urinary retention. The new device is smaller and lighter than the original system and is reported to be suited for those with lower energy requirements or small stature. The device also includes updated software and programming options. • In 2011, Medtronic InterStim System received FDA approval for the indication of chronic fecal incontinence in patients who have failed or could not tolerate more conservative treatments. • The InterStim device has not been specifically approved by the FDA for treatment of chronic pelvic pain.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies

- 02.01.04 Biofeedback
- 02.01.51 Fecal Incontinence Management
- 02.01.27 Urinary Incontinence/Voiding Dysfunction Treatments and Devices

Medically Necessary

Urinary Incontinence and Non-Obstructive Urinary Retention

A. A trial period of sacral nerve neuromodulation (SNM)/sacral nerve stimulator (SNS) with either percutaneous nerve evaluation (PNE) or a temporarily implanted lead may be considered **medically necessary** in individuals who meet **ALL** the following criteria:

   1. There is a diagnosis of at least one of the following:

      a. Urge incontinence

      b. Urgency-frequency syndrome

      c. Non-obstructive urinary retention

      d. Overactive Bladder (OAB Urgency) syndrome; **and**

   2. There is documented failure or intolerance to at least **two** conventional conservative therapies performed for a minimum of 6 months (e.g., behavioral training such as bladder training, prompted voiding, or pelvic muscle exercise training, pharmacologic treatment for at least a sufficient duration to fully assess its efficacy, and/or surgical corrective therapy; **and**

   3. Incontinence is not related to a neurologic condition (e.g., diabetic neuropathy/diabetes mellitus, detrusor hyperreflexia, multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease, stroke, spina bifida, amyotrophic lateral sclerosis [ALS]).

Note: *A successful trial of a temporary sacral nerve stimulator/neuromodulator is defined as:*

- ***Urinary retention:*** *At least a 50% reduction in catheter volume/catheterization*
- ***Urinary urge incontinence****: At least 50% reduction in one of the following: daily incontinence episodes, severity of the episodes or the number of pads/diapers used per day*
- ***Urinary urge/frequency:*** *At least 50% reduction in one of the following: number of voids daily, volume per void and frequency per void.*
- ***Overactive bladder (OAB urgency) syndrome****: At least 50% reduction in the number of daily incontinence episodes or pads used.*

B. Permanent implantation of a sacral nerve neuromodulation (SNM)/sacral nerve stimulation (SNS) device may be considered **medically necessary** in individuals who meet **ALL** the following criteria:

1. All the criteria in A (1-3) above are met; **and**

2. A trial stimulation period demonstrates at least 50% improvement in symptoms over a period of at least 1 week.

Fecal Incontinence

A. A trial period of sacral nerve neuromodulation (SNM)/sacral nerve stimulation (SNS) with either percutaneous nerve evaluation (PNE) or a temporarily implanted lead may be considered **medically necessary** in individuals who meet **ALL** the following criteria:

1. Either of the following are met:

a. There is a diagnosis of chronic fecal incontinence of greater than 2 incontinent episodes on average per week with duration greater than 6- months; **or**

b. There is a diagnosis of chronic fecal incontinence of greater than 2 incontinent episodes on average per week greater than 12- months after vaginal childbirth; **and**

2. There is documented failure or intolerance to at least two conventional conservative therapies performed for minimum of 6 months (e.g., dietary modification, defecation programs, bowel training, and pharmacologic treatment)**; and**

3. The individual has not had rectal surgery in the previous 12 months, or in the case of cancer, the individual has not had rectal surgery in the past 24 months; **and**

4. The condition is not related to an anorectal malformation (e.g., congenital anorectal malformation; defects of the external anal sphincter over 60 degrees; visible sequelae of pelvic radiation; active anal abscesses and fistulae) or chronic inflammatory bowel disease**; and**

5. Incontinence is not related to a neurologic condition (e.g., diabetic neuropathy/diabetes mellitus, detrusor hyperreflexia, multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease, stroke, spina bifida, amyotrophic lateral sclerosis [ALS]).

B. Permanent implantation of a sacral nerve neuromodulation (SNM)/sacral nerve stimulation (SNS) device may be considered **medically necessary** in individuals who meet **ALL** the following criteria:

    1. All the criteria in A (1-5) above are met; **and**

    2. A trial stimulation period demonstrates at least 50% improvement in symptoms over a period of at least 1 week.

Replacement or Revision

Replacement or revision of sacral nerve stimulation (SNS)/sacral nerve neuromodulation (SNM) may be considered **medically necessary** for an individual that meets the above criteria and the existing generator/lead/electrodes/programmer is no longer under warranty and cannot be repaired.

Investigational

Sacral nerve neuromodulation (SNM)/sacral nerve stimulation (SNS) is considered **investigational** when the above criteria is not met and for all other indications, including but not limited to the following, because safety and/or effectiveness cannot be established based on the peer reviewed medical literature:

- The treatment of chronic constipation
- The treatment of chronic pelvic pain
- The treatment of stress urinary incontinence (SUI)
- The treatment of neurogenic bladder dysfunction or neurogenic bowel dysfunction due to a neurological condition (neurologic origin) (diabetic neuropathy/diabetes mellitus, detrusor hyperreflexia, multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease, stroke, spina bifida, amyotrophic lateral sclerosis (ALS))
- The treatment other types of chronic voiding dysfunction.

Policy Guidelines

Contraindications
Individuals must not have any contraindications to using sacral nerve stimulation (SNS)/sacral nerve modulation (SNM) which includes the following:

- Individual must not have urinary obstruction
- Individual must not have current pelvic infection
- Contraindications of SNS/SNM include shortwave diathermy, microwave diathermy or therapeutic ultrasound
- Mechanical obstruction
- Inability to operate the patient programmer

- As of 2020 all new implants are MRI compatible with full-body MRI. However, some implants before the fall of 2019 do not have full MRI compatibility, so MRI evaluations and imaging must be limited to just head and neck in these individuals
- While age and comorbidities are not contraindications, there is some evidence to suggest that patients over 55 years of age with three or more chronic comorbid conditions exhibited diminished success rates for improving their voiding symptoms with SNS/SNM

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 64561 Percutaneous implantation of neurostimulator electrode array; sacral nerve (transforaminal placement):
- 64581 Open implantation of neurostimulator electrode array; sacral nerve (transforaminal placement)
- 64585 Revision or removal of peripheral neurostimulator electrode array
- 64590 Incision and subcutaneous placement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling
- 64595 Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver
- 95970 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
- 95971 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple spinal cord or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
- 95972 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex spinal cord or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

- A4290 Sacral nerve stimulation test lead, each
- C1767 Generator, neurostimulator (implantable), nonrechargeable
- C1778 Lead, neurostimulator (implantable)
- C1787 Patient programmer, neurostimulator
- C1816 Receiver and/or transmitter, neurostimulator (implantable)
- C1820 Generator, neurostimulator (implantable), non high-frequency with rechargeable battery and charging system
- C1822 Generator neurostimulator (implantable), high frequency with rechargeable battery and charging system
- C1897Lead, neurostimulator test kit (implantable)
- L8679 Implantable neurostimulator, pulse generator, any type
- L8680 Implantable neurostimulator electrode, each
- L8683 Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
- L8684 Radiofrequency transmitter (external) for use with implantable sacral root neurostimulator receiver for bowel and bladder management, replacement
- L8685 Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
- L8686 Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
- L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
- L8688 Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
- L8689 External recharging system for battery (internal) for use with implantable neurostimulator, replacement only

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POLICY HISTORY

Date	Reason	Action
June 2022	Annual Review	Policy Revised
June 2021	Annual Review	Policy Renewed
June 2020	Annual Review	Policy Revised
June 2019	Annual Review	Policy Revised
June 2018	Annual Review	Policy Revised
June 2017	Annual Review	Policy Renewed
June 2016	Annual Review	Policy Renewed
July 2015	Annual Review	Policy Revised
February 2015		Policy Revised
August 2014	Annual Review	Policy Revised
September 2013		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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