SACRAL NERVE STIMULATION FOR THE TREATMENT OF REFRACTORY URGE INCONTINENCE

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Frank V. Lefevre, M.D.
Assistant Professor
General Internal Medicine
Northwestern Medical School
and
Director of Special Assessments
Technology Evaluation Center
Blue Cross and Blue Shield Association
Chicago, Illinois

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OBJECTIVE

Sacral nerve stimulation (SNS), or sacral nerve neuromodulation, is defined as the implantation of a permanent device that modulates the neural pathways controlling bladder function. This treatment is one of several alternative modalities for patients with urge urinary incontinence who have failed conservative measures. The main objective of this technology assessment is to review the available evidence to determine whether SNS improves health outcomes of patients with refractory urge urinary incontinence.

Urge incontinence can be classified into neurologic and non-neurologic categories. This assessment will address urge incontinence that is not due to a neurologic injury or disorder, such as a cerebrovascular accident, spinal cord injury, or multiple sclerosis. SNS is also potentially a treatment for patients with other types of chronic voiding dysfunction, such as the urge-frequency syndrome, interstitial cystitis, and idiopathic chronic urinary retention. The evidence on SNS for other types of chronic voiding dysfunction will not be addressed as part of this technology assessment.

BACKGROUND

Urinary Incontinence

Urinary incontinence, defined as the involuntary loss of urine, is a common problem with a high burden of morbidity. It is estimated to affect 13 million adults in the U.S., and to account for costs exceeding $15 billion per year (Payne 1998, Fantl et al. 1996; Urinary Incontinence Guideline Panel 1992). In 1994 dollars, approximately $11.2 billion was spent on the direct treatment of incontinence and $5.2 billion on associated nursing home costs. For older adults living in the community, the prevalence of urinary incontinence has been estimated at 30%, with women affected twice as often as men (Payne 1998).

Incontinence leads to significant impairment in quality of life for affected individuals. Incontinent women report more emotional disturbances and social isolation, as compared to continent, age-matched controls (Grimby et al. 1993). In one study, approximately 20% of incontinent women abstain from social activities due to incontinence (Lam et al. 1992). In addition, urinary incontinence has been cited as one of the major precipitants for placement in a nursing home (Ouslander et al. 1982).

Voiding involves complex relationships between the nervous system, bladder, urethra, and urethral sphincters. The muscles of the urinary tract system are controlled by the parasympathetic nervous system, with additional input from central nervous system micturition centers (Weinberger 1995). Central nervous system centers perceive bladder filling and are responsible for voluntary inhibition of voiding. Activation of sacral parasympathetic nerves causes contraction of the bladder musculature and initiates the voiding reflex. In coordination with

contraction of the bladder muscles, the urinary sphincter relaxes in order to allow spontaneous voiding to occur. Interference with any of these components of voiding can lead to incontinence.

Consequently, there are numerous etiologies for urinary incontinence. The two most common categories of urinary incontinence are stress incontinence and urge incontinence (Abrams et al. 1988). Stress incontinence is characterized by loss of urine that occurs with activities that increase intra-abdominal pressure, such as coughing, sneezing, or lifting heavy objects. The underlying abnormality in SI can be either hypermotility of the bladder neck, intrinsic deficiency of the urinary sphincter, or both (Fantl et al. 1996; Urinary Incontinence Guideline Panel 1992). The majority of stress incontinence is acquired through weakening of the pelvic floor support structures as a result of aging, childbirth or other factors (NIH Consensus Statement 1989), and SNS is not a proposed treatment for this condition.

In addition to stress incontinence and urge incontinence, numerous other etiologies of incontinence exist. Reversible causes, such as urinary tract infection or medications, are managed by treating the underlying cause. Overflow incontinence occurs when the bladder cannot empty normally and becomes overdistended, such as occurs with bladder outlet obstruction as a result of prostate hypertrophy. Functional incontinence refers to the situation where no physiologic pathology is present, but incontinence occurs as a result of immobility or severe cognitive dysfunction. SNS is generally not a treatment option for these types of incontinence.

Urgency and Urge Incontinence

Urinary urgency refers to the sensation of needing to urinate, and may or may not be accompanied by incontinence. Urge incontinence occurs when patients are unable to hold urine in response to the sensation of urgency. When patients experience urgency and the need to void frequently, but do not lose urine, this is referred to as the urge-frequency syndrome.

Urgency and urge incontinence most commonly result from the inability to inhibit the voiding reflex, which is triggered by bladder volume and environmental stimuli. The voiding reflex leads to contraction of the detrusor muscle of the bladder. Following detrusor muscle contraction, if the intravesicular (bladder) pressure exceeds the urethral closure pressure, then incontinence results.

Within the category of urge incontinence, further diagnostic distinctions can be made. Swami and Abrams (1996) has divided urge incontinence into three main categories:

1) Motor urgency, which is characterized by overactivity of the bladder detrusor muscle on urodynamic testing. This is the most common category for urge incontinence.

2) Sensory urgency, which refers to the clinical syndrome of urge incontinence where no overactivity of the detrusor muscle can be demonstrated on urodynamic testing. This category may also be referred to as functional incontinence.

3) Urethral instability, which is diagnosed when a spontaneous reduction in pressure occurs in association with urgency. Urethral instability may exist as the sole abnormality in urge incontinence, or may coexist with detrusor instability (Swami and Abrams 1996).

Motor urgency, or overactivity of the detrusor muscle, is the most common underlying etiology of urge incontinence (Swami and Abrams 1996). There are two main categories of detrusor overactivity. Detrusor hyperreflexia is diagnosed when a neurologic deficit affecting bladder function is present. Neurologic deficits may be present at the central nervous system level, such as with a cerebrovascular accident or multiple sclerosis, within the spinal cord, as with spinal cord injuries, or at the peripheral nerve level, such as occurs with sacral nerve root impingement syndromes. Idiopathic detrusor instability is diagnosed when no underlying cause is identified. The underlying etiology in this condition is obscure. Possible causative factors may involve congenital abnormalities in the micturition regulatory loops, hypersensitivity to parasympathetic nerve stimulation, an imbalance of peptide or other neurotransmitters, and/or psychosomatic factors (Couillard and Webster 1995).

Treatment for Urge Incontinence

Several treatment options for urge incontinence exist, ranging from non-invasive behavioral measures to surgical procedures. In general, a staged approach to treatment is recommended for most patients, beginning with the least invasive techniques and progressing to more invasive treatments if initial measures are not successful (Fantl et al. 1996; Urinary Incontinence Guideline Panel 1992). The Agency for Health Care Policy and Research (AHCPR) issued guidelines for the management of urinary incontinence in 1992 and an updated version in 1996 (Fantl et al. 1996; Urinary Incontinence Guideline Panel 1992). These guidelines recommend that a trial of behavioral intervention be applied to all appropriate patients with urge incontinence prior to the use of more invasive treatments such as drugs or surgery.

Behavioral Treatments. Behavioral treatment requires that patients be cognitively intact and motivated to learn and practice the techniques. Castleden et al. (1985) studied factors that were predictive of success with behavioral treatments, and reported that preserved cognitive ability was the factor most strongly related to a positive outcome. Thus, behavioral treatments are not appropriate for patients with dementia or other cognitive impairments, and are more suited for community dwelling individuals, as opposed to nursing home residents.

Behavioral treatments for urge incontinence include bladder training with or without pelvic floor muscle exercises (PME). The primary goal of bladder training is to teach the patient to inhibit contractions of the detrusor muscle, thereby reducing the sense of urgency associated with an uninhibited voiding reflex. Education in the form of written, verbal or visual instruction is provided. Patients are placed on a systematic voiding schedule, which allows the bladder to adjust to increasing levels of distension. The program may also use distraction or relaxation techniques to achieve these goals. Control of fluid intake is sometimes used to aid in adhering to a voiding schedule.

In the largest controlled trial of bladder training to date (Fantl et al. 1991), 131 women were randomized to either immediate or delayed treatment. Patients in the immediate treatment group were more likely to achieve complete continence (12% of treated patients versus 3% of controls) and more likely to report a greater than 50% reduction in frequency of incontinence (75% of treated patients versus 24% of controls). This study was limited by the fact that it included patients with urge incontinence, stress incontinence and mixed types of incontinence, and only a minority of patients had only urge incontinence. However, the authors reported that there was no difference in response by diagnostic category. A review of 11 smaller studies of bladder training that treated primarily patients with urge incontinence and detrusor instability reported that fewer than 15% of patients achieved full continence and that approximately 50% experienced a reduction in incontinent episodes of 50% or more (Fantl 1998).

The addition of PME to bladder training may provide patients with an increased ability to control detrusor overactivity. PME originates from the Kegel exercises developed in the 1940s and 1950s. Patients are educated to become aware of contraction of the pelvic floor muscles and taught to contract these muscles for a defined time period, for example, 10 seconds, followed by a period of relaxation. This is repeated at a prescribed frequency, which increases over time. The AHCPR guidelines recommend that contractions be performed 30–80 times per day for a period of 8 weeks or longer (Fantl et al. 1996; Urinary Incontinence Guideline Panel 1992). Biofeedback has been used as an adjunct to bladder training or PME with the goal of improving patients' ability to learn these techniques. It has not been definitively demonstrated, however, that the addition of biofeedback to PME conveys an incremental benefit.

The delivery of behavioral treatments is not standardized. The method and intensity of instruction may vary. The method of delivery may range from brief verbal instruction by a physician in the office setting, to written materials, to multiple individual session(s) with a clinical specialist trained in delivering this treatment. The intensity of the treatment will vary both as a function of the number of training sessions employed and the frequency with which the patient practices the techniques at home.

For patients unable to control their symptoms adequately with behavioral treatment, a number of alternative therapies are available.

Pharmacologic Treatments. Pharmacologic treatment has some efficacy for treating urge incontinence, although the available literature is limited by deficiencies in methodology (Urinary Incontinence Guideline Panel 1996). The specific drug used for urge incontinence is tailored to the underlying abnormality present. For patients with detrusor instability, anticholinergic agents are the drugs of choice. Oxybutinin has been shown to be superior to other agents and is currently considered the first-line drug for this indication (Swami and Abrams 1996; Urinary Incontinence Guideline Panel 1996). The AHCPR guideline panel reviewed seven randomized trials of oxybutinin versus placebo. In 6 of 7 trials, oxybutinin was superior to placebo, with improvement in incontinent episodes ranging from 15–58% (Urinary Incontinence Guideline Panel 1996). Agents such as propantheline and imipramine are considered second-line therapy. The magnitude of benefit with these agents is probably less than with oxybutinin, and the adverse effect profile less favorable (Urinary Incontinence Guideline Panel 1996). For patients with

underlying urethral instability, alpha agonists, such as phenylpropanolamine, have been shown to have some efficacy in a small number of trials (Swami and Abrams 1996).

Surgical Treatments. Surgery is an option for patients who have continued urge incontinence causing poor quality of life and who have failed conservative treatments (Swami and Abrams 1996). Several surgical options exist, but are used uncommonly in the treatment of urge incontinence (Urinary Incontinence Guideline Panel 1996). The most common surgical approach is to augment bladder volume by enterocystoplasty, in which a portion of intestine is used to reconstruct and enlarge the bladder. This approach is best suited for patients with small bladder capacity, and is used more commonly in patients with a neurogenic origin for detrusor overactivity (Swami and Abrams 1996). The AHCPR guideline panel identified 12 studies of this procedure reporting on 403 patients. "Cure," defined as continence with spontaneous voiding, was estimated at 38%. A larger percentage of treated patients became continent, but required intermittent catheterization to manage voiding dysfunction. Significant complications of the procedure were estimated to occur in 54% of treated patients.

Enterocystoplasty is used less commonly for patients with idiopathic detrusor instability. One study of 45 patients in which the majority of patients had idiopathic detrusor instability (39/45) was identified (Kockelbergh et al. 1991). In this study, 53% of patients subjectively reported either being "cured" or "much better." Perioperative complications occurred in 42% (19/45). There was one perioperative death (2%) and one patient required a urinary diversion procedure as a result of severe complications. Following the perioperative period, significant voiding difficulties remained. Fifteen percent of patients (7/43) required intermittent self-catheterization following the procedure and another 17% (8/43) had to strain in order to void. Urinary tract infections developed in 53% (23/43) after an unspecified follow-up period.

A second class of surgical procedures is bladder denervation. These procedures involve disruption of the nerves supplying the bladder wall. The body of evidence on the efficacy of these procedures is small, and consists of uncontrolled studies, making a precise estimate of the risk-benefit ratio difficult to determine (Urinary Incontinence Guideline Panel). A short-term cure is obtained in somewhat less than half of women treated, and the relapse rate may be high.

Detrusor myomectomy, also known as auto-augmentation, is a newer procedure in which a portion of the detrusor muscle is removed from the dome of the bladder. A few studies have reported good results from this surgery (Appel 1998b) and the procedure has been performed laparoscopically.

For patients with continued severe incontinence and no other options, urinary diversion procedures can be employed. A suprapubic catheter can be surgically placed directly into the bladder and attached to an external urinary collection bag. A permanent indwelling Foley catheter is another such option. While these approaches will eliminate incontinence, they are not an acceptable option for most cognitively intact patients with incontinence. The management of an external collection device can be burdensome and unpleasant. There also is a high rate of urinary tract infections associated with theses devices.

Electrical Stimulation Therapy. Electrical stimulation is a collection of treatment modalities (Bosch and Groen 1995; Haber 1986; Moore et al. 1995), similar to behavioral therapy in that the goals are improving strength and control of the pelvic floor muscles. Different types of electrical stimulation are characterized by the physiological site of stimulation and the type of electrical impulses delivered. Non-implantable electrical stimulation, also known as pelvic floor electrical stimulation (PFES), delivers electrical impulses by vaginal or rectal probes inserted temporarily for multiple sessions of treatment (Fall and Lindstrom 1991). A number of uncontrolled studies show an apparent benefit for PFES, however, the small number of controlled trials of PFS versus placebo or PFES versus PME show conflicting results and are insufficient evidence to form definitive conclusions (Blue Cross Blue Shield Association 2000).

Several types of implantable electrical stimulation exist. One type of electrical stimulation is designed to replace innervation lost from spinal cord injury, myelomeningocele, or interstitial cystitis. In these cases, transcutaneous electrical nerve stimulation or implanted electrodes are placed to direct impulses to the bladder wall, pelvic nerves, sacral roots or spinal cord to assist patients in the control over micturition. This technology assessment deals specifically with sacral nerve stimulation (SNS).

Sacral Nerve Stimulation

The SNS device consists of an implantable pulse generator that delivers controlled electrical impulses. This pulse generator is attached to wire leads that connect to the sacral nerves, most commonly the S3 nerve root. Two external components of the system help control the electrical stimulation. A control magnet is kept by the patient and can be used to turn the device on or off. A console programmer is kept by the physician and used to adjust the settings of the pulse generator.

Prior to implantation of the permanent device, patients undergo a peripheral nerve stimulation test to estimate potential response to SNS. This procedure is done under local anesthesia, using a test needle to identify the appropriate sacral nerve(s). Once identified, a temporary wire lead is inserted through the test needle and left in place for several days. This lead is connected to an external stimulator, which is carried by the patient in their pocket or belt. The patient then keeps track of voiding symptoms while the temporary device is functioning. The results of this test phase are used to determine whether the patient is an appropriate candidate for the permanent device. If the patient shows a 50% or greater reduction in incontinence frequency, they are deemed eligible for the permanent device. According to data from the manufacturer, approximately 63% of patients have a successful peripheral nerve evaluation and are thus candidates for the permanent SNS.

The permanent device is implanted under general anesthesia. An incision is made over the lower back and the electrical leads are placed in contact with the sacral nerve root(s). The wire leads are extended through a second incision underneath the skin across the flank to the lower abdomen. Finally, a third incision is made in 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 that patient. The patient can switch the pulse generator

between on and off by placing the control magnet over the area of the pulse generator for 1–2 seconds.

FDA status. The Medtronic® Interstim Sacral Nerve Stimulation (SNS)™ system originally received FDA premarket application (PMA) approval for marketing on September 29, 1997 for the indication of urinary urge incontinence in patients who have failed or could not tolerate more conservative treatments. On April 15, 1999, the system received supplemental PMA approval for use in patients with urinary retention, and significant symptoms of urgency/frequency in patients who have failed or could not tolerate more conservative treatments. No other implantable SNS device currently has FDA approval.

Methodologic Considerations

The available literature evidence consists mostly of single-armed clinical series of treatment with SNS (Dijkema et al. 1993; Elabbady et al. 1994; Bosch and Groen 1995; Shaker and Hassouna 1998). Evidence reported from such single-armed clinical studies tends to overestimate treatment effect (Sacks et al. 1983; Colditz et al. 1989). The pretest-posttest design (the "before-after" study), often employed in clinical series, is the comparison of observations at baseline to observations that occur after an intervention. A major limitation in this type of study design is that rival sources of explanation for changes in outcomes are numerous and uncontrolled. For example, before-after studies do not account for placebo effects, the natural history of the disorder being studied, or other modifying factors that may have an effect on outcomes. For incontinence, there are numerous factors that may impact on the outcomes that are measured, such as education, medication use, activity level, and expectations for treatment. In a trial without concurrent controls, it is impossible to ascertain how much of the improvement seen is due to these types of factors, as opposed to the effect of the intervention.

Campbell and Stanley published a classic handbook on research methodology that still provides a solid framework for evaluating the validity and generalizability of scientific evidence (Campbell and Stanley 1966). The Campbell and Stanley framework classifies clinical series research design as pre-experimental. All the pre-experimental designs are weak forms of scientific research design because they are subject to extraneous factors that provide alternative explanations of the results. When alternative explanations are present, an experiment is ambiguous because the extraneous factors interfere with the conclusion or inferences to be drawn. While clinical series often provide descriptive information and the historical interest in framing a research question, the lack of internal validity excludes studies using a clinical series design as scientific evidence (Guyatt et al. 1994; Sackett 1979; Feinstein 1985; Campbell and Stanley 1966). Clinical series may also provide some information on the durability of a treatment effect, given that efficacy has been established in well-designed, controlled trials of shorter duration. Expert panels in reviewing scientific evidence have ranked the quality of this type of evidence in the lowest category of rigor (Fantl et al. 1996).

In addition, there are several concerns specific to the evaluation of efficacy in incontinence. The measurement of the frequency of incontinence is limited both by inherent variability in the condition itself, and by potential inaccuracies in the available measurement instruments. For

patients with stress incontinence, the specific activities performed during a given time period will impact on the frequency of incontinence. Day-to-day variability in activities may be associated with variability in the frequency of incontinence. Other variables, such as fluid or caffeine intake, may also contribute to underlying variability in the condition.

Also, the measurement instruments available to quantitate outcomes of incontinence are not ideal (Fantl et al. 1996). Patient recorded diaries have a fair amount of subjectivity. Adequacy of documentation may introduce an additional level of variability to the data. The pad test, while perhaps more objective than patient reported diaries, may be less useful clinically since the maneuvers performed during this test may or may not correspond to the usual types of activities performed by patients. The precision and reproducibility of the pad test is not well reported in the literature.

As with most medical interventions, there is expected to be some degree of placebo response in clinical trials of treatment for incontinence. For example, in a recent well-designed trial comparing PME to drugs (Burgio et al. 1998), a placebo "drug" group was included. This placebo group had a 39.4% improvement in the frequency of incontinence by patient reported diary.

Because of the above methodologic considerations, clinical trials with concurrent controls are needed to demonstrate the efficacy of treatment for urge incontinence. Randomized controlled trials with adequate numbers of patients are the ideal types of studies that minimize bias and confounding. Controlled trials that are nonrandomized, while prone to selection bias, may also provide sufficient evidence of efficacy if the comparability of the treatment arms can be adequately assessed and is confirmed as acceptable. Trials without concurrent controls, however, have too great a potential for bias to allow conclusions on the relevant assessment questions. Thus, this assessment will be restricted to controlled trials, either randomized or non-randomized, involving treatment with SNS for urge incontinence.

METHODS

Search Methods

The MEDLINE database was searched for the periods of 1966 through March 2000, using the Medical Subject Heading (MeSH) term "urinary incontinence" and the textwords "sacral nerve stimulation." A search was also performed using the textwords "pelvic floor stimulation," linked with "urinary incontinence." This search was limited to English language articles reporting on human subjects. All articles describing the use of sacral nerve stimulation were retrieved. Bibliographies of recent review articles and clinical trials were reviewed. Additional searches of *Current Contents* were also performed.

Study Selection

Selection criteria for inclusion in this assessment included the following:

1. Full-length, peer-reviewed articles reporting on outcomes of treatment with SNS;
2. Included patients with urge urinary incontinence refractory to conservative treatments(behavioral treatments and/or medications);
3. Included relevant health outcome measures (percent change in incontinent episodes by patient diary, percent of patients dry, percent of patients with >50% improvement in incontinence)
4. Included a concurrent comparison group not treated with SNS;
5. Adequate description of the patient population, including diagnostic criteria for refractory urge incontinence;
6. Adequate description of the treatment course, including peripheral nerve screening test, duration of follow-up.

FORMULATION OF THE ASSESSMENT

Patient Indications

The main indication for this assessment is adults with self-reported involuntary loss of urine, with an objective diagnosis of urge incontinence by urodynamic testing, who have failed or not tolerated conservative treatment. Conservative treatment will consist of behavioral interventions, such as bladder training and pelvic floor muscle exercises, and pharmacologic treatment. This group potentially includes patients both with neurologic disorders such as MS, spinal cord lesions, cerebrovascular accidents (detrusor hyperreflexia) and without neurologic disorders (idiopathic detrusor instability). This assessment will not address patients who have urge incontinence as a result of neurologic injury or illness.

Technologies to Be Compared

SNS can be compared to continued conservative treatment(s), to various bladder surgical treatments, and to urinary diversion procedures (permanent catheterization). Some patients who fail conservative treatments (behavioral and/or pharmacologic therapy) are surgical candidates and some are not. Therefore, this assessment will attempt to determine whether SNS has a beneficial treatment effect in patients who continue to do poorly after an adequate trial of conservative treatment. It will also attempt to compare the relative efficacy of SNS versus surgery in patients who are surgical candidates, and to the option of permanent urinary diversion.

Health Outcomes

The main outcome measure used in studies of incontinence is the change in the number of incontinent episodes, usually measured as episodes per week. Study patients keep voiding diaries that include recording the episodes of voiding and urinary incontinence, number of pads used per day, nocturnal voids and urgency episodes without incontinence. The percent change in number of incontinent episodes is calculated using the following equation:

$$\frac{\text{pretreatment episodes/period - posttreatment episodes/period}}{\text{pretreatment episodes/period}} \times 100$$

This outcome measure, *percent change* in the frequency of incontinent episodes is the most consistently reported outcome and will be the main outcome measure used for comparing results across studies. Derived from change in the number of incontinent episodes are percent cure and/or percent of patients who improve. Patients who become dry (i.e., no longer experience incontinence following treatment) are considered cured of incontinence. The proportion of patients with 100% reduction in incontinence is the *percent cure* reported in a study. A reduction of leakage episodes by 50% has been defined by the International Continence Society as a clinically significant improvement (Blaivas et al. 1997). The proportion of patients with 50% or greater reduction in incontinent episodes is the percent of patients with improvement reported in a study.

In addition to these health outcomes, clinical examinations often include measuring perineal muscle strength and/or urodynamic testing. These types of intermediate outcomes do not represent true health outcomes of interest and, thus, will not be considered primary to this assessment.

Subjective assessments include symptom scales and the Incontinence Impact Questionnaire (Shumaker et al. 1994). These types of patient reported outcomes have not been commonly used in studies to date and, thus, also will not be considered primary to this assessment. General functional status instruments (SF-36) have been included in some of the studies.

The following adverse outcomes have been reported or are potential problems, and will be considered in this assessment:

1) pain at the site of the implanted leads or the implanted pulse generator;
2) infection/skin irritation at the implant sites;
3) lead migration necessitating repeat surgical procedure for revision or replacement;
4) adverse change in bowel function;
5) numbness or other adverse electrical sensation in distribution of stimulated nerves;
6) pelvic/vaginal pain and/or cramping;
7) adverse change in menstrual or sexual functioning;
8) nerve injury at implantation site, and;
9) allergic reaction to device.

Specific Assessment Question

Does sacral nerve stimulation improve health outcomes in patients with refractory urge incontinence?

REVIEW OF EVIDENCE

The evidence for this assessment consists of one published, randomized controlled trial (RCT) (Schmidt et al. 1999). The methodologic aspects of this trial are summarized in Table 1a. This manufacturer supported trial evaluated the safety and effectiveness of the Medtronic SNS System for treatment of urinary urge incontinence. Data from the published article was supplemented

with data submitted to the FDA as part of the approval process and from data supplied by Medtronic, Inc. This supplemental data included extensive reporting on adverse events associated with the technology.

The study involved 16 sites, 9 in Europe and 7 in North America, with an identical study protocol across sites. Patients were randomized to either an immediate implant group or a delayed implant group. The delayed group served as the control arm where participants were offered implantation after six months of follow-up. Eligible patients for the entire study had either urge incontinence, chronic idiopathic urinary retention, or the urgency/frequency syndrome. Patients who had neurologic conditions (multiple sclerosis, spinal cord lesions, cerebrovascular accident) and detrusor hyperreflexia were excluded. The present results are restricted to only the 155 urge incontinence patients.

The data from this clinical trial was reported in three parts. First, the results of the comparative portion of the trial was presented, in which patients receiving immediate SNS were compared to control patients, i.e., in the delayed implant group. Second, a cohort analysis was presented, in which results for all patients receiving SNS, both in the immediate and delayed arm, were pooled, with outcomes evaluated for all patients in both groups who had reached the 6 month, 12 month, and 24 month follow-up period. Third, a therapy evaluation test was presented. In this phase, patients who had reached 6 months of follow-up had their SNS systems turned off, thereby, serving as their own controls. Endpoints were reassessed with the SNS turned off and compared with endpoints obtained at the 6-month follow-up period.

The 155 urge incontinent patients were 80.6% female (n=125). Many of these patients ultimately were not eligible for permanent implantation or did not have complete data at six months. The percentage of males in the final data sets is not specified, but there are probably only a very small number of men included in the final data. This makes it difficult to draw any definitive conclusions specific for men at this time. On the other hand, there are no physiologic reasons why treatment would be expected to differ by gender.

The average age was 46.6 ± 13.0 years, with a range of 20.2 to 78.9 years. This population would include some patients in the Medicare age group, but this would be a minority of the total number of patients. The duration of urinary symptoms averaged 9.0 years, ranging from 0.6 to 35.4 years. The patients showed evidence of extensive prior treatment, with a total of 706 prior non-surgical procedures and 208 surgeries in 155 patients. However, there was a relatively low percentage of patients who reported previous behavioral treatment (36%), which today is considered first line treatment for most patients with urge incontinence. The two groups were similar in number of leakages per day, severity of leakages, and replacement pads used.

Among the 155 urge incontinent patients, 57 patients did not qualify for randomization. Fourteen patients did not complete baseline diaries and were removed from the study. Another 43 patients showed less than 50% response on the peripheral nerve evaluation test and thus failed the permanent implantation inclusion criteria. A total of 98 patients were randomized into the immediate implant or delayed implant groups of the trial.

Follow-up evaluations took place at 1, 3, 6 and 12 months post-implant and thereafter, once every 6 months. Voiding diaries were collected at all follow-up appointments. Urodynamic testing was conducted at baseline and 6 months. Quality of life assessments (SF-36, Beck depression index) were administered at baseline and each follow-up visit after 3 months. The immediate implant and delayed implant groups were compared at 3 and 6 months post-randomization.

Results are reported on 76 of the 98 randomized patients who completed 6 months of follow-up prior to the closure of the database, comparing 34 immediate implant (treatment) patients with 42 delayed implant (control) patients. At the 6 month follow-up, 18 patients in the SNS group (35%) and 4 in the control group (8.7%) did not have complete data available, although all these patients did not discontinue treatment. Analysis was performed using group sequential data analysis, which accounts for the patients without complete data (dropouts) and for interim data analysis.

These main outcomes from this trial are summarized in Table 1b. The SNS patients had consistently superior outcomes on all of the major endpoints examined. Nearly half of the SNS patients did not experience any further episodes of incontinence, and therefore were considered cured. Approximately three-quarters of the SNS patients showed a clinically significant response, i.e. at least was a 50% reduction in the frequency of incontinent episodes. On the outcome of mean leaks/day, there was an improvement from a baseline average of 9.7 per day to 2.6 per day after six months of treatment. In the delayed group, there was a 21% worsening in the average number of reported leaks per day from 9.3 per day to 11.3 per day. This apparent worsening of incontinence in the control group is likely to result from instability in the measures used to quantitate incontinence, and is also likely to make the group comparisons appear more favorable toward SNS. However, the degree of worsening seen in the control group is small relative to the degree of benefit seen in the SNS group.

Quality of life measurements were superior for implant group patients on some components. Subscores of the SF-36 were significantly improved on the measures of physical functioning and general health. Other subscores of the SF-36 improved relative to the delayed implant group, but did not reach statistical significance. Collapsed measures of the mental component and the physical component of the SF-36 were not significantly different between groups. There was also no significant difference in the Beck depression index between the two groups.

In summary, this was a rigorous multicenter randomized clinical trial in a well-defined patient population. Multiple outcome measures were examined, and all endpoints showed differences in favor of SNS that were both clinically and statistically significant. It is unlikely that bias can account for the magnitude of effect seen in this trial. Although there were a large number of patients in the SNS group who did not have complete data at 6 months (18/54), these dropouts were accounted for in the statistical analysis. There was a potential for performance bias, given the inequality in intensity of treatment between the groups. However, an inequality in the

Table 1a. Randomized controlled trial of SNS versus control – methodologic features

Study/year	Patient characteristics	Group Allocation	Treatment	Dropouts	Outcome Measures	Possible threats to validity
Schmidt 1999	155 patients with refractory urge incontinence from 16 clinical centers, 80% female, 20% male. Mean age 46.6 ± 13.0. All pts 'refractory to standard medical therapy': 99% previous tx: 93% drug tx 36% non-surgical 57% surgical tx	Pts with successful test stimulation phase (n=98) randomized to SNS or delayed SNS.	SNS – Surgery to implant SNS device. Follow-up evaluations at 1,3, 6 mths and then q6mth. Control (delayed implant) – F/u visits without treatment at 1,3 and 6mth. SNS implantation at 6mths. Therapy evaluation test – At 6mths post-implantation, device turned off for a minimum of 3 days, then restarted.	6 mths*: SNS - 18/52 (35%) Ctrl – 4/46 (8.7%) * number of pts without complete data at 6mth f/u	Pt recorded voiding diaries completed throughout course of study. SF-36 functional status assessment at baseline and 6mth	Potential for performance bias

Table bibliography

Schmidt RA, Jonas U, Oleson KA et al. (1999). Sacral nerve stimulation for treatment of refractory urinary urge incontinence. *J Urol*, 162:352-357.

Table 1b. Randomized controlled trial of SNS versus control – outcomes

Study/year	Patients/ Groups	Pt recorded diaries						Functional Status outcomes (SF-36)			
		Measure	Pre-	Post-	% change[1]	% pts improv[2]	% cure[3]	Measure	Pre	Post	p value[4]
Schmidt 1999	SNS (n=34)	Leaks/d	9.7	2.6	73% *	76% *	47%*	Physical Functioning	47.9	66.0	<0.001
								Role physical functioning	28.2	49.2	NS
								Bodily Pain	46.5	57.3	NS
								General health	45.7	64.5	<0.001
								Vitality	43.0	53.6	NS
								Social functioning	51.6	53.5	NS
								Mental health functioning	61.6	65.9	NS
								Role emotional health	54.8	75.3	NS
	Control (n=42)	Leaks/d	9.3	11.3	-21%	5%	0%				
								Physical Functioning	55.4	48.5	NS
								Role physical functioning	34.7	38.2	NS
								Bodily Pain	53.2	51.4	NS
								General health	53.8	51.5	NS
								Vitality	50.7	51.8	NS
								Social functioning	51.0	53.0	NS
								Mental health functioning	66.0	64.9	NS
								Role emotional health	50.5	49.5	NS

* Statistically significant difference as compared to control group (P<0.0001)

[1] % change – Defined as the percent decrease in the frequency of incontinence over a specified time period, calculated by the following equation:

$$\frac{\text{pretreatment episodes/period - posttreatment episodes/period}}{\text{pretreatment episodes/period}} \times 100$$

[2] % pts improv – Defined as the percentage of patients with 50% or greater decrease in the frequency of incontinence, as calculated by the previous equation.

[3] % cure – Defined as the percentage of patients with 100% decrease in frequency of incontinence, i.e., no incontinent episodes over the specified time period.

[4] p-value for change in SNS group compared to change in control group, by repeated measures ANOVA

Table 2 - Results of cohort analysis from clinical trial

Study/year	Leaks/day at 6 months (n=58)					Leaks/day at 12 months (n=38)					Leaks/day at 18 months (n=25)				
	Pre-	Post-	% change[1]	% pts improv[2]	% cure[3]	Pre-	Post-	% change[1]	% pts improv[2]	% cure[3]	Pre-	Post-	% change[1]	% pts improv[2]	% cure[3]
Schmidt 1999	10.7	2.8	74%	74%	47%	11.1	2.5	77%	79%	45%	11.5	3.5	73%	NR	NR

[1] % change – Defined as the percent decrease in the frequency of incontinence over a specified time period, calculated by the following equation:

$$\frac{\text{pretreatment episodes/period - posttreatment episodes/period}}{\text{pretreatment episodes/period}} \times 100$$

[2] % pts improv – Defined as the percentage of patients with 50% or greater decrease in the frequency of incontinence, as calculated by the previous equation.
[3] % cure – Defined as the percentage of patients with 100% decrease in frequency of incontinence, i.e., no incontinent episodes over the specified time period.

placebo effect among groups cannot account for either the magnitude or duration of effect reported. Thus it is possible to conclude that SNS is efficacious in improving incontinence for patients with refractory urge incontinence.

Cohort Analysis. Results for all implant and delay group patients were combined to examine the outcomes 6, 12, and 24 months post-implant. This yielded a slightly larger overall group with a longer duration of follow-up. Results of this analysis are summarized in Table 2. These outcomes are very similar to those reported for the treatment group of the randomized portion of the study, and indicate that the beneficial outcomes were maintained for at least 24 months.

Therapy Evaluation Test. After 6 months of implantation, the stimulation was turned off to compare urge incontinence on and then off the electrical stimulation. This portion of the study was intended to provide further evidence that the improvement in urge incontinence was a function of the electrical stimulation provided by the implanted device, and to show that the effects of SNS were reversible. After the electrical stimulation was turned off, patients were allowed to re-equilibrate for a period between 3 and 30 days. Patients then completed the voiding diary over a seven-day period. Data were available from 52 patients. After the device was turned off, the number of leaking episodes per day, the severity of the leaking episodes, and the number of pads/diapers per day returned to roughly the baseline levels prior to SNS implantation (Table 3).

Adverse events. The manufacturer's data presented to the FDA contained extensive information on adverse events. This safety data was reported on all patients treated with SNS, which included the 155 patients with urge incontinence as well as patients with other potential indications for SNS. The adverse effect rates were high, although most events were not clinically serious and resolved with treatment or surgical revision.

First, data was reported examining adverse events related to the test stimulation procedure. These results are summarized in Table 4a. There were 664 test procedures conducted on 458 patients. Adverse events were catalogued as either device or therapy related. Ninety-eight of the 458 test patients (21.4%) experienced a total of 126 adverse events. The types of problems were not serious complications but matters of inconvenience. There were 26 adverse events that were device related occurring in 25 (5.5%) of the 458 patients. Six of the 26 events occurred as a result of mishandling; all events but one (detachment of the lead) were resolved. There were 92 adverse events that were therapy related occurring in 81 (17.7%) of the 458 patients. All but one event (temporary pain) was resolved.

Complications related to the implantation of the permanent device were next reported. A total of 157 patients received the permanent device and were evaluated for adverse events post-implantation. These adverse event rates are summarized in Table 4b. Among the 157 patients, 83 (52.9%) patients experienced 168 adverse events.

Local pain following implantation can often be treated by adjustments in the current amplitude and frequency of the stimulation. Irritation at the site of the generator can usually be resolved by moving the generator to a different location. Movement of the electrode, faulty contact points on

Table 3. Results of therapy evaluation test

Patients	Outcome Measures	Baseline	6-Months Post-Implantation	Stimulation OFF	Stimulation ON
52 patients who completed six months of therapy, drawn from 98 randomized patients.	Leaking episodes per day	10.8 ± 6.3	2.9 ± 5.0	9.5 ± 6.4*	3.0 ± 4.7**
	Severity of leaking	2.0 ± 0.6	0.8 ± 0.8	1.9 ± 0.8*	0.7 ± 0.8**
	Absorbent pads/diapers replaced due to leaking	6.3 ± 4.4	1.2 ± 2.2	5.8 ± 4.7*	1.4 ± 2.4**

*P<0.0001 compared to 6 month post-implantation frequency

**p<0.0001 compared to stimulation OFF

Table 4a. Adverse events associated with peripheral nerve evaluation test

Event type	**Events**	Number and percent of patients (N= 458)	Number of events (n = 26)	Events resolved
Device-Related	Peripheral nerve evaluation lead disconnection at proximal end of external screener	16 (3.5%)	17	17
	Dislodged ground pad	2 (0.4%)	2	2
	Unable to pass lead through needle	1 (0.2%)	1	1
	Mishandling (detachment of lead at distal end, obstructed needle, incorrect connection of cable, transient electric shock, broken screener)	6 (1.2%)	6	6
Therapy-Related	Peripheral nerve evaluation lead migration	56 (12.2%)	66	66
	Temporary pain (soreness with needle puncture)	16 (3.5%)	17	16
	Superficial infection or skin irritation	4 (0.9%)	4	4
	Adverse change in bowel function	3 (0.6%)	3	3
	Adverse change in voiding	1 (0.2%)	1	1
	Irritation at ground pad site	1 (0.2%)	1	1
Patient-Related **		6 (1.3%)	8	8
	Total	**98 (21.4%)***	**126**	**124**

*Several patients experienced more than one event

** Patient-related adverse events were untoward events which were classified by the researchers as not attributed to the SNS device. Examples of these include headache, dizziness, small bowel obstruction, tumor, perianal fistula, adhesions, patient fall, lightning strike, etc.

Table 4b. Adverse events post-implantation of SNS

Event type	**Event**	Number/percent of patients (N = 157)	Number of Events	Events Resolved
Device-Related	Lead fracture	1 (0.6%)	3	2
Therapy-Related	Pain at implant site (back, buttocks, legs)	30 (19.1%)	33	30
	Pain at pulse generator site	25 (15.9%)	27	22
	Lead migration	11 (7.0%)	14	12
	Infection or skin irritation	9 (5.7%)	11	10
	Technical problem	8 (5.1%)	11	9
	Sensation of transient electric shock	8 (5.1%)	10	10
	Adverse change in bowel function	8 (5.1%)	8	8
	Allergic reaction	1 (0.6%)	1	1
	Aggravation of baseline symptoms	1 (0.6%)	1	0
	Other (numbness, vaginal cramping, inability to have orgasm, menstrual bleeding, trauma to pulse generator)	6 (3.8%)	6	5
Patient-Related **		34 (21.7%)	43	43
Total		**83 (52.9%)***	**168**	**152**

*Several patients experienced more than one event

** Patient-related adverse events were untoward events which were classified by the researchers as not attributed to the SNS device. Examples of these include headache, dizziness, small bowel obstruction, tumor, perianal fistula, adhesions, patient fall, lightning strike, etc.

Table 4c. Post-implant revision procedures

Revision type	Number of patients	Number of events	Number of surgeries
Permanent explant Pain at implant site (3) Change in bowel function (1) Infection (2)	6	6	6
Temporary explant/reimplantation Pain at implant site (1) Infection (2) Allergic reaction (1)	4	4	8 (4 explant/4 reimplant)
Device exchange Technical problem (6) Lead migration (10) Change in bowel function (1) Pain at implant site (3)	14	20	19 (1 procedure pending)
Reposition (leads or extension) Pain at implant site (6) Change in bowel function (3) Lead extension/migration (3) Technical problem (4) Transient electric shock (1)	16	17	16 (1 procedure pending)
Reposition (IPG) Pain at IPG site (25)	23	25	22 (3 procedures pending)
Total	**51***	**72**	**76**

*Several patients experienced more than one event

the electrode, faulty placement of the electrode, defects in isolation of the electrode and fracture of the lead may require reoperation. Technical problems include kinking of the cable, fracture of the cable, and excessive tension in the tracking of the cable. These problems require redirection of the wire or replacement cabling.

Surgical re-intervention (i.e., repositioning or replacement) for revision of the device was required in 51 (32.5%) of the 157 patients, totally 72 revision procedures (Table 4c). Six patients had the implant permanently removed. Four patients each had two surgeries, one each for pain, skin irritation and an allergic reaction and one for re-implantation. Pain at the implant site was surgically corrected in 13 (21%) of the patients, the remainder were managed without surgical intervention. Resolution of the adverse event was successful in 69 (92%) of the 75 surgical procedures.

Potentially serious operative complications can include inadvertent puncture of the bowel, pelvic abscess, severing of a nerve, severing of a blood vessel creating a hematoma, infection along the nerve creating an encephalitic or peripheral neuritis problem, chronic long-term pain, urinary tract infections, seromas, or functional deficits due to long term exposure to artificial electrical stimulation. None of these types of complications were reported in the trial.

Replacements and repositioning resulted in several re-operations. The non-device related events included 3 urinary tract infections and 1 cerebrovascular accident.

SUMMARY

Adequacy of evidence. The main piece of evidence for this assessment is a single randomized, controlled trial sponsored by the manufacturer as part of the FDA approval process. This was a multicenter trial, enrolling patients with severe urge incontinence who had failed extensive prior treatments. The study methodology, including inclusion and exclusion criteria, was well-described. A variety of standardized outcome measures, both clinical and functional status, were employed. Of 155 potentially eligible patients, 98 completed a successful test stimulation phase and were randomized to immediate or delayed SNS.

Results showed that patients receiving the implant had markedly better outcomes than did the control patients. Approximately half of the patients treated with SNS become dry, and three-quarters experienced at least 50% reduction in incontinence. The therapy evaluation test, in which the device is turned off and patients thus serve as their own controls, provided further evidence that the effect on incontinence is due to electrical stimulation, and demonstrates that the effect of SNS is reversible. The cohort analysis of the clinical trial provides some evidence that the effect of SNS is maintained for up to 2 years.

The results seen from this trial represent are unlikely to result from bias. Although there were a large number of patients in the SNS group who did not have complete data at 6 months (18/54), these dropouts were accounted for in the statistical analysis. There was a potential for performance bias, given the inequality in intensity of treatment between the groups. However, an inequality in the placebo effect among groups cannot account for either the magnitude or duration

of effect reported. Thus it is possible to conclude that SNS is efficacious in improving incontinence for patients with refractory urge incontinence.

Benefits versus risks. The improvement in incontinence is weighed against the adverse event rate for permanent implantation of the device to determine the net health outcome benefit. The overall adverse event rate is high. Approximately 20% of patients will experience an adverse event during the peripheral nerve evaluation test, and approximately 50% of patients will experience one or more adverse events following permanent implantation. Most of these events are minor complications and either resolve with treatment or with revision of the device. The most common adverse event is post-implant pain, either at the site where the pulse generator is implanted (16%), or at the site of lead implantation to the sacral nerves (19%). Infection, adverse changes in bowel function, lead migration, and a sensation of an electric shock occurred in the clinical trial with a frequency of 5-7%. Approximately one-third of treated patients required additional surgical procedures for revision or replacement of the device due to one or more adverse events. More serious clinical complications can potentially result from the procedure but were not reported in any of the studies to date. Therefore, it appears that the benefits of SNS outweigh the harms. Although both risks and benefits are common, the benefits are relatively large and the risks relatively minor.

Magnitude of benefit. It is likely that SNS is a more effective treatment option than available alternatives for this specific patient population. The main alternative to SNS for refractory urge incontinence is bladder surgery. The most common surgical procedure for urge incontinence, enterocystoplasty, involves reconstruction of the bladder using a portion of bowel. An estimate by AHCPR of the cure rate for this procedure (Urinary Incontinence Guideline Panel 1996), when defined as achieving continence with spontaneous voiding, was placed at 38%. A larger percentage of patients achieve continence but with the tradeoff of requiring intermittent catheterization. The procedure has considerable morbidity, with complications estimated in 54% of patients, some of which are life-threatening. Other surgical procedures, such as partial denervation of the bladder or detrusor myomectomy, are in evolution, and a smaller body of outcome literature exists, limiting the ability to make useful comparisons.

Urinary diversion procedures, such as suprapubic catheterization or permanent Foley catheter use, can be used as alternatives in patients who fail other treatments. Urinary diversion necessitates that patients carry a urinary collection bag, and are associated with high rates of urinary tract infection. These factors result in a substantial negative impact on quality of life, thus rendering these approaches a last resort for patients who have exhausted all other options.

Relevance to Medicare population. While this trial included a broad range of ages, the majority of patients were not in the Medicare age group. The mean age was 46.6 ± 13.0 years. There was no breakdown of results by age group, as this trial was likely to be too small to allow such subgroup analysis. Thus, it is not possible to say with certainty that these results apply to the Medicare population. However, it is likely that an elderly population will respond in a similar manner to those patients in the trial. There are no physiologic reasons to expect that elderly patients will respond differently, and there is no evidence to suggest that efficacy of treatment for urge incontinence differs according to age.

There are several issues regarding SNS that the current data does not answer. The protocol for which other treatments should be attempted before proceeding to SNS implantation is not clearly defined. Although all patients in the trials had previous treatments over a relatively long period of time, the specific treatments for each patient varied. For example, although over 90% of patients had been treated with drugs and more than half had undergone prior surgeries, only 36% of patients were reported to have non-surgical medical treatment. Non-surgical medical treatment includes behavioral treatments, which are currently recommended as first line therapy for patients with urge incontinence. This apparent discrepancy in prior treatments probably results from changes in practice patterns over long periods of time and/or geographic variations in treatment approaches.

A second issue is that the training and proficiency of physicians performing the procedure is in evolution. This is a new approach to the treatment of urge incontinence and there is a learning curve involved in performing the procedure. The manufacturer currently sponsors one and one half day training sessions to teach physicians the procedure. This training is intended for experts in incontinence who work in centers of excellence and nor for the general urologic or gynecologic community. It is too early in the dissemination process to determine the extent to which this technique will be ultimately diffused throughout the medical community. A learning effect may also be seen in terms of adverse events. The adverse event rate and need for subsequent revisions may improve over time as physicians become more familiar with potential problems and ways in which they might be minimized.

Patients have not been followed long enough to investigate issues surrounding battery life and additional surgery for battery replacement, as current data extends only to two years in a very small number of patients. Additional procedures and/or revisions may be required in order to maintain clinical benefit over a longer time period.

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