# SACRAL NERVE STIMULATION FOR THE TREATMENT OF URINARY URGENCY/FREQUENCY IN ADULTS

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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 proposed for patients with urinary urgency/frequency who have failed or cannot tolerate more conservative treatments. The objective of this technology assessment is to review the available evidence to determine whether SNS improves health outcomes of adult patients with refractory urinary urgency/frequency.

Urinary urgency/frequency can be classified into neurologic and non-neurologic categories. This technology assessment will address urinary urgency/frequency 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 indications, such as urge incontinence and non-obstructive urinary retention. The evidence on SNS for the treatment of other types of chronic voiding dysfunction will not be addressed as part of this technology assessment.

BACKGROUND

### Urinary Urgency/Frequency

Urgency is described as a powerful sensation to void, regardless of bladder volume (Brubaker and Sand 1989). The voided volumes observed with urgency are typically considerably lower than cystometric capacity. Urgency may be associated with urge incontinence, which is the involuntary loss of urine associated with a strong desire to void. Frequency is defined as voiding at intervals of 2 hours or less, or more than 7 times per day (Brubaker and Sand 1989).

Although underlying causes of urgency/frequency are unknown, age-related causes are suspected (Brubaker and Sand 1989). Anatomic changes include the squamous epithelium of the outer urethra gradually changing to pseudostratified columnar epithelium. In addition, there is decreasing relative volume of striated muscle and vascular component of the urethra. These anatomic changes may make the urethra more vulnerable to infectious and inflammatory insults. Increasing exposure to suspected iatrogenic causes of urgency-frequency occurs with age. Transurethral catheterization, surgery, urethral instrumentation, and pelvic irradiation occur more frequently in older women. Additional areas of research for etiologies include viral infection, retained bacterial DNA in the bladder tissue after infection, damage to the bladder mucosa or glycosaminoglycan protective layer, neurally mediated inflammation and/or ischemia, and autoimmune disease (Jones and Nyberg 1997).

Diagnoses observed with urgency-frequency symptoms include: infectious cystourethritis, interstitial cystitis, detrusor instability, urethral instability, urethral diverticula, urinary tract neoplasms, pelvic malignancies and treatment, and urethral syndrome (Brubaker and Sand 1989). While urgency/frequency primarily affects females, non-bacterial prostatitis and prostatodynia in males are associated with identical irritative voiding symptomology (Mears 1992).

In a survey of healthy women aged 30 to 64 years, 20% reported having urgency/frequency (Tapp and Cardozo 1986). In another survey of 1,150 non-institutionalized elderly women, 23% reported voiding more than 8 times per day (Diokno et al. 1986). Of the 164 women that subsequently underwent urodynamic testing, 9.8% of patients reporting frequency were found to have unstable bladders (Diokno et al. 1988). The prevalence of interstitial cystitis and urethral syndrome in the U.S. is estimated at about 450,000 (Koziol et al. 1993). The prevalence of non-bacterial prostatitis and prostatodynia is estimated at about 405,000 males (Schaeffer et al. 1981).

**Conservative Treatments for Urgency/Frequency**

As first-line therapy, patients undergo diet modification and behavioral therapy. Bladder retraining uses a series of steps to achieve longer periods between voiding, increase bladder capacity, and reduce discomfort. In an uncontrolled study of 21 interstitial cystitis patients, 71% of patients reported a 50% decrease in their symptoms with this approach (Parsons and Koprowski 1991). Behavioral therapy consists of diary keeping, timed voiding, controlled fluid intake, and pelvic floor muscle training. Biofeedback is another conservative treatment that has been used (Wyndaele et al. 1997).

Pharmacologic treatment includes tricyclic antidepressants, which are known to have an anticholinergic effect and calm an overactive bladder (Owens and Karram 1998). Eleven of 22 patients with voiding dysfunction (including urgency/frequency patients) became symptom-free using amitriptyline (Pranikoff et al. 1998). However, adverse effects caused 4 study participants to discontinue drug therapy. Anticholinergics also have been prescribed for urgency/frequency (Owens and Karram 1998).

Instillation of dimethyl sulfoxide (DMSO) via catheter for 10–20 minutes once per week, for 6 to 8 weeks, is another non-surgical treatment of urgency/frequency. Remission has been reported in 34–40% of interstitial cystitis patients in uncontrolled trials (Parsons 1996). Heparin has been another instillation agent, administered 3 times per week with 50% of 48 patients remaining in remission after 1 year of therapy (Parsons et al. 1994).

Hydrodistention has been used to treat pain and discomfort with urgency/frequency (Pontari et al. 1997). In this procedure, a balloon catheter is inserted into the patient's bladder and filled with water, causing a distension or stretching of the bladder (Lloyd et al. 1992). Although this type of therapy requires anesthesia, it can be performed in an outpatient setting. Hydrodistention has been reported to relieve symptoms in approximately 60% of patients for 4 to 12 months (Parsons 1996).

Surgical interventions for urgency/frequency patients include augmentation cystoplasty or a cystectomy with or without diversion or orthotopic augmentation. Surgery generally is reserved for difficult to treat cases that do not respond to less-invasive intervention (Couillard and Webster 1995; Wall 1990; Langer et al. 1988; Pontari et al. 1997). In augmentation cystoplasy, part or most of the bladder is removed and a new bladder is formed with a section of the patient's bowel, intestine, or stomach. Urine continues to be stored in the neobladder and emptied through the existing urethra or surgically formed opening.

Patients who fail conservative therapy or elect not to undergo surgery, default to managing their voiding dysfunction through frequent voiding, fluid restriction, and by making significant lifestyle adjustments.

**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 on their 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 primary voiding diary parameters, he or she is deemed eligible for the permanent device. According to data from the manufacturer, approximately 45% of patients (260/581) with chronic voiding dysfunction (urge incontinence, urinary retention and urgency/frequency) had a successful peripheral nerve evaluation and were 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 U.S. Food and Drug Administration (FDA) 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.

METHODS

### Search Methods

The MEDLINE database was searched for the periods of 1966 through July 2000, using the Medical Subject Headings (MeSH®) term "urination disorders" and the text words "sacral" "stimulat*." 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 urinary urgency/frequency refractory to conservative treatments (behavioral, pharmacologic, and/or surgical treatments);
3. included relevant health outcome measures (voids/day, volume voided/void, and degree of urgency prior to void)
4. included a concurrent comparison group not treated with SNS;
5. adequate description of the patient population, including diagnostic criteria for refractory urgency/frequency;
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 significant symptoms of refractory urinary urgency/frequency characterized by frequent voids (defined as 7 times per day) that are associated with a strong desire to void (urgency). Patients will have failed or been unable to tolerate prior conservative treatment, for example, behavioral interventions, pharmacologic treatment, and surgery. This group potentially includes patients both with neurologic disorders, such as multiple sclerosis, spinal cord lesions, cerebrovascular accidents, (detrusor hyperreflexia) and without neurologic disorders (idiopathic detrusor instability). However, this Assessment will not address patients who have urinary dysfunction as a result of neurologic injury or illness.

### Technologies to Be Compared

This Assessment will compare SNS to continued conservative management in patients who continue to do poorly after an adequate trial of conservative treatment.

### Health Outcomes

Three main outcome measures are reported in the study of urinary urgency/frequency. Study patients keep voiding diaries that include recording: 1) the number of voids per day, 2) voided

volume per void, and 3) the degree of urgency prior to void (the subject ranks the sensation/desire to void as 0 - “none” (no urge), 1 - “mild,” 2 - “moderate,” or 3 - “severe”). Patients are asked to keep a record of their voiding behavior for 4 days prior to each visit. If the diary is not correctly maintained, patients are given another opportunity to do so by recording their voiding behavior for the 4 days after the visit.

In addition to these health outcomes, clinical examinations may include urodynamic testing. This type of intermediate outcome does not represent true health outcomes of interest and, thus, 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**

Compared to continued conservative management, does sacral nerve stimulation improve health outcomes in patients with refractory urinary urgency/frequency?

REVIEW OF EVIDENCE

The evidence meeting inclusion criteria for this assessment consists of one published, randomized, controlled trial (RCT) (Hassouna et al. 2000). 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 refractory urinary urgency/frequency. Data from this published article were supplemented with data submitted to the FDA as part of the approval process, data supplied by the manufacturer, and a published, long-term, single-arm clinical series (referred to as the “cohort study” in this assessment) (Siegel et al. 2000). The supplemental data from the manufacturer included reporting on adverse events associated with the technology.

The RCT involved 12 sites in Europe and North America, with an identical study protocol across sites. Based on prior agreement with the FDA, patients included in this study were selected based on symptoms (7 or more voids per day) instead of diagnostic categories. Study candidates older than 16 years who were refractory to standard medical therapies underwent baseline evaluation

**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 |
|---|---|---|---|---|---|---|
| Hassouna et al. 2000 | 222 patients with urgency/frequency, all pts 'refractory to standard medical therapy'<br><br>SNS (n=47)<br>85% female<br>Mean age 38.3 ± 11.2<br>98% previous tx:<br>94% drug tx<br>60% non-surgical<br>68% surgical tx<br><br>Control (delayed implant) (n=33)<br>94% female<br>Mean age 40.2 ± 10.5<br>97% previous tx:<br>97% drug tx<br>58% non-surgical<br>76% surgical tx | Pts with successful test stimulation phase (n=80) randomized to SNS or delayed SNS. | SNS – Surgery to implant SNS device. Follow-up evaluation at 6 months.<br><br>Control (delayed implant) – Follow-up visit without treatment at 6 months. SNS implantation at 6 months. | SNS<br>2/26<br>(7.7%)<br><br>Control<br>7/33<br>(21.2%) | Patient recorded voiding diaries completed 4 days prior to baseline and 6-months follow-up: voids/day, volume voided/void, degree of urgency prior to void.<br><br>SF-36 functional status assessment at baseline and 6-months follow-up. | Potential for performance bias |

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

| Study/year | Patients/ Groups | Baseline | 6 Months | Reduction (normal) 100% | ³50% | <50% | None | p value* | Functional Status Outcomes (SF-36) Measure | Score | p value* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hassouna et al. 2000 | Urgency /Frequency SNS (n=25) | Voids/Day | | | | | | | Physical Functioning | 77 | 0.0001 |
| | | 16.9 ± 9.7 | 9.3 ± 5.1 | 15% | 40% | 32% | 8% | 0.0001 | Role physical functioning | 51 | 0.01 |
| | | | | | | | | | Bodily Pain | 60 | 0.01 |
| | | | | | | | | | General health | 61 | 0.003 |
| | | Volume Voided/Void | | | | | | | Vitality | 55 | 0.01 |
| | | 118 ± 74 ml | 226 ± 124 ml | n.a. | 64% | 28% | 4% | 0.0001 | Social functioning | 77 | 0.002 |
| | | | | | | | | | Mental health functioning | 71 | 0.01 |
| | | | | | | | | | Role emotional health | 62 | NS |
| | | Degree of Urgency Prior to Void | | | | | | | | | |
| | | 2.2 ± 0.6 | 1.6 ± 0.9 | | | | | 0.01 | | | |
| | Urgency /Frequency Control (n=26) | Voids/Day | | | | | | | Physical Functioning | 48 | |
| | | 15.2 ± 6.6 | 15.7 ± 7.6 | 0% | 4% | 32% | 64% | | Role physical functioning | 30 | |
| | | | | | | | | | Bodily Pain | 34 | |
| | | | | | | | | | General health | 46 | |
| | | Volume Voided/Void | | | | | | | Vitality | 36 | |
| | | 124 ± 66 ml | 123 ± 75 ml | n.a. | 8% | 23% | 69% | | Social functioning | 43 | |
| | | | | | | | | | Mental health functioning | 62 | |
| | | | | | | | | | Role emotional health | 71 | |
| | | Degree of Urgency Prior to Void | | | | | | | | | |
| | | 2.4 ± 0.5 | 2.3 ± 0.5 | | | | | | | | |

*Treatment versus control group at 6 months; because at the 6-month follow-up, 15 patients in the SNS group (38.5%) and 7 in the control group (21.2%) did not have complete data available, analysis was performed using group sequential data analysis.

to rule out treatable etiologies. Pre-study evaluation included medical and urological history, physical examination, urodynamic testing and completion of two 3-day voiding diaries. Patients with a bladder capacity of at least 100 mL and normal upper tracts were enrolled in the study. Patients who had neurologic conditions (multiple sclerosis, spinal cord lesions, cerebrovascular accident) and detrusor hyperreflexia were excluded. In addition, patients with primary stress incontinence and primary pelvic pain symptoms were excluded. 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 6 months of follow-up.

The data for the FDA PMA supplement were reported in three parts. First, the results of the RCT (Hassouna et al. 2000) were presented, in which patients receiving immediate SNS were compared to control patients, i.e., in the delayed implant group. Second, results from the cohort study (Siegel et al. 2000) were 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 24-month follow-up period. Third, a therapy evaluation test was presented (FDA PMA supplement). 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.

Of the 220 urgency/frequency patients enrolled for study, 80 (36.3%) were eligible for randomization and permanent implantation of device. Eight patients, all in the treatment group, had not reached 6 months of follow-up for the study. Thirteen patients, all in the treatment group, were not implanted. At 6 months of follow-up, the drop-out rate for the treatment group was 2/26 or 7.7% (1 patient did not complete the diary and 1 patient was explanted and left the study). The drop-out rate for the control group was 7/33 or 21.2% (5 patients did not complete the study and 2 left the study). The difference in drop-out rates between treatment and control groups although substantial, is not statistically significant p=0.152 (by chi-square test). Eighty-five percent of the treatment group and 94% of the control group were female. Since there was only a very small number of men included in the final data, any definitive conclusions specific for men would be difficult at this time. However, there are no physiologic reasons why treatment would be expected to differ by gender.

The average age for the treatment group was 38.3 ± 11.2 years and for the control group was 40.2 ± 10.5 years. Of the treatment group, 98% had frequency symptoms averaging 7.1 ± 8.3 years, while 91% of the control group had frequency symptoms averaging 9.1 ± 8.8 years. Urgency symptoms were exhibited by 85% of the treatment group for 7.2 ± 8.7 years, while 97% of the control group exhibited 8.9 ± 8.5 years of urgency symptoms. The patients showed evidence of extensive prior treatment, with 94% of treatment patients and 97% of controls with prior pharmacologic treatment. In addition, 68% of treatment patients and 76% of controls had surgical therapy. Non-surgical therapy was 60% for the treatment group and 58% for the control group. However, these results indicate that behavioral treatment, which currently is considered first line treatment (at least for urinary incontinence) was not universally attempted.

Follow-up evaluations took place at 6, 12, 18, and 24 months post-implant. 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 6 months. The immediate implant and delayed implant groups were compared at 6 months post-randomization.

Results are reported on 51 patients at 6 months of follow-up, comparing 25 immediate implant (SNS treatment) patients with 26 delayed implant (control) patients. At the 6-month follow-up, 15 patients in the SNS group (38.5%) and 7 in the control group (21.2%) did not have complete data available. Analysis was performed using group sequential data analysis, with a significance level of p=0.01 (based on accrual, alpha, and maximum sample size) to judge the statistical significance of the primary variables.

The main outcomes from the randomized trial are summarized in Table 1b. The SNS patients had consistently superior outcomes that were statistically significant on all of the major endpoints examined. Voids/day decreased from 16.9 ± 9.7 to 9.3 ± 5.1, with no such corresponding reduction in the control group. Fifteen percent of SNS patients compared to 0% of controls achieved normal urinary frequency, while 40% of SNS patients showed at least a 50% reduction in frequency compared to 4% of controls. Volume voided/void increased from 118 ± 74 ml to 226 ± 124 ml in SNS patients, with no such corresponding increase in control patients. Sixty-four percent of SNS patients saw at least a 50% increase in their volume voided/void compared to 4% of controls. Degree of urgency prior to void decreased from a score of 2.2 ± 0.6 to 1.6 ± 0.9, while remaining relatively constant in controls. With regard to degree of urgency prior to void, the authors also report "clinical success" of 88% in the SNS group versus 32% in the control group. However, since this measure by definition could include subjects with increased voided volumes without necessarily having decreased urgency, the utility of this measure is questionable. Quality of life measurements were significantly improved for implant group patients on 7 of the 8 subscores of the SF-36.

Cohort Study. Results for all implant and delay group patients were combined to examine the outcomes 6, 12, 18, and 24 months post-implant. This yielded a slightly larger overall group with a longer duration of follow-up. Results of this analysis at 24 months are summarized in Table 2. Fifty-six percent of patients demonstrated at least a 50% reduction in voids per day at 24 months (n=29), while 32% had returned to within normal range. Forty-eight percent of patients showed at least a 50% increase in volume voided/void. 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. (The authors did not report degree of urgency score at 24 months, rather "clinical improvement," which did not necessarily reflect a reduction in degree of urgency.)

**Table 2. Results of cohort study**

| Study/year | Diary Variable | Baseline | 24 Months Post Implantation n=29 | P value |
|---|---|---|---|---|
| Siegel et al. 2000 | voids/day | 17.7 ± 8.6 | 10.6 ± 6.6 | 0.0001 |
| | volume voided (mL)/void | 132.5 ± 93.6 | 225.0 ± 162 | 0.0001 |

Therapy Evaluation Test. After 6 months of implantation, the stimulation was turned off to compare urgency/frequency 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 7-day period. Data were available from 37 patients. After the device was turned off, the primary endpoints showed statistically significant reductions from treatment, returning to approximately 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 (Tables 4a and b). These safety data were reported on all patients treated with SNS (n=581), which included the patients with urgency/frequency (n=220), as well as patients with other potential indications (urge incontinence [n=184] and non-obstructive urinary retention [n=177]) for SNS. The adverse effect rates were high, although most events were not clinically serious and resolved with treatment or surgical revision.

First, data were reported examining adverse events related to the test stimulation procedure. These results are summarized in Table 4a. There were 914 test procedures conducted on 581 patients. Adverse events were catalogued as either device or therapy related. One hundred thirty-five of the 581 test patients (23.2%) experienced a total of 181 adverse events. The types of problems were not serious complications but matters of inconvenience. There were 143 adverse events that were device-related occurring in 15.6% of the 581 patients. There were 35 adverse events that were therapy-related occurring in 3.8% of the 581 patients. All events were resolved.

Complications related to the implantation of the permanent device were next reported. A total of 219 patients received the permanent device and were evaluated for adverse events post-implantation. These adverse event rates are summarized in Table 4b. Among the 219 patients, 113 (51.6%) patients experienced 201 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 the electrode, faulty placement of the electrode, defects in isolation of the electrode, and fracture of the lead may require re-operation. 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.

**Table 3. Results of therapy evaluation test**

| Study/year | Diary Variable (mean) | Baseline (No Stimulation) | 6-Months Post-Implantation (Stimulation On) | Therapy Evaluation (Stimulation Off) | P value (On vs Off) |
|---|---|---|---|---|---|
| Data from manufacturer (n=37) | voids/day | 16.3 | 8.8 | 13.5 | 0.0001 |
| | void volume (ml)/void | 127 | 230 | 147 | 0.0001 |
| | degree of urgency prior to void | 2.3 | 1.7 | 2.2 | 0.0001 |

**Table 4a. Adverse events associated with peripheral nerve evaluation test in 581 patients1**

| Event type | Events | Number of events | Events resolved |
|---|---|---|---|
| Device-Related | Suspected lead migration | 108 | 108 |
| | Technical problem | 24 | 24 |
| | Suspected device problem | 10 | 10 |
| | Transient electric shock | 1 | 1 |
| Therapy-Related | New pain | 19 | 19 |
| | Skin irritation | 6 | 6 |
| | Adverse change in bowel function | 4 | 4 |
| | Infection at lead site | 3 | 3 |
| | Adverse change in voiding function | 3 | 3 |
| | | | |
| Other [2] | | 3 | 3 |
| | **Total [3]** | **181** | **181** |

[1] With 914 test procedures.
[2] Other adverse events included affected equilibrium, poor rubber pad adhesion, and syncope.
[3] Several patients experienced more than one event.

**Table 4b. Adverse events post-implantation of SNS in 219 patients**

| Event type | Event | Number of Events | Events Resolved |
|---|---|---|---|
| Device-Related | Pain at implant site (back, buttocks, legs) | 46 | 43 |
| | Suspected device problem | 14 | 12 |
| | Technical problem | 4 | 4 |
| Therapy-Related | New pain | 23 | 19 |
| | Suspected lead migration | 19 | 18 |
| | Infection | 18 | 18 |
| | Pain at lead site | 15 | 12 |
| | Transient electric shock | 14 | 13 |
| | Adverse change in bowel function | 7 | 7 |
| | Persistent skin irritation | 2 | 2 |
| | Change in menstrual cycle | 2 | 2 |
| | Suspected nerve injury | 1 | 1 |
| | Change in voiding function | 1 | 1 |
| | Device rejection | 1 | 1 |
| Other [1] | | 34 | 30 |
| **Total [2]** | | **201** | **183** |

[1] Change in sensation of stimulation (9), Grand mal seizure when stimulation inactivated (1), Hematoma or seroma (1), Urinary hesitancy (1), IPG turns ON and OFF (2), Lack of orgasm (1), Lack of efficacy (2), Numbness and tingling (3), Foot/leg movement (6), Strong anal sensation (1), Unable to perceive stimulation (2), Stress urinary incontinence (1), Swollen feeling in abdomen (1), Vaginal cramps (1), Superficial connection (1), Possible skin perforation at IPG (1).

[2] Several patients experienced more than one event.

SUMMARY

Adequacy of evidence. The evidence meeting inclusion criteria for this assessment is one published, randomized controlled trial (RCT). This manufacturer-supported trial evaluated the safety and effectiveness of the Medtronic SNS System® for treatment of refractory urinary urgency/frequency. Data from this published article were supplemented with data submitted to the FDA as part of the approval process, data supplied by Medtronic, Inc., and a published, long-term, single-arm cohort study.

The RCT involved 12 sites in Europe and North America. 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. Patients who had neurologic conditions (multiple sclerosis, spinal cord lesions, cerebrovascular accident) and detrusor hyperreflexia were excluded. Of the 220 urgency/frequency patients enrolled for study, 80 (36.3%) were eligible for randomization and ultimately permanent implantation of device. At 6 months follow-up, data on 51 patients were available; because 15 patients in the SNS group (38.5%) and 7 in the control group (21.2%) did not have complete data available, analysis was performed using group sequential data analysis.

Eighty-five percent of the treatment group and 94% of the control group were female. The average age for the treatment group was 38.3 ± 11.2 years and for the control group was 40.2 ± 10.5 years. Of the treatment group, 98% had frequency symptoms averaging 7.1 ± 8.3 years, while 91% of the control group had frequency symptoms averaging 9.1 ± 8.8 years. Urgency symptoms were exhibited by 85% of the treatment group for 7.2 ± 8.7 years, while 97% of the control group exhibited 8.9 ± 8.5 years of urgency symptoms. The patients showed evidence of extensive prior treatment, with 94% of treatment patients and 97% of controls with prior pharmacologic treatment. In addition, 68% of treatment patients and 76% of controls had surgical therapy. Non-surgical therapy was 60% for the treatment group and 58% for the control group.

The SNS-treated patients had consistently better outcomes that were statistically significant on all of the major endpoints examined. Voids per day decreased from 16.9 ± 9.7 to 9.3 ± 5.1, with no such corresponding reduction in the control group. Fifteen percent of SNS patients compared to 0% of controls achieved normal urinary frequency, while 40% of SNS patients showed at least a 50% reduction in frequency compared to 4% of controls. Volume voided per void increased from 118 ± 74 ml to 226 ± 124 ml in SNS patients, with no such corresponding increase in control patients. Sixty-four percent of SNS patients saw at least a 50% increase in their volume voided per void compared to 4% of controls. Degree of urgency prior to void decreased from a score of 2.2 ± 0.6 to 1.6 ± 0.9, while remaining relatively constant in controls. Quality of life measurements were significantly improved for implant group patients on seven of the eight subscores of the SF-36.

This was a sufficiently rigorous, multicenter, randomized clinical trial in a reasonably well-defined patient population. 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 symptoms of patients with refractory symptoms of urinary urgency/frequency.

The cohort trial, in which data on the implant's effects were combined from the immediate and delayed implant groups, demonstrated that the beneficial effects are maintained for at least 24 months. The therapy evaluation phase of the trial further supported the efficacy of the device and demonstrated that the effect was reversible, since the frequency of incontinence returned to roughly baseline levels after the device was turned off.

Benefits versus risks. The improvement in symptoms for patients treated with SNS is weighed against the adverse event rate for permanent implantation of the device to determine if net health outcome is improved. The degree of improvement seen in all of the studies examined is large, for a population that has failed extensive prior treatment. The improvement in urgency/frequency symptoms improve patients' overall quality of life as well, as demonstrated by significant differences on seven of eight SF-36 subscores.

The reported test stimulation procedure adverse event rate was high, at 23.2%; however, the types of problems were not serious complications and all events were resolved. Complications related to the implantation of the permanent device were reported to be 51.6%. Ninety-one percent of these complications were resolved. Surgical re-intervention (i.e., repositioning or replacement) for revision of the device was required in 33.3% of patients. One suspected nerve injury and one hematoma or seroma were reported.

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. Therefore, it is possible to conclude that SNS improves the net health outcome in patients with urgency/frequency.

Magnitude of benefit. The technology was applied in patients refractory to or unable to tolerate prior conservative therapy. Patients, who fail conservative therapy or elect not to undergo surgery, continue to manage their voiding dysfunction through frequent voiding, fluid restriction, and limitations or adjustments in their daily activities. Patients with urinary urgency/frequency symptoms, which are not due to a neurologic condition, who have failed previous conservative treatments, and who have had a successful peripheral nerve evaluation test appear to derive benefit from SNS that is not available to them with other currently available conservative therapies.

Relevance to Medicare population. While the RCT included patients who were within a broad range of ages, the majority of patients were not in the Medicare age group. The mean age of patients treated with SNS was 38.3 $\pm$ 11.2 years and the mean age of control patients was 40.2 $\pm$ 10.5 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 urgency/frequency differs according to age. Also, 85% of the treatment group and 94% of the control group were female. Since there was only a very small number of

men included in the final data, any definitive conclusions specific for men would be difficult at this time. However, there are no physiologic reasons why treatment would be expected to differ by gender.

There are several issues regarding SNS that the current data do 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 approximately 60% 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 not 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.

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