ORIGINAL CONTRIBUTION

Long-term Efficacy and Safety of Sacral Nerve Stimulation for Fecal Incontinence

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BACKGROUND AND OBJECTIVE: Sacral nerve stimulation is effective in the treatment of urinary incontinence and is currently under Food and Drug Administration review in the United States for fecal incontinence. Previous reports have focused primarily on short-term results of sacral nerve stimulation for fecal incontinence. The present study reports the long-term effectiveness and safety of sacral nerve stimulation for fecal incontinence in a large prospective multicenter study.

DESIGN AND METHODS: Patients with fecal incontinent episodes more than twice per week were offered participation in this multicentered prospective trial. Patients showing ≥50% improvement during test stimulation were offered chronic implantation of the InterStim Therapy system (Medtronic; Minneapolis, MN). The aims of the current report were to provide 3-year follow-up data on patients from that study who underwent sacral nerve stimulation and were monitored under the rigors of an Food and Drug Administration-approved investigational protocol.

RESULTS: One hundred thirty-three patients underwent test stimulation with a 90% success rate, of whom 120 (110 females) with a mean age of 60.5 years and a mean duration of fecal incontinence of 7 years received chronic implantation. Mean length of follow-up was 3.1 (range, 0.2–6.1) years, with 83 patients completing all or part of the 3-year follow-up assessment. At 3 years follow-up, 86% of patients ($P < .0001$) reported ≥50% reduction in the number of incontinent episodes per week compared with baseline and the number of incontinent episodes per week decreased from a mean of 9.4 at baseline to 1.7. Perfect continence was achieved in 40% of subjects. The therapy also improved the fecal incontinence severity index. Sacral nerve stimulation had a positive impact on the quality of life, as evidenced by significant improvements in all 4 scales of the Fecal Incontinence Quality of Life instrument at 12, 24, and 36 months of follow-up. The most common device- or therapy-related adverse events through the mean 36 months of follow-up included implant site pain (28%), paresthesia (15%), change in the sensation of stimulation (12%), and infection (10%). There were no reported unanticipated adverse device effects associated with sacral nerve stimulation therapy.

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CONCLUSIONS: Sacral nerve stimulation using InterStim Therapy is a safe and effective treatment for patients with fecal incontinence. These data support long-term safety and effectiveness to 36 months.

KEY WORDS: Fecal incontinence; Sacral nerve stimulation; Therapy; InterStim therapy; Fecal leakage.

During the past 20 years, numerous new options have arisen for the treatment of fecal incontinence (FI), including the injection of substances into the submucosa and into the intersphincteric space,[1–3] stimulated graciloplasty,[4–6] artificial bowel sphincter,[7–9] and, most recently, sacral nerve stimulation (SNS).[10–12] The fact that so many new developments have been championed attests to the lack of a panacea of any single intervention, at least in part because of the multifactorial nature of FI. However, the efficacy, as well as the morbidity profile, of these new techniques and technologies also significantly limit their use. As an example, the high morbidity rates reported with both the dynamic graciloplasty[13,14] and the artificial bowel sphincter[7,15] have limited their appeal. Conversely, SNS has been associated with a vastly lower morbidity,[16] perhaps at least in part because the instrumentation and the surgical sites are well away from the anus.

Because of the relative simplicity of SNS, as well as the comparatively acceptable risk profile, the question of efficacy becomes the most important facet of data analyses. Few authors have assessed the long-term efficacy of SNS. The longest follow-up was recently reported by Matzel and coworkers,[17] who had a minimum follow-up of 7 years and a mean follow-up of 10 years in a retrospective study including 9 patients. They reported a success rate of 66%.

The lack of large multicenter trials including substantial numbers of patients with long-term follow-up of SNS is striking. Despite the relative dearth of published data in this regard, the studies have shown concordance with the maintenance of this salutary effect in terms of significant decreases in actual incontinence and dramatic objective improvements in quality of life. The first Food and Drug Administration (FDA)-regulated multicenter prospective study was recently published.[18] This analysis of 120 patients revealed a success rate of approximately 80% at a relatively short follow-up of 12 months postimplant. A subsequent publication from the same group noted a low morbidity, including a limited infection rate at 10.8%.[16] The question is whether this dramatic improvement in incontinence and quality of life is sustained over a lengthier follow-up. Accordingly, the aims of the current report were to provide 3-year follow-up data on patients from that study who underwent SNS and were monitored under the rigors of an FDA-approved investigational protocol.

PATIENTS AND METHODS

Study Design and Objectives

This prospective nonrandomized study was conducted in 14 centers in the United States, 1 in Canada, and 1 in Australia from 2002 through 2010. Patients with FI received SNS using InterStim Therapy (Medtronic, Minneapolis, MN), and they were thereafter followed up with a standardized protocol at predetermined intervals to evaluate the efficacy and safety of the therapy. The study protocol was approved by the FDA and the institutional review boards at all participating institutions. The present article provides a report of the study results using data from all patients who had or would have completed 3 years of follow-up at the time of data cutoff for this article. Patients underwent permanent implant of the SNS device between 2001 and 2008. The cutoff date for this article was February 8, 2010. Some of these results have been previously reported after 12 months of follow-up.[18]

Study Patients

Inclusion and exclusion criteria and surgical procedures have been previously described.[18] All patients had failed or were not candidates for more conservative medical treatments and were 18 years of age or older (no upper limit). All patients had chronic FI, defined as more than 2 incontinent episodes of frank fecal incontinence of fecal material per week for a duration of longer than 6 months (1 year post-vaginal childbirth). Fecal staining did not qualify as incontinence episodes.

Surgical Procedures

Qualified patients underwent a staged implant procedure.[18] Adequate motor/sensory response was tested in the foramen of S2, S3, and/or S4. A quadripolar electrode was placed in the foramen with the best response and connected, via a percutaneous extension kit, to an external test stimulator. Patients underwent the subchronic test stimulation for 10 to 14 days and were asked to complete a daily bowel diary. Patients achieving $\geq$50% reduction in the number of incontinence episodes per week and/or $\geq$50% reduction in the number of incontinence days per week were offered the implantation of a permanent neurostimulation device.

At the permanent implantation, the percutaneous extension was removed and replaced by a shorter extension connected to an internal pulse generator placed subcutaneously in a pocket in the gluteal area. The pulse generator was activated after the procedure.

Assessments at Baseline and at Follow-up Visits

Baseline assessments included appropriate history and physical evaluation, anorectal manometry, pudendal nerve terminal motor latency measurement, endoanal ultrasound, bowel diary, and assessments of FI severity and

quality of life. Follow-up visits for efficacy assessment were scheduled at 3 months, 6 months, 12 months, and annually thereafter.

Patients were asked to complete a bowel diary at baseline, during subchronic test stimulation, and at all follow-up visits. This 5-question diary collected the following data pertaining to each bowel episode: amount of incontinence, urgency, ability to defer defecation, occurrence of the episode during sleep, and stool consistency.[18,19] The diary was filled out for a period of 10 to 14 consecutive 24-hour periods.

Patients were asked to complete the American Society of Colon and Rectal Surgery Fecal Incontinence Quality of Life Questionnaire (FIQOL),[20] fecal incontinence severity index (FISI),[21] and a survey question on pad use at baseline and all follow-up visits.

Adverse events were collected at surgical procedures, during subchronic test stimulation, at all follow-up visits, and when the patient contacted the investigator for any type of symptoms or problems between the scheduled follow-up visits. All undesirable clinical symptoms and events of any kind were classified as adverse events irrespective of whether they were deemed to be device/therapy related or not. The cause of the adverse event was classified by an Adverse Events Committee as being device related (the event is caused by a suspected device malfunction), therapy related (the event is directly or indirectly caused by the surgical implantation procedure, or is associated with the presence and/or use of the device), or related to the subject's underlying diagnosis or a new diagnosis unrelated to the device.

Statistical Analysis

The software package SAS version 9.1 (SAS Institute, Inc., Cary, NC) was used for all data analysis. Efficacy results were presented for each follow-up visit through 36 months for subjects who completed the relevant assessments at the visit (complete case analysis). The therapeutic success rates (proportions of subjects with ≥50% reduction in incontinent episodes per week or incontinent days per week) were also evaluated by using 2 alternative methods on the intention-to-treat basis: the last-observation-carried-forward method where missing 3-year data were imputed using data from the preceding visit, and the modified worst case analysis where subjects with missing 3-year data were considered failures, unless data were collected at a subsequent visit that would then be used to substitute for the missing 3-year data. Changes from baseline to follow-up in FI symptoms, FISI scores, and FIQOL scores were evaluated with either the paired *T* test or the Wilcoxon signed rank test after testing for data normality. The success rates were compared against a null value of 50% by using the exact binomial test for a one-sample proportion. Reduction in fecal incontinent episodes per week or incontinent days per week was also classified into 5 categories: 100% (perfect continence), 75% to 100%, 50% to 75%, 0% to 50%, and ≤0% (no improvement or worsening). Subjects' responses to key questions of the FIQOL and FISI questionnaires and a survey question on pad use were summarized and compared between the baseline and follow-up visits. The most frequently reported adverse events related to the SNS device or therapy, cumulative through the time of data cutoff for this article, were presented in terms of the percentage of subjects experiencing each event. All subjects receiving the SNS intervention were included in the adverse events analysis (133 subjects underwent subchronic testing and 120 received chronic implant).

RESULTS

Patients

A total of 285 patients with chronic FI were evaluated for potential enrollment at 16 institutions, and 152 patients were excluded from further participation in the study.[18] A total of 133 patients underwent acute test stimulation. The acute test stimulation failed in 3 patients, 9 patients did not achieve sufficient improvement at the subchronic test stimulation, and one patient withdrew consent. A total of 120 patients underwent implantation of a chronically implanted device.

All 120 patients had achieved ≥50% improvement of symptoms during the subchronic test phase, and these 120 patients are the subject of the balance of this report. Mean age was 60.5 (range, 30–88) years, and patients reported a mean duration of FI at baseline of 7 (range, 1–44) years. Ninety-two percent of the patients were females, and the etiologies of FI included obstetric trauma (n = 55), postsurgical (n = 25), noniatrogenic trauma (n = 3), and other

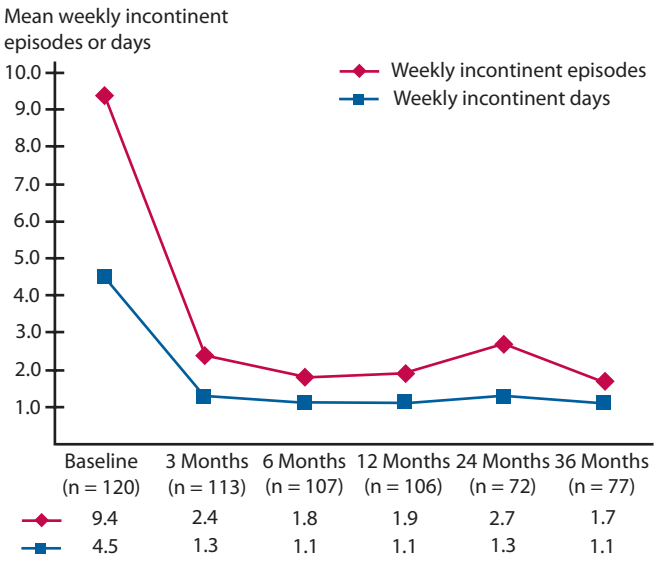

FIGURE 1. Frequency of incontinent episodes or days per week. All paired tests comparing follow-up to baseline had a *P* value of less than .0001.

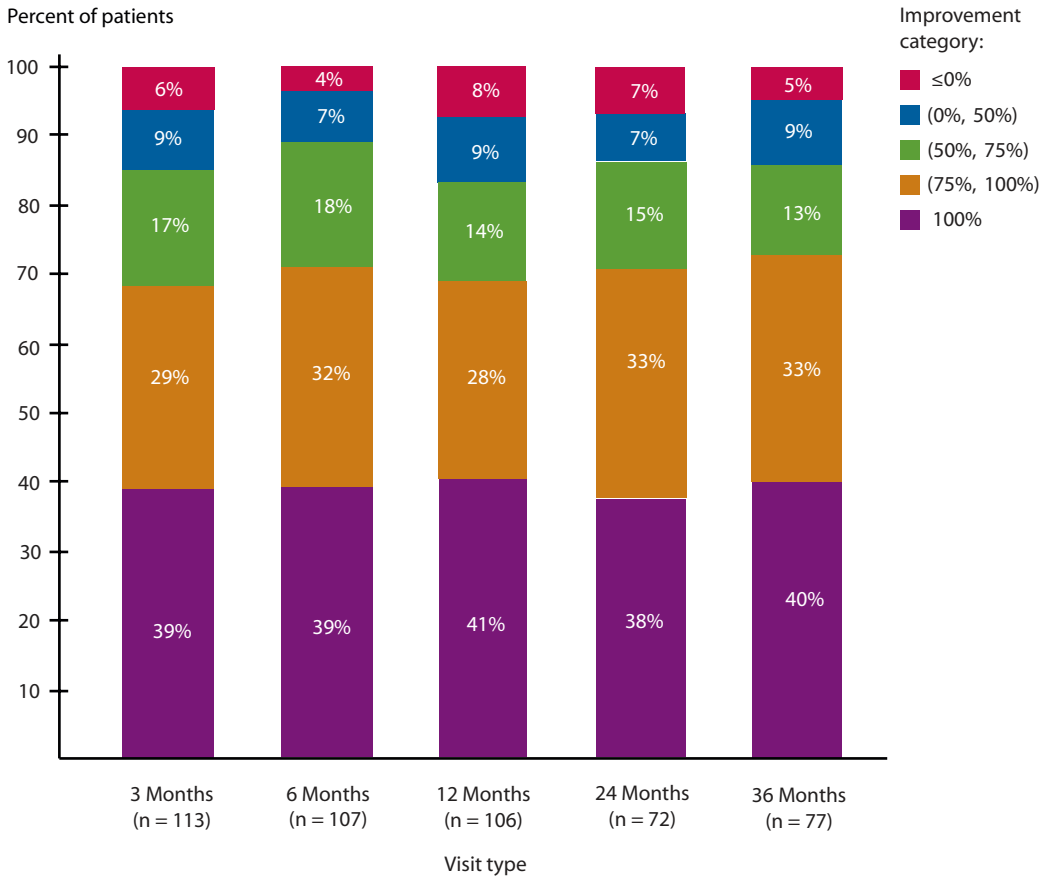

FIGURE 2. Improvement categories in weekly incontinent episodes. All exact-binomial tests comparing the success rate (proportion of subjects with ≥50% reduction in weekly incontinent episodes) at follow-up against a null value of 50% had a *P* value of less than .0001.

(n = 37). Previous surgical procedures and concurrent medical disorders have been reported previously.[18] At baseline, mean resting anal pressures were recorded at an average of 37 (range, 85–101) mmHg, mean squeeze pressures at an average of 51 (range, 6–172) mmHg, right-sided pudendal latency at an average of 2.5 (range, 0–5) ms, and left-sided pudendal latency at an average of 2.7 (range 0–11) ms. Pudendal latencies were unobtainable in 10 patients on the right side and in 11 patients on the left side. Endoanal ultrasound demonstrated a defect in the internal anal sphincter in 22 patients and in the external anal sphincter in 14 patients.

Follow-up

At the time of data cutoff for this article, the mean length of follow-up in the 120 patients with implants was 3.1 (range, 0.2–6.1) years, with 83 patients completing all or part of the 3-year follow-up assessment. A total of 37 patients had exited the study at the time of data cutoff. Reasons for study exit included terminal illness of the local principal investigator (n = 14), lack of efficacy (n = 6), death not related to device or therapy (n = 4), withdrawal of consent (n = 3), persistent skin irritation (n = 2), implant site infection (n = 2), suspected device problem (n = 1), posterior pain (n = 1), rectal prolapse (n = 1), diarrhea (n = 1), subject being monitored by nonstudy physician (n = 1), and subject lost to follow-up (n = 1).

Effect on FI Symptoms

SNS therapy significantly decreased ($P < .0001$) the frequency of incontinent episodes or days per week (Fig. 1). The number of incontinent episodes per week decreased from a mean of 9.4 at baseline to 1.7 at 3 years, and the number of incontinent days per week decreased from a mean of 4.5 at baseline to 1.1 at 3 years. FI symptoms were significantly improved in the majority of patients within 3 months of receiving SNS therapy, and this beneficial effect was sustained and stable over the course of follow-up for 3 years (Figs. 2 and 3). At 3 years of follow-up, 86% of patients ($P < .0001$) reported ≥50% reduction in the number of incontinent episodes per week compared with baseline (Fig. 2), and 78% of patients ($P < .0001$) reported ≥50% reduction in the number of incontinent days per week compared to baseline (Fig. 3). Approximately 70% of patients reported ≥75% reduction in incontinent episodes, with 40% reporting perfect continence, at each

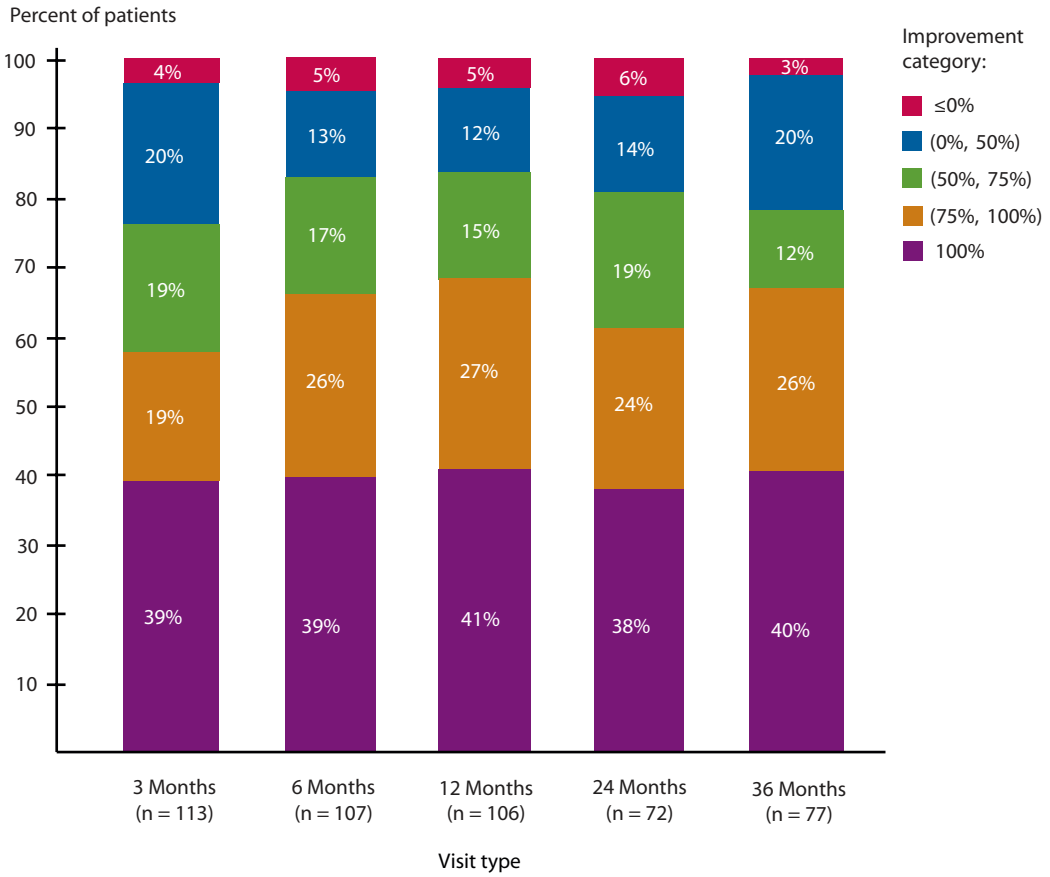

FIGURE 3. Improvement categories in weekly incontinent days. All exact-binomial tests comparing the success rate (proportion of subjects with ≥50% reduction in weekly incontinent days) at follow-up against a null value of 50% had a *P* value of less than .0001.

follow-up visit; and this therapeutic effect was stable over time (Figs. 2 and 3).

Results remained robust in an analysis where missing 3-year data were imputed by use of the last-observation-carried-forward method, with 79% of patients ($P < .0001$) experiencing ≥50% reduction in the number of incontinent episodes per week and 74% of patients ($P < .0001$) experiencing ≥50% reduction in the number of incontinent days per week. In a more conservative modified worst case analysis, where all subjects missing 3-year data were considered failures unless they had data at a later visit, 59% of patients ($P = .055$) experienced ≥50% reduction in the number of incontinent episodes per week and 53% of patients ($P = .52$) experienced ≥50% reduction in the number of incontinent days per week.

The therapy also improved ($P < .0001$) the FISI score (Fig. 4), which measures the leakage of gas, mucus, and liquid and solid stool; this improvement was stable over time.

Effect on Quality of Life

SNS improved quality of life, demonstrated by significant improvement ($P < .0001$) in all 4 scales of the FIQOL instrument from baseline to 3 years (Fig. 5). This improvement is characterized when analyzing key questions in the FIQOL instrument (Figs. 6–8). Figure 6 demonstrates that

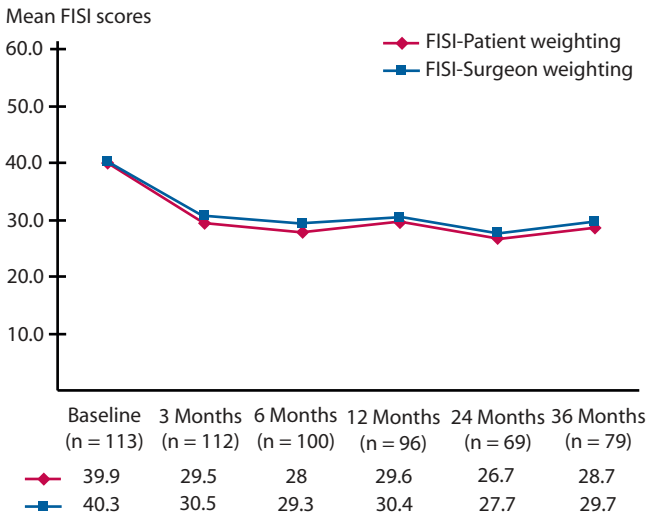

FIGURE 4. Fecal incontinence severity index (FISI) assessment. All paired tests comparing follow-up to baseline had a *P* value of less than .0001.

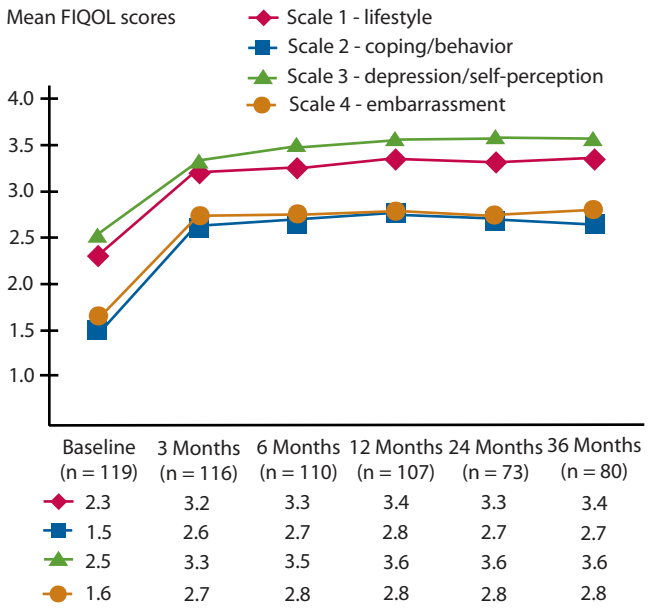

FIGURE 5. Fecal incontinence quality of life (FIQOL) assessment score. All paired tests comparing follow-up with baseline had a *P* value of less than .0001.

the therapy was successful in reducing passive FI symptoms: at baseline 60% of patients leaked stool without even knowing it most of the time; after 3 months of SNS therapy this number was reduced to only about 10%, and the effect was sustained through 3 years of follow-up. Figure 7 demonstrates the significant effect of the therapy on reducing patients' worries about their FI symptoms, and Figure 8 demonstrates the therapy's beneficial effect on the patients' planning of their daily activities.

The therapy also decreased the use of protective pads (Fig. 9). Approximately 30% of patients reported no use of protective pads after 3 months of SNS therapy, compared with only 3% at baseline, and the effect was sustained through 3 years of follow-up.

Adverse Events

Adverse events cumulative through an earlier data cutoff date and details on implant site infections have been reported previously.[16,18]

At the time of data cutoff for this article, a total of 334 adverse events were reported in 99 patients that were considered to be related to the device or therapy, with the majority (67%) of these adverse events occurring within the first year of implant. The vast majority of these adverse events required no or minimal interventions, such as medication.

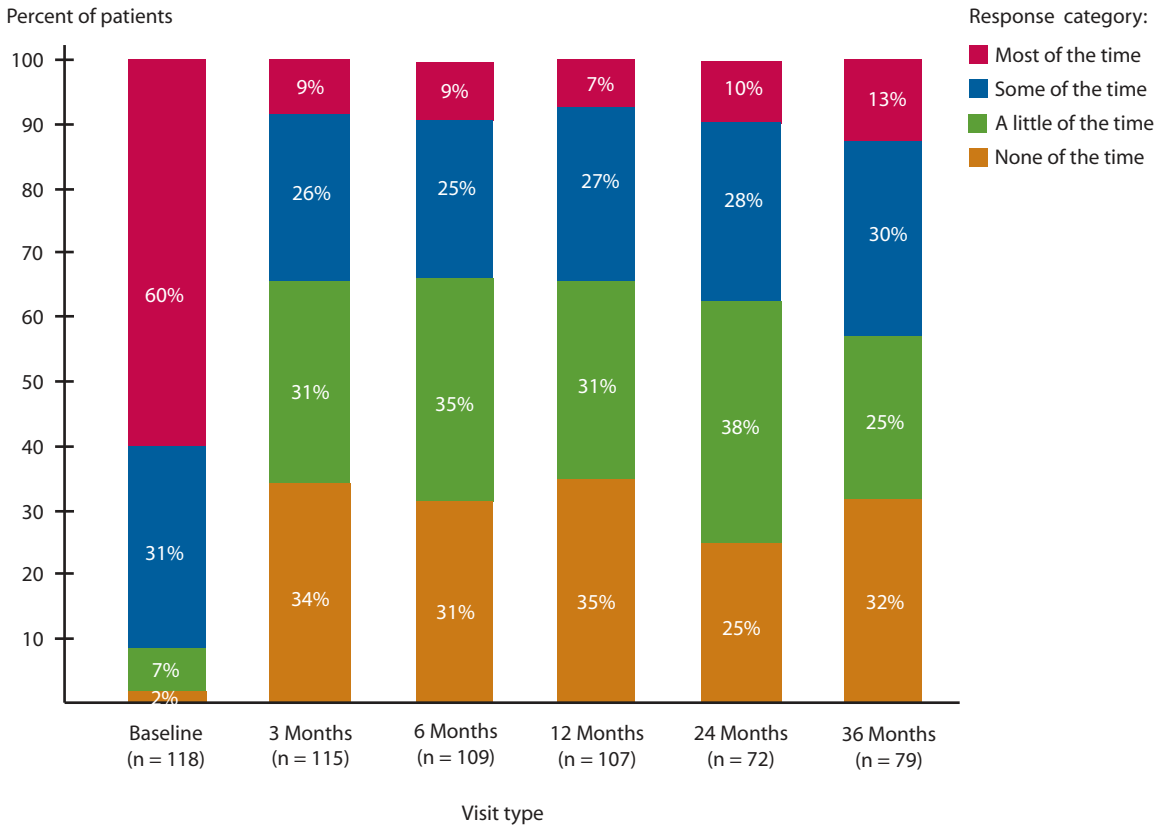

FIGURE 6. "I leak stool without even knowing it"–response categories.

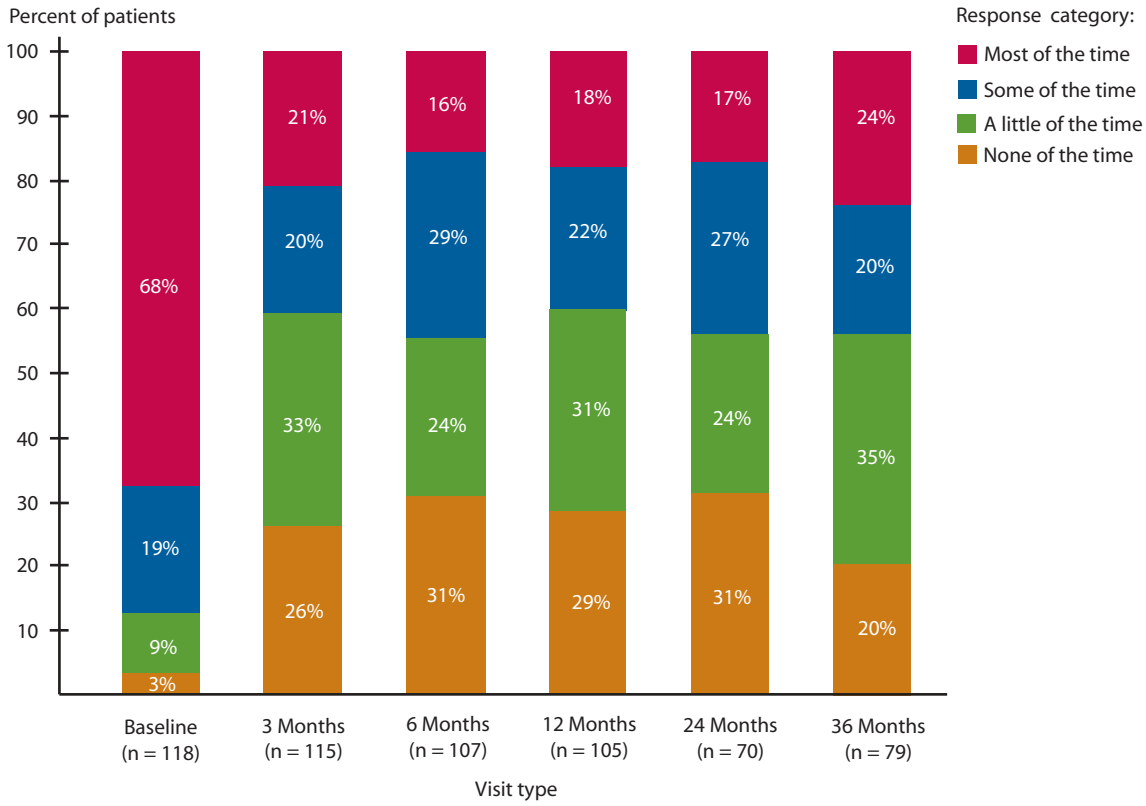

FIGURE 7. "I worry about not being able to get to the toilet in time"–response categories.

The most frequently reported adverse events related to the device or therapy occurring after chronic implantation (n = 120 patients), cumulative through the data cutoff date for this article, included implant site pain (28%), paresthesia (15%), change in the sensation of stimulation (12%), implant site infection (10%), urinary incontinence (6%), diarrhea (6%), and extremity pain (6%). Treatment of implant site pain included neurostimulator reprogramming (n = 16), medication,[10] no treatment,[10] neurostimulator and lead explant,[3] and neurostimulator revision.[6] Of the 12 infection events, 1 infection was a superficial yeast infection that resolved spontaneously, 5 infections resolved with medication, and 6 infections required surgical intervention (5 device explants and 1 device replacement).

DISCUSSION

The present study demonstrates that SNS provides symptomatic relief in a majority of patients with FI and that this improvement is sustained at long-term follow-up after 3 years in a rigorous FDA-regulated study. Previous reports have mainly been single-institution reports and have included smaller numbers of patients.[22–24] Some of these studies have presented long-term efficacy data. In 2009, Altomare et al[25] reported a 74% success rate after 5 years in 52 patients. Matzel et al[17] reported recently that 6 of 9 patients had a sustained effect after a minimum 7 years of stimulation, and Michelsen et al[12] reported that 10 patients had a sustained effect of SNS treatment after 6 years of treatment. Results in the present study are similar to those obtained in a smaller prospective multicenter study reported earlier.[19] In that smaller study,[19] 34 patients underwent implantation, resulting in an improvement in the frequency of incontinence episodes and improved quality of life in up to 2 years of follow-up.

In the present study, 77 of 120 patients (64%) completed a bowel diary assessment at the 3-year follow-up. The number of patients (n = 43) who were unavailable to provide 3-year data will have an impact on the efficacy results in varying degrees, depending on which type of efficacy analysis is selected. Limiting the analysis to the 77 patients who completed a 3-year bowel diary results in a 86% success rate (≥50% reduction in incontinent episodes) (Fig. 2). This analysis, however, does not take into account the efficacy achieved in patients with missing 3-year data. Six of these patients were exited from the study because of a lack of efficacy. The last observation-carried-forward analysis uses the most recent data collected as end point data when the 3-year data are missing. This analysis will thus take into account patients who have been exited before the 3-years cutoff because of lack efficacy. On the other hand, the analysis extrapolates that the function will

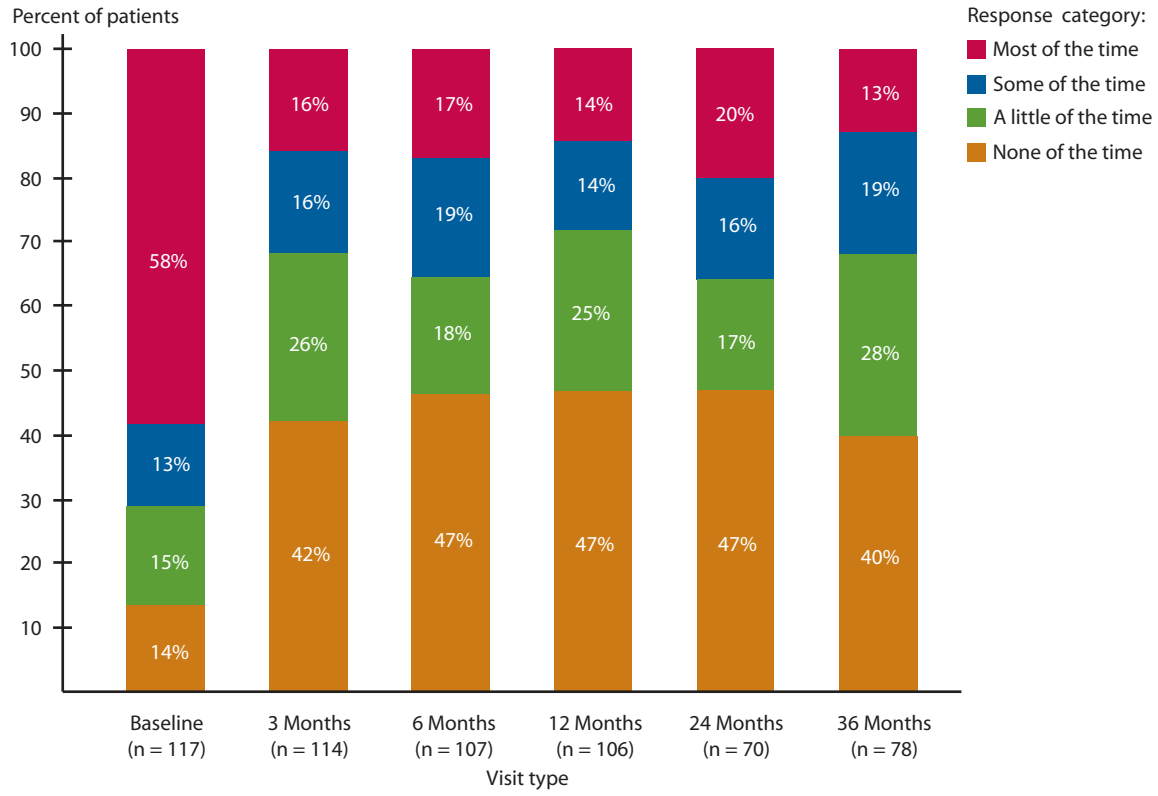

FIGURE 8. "It is important to plan my schedule (daily activities) around my bowel pattern"–response categories.

remain stable over time when the 3-year cutoff is not achieved, which may not be correct in all patients. By the use of this method, the therapeutic success rate remained high at 79%. The modified worst case analysis treats all subjects with missing 3-year data as failures, unless they have data at a later visit. This method is quite stringent and conservative, considering that the exclusion of 14 patients was because of the terminal illness of the local principal investigator. These patients may have sustained the effect of the therapy, but could not be evaluated because the research site had to be closed. With the use of this method, the therapeutic success rate still remained satisfactory at 59%.

All 3 evaluation methods used have different types of bias. The intention-to-treat and last-observation-carried-forward methods demonstrate success rates similar to previous reports.[19,23,24,26] These methods may give a falsely positive impression, however, as indicated above. The 59% success rate found when using the modified worst case analysis is lower than previous reports, but this result still demonstrates a sustained effect from SNS. No other treatment option has been able to demonstrate similar success rates.

Perhaps even more important, the decrease in FI symptoms also translated into an improvement in quality of life at long-term follow-up (Fig. 5). The American Society of Colon and Rectal Surgery FIQOL instrument was used for assessment. The previously reported excellent 1-year results[18] were sustained 2 years later at the long-term 3-year follow-up. The improvement in quality of life underscores the improvement of quality of life found in previous smaller studies.[19,27,28] The FIQL instrument is validated, but abstract to interpret. The impact on daily life can be seen when individual questions in the instrument are studied separately. Figure 7 demonstrates the effects on patients' worries and daily activities, but, at the same time, it is important to remember that the instrument is not validated to be used in this fashion.

The mechanism of SNS remains undefined. Studies have suggested a variety of different factors, including improved sensory function, improved anal sphincter function, improved rectal motility, and/ or central nervous system effects.[29,30] Some authorities have questioned whether the effects of SNS may be due to placebo effect, because the patients in most studies have known that they received active treatment. Several prior studies[28,31] have looked at this problem and indicate that SNS seems to have a definitive effect on symptoms. A significant decrease in the intensity of incontinence symptoms has been noted when the stimulator is turned on, in comparison with the periods when the stimulator is turned off.[28] Positive gains sustained for 3 years, as shown in the present study, add to this body of evidence, making the placebo effect an unlikely explanation.

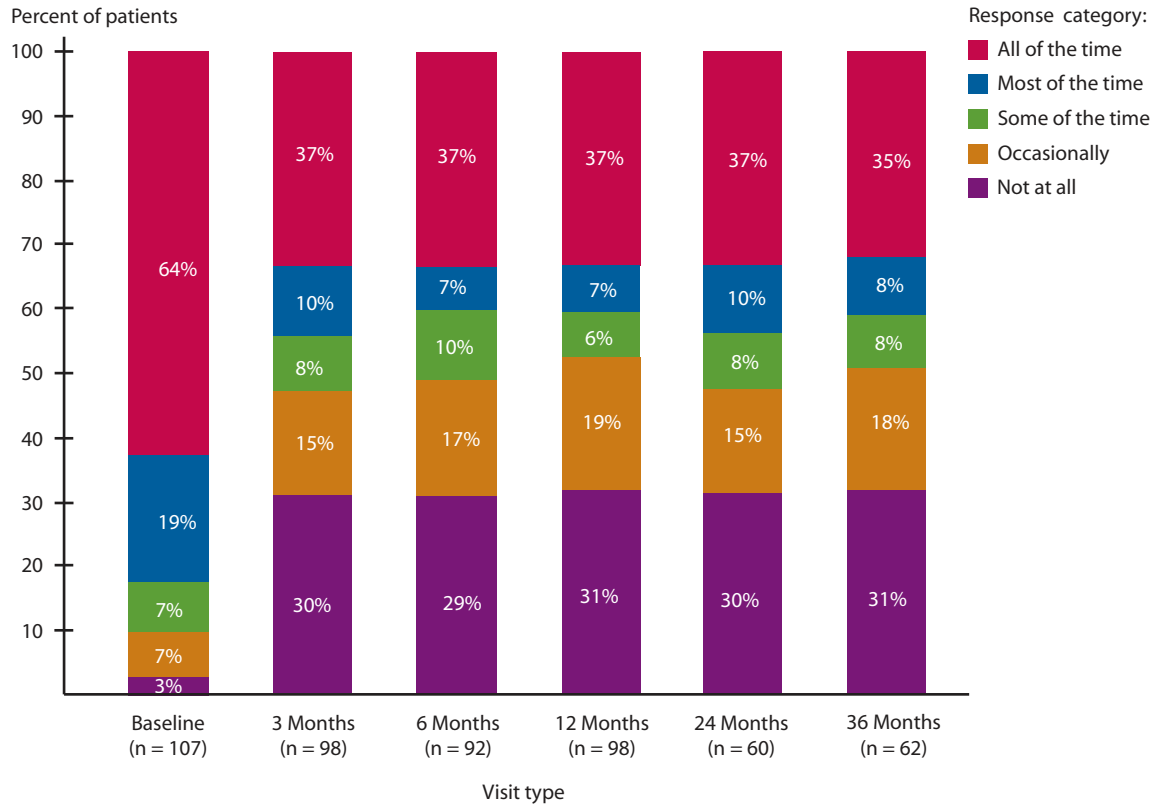

FIGURE 9. Use of protective pads.

Initially, the indications for use of SNS were strict and usually limited to patients with intact sphincters or limited sphincter injuries as in the present study. The subchronic test phase is unique to SNS and is associated with a low morbidity, thus allowing the treatment to be safely tested to identify suitable candidates for the therapy. The previous rigorous criteria for SNS treatment have therefore been replaced with a pragmatic trial philosophy with significantly less restrictive indications.

The current study was limited to patients with intact sphincters or limited sphincter injuries. Recently, a few smaller studies have indicated that SNS may also be effective in patients with anal sphincter defects.[32,33] Likewise, patients with loose stools or irritable bowel syndrome have frequently been excluded from SNS studies. A recent study demonstrated that SNS may also be effective for these patients.[34] In the future, it will therefore be interesting to study the effect of SNS in these patients.

SNS has a high success rate in most patients. In the present study, 40% of patients had a complete resolution of their symptoms, whereas 70% had at least a 75% reduction in symptoms. Moreover, if the SNS is not effective, other additional treatment options may be possible. With the arrival of other new modalities for the treatment of FI, a combination of 2 or 3 modalities in the same patient will be increasingly common. In the future, it will be important to evaluate the outcomes after treatment with SNS and other modalities, such as injectables and pelvic floor repair.

SNS is a relatively safe procedure.[12,35–40] Infection occurred in 12 patients after implantation in this study, an incidence similar to that noted in prior studies. This result differs from our prior report of postimplant infection in 13 patients (10.8%).[16] The present report of 12 patients (10%) reflects a data clarification received since the time of original analysis in which the onset date of one infection was determined by the investigational site to have occurred during the test stimulation phase. The consequences of the infections were controlled in all patients, and the infections did not lead to any permanent morbidity other than a need for surgical intervention in 6 patients. Theoretically, any surgical procedure such as SNS could cause serious complications, but the incidence of such events has been low.[35–40]

In summary, the present study demonstrates that SNS provides a significant sustained long-term improvement in FI symptoms in the majority of patients.

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APPENDIX

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