Five-Year Followup Results of a Prospective, Multicenter Study of Patients with Overactive Bladder Treated with Sacral Neuromodulation

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Purpose: We evaluated the therapeutic success rate, changes in quality of life and safety of sacral neuromodulation 5 years after InterStim™ implantation. Included in study were subjects with bothersome symptoms of overactive bladder, including urinary urge incontinence and/or urgency-frequency, in whom at least 1 anticholinergic medication failed and 1 medication had not been tried.

Materials and Methods: Therapeutic success was defined as a urinary urge incontinence or urgency-frequency response of 50% or greater improvement in average leaks or voids per day, or return to normal voiding, defined as fewer than 8 voids per day. Quality of life was evaluated by ICIQ-OABqol (International Consultation on Incontinence Modular Questionnaire). Safety was evaluated through adverse events.

Results: Of the 340 subjects who completed the test stimulation 272 had an implant, of whom 91% were female. Mean age was 57 years. At baseline 202 subjects with urinary urge incontinence had a mean ± SD of 3.1 ± 2.7 leaks per day and 189 with urgency-frequency had a mean of 12.6 ± 4.5 voids per day. The 5-year therapeutic success rate was 67% (95% CI 60–74) using modified completers analysis and 82% (95% CI 76–88) using completers analysis. Subjects with urinary urge incontinence had a mean reduction from baseline of 2.0 ± 2.2 leaks per day and subjects with urgency-frequency had a mean reduction of 5.4 ± 4.3 voids per day (each completers analysis $p < 0.0001$). Subjects showed improvement in all ICIQ-OABqol measures ($p < 0.0001$). The most common

Abbreviations and Acronyms

AE = adverse event

BoNT = intradetrusor onabotulinum toxin

ICIQ-OABqol = International Consultation on Incontinence Modular Questionnaire-OAB Symptoms QOL

OAB = overactive bladder

PTNM = percutaneous tibial nerve modulation

QOL = quality of life

ROSETTA = Refractory Overactive Bladder: Sacral Neuromodulation vs Botulinum Toxin Assessment

SNM = sacral neuromodulation

UF = urgency frequency

UI = urinary incontinence

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device related adverse events were an undesirable change in stimulation in 60 of the 272 subjects (22%), implant site pain in 40 (15%) and therapeutic product ineffectiveness in 36 (13%).

Conclusions: This multicenter study shows that sacral neuromodulation had sustained efficacy and quality of life improvements, and an acceptable safety profile through 5 years in subjects with overactive bladder.

Key Words: urinary bladder, overactive; urinary incontinence; electrodes, implanted; quality of life

Overactive bladder is a common chronic condition which negatively impacts the QOL of 10% to 30% of the population.[1] Symptom control for a long time is usually needed for satisfactory management. While treatments such as behavioral therapy, biofeedback, physical therapy and oral medications are typically offered as first and second line remedies, a substantial proportion of patients continue to experience enough bother to seek further therapeutic options.[2]

Advanced treatment options, including SNM, PTNM and BoNT injection, have been incorporated into treatment guidelines.[2,3] Sparse data exist regarding the long-term efficacy of PTNM and BoNT beyond 3 years.[4,5] While several groups have documented the long-term efficacy of SNM,[6–10] most studies were single center and retrospective that lacked rigorous analysis or were limited due to incomplete followup. The InSite for OAB study reflects current standard practices, including minimally invasive techniques, routine fluoroscopy and exclusive use of staged implantation of the tined lead.

The InSite for OAB trial was designed to be implemented in 2 phases. Phase 1 was a prospective, multicenter, randomized trial comparing SNM to standard medical therapy at 6 months.[11] It provided level 1 evidence of the objective and subjective superiority of SNM over standard medical therapy in patients with OAB who had previously experienced insufficient relief after trialing a median of 2 anticholinergic medications. Phase 2 was a prospective evaluation of the safety and efficacy of SNM during 5 years. The primary objective of this portion of the study satisfied the FDA (Food and Drug Administration) post-approval requirements to evaluate the tined lead. Results in subjects followed through 1 and 3 years have been previously reported.[12,13]

This study represents the completion of the InSite for OAB trial at 5 years, including all subjects from the 2 phases.

METHODS

Enrollment criteria and design were published previously.[11–13] Subjects had a primary diagnosis of OAB as demonstrated on a 3-day voiding diary with 8 or more voids per day, considered UF, and/or 2 or more involuntary leaking episodes in 72 hours, considered UI. Subjects experienced previous treatment failure with at least 1 anticholinergic medication and had at least 1 medication untried. Institutional review boards approved the protocol and informed consent forms were signed prior to participation. All subjects underwent a staged implant procedure with the InterStim™ System, including neurostimulator models 3023 and 3058, and lead models 3093 and 3889. Test stimulation success was defined as improvement from baseline, including 50% or greater improvement in the average number of voids per day or a return to normal voiding, considered fewer than 8 voids per day, in subjects with UF and 50% improvement in the average number of leaks per day in subjects with UI. After completion of test stimulation, those who met success criteria were implanted with the neurostimulator.

Subjects returned for visits after implantation at 3, 6 and 12 months, and yearly thereafter out to 5 years. Electronic voiding diaries were used which allowed collection of real time OAB data. QOL was assessed using the validated ICIQ-OABqol, which evaluates total health related QOL and 4 subscales, including concern, coping, sleep and social.[14] Responses to the interference question on ICIQ-OABqol measured how much urinary symptoms interfere with everyday activities. Other patient reported outcome tools used included MLUTSsex (Male Lower Urinary Tract Symptoms-Sex),[15] FLUTSsex (Female Lower Urinary Tract Symptoms-Sex),[16] BDI-II (Beck Depression Inventory II)[17] and a visual analog scale for pelvic pain.

The primary safety objective was to demonstrate that the upper bound of the 95% CI for the cumulative 5-year rate of AEs related to the tined lead that required surgery was less than 33%. Device related AEs were defined as those related to the implant procedure, therapy, device or implant site. A clinical events committee reviewed and adjudicated all AEs.

Various outcome measures were evaluated to determine the 5-year efficacy of SNM, including the success rate for OAB, UI and UF subgroups, and the absolute change in leaking and voiding frequency from baseline as well as trends in these measures with time.

Two analyses were done of the success rate at 5 years. The first one was a modified completers analysis evaluating all subjects who received a full system implant and had a baseline and 5-year evaluation or withdrew early from study due to a device related AE or

lack of efficacy resulting in explantation. For these early withdrawals missing data were imputed to the baseline assessment and these cases were considered failures. Implanted subjects who withdrew for reasons unrelated to the device were excluded from the primary efficacy analysis. The second (sensitivity) analysis was a completers analysis which included all implanted subjects with diary data at baseline and 5 years. Descriptive statistics are reported, and p values of paired comparisons between baseline and visits through 5 years for leaking and voiding episodes per day were determined using the Wilcoxon signed rank test. To assess the trend of efficacy with time outcomes were evaluated in subjects with data available at baseline and each followup.

To assess QOL data were analyzed as changes from baseline to followup visits. No data were imputed for missing values and descriptive statistics are reported. Within treatment comparisons were made using the Wilcoxon signed rank test. All subjects with a device implant and the required outcome data at baseline and followup visits were included.

Published scoring criteria were followed for ICIQ-OABqol.[14] The ICIQ-OABqol question, "Overall, how much do your urinary symptoms interfere with your everyday life?" was measured on a scale of 0 to 10 with a lower score indicating less OAB symptom interference. Based on the difference between scores at followup visits and baseline the percent of subjects is reported in each category as worsened (2 or greater), no change (−1 to 1), improved (−4 to −2) and greatly improved (−5 or less).

Safety through 5 years was evaluated by reported AEs. The primary safety objective of 5-year AEs related to the tined lead that required surgery is reported as the Kaplan-Meier estimate of the survival function at 5 years with the 95% CI based on the Greenwood SE. Descriptive statistics were used to report the most common device related AEs and surgical intervention rates. All statistical tests were examined for significance at the 0.05 level. SAS®, version 9.2 was used for all analyses.

RESULTS

Overall 340 subjects received test stimulation and 272 (80%) were implanted with the InterStim System. The table lists baseline demographics.

Using the modified completers analysis in 183 of the 272 subjects the overall OAB response rate demonstrating therapeutic success was 67% at 5 years. The UI response rate was 64% in subjects characterized with UI at baseline. These subjects had an average ± SD reduction of 1.7 ± 2.1 leaks per day compared to baseline ($p < 0.0001$). Complete continence at 5 years was achieved in 38% of subjects. In those with UF a therapeutic response rate of 57% was observed. These subjects had an average reduction of 4.4 ± 4.4 voids per day from baseline ($p < 0.0001$).

Baseline demographics

No. pts	272	
No. female (%)	248	(91)
No. male (%)	24	(9)
No. race (%):		
Caucasian	243	(89)
African American	19	(7)
Asian/Caucasian	1	(less than 1)
American Indian or Alaska native/Caucasian	2	(less than 1)
American Indian or Alaska native	1	(less than 1)
Native Hawaiian or other Pacific Islander	1	(less than 1)
Other	5	(2)
No. primary prestudy diagnosis (%):		
Urge incontinence	157	(58)
Urgency-frequency	110	(40)
Interstitial cystitis	5	(2)
No. diary OAB qualification (%):*		
UI + UF	128	(47)
UI only	74	(27)
UF only	61	(22)
Mean ± SD age at implantation	57.0 ± 14.2	
Mean ± SD yrs since diagnosis	8.3 ± 9.9	
OAB medications tried prior to implant (%):†		
1	60	(22)
2	84	(31)
3	56	(21)
4–7	67	(25)
Mean ± SD baseline leaks/day (No. pts)‡	3.1 ± 2.7 (202)	
Mean ± SD pads replaced/day (No. pts)	1.7 ± 2.2 (202)	
Mean ± SD leak urgency (No. pts)§	3.0 ± 0.8 (202)	
Mean ± SD No. baseline voids/day (No. pts)‡	12.6 ± 4.5 (189)	
Mean ± SD ml voided vol/void (No. pts)¶	159.1 ± 87.1 (154)	
Mean ± SD urgency voids (No. pts)§	3.0 ± 0.5 (189)	

* Baseline value not available in 9 subjects.
† Five subjects did not use medication prior to implantation as protocol deviation or contraindication to OAB medication.
‡ Including only subjects with UI (leaks) and/or UF (voids) at baseline.
§ Void and leak urgency rated as 1—no urgency, 2—mild, 3—moderate, 4—severe.
¶ In subjects reporting volume of at least 50% of voids.

Using completers analysis with no imputation of missing data in 150 of the 272 subjects the overall OAB response rate demonstrating therapeutic success at 5 years was 82% (fig. 1). The UI response rate was 76% in those characterized with UI at baseline. These subjects had an average reduction of 2.0 ± 2.2 leaks per day compared to baseline ($p < 0.0001$). Complete continence at 5 years was achieved in 45% of subjects. In subjects with UF a therapeutic response rate of 71% was observed. The mean reduction in voids per day was 5.4 ± 4.3 ($p < 0.0001$). Response rates and mean reductions in leaks and voids showed the sustained efficacy of SNM through 5 years.

Sustained QOL improvements were reported from baseline to 5 years in all ICIQ-OABqol domains. All were statistically significant ($p < 0.0001$, fig. 2). At 5 years 84% of subjects reported an improved or greatly improved urinary symptom interference score (fig. 3). The impact on sexual function was evaluated with the MLUTSsex and FLUTSsex questionnaires. There was significant improvement from baseline to 5 years

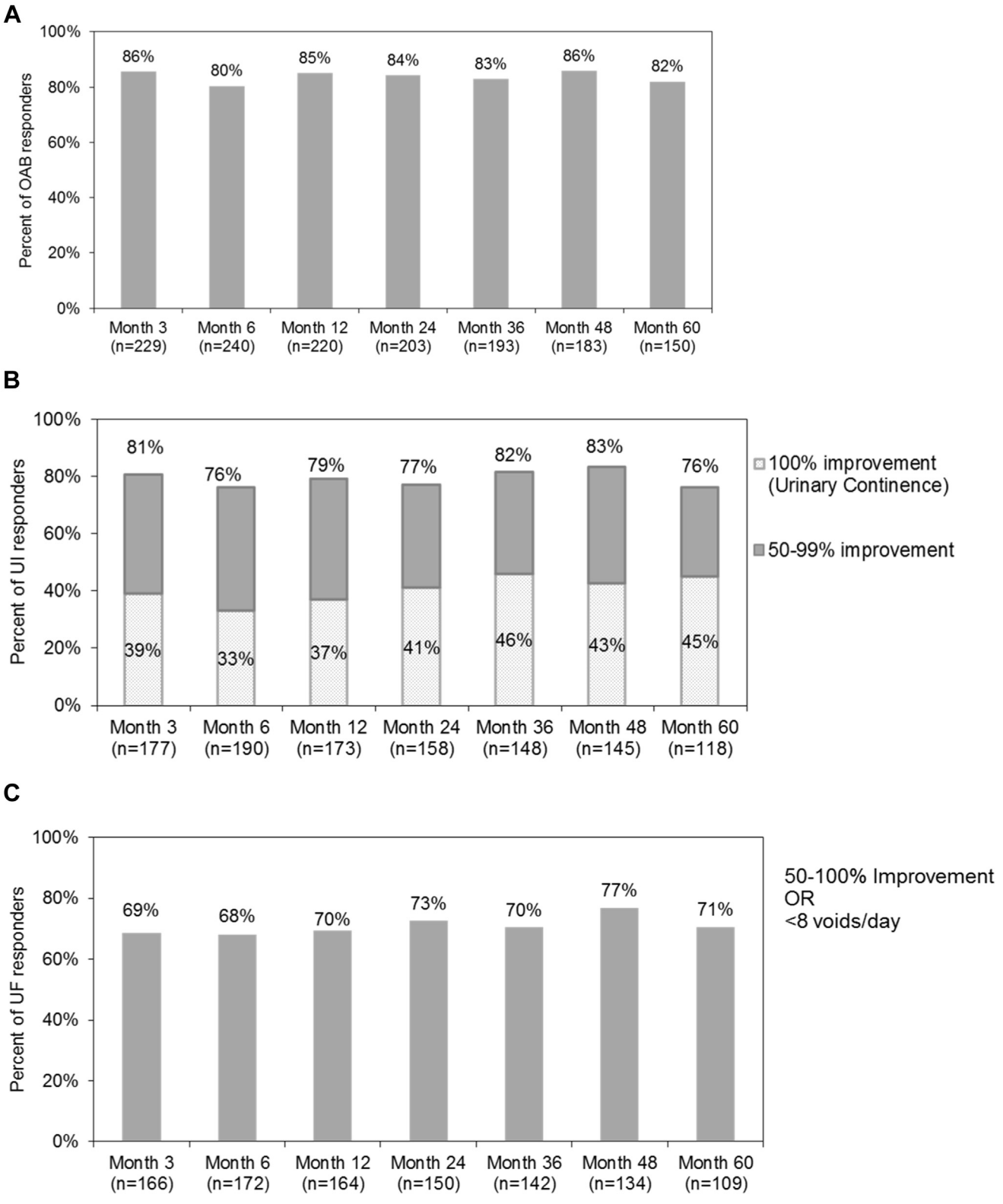

Figure 1. OAB therapeutic success rate with time determined by completers analysis in subjects with diary data at baseline and followup visits. *A*, OAB response was defined as 50% or greater improvement in leaks per day in UI subjects and 50% or greater improvement in voids per day or return to normal voiding frequency of fewer than 8 voids per day in UF subjects. *B*, UI response. *C*, UF response.

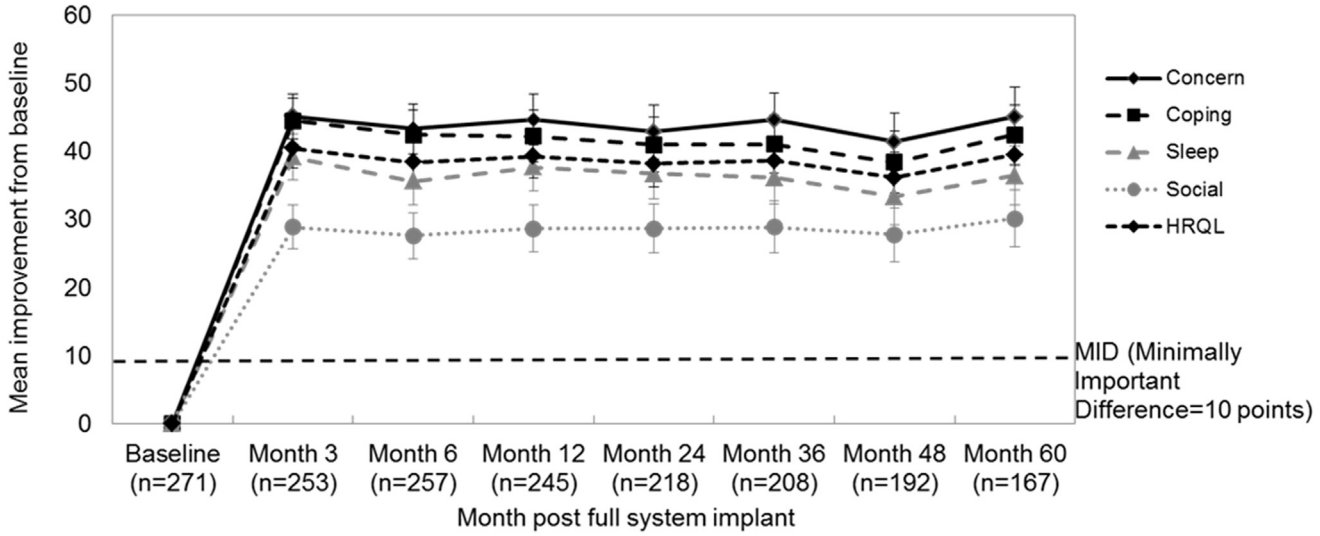

Figure 2. ICIQ-OABqol improvement from baseline with time. Baseline values were 33.8 for concern, 37.0 for coping, 37.6 for sleep, 62.8 for social and 41.4 for health related QOL (*HRQL*). All 4 subscales and total health related QOL showed greater improvement at followup visits vs baseline (all p <0.0001). Minimally important difference (*MID*) is smallest score change perceived to be beneficial to patients which is often used to determine whether score changes are considered clinically significant.[14] ICIQ-OABqol subscale minimally important difference was suggested to be 10 points. Error bars indicate 95% CI.

in 155 females (p <0.0001) but no significant change in males was found, which have been due to the small sample size of 8 men. Depression measured by BDI-II significantly improved from baseline to 5 years in 168 subjects (p <0.0001). The visual analog scale for pelvic pain also significantly improved from baseline to 5 years in 166 subjects (p <0.0001).

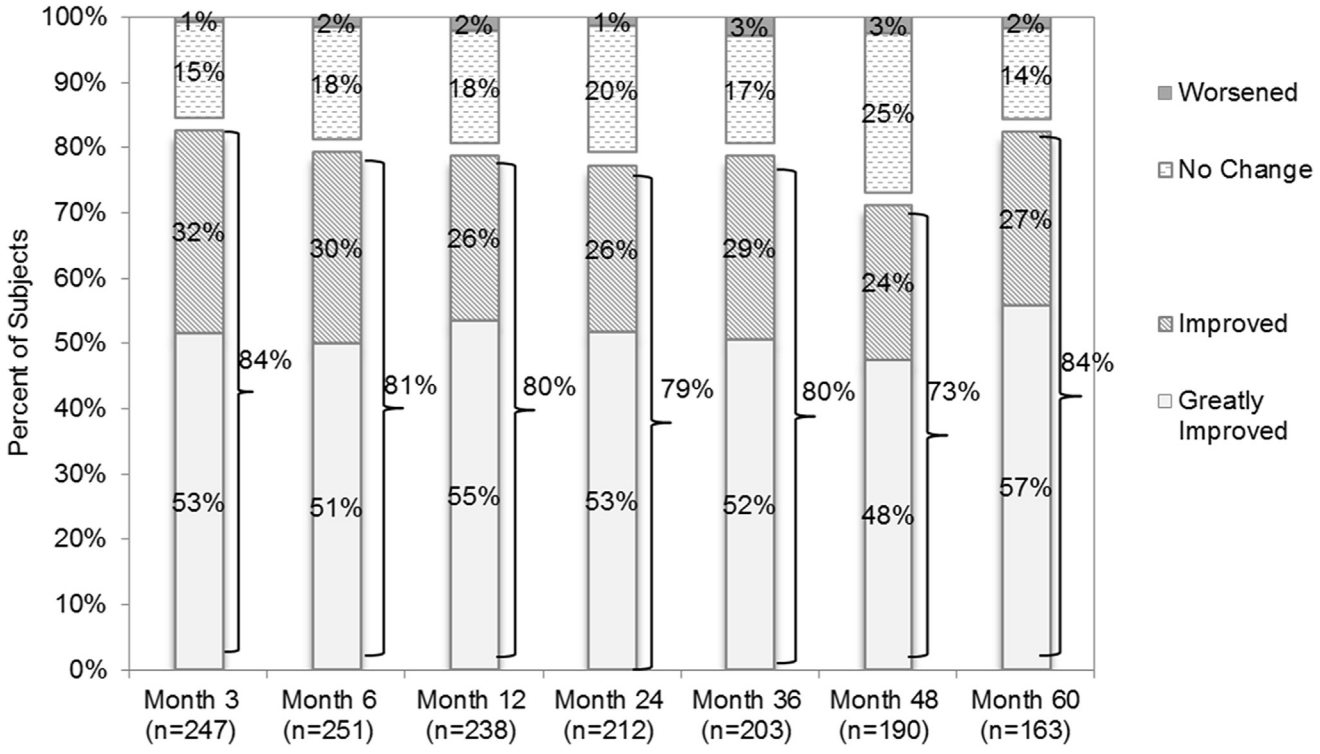

Figure 3. Urinary symptom interference according to ICIQ-OABqol question, "Overall, how much do your urinary symptoms interfere with your everyday life?"[11]

Based on the 140 subjects who reached the 5-year visit and had programming data available 60.7% were programmed to an amplitude of less than 2 V. In most subjects the pulse width was 210 μseconds, in 63.6% the rate was programmed to 14 Hz and 67.9% were on continuous stimulation.

The 5-year cumulative rate of AEs related to the tined lead that required surgery after full system implantation was 22.4% (95% CI 16.6–27.7), which fulfilled the primary safety objective. There were no unanticipated adverse device effects. In subjects with a fully implanted system an undesirable change in stimulation was the most common AE, which occurred in 60 of 272 (22%), followed by implant site pain in 40 (15%) and therapeutic product ineffectiveness in 36 (13%). All other device related AEs which developed upon or after implantation were reported in fewer than 6% of subjects. One event, implant site erosion, was classified as serious but it resolved.

Surgical interventions were also reported, including revision, replacement and permanent explantation of any device component. A subject could have experienced multiple types of surgical interventions and an intervention could have been due to multiple reasons, such as an AE, patient request, lack or loss of efficacy or battery replacement. Surgical intervention was performed in 84 subjects (30.9%) due to an AE and 91 (33.5%) underwent a surgical intervention due to battery replacement.

In all 272 implanted subjects the permanent explantation rate was 19.1% (95% CI 14.1–23.9) at 5 years. The top reason reported by investigators for permanent explantation was an AE in 30 of the 272 subjects (11.0%), which was most often an ineffective therapeutic product (7 of 272 or 2.6%). Other reasons included subject need for magnetic resonance imaging, lack or loss of efficacy and withdrawal of subject consent. Of the permanent explants 23 (8.5%) were associated with a lack or loss of efficacy. Surgical intervention was performed in 91 subjects (33.5%) due to lack or loss of efficacy after full system implantation.

DISCUSSION

OAB is a common, chronic condition which significantly impacts QOL. Therefore, it is important for successful therapy to achieve substantial and sustained symptom relief. This prospective study demonstrated the sustained efficacy and safety of SNM in subjects with OAB after 5 years of treatment. The therapeutic success rate was 82% at 5 years and 85% at 1 year,[13] which strongly demonstrates long-term durability in patients with SNM in clinical practice.

The 60-month dry rate in the 118 patients with UI was 45%, which is considerably higher than the dry rate at 6 months reported in the recent ROSETTA trial comparing SNM to BoNT 200 U (174 patients or 2% vs 190 or 20%).[18] Speculations on the reasons for this contrast include differences in analysis methods, the high rate of experience among InSite for OAB study implanters, predominant use of the 3889 lead vs the 3093 lead (with an extended number 1 electrode, now discontinued) that was exclusively used in the ROSETTA trial and the opportunity in InSite to adjust for suboptimal responses via reprogramming or lead revision. The mean decrease in leaks and voids per day was 2.0 and 5.4 at 60 months in the current study vs 3.3 and not reported in the ROSETTA study at 6 months.[18] The differences could be due to purposeful selection of patients with more severe UI in ROSETTA (baseline mean of 5.4 leaks per day) and excluding those with UF only to justify the BoNT dose used in the treatment arm. Subanalysis of patients in InSite for OAB showed that SNM was effective in treating severe and less severe UI and UF at 12 and 24 months of followup.[19]

Improvements in QOL, sexual function in female subjects and pelvic pain measures were also sustained during 5 years. The rate of device related AEs and surgical intervention remained significantly lower than in previously published studies using older techniques and devices[20] but must be acknowledged as a consideration when evaluating candidates for this therapy. Investigators were required to report all undesirable, device related changes experienced in subjects regardless of clinical significance. In addition, the clinical events committee had a rigorous process for AE adjudication. The fact that a third of the device related AEs developed within the first 12 months of implantation may suggest that further refinements of lead placement technique or patient selection could result in improvements in the safety profile.[21]

During the long followup of 5 years more subjects elected to replace the device than have it permanently explanted. Most AEs were minor and could be treated with noninvasive measures. With time it is expected that all subjects who have been successfully treated will need device replacements to maintain the benefit due to the nature of treatment and the underlying chronic condition. Most surgical interventions were performed to allow for continuation of the therapy. Less than 20% of all implanted subjects underwent permanent explantation for various reasons, including AEs, patient request and lack or loss of efficacy.

Few groups have reported outcome data or continuation rates of other advanced OAB treatments

beyond 36 months. In the multicenter STEP (Sham Effectiveness in Treatment of Overactive Bladder Symptoms) study 50 of 60 subjects were enrolled and PTNM outcomes were documented in 29 (58%) at 36 months.[5] Although only a small number of subjects were included, PTNM showed safety with sustained improvements after 3 years. In a single center study measuring the long-term outcome of of BoNT for the treatment of OAB 137 of 268 subjects were followed 36 months or longer.[4] In that series, 61.3% of subjects had discontinued therapy by 36 months, including initial therapy failures. The main reasons for study discontinuation were tolerability issues, including the need for intermittent catheterization and urinary tract infections.

Initial costs are predictably lower for PTNM and BoNT than for SNM. To be more cost-effective it is necessary for SNM to provide a long-term benefit. Previous studies have shown that SNM becomes more cost-effective than BoNT after 3 to 5 years, indicating that SNM may be comparatively cost saving in the long term.[22,23] This advantage could be magnified by technological advances, including longer lasting batteries.

The strengths of the InSite for OAB study include the large number of subjects with protocol mandated followup and the rigorous modified completer analysis including subjects who withdrew for lack of benefit or device related complications as treatment failures. Additionally, the fact that private practice and academic centers contributed subjects reflects real world experience with the therapy and, thus, the results are more generalizable.

Limitations include the homogeneous population with a minority of male subjects, which could detract from generalizability. Furthermore, centers could follow individual protocols regarding perioperative antibiotics, lead choice and procedure techniques. Although this approximates what is occurring in general practice with SNM therapy, this lack of standardization along with the potential impact on infection rates, device related complications and ultimate therapy success or failure rates may have impacted the overall study results.

CONCLUSIONS

InterStim therapy provides a durable treatment effect from implantation to 5 years. Statistically significant treatment effects from baseline to 5 years were found in the cardinal symptoms of OAB (leaks and/or voids) and in QOL. In addition, the InSite for OAB study showed an InterStim therapy safety profile that indicates a low rate of serious device related AEs and types of device related AEs that are consistent with product labeling and the published literature.

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EDITORIAL COMMENT

This is an important study because sacral neuromodulation as a treatment modality in patients with OAB symptoms, and the long-term results and potential side effects are still questioned. When choosing between botulinum toxin injections and sacral neuromodulation as alternatives in the same group of patients, additional information is necessary on long-term efficacy and side effects. Also, in the ongoing debate on the cost-effectiveness of the 2 therapies data on long-term clinical efficacy are mandatory (reference 18 in article).

In this series of 272 implanted patients the 82% 5-year success rate is definitely impressive since implantation was not performed only at high volume centers. Furthermore, the rate of device related adverse events remained significantly lower than in an earlier 5-year followup study (reference 20 in article), indicating that technical developments have ameliorated the outcome. However, a third of the adverse events developed within the first 12 months after implantation. Thus, further refinement of the implantation technique may enhance the safety profile, which may favor high volume centers. As 33.5% of patients needed a battery change, a longer lasting or rechargeable battery is needed.

This study confirms that sacral neuromodulation should be a therapeutic modality that must be offered to any patient with overactive bladder symptoms in whom conservative therapy has failed.

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