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Results of a Prospective, Randomized, Multicenter Study Evaluating Sacral Neuromodulation With InterStim Therapy Compared to Standard Medical Therapy at 6-Months in Subjects With Mild Symptoms of Overactive Bladder

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Aims: This prospective, randomized, multicenter trial evaluated the 6-month success rate of sacral neuromodulation (SNM) with InterStim® Therapy versus standard medical therapy (SMT) for overactive bladder (OAB). **Methods:** Enrolled subjects discontinued OAB medications prior to and during baseline data collection and were randomized 1:1 to SNM or SMT. Subjects had bothersome symptoms of overactive bladder (OAB) including urinary urge incontinence ($\geq$2 leaks/72 hr) and/or urgency-frequency ($\geq$8 voids/day). Subjects failed at least one anticholinergic medication, and had at least one medication not yet attempted. The primary objective was to compare OAB therapeutic success rate at 6 months between SNM and SMT. **Results:** Overall, 147 subjects were randomized (70 to SNM and 77 to SMT); 93% were female and mean age was 58. The primary intent to treat analysis showed OAB therapeutic success was significantly greater in the SNM group (61%) than the SMT group (42%; $P = 0.02$). In the as treated analysis, OAB therapeutic success was 76% for SNM and 49% for SMT ($P = 0.002$). The SNM group showed significant improvements in quality of life versus the SMT group (all $P < 0.001$) and 86% of SNM subjects reported improved or greatly improved urinary symptom interference score at 6 months, compared to 44% for SMT subjects. The device-related adverse event rate was 30.5% and the medication-related adverse event rate was 27.3%. **Conclusions:** This study demonstrates superior objective and subjective success of SNM compared to SMT. SNM is shown to be a safe and effective treatment for OAB patients with mild to moderate symptoms. *Neurourol. Urodynam. 34:224–230, 2015.* © 2014 Wiley Periodicals, Inc.

Key words: anticholinergic; overactive bladder; sacral neuromodulation; urgency frequency; urinary incontinence

INTRODUCTION

Overactive bladder (OAB) is an umbrella term that covers several lower urinary tract symptoms including urinary urgency, frequency, nocturia, and urgency incontinence.[1] A recent study estimated that one in three adults over 40 suffers from moderate to severe OAB with the prevalence increasing with age.[2] Although not life threatening, it does have a significant impact in most domains of quality of life.[3] Additionally, specific medical conditions are associated with OAB, including a higher incidence of urinary tract and perineal skin infections, clinical depression, as well as a higher risk of falls and hip fractures, increasing by 28% and 32%, respectively.[4] Recently the American Urological Association published treatment guidelines for OAB.[5] This is a three-tiered algorithm that places behavioral therapy in the first tier, pharmacological therapy in the second tier and sacral neuromodulation (SNM) as the only recommended therapy in the third tier. However, persistence and adherence with pharmacological therapy are suboptimal. A recent study indicated that over 50% of subjects with OAB discontinued pharmacotherapy (regardless of the particular agent) due to lack of efficacy or intolerable side effects at 12 months.[6]

SNM has been FDA-approved for the treatment of urgency incontinence (UI) since 1997, for urgency-frequency (UF) since 1999, and is recognized an effective treatment for refractory

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TABLE I. Inclusion and Exclusion Criteria

Inclusion criteria
Diagnosis of OAB as demonstrated on a 3-day voiding diary demonstrating greater than or equal to 8 voids/day and/or by having a minimum of two involuntary leaking episodes in 72 hr
Male or female and 18 years of age or older
Failed or are not a candidate for more conservative treatment (e.g., pelvic floor training, biofeedback, behavioral modification)
Failed or could not tolerate at least one anticholinergic or antimuscarinic medication AND have at least one anticholinergic or antimuscarinic medication not yet attempted
On current regimen of OAB medications or have not been on any OAB medications, for at least 4 weeks prior to beginning the baseline voiding diary
Exclusion criteria
Severe or uncontrolled diabetes or diabetes with peripheral nerve involvement.
Concomitant medical conditions which would limit the success of the study procedure
Skin, orthopedic or neurologic anatomical limitations that could prevent successful placement of an electrode
Neurological diseases such as multiple sclerosis, clinically significant peripheral neuropathy or complete spinal cord injury (e.g., paraplegia)
Knowledge of planned MRIs, diathermy, microwave exposure, high output ultrasonic exposure, or RF energy exposure
Urinary tract mechanical obstruction such as benign prostatic hypertrophy, cancer, or urethral stricture
Symptomatic urinary tract infection
Implantable neurostimulators, pacemakers, or defibrillators
Primary stress incontinence or mixed incontinence where the stress component overrides the urge component
Treatment of urinary symptoms with botulinum toxin therapy in the past 12 months
Life expectancy of less than 1 year
Pregnant or planning to become pregnant or are a woman of child-bearing potential who is not using a medically acceptable method of birth control

OAB.[7,8] The only commercially available form of SNM is InterStim® (Medtronic, Minneapolis, MN). InterStim functions by delivering mild electrical impulses to the sacral nerve roots via an implanted neurostimulator and lead typically placed adjacent to the 3rd sacral nerve root, which allows for communication with the neural system controlling effector organs (bladder) and muscles (sphincters) innervated by the sacral nerves. Original studies demonstrating the effectiveness of SNM used an older, more invasive surgical approach, and while significant benefit was achieved, randomized studies enrolling a contemporary subject population utilizing newer minimally invasive techniques, including the tined lead, are scarce.

The InSite trial is a prospective, multicenter, FDA-mandated post-approval study to evaluate safety of the tined lead at 5 years. The study included an effectiveness analysis that compared OAB therapeutic success in a subset of subjects randomized to SNM or standard medical therapy (SMT) of anticholinergic or antimuscarinic medication and followed for 6 months. The primary hypothesis of the randomized portion was that SNM is superior to SMT in this population where at least one medication had been tried, but other pharmacologic agents were still available. As this is an ongoing trial, the quality and duration of treatment benefit and safety in this less severe study population will continue to be evaluated.

MATERIALS AND METHODS

Study Design and Procedures

Enrolled subjects met all inclusion and none of the exclusion criteria (Table I). The research protocol was approved by institutional review boards and participants gave written informed consent prior to initiation into the study. Previous treatment failure consisted of inadequate symptom control and/or unacceptable adverse drug events with at least one anticholinergic medication.

After enrollment, subjects completed baseline electronic diary information and questionnaires and were randomized to SNM or SMT in a 1:1 ratio. All subjects were required to discontinue OAB medications for 4 days prior to their initial voiding diary. Subjects randomized to SNM with full system implant were required to remain off OAB medications from test stimulation through 6 months. Subjects randomized to SMT started the next recommended antimuscarinic medication per physician discretion, or restarted the discontinued medication.

Subjects randomized to SNM underwent a staged procedure using the InterStim® Therapy system[a] requiring a 14-day test stimulation period. If successful test stimulation was demonstrated [$\geq$50% improvement from baseline in average leaks/day or voids/day or a return to normal voiding ($<$8 voids/day)] based on voiding diary parameters, the neurostimulator was implanted. Details of the implant procedure have been previously reported.[9] Subjects who failed to show a successful response during test stimulation were allowed to repeat a test stimulation procedure on one additional occasion. Subjects randomized to SNM who never received a full system implant continued follow up through the 6-month visit and were analyzed in the SNM group (intent to treat analysis).

Outcomes

The primary outcome measure, OAB therapeutic success, was determined using voiding diaries collected at the 6-month follow-up visit. To be considered a success, subjects with both UI and UF had to demonstrate either a $\geq$50% improvement in average leaks/day or voids/day from baseline or a return to normal voiding frequency ($<$8 voids/day). A subject was only counted once if s/he met the definition of success for both voids and leaks. A Clinical Events Committee reviewed all adverse events.

Additional a priori objectives were to compare QOL measures between groups at 6 months using the following validated questionnaires: International Consultation on Incontinence Modular Questionnaire (ICIQ)-OABqol including a single item on urinary symptom interference; ICIQ—Male/Female Lower Urinary Tract Symptoms-Sex[10]; Beck Depression Inventory II; and a Visual Analog Scale for pelvic pain.

Sample Size and Statistical Analyses

A total of 94 subjects (47 per group) were required to provide 80% power for a two-tailed, alpha = 0.05 comparison of

[a] Neurostimulator models 3023 and 3058. Lead models 3093 and 3889.

6-month OAB therapeutic success rates, assuming 53% for SNM and 23% for SMT. Success rates were estimated from previous studies with adjustment for a fraction of SNM subjects who did not receive a system implant. In order to meet the required 94 subjects needed to complete follow-up, 132 subjects were planned to be randomized to account for attrition and ensure the requirement could be sufficiently met. All subjects were analyzed in the group to which they were assigned, regardless of treatment received. Subjects who failed to complete follow-up were assumed to be treatment failures. A sensitivity analysis based on the treatment that subjects received (hereafter, "as treated") was also conducted on the primary analysis, and only included those subjects with both baseline and follow-up measurements. All other efficacy analyses are also reported similarly. Therapeutic success results are reported as sample proportions. QOL results were calculated by subtracting baseline from 6 months. Published scoring criteria[11] were used whenever possible. Overall assessment on interference change is categorized as worsened, no change, improved, and greatly improved. Safety was evaluated through adverse events and statistical comparisons were made between SNM subjects with full system implant and SMT subjects without an implant.

Between group differences were tested using Fisher's Exact test for categorical variables and Wilcoxon's rank sum test for continuous or ordinal variables. All statistical tests were examined for significance at the 0.05 level, with no adjustments for multiple testing. SAS software (version 9.2, SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Between November 2007 and June 2010, 243 subjects were enrolled from 38 sites; 147 were randomized, 70 were allocated

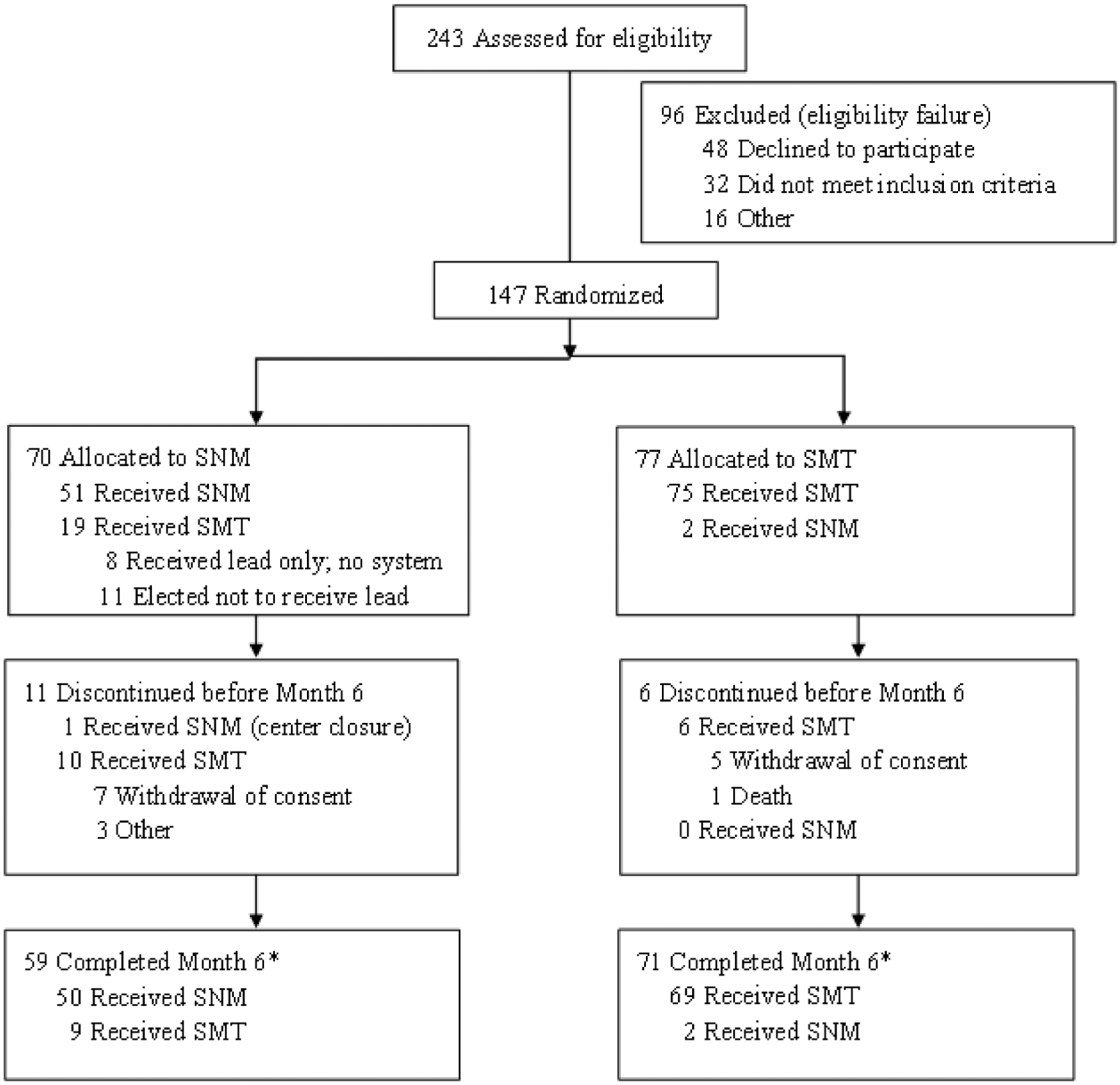

Fig. 1. Subject flow diagram. *Not all subjects who completed Month 6 completed all required assessments

to SNM and 77 to SMT (Fig. 1). Study outcome data remained blinded until follow-up of the randomized subjects was completed. There were no significant differences between the groups in demographics, baseline assessments, or medical history (Table II). Subjects tried a median of two OAB medications prior to study enrollment. Of the 70 subjects randomized to SNM, 59 underwent test stimulation, and 51 (86%) received a full system implant.

Nearly all SMT subjects (96.1%) used OAB medication between randomization and six months and 70% used medications on at least 80% of the days during the 6-month period. In many cases, subjects used more than one medication during the follow-up period. Only two (3.9%) SNM subjects with full system implant used medications between test stimulation and 6 months.

Primary Outcome

For the primary analysis using ITT (Fig. 2A), the OAB therapeutic success rate at 6 months was 61% for SNM compared to 42% for SMT ($P = 0.02$). Similar findings were demonstrated in the as treated analysis, with OAB success rates of 76% for SNM and 49% for SMT ($P = 0.002$). These data support the primary hypothesis that SNM is superior to SMT in the treatment of OAB. For subjects with UI at baseline, 71% of SNM and 47% of SMT subjects demonstrated therapeutic success ($P = 0.03$). Complete continence was almost doubled in the SNM group compared to the SMT group (39% vs. 21%, respectively, $P = 0.06$; Fig. 2B). For subjects with UF at baseline, normal voiding patterns (<8 voids/day) were achieved in 61% of SNM subjects and 37% of SMT subjects ($P = 0.04$; Fig. 2C).

TABLE II. Baseline Demographics and Medical History*

Demographic	SNM (n = 70)	SMT (n = 77)
Gender		
Female	66 (94%)	71 (92%)
Male	4 (6%)	6 (8%)
Race		
White	61 (87%)	70 (91%)
Black	7 (10%)	7 (9%)
Asian/White	1 (1%)	0 (0%)
Other	1 (1%)	0 (0%)
Primary pre-study diagnosis		
Urge incontinence	44 (63%)	46 (60%)
Urgency-frequency	26 (37%)	31 (40%)
OAB qualification per study diary		
Urinary incontinence only	25 (36%)	27 (35%)
Urgency frequency only	19 (27%)	16 (21%)
Both	26 (37%)	34 (44%)
Secondary diagnoses		
Stress incontinence	36 (51%)	32 (42%)
Urinary frequency	29 (41%)	29 (38%)
Urinary urge incontinence	17 (24%)	23 (30%)
Interstitial cystitis	4 (6%)	9 (12%)
Retention	0 (0%)	3 (4%)
Pelvic pain	1 (1%)	2 (3%)
None	8 (11%)	8 (10%)
Number of previous medications		
1	20 (29%)	17 (22%)
2	21 (30%)	28 (36%)
3	14 (20%)	14 (18%)
4–7	15 (21%)	18 (23%)
Age at consent (yrs)	60.4 ± 14.4	57.1 ± 15.3
Years since diagnosis	9.2 ± 10.5	7.4 ± 7.1
Baseline leaks/day	2.4 ± 1.7 (n = 51)	2.7 ± 1.9 (n = 61)
Pads replaced/day	1.1 ± 1.1 (n = 51)	1.5 ± 1.5 (n = 61)
Urgency of leaks[a]	3.0 ± 0.8 (n = 51)	3.1 ± 0.8 (n = 61)
Baseline voids/day	11.2 ± 2.9 (n = 45)	11.9 ± 4.3 (n = 50)
Void volume/void (ml)[b]	157.2 ± 77.0 (n = 37)	159.2 ± 87.9 (n = 36)
Urgency of voids[a]	2.9 ± 0.4 (n = 45)	3.0 ± 0.5 (n = 50)

*Plus-minus values are mean ± SD. None of the characteristics differed significantly between groups.
[a]Urgency of each leak and void was rated on the following scale: 1 = no urgency, 2 = mild, 3 = moderate, 4 = severe.
[b]Void volume was only summarized for subjects reporting volume on at least 50% of their voids.

Additional Outcomes

Changes from baseline in OAB QOL between groups showed greater improvement in SNM compared to SMT (all $P < 0.001$, Fig. 3A). Eighty-six percent of SNM subjects reported improved or greatly improved urinary symptom interference score at 6 months, compared to 44% for SMT subjects (Fig. 3B). SNM females had a greater improvement in sexual function than SMT ($P < 0.05$). Additionally, SNM demonstrated a greater improvement in depression compared to SMT ($P = 0.01$).

Safety was evaluated through adverse event (AE) analysis. There were no unanticipated adverse device effects. Device-related AEs (related to surgery, therapy, device, or implant site) occurred in 30.5% (18/59) of subjects with a lead implant and none were serious. OAB medication-related events occurred in 27.3% (21/77) of SMT subjects and none were serious. Statistical comparisons were made between 51 SNM subjects with full system implant and 75 SMT subjects without an implant. The SNM group had a higher number of urinary tract infections compared to the SMT group ($P = 0.01$); about one third of the events occurred prior to lead implant in the SNM group. The serious AE rates for both groups were not significantly different and were low, 9.8% (4/51) in SNM and 5.3% (4/75) in SMT. One SMT subject died during the study due to an unrelated cerebrovascular aneurysm. The most common device-related AE's in SNM subjects were undesirable change in stimulation 10.2% (6/59), implant site pain 8.5% (5/59), lead migration/dislodgment 3.4% (2/59), and implant site infection 3.4% (2/59). The three most common medication-related AEs in SMT subjects were constipation 9.1% (7/77), drug toxicity 6.5% (5/77), and dry mouth 5.2% (4/77). For the 51 SNM subjects with full system implant, the 6-month post-implant surgical intervention rate was 3.9% (2/51).

DISCUSSION

This prospective, multi-center, randomized clinical trial provides level-one evidence for the objective and subjective superiority of SNM over SMT among refractory patients with mild to moderate symptoms of OAB. It also confirms the safety of currently used techniques for SNM. For the primary outcome, 61% of SNM subjects demonstrated therapeutic success at 6 months versus 42% of the SMT subjects using an intent to treat analysis ($P = 0.02$). The significant difference between success rates using this conservative analysis emphasizes the strength of the results. Predictably, therapeutic success was more robust in subjects actually receiving SNM versus SMT (76% response in the SNM group and 49% in the SMT group, $P = 0.002$, as treated analysis). The differences demonstrated between the as treated groups is a more realistic reflection of that expected in routine patient care. The rate of complete continence was nearly doubled in the SNM group (39% vs. 21%), and this trended towards statistical significance ($P = 0.06$).

In contrast to early InterStim publications, this study population had less severe OAB symptoms based on voiding diaries.[7,8,12] InSite subjects had a low mean number of baseline leaks/day (2.6) and voids/day (11.6), compared to the MDT-103

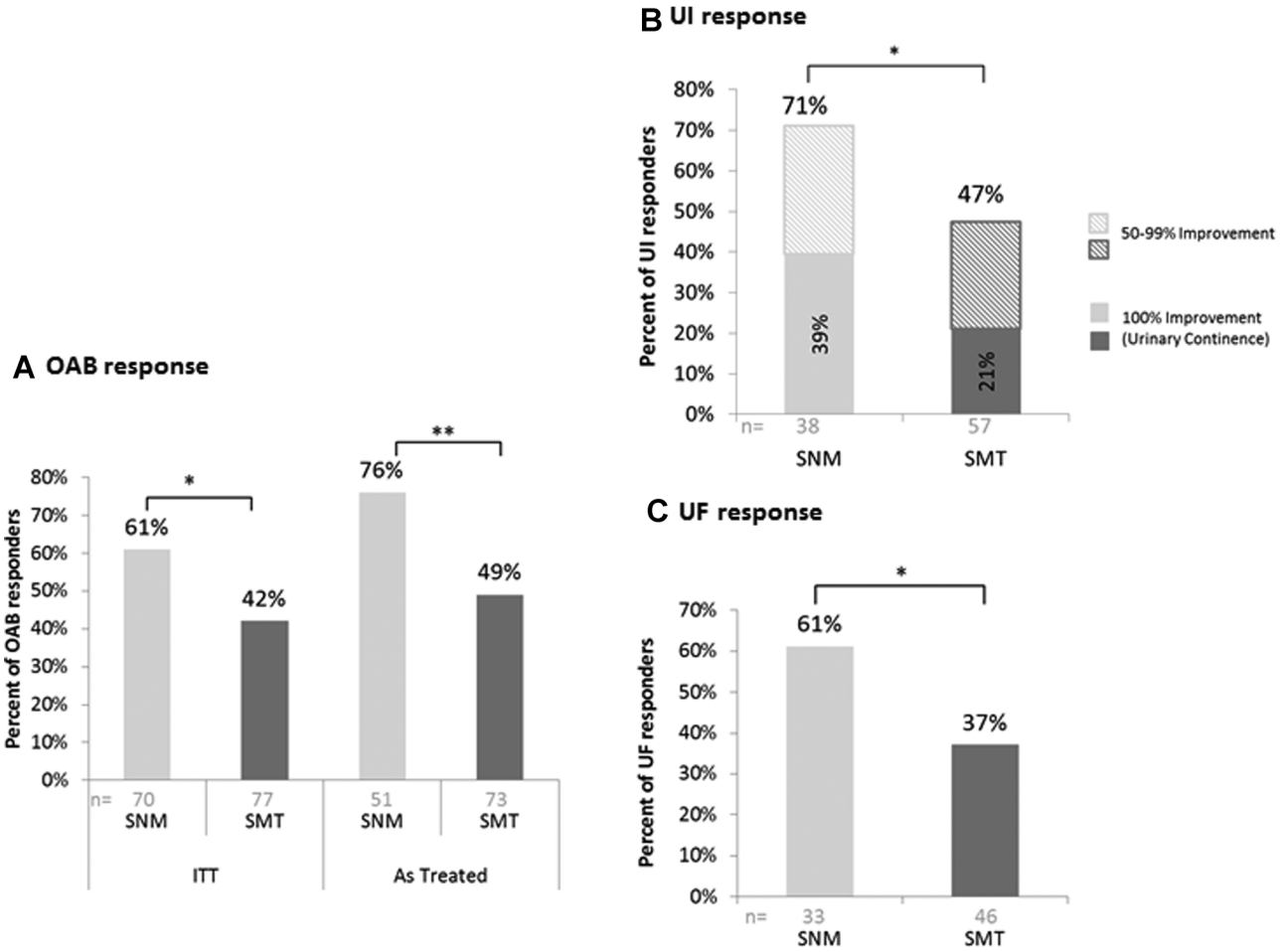

Fig. 2. Overactive bladder therapeutic response. **Panel A**: Intent to Treat (ITT): Includes all randomized subjects (including SNM subjects not implanted). Data for subjects without 6-month diary data were assumed to be treatment failures. As Treated: Includes subjects with diary data at baseline and 6 months (124/147); subjects are grouped based on treatment received: SNM includes all implanted subjects, SMT includes all subjects not implanted. **Panels B** and **C**: UI responder was defined as ≥50% improvement in leaks/day. UF responder was defined as ≥50% improvement in voids/day or a return to normal voiding frequency (<8 voids/day). $^{*}P < 0.05$; $^{**}P < 0.01$.

trial where subjects had a mean of 9.5 leaks[8] and 16.0 voids[7] per day at baseline. These new findings indicate SNM is an effective therapy in refractory subjects with less severe OAB symptoms who experienced inadequate symptom control and/or unacceptable adverse drug events with at least one anticholinergic medication, and does not require failing all medications before offering as a therapeutic option.

In addition to the objective improvements, this study also demonstrated a significant difference in subjective measures, favoring SNM over SMT. All domains of the ICIQ-OABqol showed greater improvement in the SNM group compared to the SMT group (all $P < 0.001$). For the domains of Concern, Coping, Sleep and HRQL, score changes for SNM were greater than 3.5 times the minimally important difference (MID); while in the SMT group, the score changes were 1–1.5 times the MID. In addition there were greater improvements in sexual function for females and depression scores for SNM compared to SMT.

Recent published multicenter trials for other OAB therapies demonstrated a failure to meet their primary efficacy outcome comparison to anticholinergic medication, indicating they were not more efficacious than drug. The Orbit trial randomized 100 subjects to SMT versus percutaneous tibial nerve stimulation (PTNS). While the subjective improvement was greater for PTNS, the objective changes measured were not significantly different.[13] In the ABC trial, subjects were randomized to either anticholinergic therapy versus a single dose of 100 units of intravesical onabotulinum toxin (BoNT) injected at 20 sites.[14] The study demonstrated no significant difference in the primary outcome of number of incontinence episodes, nor secondary outcomes of QOL between the two treatments at 6 months. While there is yet to be a completed trial comparing either PTNS or intravesical BoNT to SNM, these recent studies provide a context for comparison. PTNS and BoNT did not show an objective benefit compared to SMT, while this trial showed SNM to be objectively and subjectively superior to SMT. An additional alternative OAB treatment (mirabegron, a β3 adrenergic agonist) has been recently approved although efficacy has not been evaluated in comparison to SNM or other treatment options.

The rate of device-related AEs observed in the InSite study are improved compared to those reported earlier.[7,8,15,16] Importantly, only a small number of reported AE's in the two groups were serious. Two subjects discontinued due to an AE, but only one of these was device-related (infection of the incisional site and device tract).

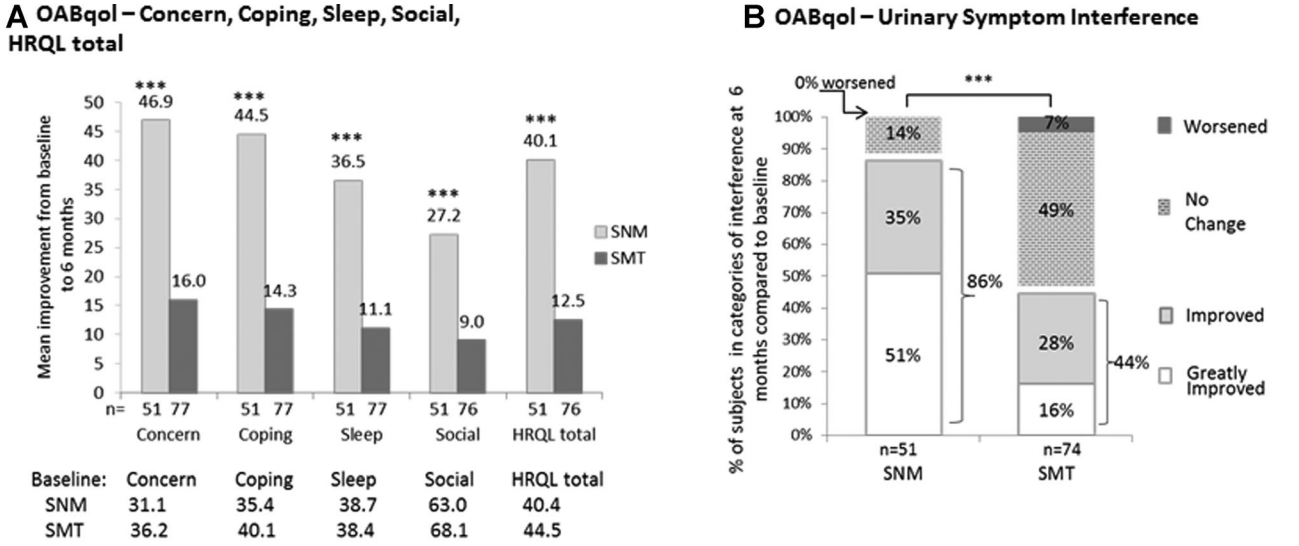

Fig. 3. Results of OAB quality of life comparison between SNM and SMT at 6 months from baseline. As shown in **Panel A**, all measures (Concern, Coping, Sleep, Social, and HRQL total) showed greater improvement at 6 months in the SNM group compared to the SMT group (all $P < 0.001$). MID, minimally important difference. The MID is the smallest score change that is perceived beneficial to patients and is often used to determine whether changes in scores are considered clinically significant.[17] The MID for the OABqol subscales has been suggested to be 10 points.[18] As shown in **Panel B**, there is a significant difference between SNM and SMT in improvement of urinary symptom interference from baseline at 6 months ($P < 0.001$). $^{***}P < 0.001$; between group comparison.

The primary strength of this study is its prospective, randomized design, which provides level-one evidence of the benefit of SNM over SMT in a population of subjects with relatively milder symptoms of OAB. Additionally, the large number of academic and private practice centers enrolling subjects make the data more generalizable and reflective of outcomes from standard clinical practice. A weakness of the study is the homogenous, predominantly Caucasian subject population, making the results less generalizable to the overall population. Additionally, the lack of blinding of randomized treatment must be acknowledged as a potential weakness. It was deemed very difficult to include in the current study due to the inability to blind patients from sensing stimulation and the ethical considerations of a sham device implantation for an approved therapy as well as the fact that a blinded assessment of the therapy had occurred previously as part of the original device approval trial.

The response to SMT measured in this study was higher than expected. Some possible explanations include the study aim to focus on subjects with less severe symptoms and the use of newer pharmacological options. Subjects with severe symptoms, or who were motivated to receive SNM instead of SMT, were eligible to obtain neuromodulation outside of the protocol as a standard treatment. Additionally, careful monitoring of compliance, improved tolerability of newer agents, and the opportunity to switch medications within SMT may have played a role in the outcomes. Even with the high rate of benefit from SMT measured in this study, there was a 20–30% advantage for SNM.

CONCLUSION

This study demonstrates that SNM provides superior objective and subjective outcomes compared to SMT for symptoms of UI and UF. Additionally, there was an improved AE profile for SNM than previously reported. This subject population was a less severe and refractory group than previously studied, demonstrating that SNM is a successful option for subjects who experienced inadequate symptom control and/or unacceptable adverse drug events with at least one anticholinergic medication throughout the OAB spectrum. This study suggests that after unsuccessful treatment with one or more anticholinergic medications, OAB subjects are more likely to benefit from SNM than an additional anticholinergic as a next step.

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