

# Randomized Trial of Percutaneous Tibial Nerve Stimulation Versus Sham Efficacy in the Treatment of Overactive Bladder Syndrome: Results From the SUMiT Trial

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## Abbreviations and Acronyms

GRA = global response assessment

OAB = overactive bladder syndrome

OAB-q = OAB questionnaire (short form)

OrBIT = Overactive Bladder Innovative Therapy

PTNS = percutaneous tibial nerve stimulation

SUMiT = Study of Urgent PC versus Sham Effectiveness in Treatment of Overactive Bladder Symptoms

TENS = transcutaneous electrical nerve stimulation

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**Purpose:** The Study of Urgent® PC vs Sham Effectiveness in Treatment of Overactive Bladder Symptoms (SUMiT) was a multicenter, double-blind, randomized, controlled trial comparing the efficacy of percutaneous tibial nerve stimulation to sham through 12 weeks of therapy. The improvement in global response assessment, voiding diary parameters, and overactive bladder and quality of life questionnaires was evaluated.

**Materials and Methods:** A total of 220 adults with overactive bladder symptoms were randomized 1:1 to 12 weeks of treatment with weekly percutaneous tibial nerve stimulation or sham therapy. Overactive bladder and quality of life questionnaires as well as 3-day voiding diaries were completed at baseline and at 13 weeks. Subject global response assessments were completed at week 13.

**Results:** The 13-week subject global response assessment for overall bladder symptoms demonstrated that percutaneous tibial nerve stimulation subjects achieved statistically significant improvement in bladder symptoms with 54.5% reporting moderately or markedly improved responses compared to 20.9% of sham subjects from baseline ( $p < 0.001$ ). All individual global response assessment subset symptom components demonstrated statistically significant improvement from baseline to 13 weeks for percutaneous tibial nerve stimulation compared to sham. Voiding diary parameters after 12 weeks of therapy showed percutaneous tibial nerve stimulation subjects had statistically significant improvements in frequency, nighttime voids, voids with moderate to severe urgency and urinary urge incontinence episodes compared to sham. No serious device related adverse events or malfunctions were reported.

**Conclusions:** This pivotal multicenter, double-blind, randomized, sham controlled trial provides level I evidence that percutaneous tibial nerve stimulation therapy is safe and effective in treating overactive bladder symptoms. The compelling efficacy of percutaneous tibial nerve stimulation demonstrated in this trial is consistent with other recently published reports and supports the use of peripheral neuromodulation therapy for overactive bladder.

**Key Words:** urinary bladder; urinary bladder, overactive; electric stimulation therapy; tibial nerve; urinary incontinence, urge

OVERACTIVE bladder syndrome significantly impacts the lives of those affected with an overall prevalence in

the United States of 16.5%.<sup>1</sup> Of the approximately 34 million people affected, the incidence of OAB is in-

creasing along with the aging baby boomer population.<sup>2</sup> OAB symptoms may decrease quality of life, increase social isolation, and result in increased morbidity such as falls and fractures.<sup>3</sup> Following behavioral and pelvic floor therapies, antimuscarinic agents are the mainstay of treatment. However, lack of efficacy, side effects and costs appear to limit the adherence to this therapy, and ultimately limit benefit for many patients.<sup>4</sup> Surgical treatment such as augmentation cystoplasty is invasive and is increasingly limited to rare cases. Neuromodulation of the sacral nerves requires a permanent surgical implant with up to a 40% complication rate in 5 years.<sup>5,6</sup> Pudendal nerve stimulation has recently been more closely studied but also requires surgical implantation.

Historically Stoller reported the use of PTNS as early as 1987 for lower urinary tract symptoms. Several other investigators have since reported compelling results with the use of PTNS for the treatment of OAB, some of which have provided highly favorable comparisons to pharmacotherapy.<sup>7–15</sup> According to the published literature, subjects with OAB in placebo controlled drug trials have a placebo response rate varying from 9% to 64% for some urinary incontinence symptoms.<sup>16,17</sup> Of note, the impact of a validated placebo response during therapy with implantable neuromodulators for sacral and pudendal nerves has not been studied to date to our knowledge, as prior studies of implanted neuromodulators have used an on/off design in implanted treatment responders.<sup>18</sup>

This pivotal level I study reports the outcomes of a multicenter trial to assess the efficacy of PTNS compared to a validated sham intervention in subjects with OAB. The previously published validated sham intervention simulates PTNS treatment sensory effects without delivering a therapeutic effect and maintains the double-blind study design.<sup>19</sup> This unique validated study design is the first randomized and controlled neuromodulation study, and specific to PTNS corroborates existing published PTNS efficacy data.

## MATERIALS AND METHODS

The SUMiT trial was an institutional review board approved, double-blind, randomized, controlled trial conducted by urologists, urogynecologists, gynecologists and nurse practitioners across 23 geographically diverse clinical centers in the United States (Appendix 1). The primary end point of this trial was to assess the efficacy of PTNS compared to an inactive sham intervention in subjects with overall OAB symptoms in an intent to treat analysis. A responder was defined as reporting bladder symptoms as moderately or markedly improved on a 7-level GRA at week 13 after completing 12, 30-minute, consecutive weekly intervention sessions. Secondary end points included change in individual GRA subset symp-

tom components (urgency, frequency and urinary urge incontinence), 3-day voiding diary parameters (frequency, nighttime voids, voids with moderate to severe urgency, urinary urge incontinence episodes and voided volume), OAB-q scores and SF-36<sup>TM</sup> quality of life scores at week 13 compared to baseline.<sup>20–22</sup> To test the validity of the sham at the end of the trial, subjects were also asked to identify which intervention they believed they received during the study.

From September 2008 to January 2009 subjects were recruited by investigator sites assisted by limited recruitment advertising. The study inclusion and exclusion are given in Appendix 2. During the course of the trial concomitant OAB medical therapies were not used. On-site training of investigators and research staff included study protocol lecture, demonstration of blinding apparatus setup, use of the Urgent PC system according to manufacturer instructions for use, and use of a TENS unit (Biostim M7 TENS unit, Biomedical Life Systems, Vista, California) and Streitberger placebo needles (Asia-Med, Munich, Germany) for sham subjects.<sup>23</sup> Subjects and study coordinators who administered questionnaires and reviewed voiding diary outcome measures were blinded to the assigned treatment intervention throughout the trial. All subjects were randomized 1:1 at the first intervention visit to PTNS or sham using a random block design stratified by investigational site.

During the intervention session subjects were in a comfortable seated or reclining position with lower extremities blocked and draped from view. All subjects had 3 electrode pads placed as shown in figure 1 to standardize the perception of the intervention between the 2 treatment arms. Additionally, all subjects were informed that they may or may not feel a sensory stimulus effect on their lower extremities as a result of the intervention. Subjects in both study groups received 12 weekly 30-minute intervention sessions and were queried about adverse events.

For PTNS subjects a 34 gauge needle electrode was inserted at a 60 degree angle approximately 5 cm cephalad to the medial malleolus and slightly posterior to the tibia (fig. 1, A). A PTNS surface electrode was placed on the ipsilateral calcaneus as well as 2 inactive sham surface electrodes, 1 under the little toe and 1 on the top of the foot. When the PTNS lead set was connected to the Urgent PC stimulator, a current level of 0.5 to 9 mA at 20 Hz was selected based on each subject's foot and plantar motor and sensory responses.

In the sham group a Streitberger placebo needle was used to simulate the location and sensation of PTNS needle electrode insertion. The Streitberger 2-piece needle is

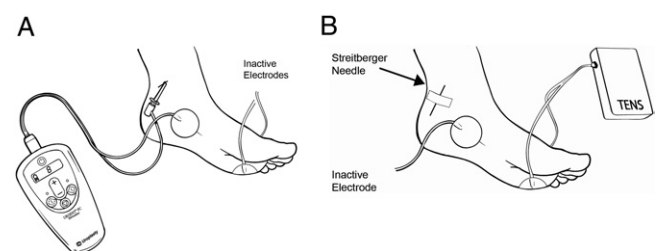
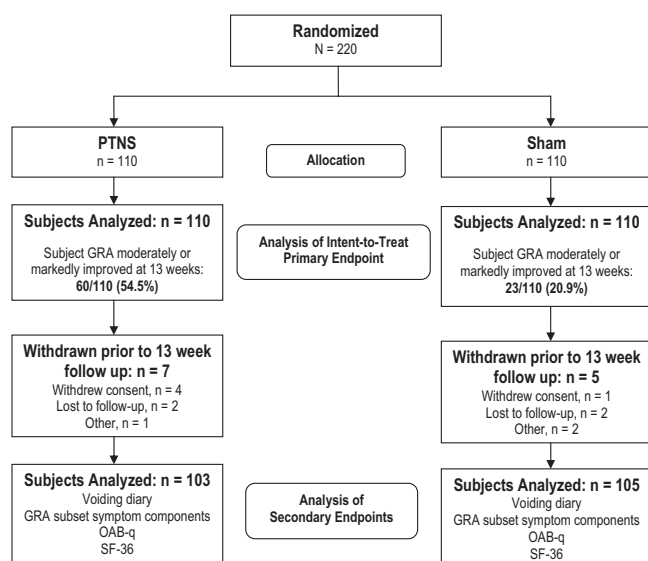


Figure 1. PTNS (A) and sham (B) setup



**Figure 2.** CONSORT diagram (Consolidated Standards of Reporting Trials).

comprised of a needle handle and blunt tip needle shaft, and causes the sensation of a slight prick when touched to the skin. However, the blunt tip needle shaft retracts into the handle as it appears to enter the skin, with no puncturing of the skin actually occurring. Therefore, no tibial nerve stimulation could occur without the insertion of a needle close to the tibial nerve. An inactive PTNS surface electrode was placed on the ipsilateral calcaneus. Two active TENS surface electrodes were placed, 1 under the little toe and 1 on the top of the foot. Sham stimulation parameters were determined based on subject first sensory level of localized stimulation through a TENS unit (fig. 1, B). Care was taken to avoid surface electrode placement over reflexology areas for major organs or the tibial nerve. The audible sounds produced by the Urgent PC stimulator in the PTNS treatment arm were also reproduced during the sham intervention to decrease auditory variation between study arms. Thus, the sham group received an intervention similar to the PTNS group without receiving active therapy.

A sample size estimate of approximately 214 subjects, 107 per study arm, was calculated using a 2-sided Fisher's exact binomial test based on an estimated 60% responder rate in the PTNS group and a 40% responder rate in the sham group with a 5% significance level and 80% power. An intent to treat analysis which counted any subject not assessed at 13 weeks as a failure was planned for the study primary end point. Data were entered into a double entry, password protected Clindex® Clinical Trial and Data Management System. All data including voiding diaries were analyzed by an independent biostatistician (Integra Group, Brooklyn Park, Minnesota) using SAS® version 9.2. Mean values were analyzed for significant change using a 2-sided paired t test and proportions were analyzed using chi-square methodology. Median values were analyzed using a Wilcoxon signed rank test with  $p < 0.05$  considered statistically significant.

**Table 1.** Subject baseline characteristics

	PTNS	Sham
Mean $\pm$ SD body mass index	29.1 $\pm$ 6.8	30.1 $\pm$ 7.8*
No. white subjects (%)	102 (92.7)	103 (93.6)
Mean $\pm$ SD yrs OAB history	10.2 $\pm$ 11.5	9.8 $\pm$ 10.4
No. use of OAB medication within 6 mos (%)	72 (66.4)	76 (69.1)

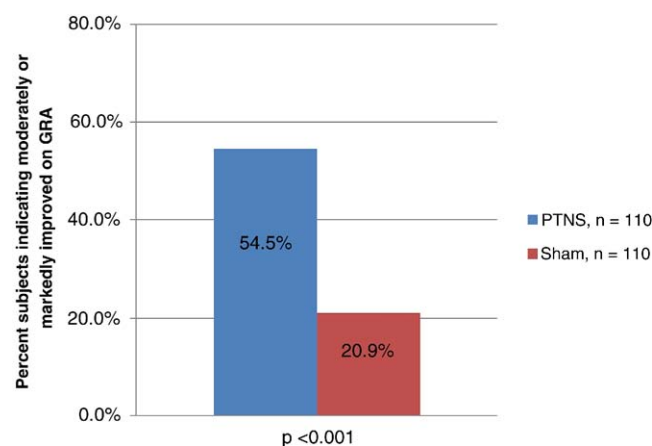
No significant differences between treatment arms.

\* Of 107 subjects.

## RESULTS

A total of 220 ambulatory adult subjects were enrolled and randomized with 110 subjects in each arm (fig. 2). Baseline characteristics were homogeneous across intervention arms with females accounting for 86 (78.2%) PTNS subjects and 88 (80.0%) sham subjects. Mean age of subjects was 62.5 and 60.2 years, with 56 (50.9%) and 46 (41.8%) older than 65 years for PTNS and sham subjects, respectively (table 1).

An intent to treat analysis of the primary end point demonstrated 54.5% (60 of 110) of PTNS subjects compared to 20.9% (23 of 110) of sham subjects responding to the GRA as being moderately or markedly improved on overall bladder symptoms from baseline (fig. 3). The primary end point analysis showed that PTNS was effective and statistically significant ( $p < 0.001$ ) compared to the sham for improvement in overall bladder symptoms. The primary end point in an as-followed completer analysis of those subjects assessed at 13 weeks demonstrated similar statistically significant results with 58.3% (60 of 103) of PTNS subjects compared to 21.9% (23 of 105) of sham subjects reporting GRA as being moderately or markedly improved on overall bladder symptoms from baseline (table 2). Assessment of treatment effects for the primary efficacy end point by investigational site showed no evidence of a significant association between investigational site and treatment outcome.



**Figure 3.** Intent to treat analysis comparing PTNS and sham GRA at week 13 assessment.

**Table 2.** GRA improvement at 13 weeks compared to baseline

	No./Total No. PTNS (%)	No./Total No. Sham (%)	p Value
Overall bladder symptoms (intent to treat)	60/110 (54.5)	23/110 (20.9)	<0.001
Overall bladder symptoms	60/103 (58.3)	23/105 (21.9)	<0.001
Urinary urgency	44/103 (42.7)	24/105 (22.9)	0.003
Urinary frequency	49/103 (47.6)	23/105 (21.9)	<0.001
Urinary urge incontinence	39/103 (37.9)	23/104 (22.1)	0.02

The secondary end point of the GRA subset symptom components for urinary urgency, frequency and urge incontinence demonstrated that PTNS subject results were statistically significant for improvement on all GRA subsets compared to sham. This finding was determined by subject responses of moderately or markedly improved after 13 weeks.

The 3-day voiding diary daily results showed PTNS to be statistically superior to sham in reducing frequency, urinary urge incontinence episodes, nighttime voids, urgency episodes and voids with moderate to severe urgency (table 3). For voided volume PTNS subjects had a statistically significant increase in voided volume from baseline to 13 weeks, whereas the sham group did not. The difference between groups was not statistically significant for voided volume.

The condition specific OAB-q symptom severity score and quality of life scores showed statistically significant improvement in the PTNS group compared to the sham group (table 4). The SF-36 general health survey quality of life scores showed statistically significant improvement from baseline compared to 13 weeks in the PTNS group in the physical ( $p = 0.002$ ) and mental ( $p = 0.049$ ) domain scales. The sham arm did not show statistically significant improvement

**Table 4.** OAB-q change from baseline at 13 weeks

	Symptom Severity Score*	Health Related Quality of Life Score†
PTNS:		
No.	101	103
Mean $\pm$ SD change	$-36.7 \pm 21.5$	$34.2 \pm 21.3$
Sham:		
No.	102	105
Mean $\pm$ SD change	$-29.2 \pm 20.0$	$20.6 \pm 20.6$
Difference (PTNS – sham)	$-7.5 \pm 20.7$	$8.2 \pm 21.0$
p Value	0.01	0.006

\* Lower score is better score.

† Higher score is better score.

from baseline compared to 13 weeks, nor was the difference between groups statistically significant. At 13 weeks the percent of subjects who correctly identified their randomized intervention assignment was equivalent between the study groups (52% in the PTNS group and 58% in the sham group), confirming the validity of the sham model.

In total 6 PTNS subjects reported 9 mild or moderate treatment related adverse events consisting of ankle bruising (1 of 110, 0.9%), discomfort at the needle site (2 of 110, 1.8%), bleeding at the needle site (3 of 110, 2.7%) and tingling in the leg (1 of 110, 0.9%). No local treatment related adverse events were reported in the sham group. In addition, no systemic adverse events were experienced in either group.

## DISCUSSION

The results of this study provide strong scientific evidence that the therapeutic effect of PTNS is due to the stimulation of the posterior tibial nerve and is not due to a placebo effect. The intent to treat primary end

**Table 3.** Voiding diary parameters at baseline and 13 weeks

	Baseline	13 Wks	Change From Baseline	p Value	Difference (PTNS – sham)	p Value
Mean $\pm$ SD PTNS:						
Frequency*	$12.3 \pm 3.2$	$9.8 \pm 2.8$	$-2.4 \pm 2.5$	<0.001	$-0.9 \pm 2.5$	0.01
Nighttime voids†	$2.9 \pm 1.6$	$2.1 \pm 1.4$	$-0.7 \pm 1.2$	<0.001	$-0.4 \pm 1.3$	0.04
Voided vol‡	$169.5 \pm 78.9$	$183.0 \pm 75.6$	$11.4 \pm 45.0$	0.01	$5.5 \pm 42.1$	0.35
Mean $\pm$ SD sham:						
Frequency	$12.4 \pm 3.0$	$11.0 \pm 3.1$	$-1.5 \pm 2.4$	<0.001		
Nighttime voids	$2.9 \pm 1.7$	$2.6 \pm 1.6$	$-0.3 \pm 1.4$	0.02		
Voided vol	$168.7 \pm 84.0$	$172.6 \pm 90.6$	$5.9 \pm 39.0$	0.13		
Median PTNS:						
Moderate to severe urgency§	8.3	3.7	-3.7	<0.0001		<0.001
Urge incontinence	3.0	0.3	-1.3	<0.0001		0.002
Median sham:						
Moderate to severe urgency	8.0	5.0	-2.0	<0.0001		
Urge incontinence	1.8	1.0	-0.3	<0.0001		

\* Measured by average number of intentional voids per day (day and night in 3-day voiding diary).

† Measured by average number of waking episodes per day (in 3-day voiding diary).

‡ Average voided volume per void (CC) from the 3-day voiding diary (99 for PTNS, 102 for sham due to incomplete diary completion for this measuring parameter).

§ Measured by the median number of voids per day (in 3-day voiding diary).

|| Measured by median number of incontinence episodes accompanied by moderate to severe urgency per day (day and night in 3-day voiding diary).



point of the study demonstrated that 54.5% of PTNS subjects and 20.9% of sham subjects reported GRA as being moderately or markedly improved in their overall bladder symptoms from baseline. The primary end point calculation used a conservative intent to treat analysis where all subjects lost to followup were analyzed as failures to limit bias to the success rate caused by patient dropouts.

With PTNS there was a statistically significant improvement in all GRA subset components compared to the sham intervention. Additionally, objective voiding diary parameters of frequency, urinary urge incontinence episodes, nighttime voids, urgency episodes and voids with moderate to severe urgency were statistically significant in the PTNS group compared to sham. OAB-q and SF-36 quality of life questionnaires provided further support of the primary and other secondary end points for the efficacy of PTNS.

This is the first neuromodulation study to use a published validated sham component.<sup>19</sup> When subjects were asked which intervention they believed they received during the study, there was no statistical difference between the groups. This finding confirms that neither group knew which treatment they received, and affirms the integrity of the sham technique and design, further strengthening the validity of these results.

A strength of this study design is the use of a validated realistic sham intervention which would be difficult to replicate for implantable neuromodulation systems that require surgical placement. An advantage of PTNS is that it does not require surgical implantation of a power supply, leads or electrodes, or the use of prophylactic antibiotics.

The results of this study provide level I evidence that PTNS is safe and effective in improving OAB. A recent multicenter, randomized trial (OrBIT Trial) demonstrated that a series of 12 weekly PTNS treatments was comparable to extended-release tolterodine in treating OAB symptoms.<sup>7</sup> A long-term followup of the OrBIT Trial evaluated the durability of PTNS benefits and found that 96% of 12-week responder subjects who continued periodic treatments sustained OAB symptom improvements at 1 year followup.<sup>24</sup> No significant PTNS related adverse events were noted in these trials.

A limitation of this study is the relatively short followup period of 12 weeks. However, the 12-week followup corresponds to the recommended treatment protocol for PTNS and additional clinical improvement in the sham arm was not expected to increase after this followup period. This is also the usual therapeutic interval used for OAB drug trials.

PTNS represents an excellent option for patients who are unwilling or unable to tolerate systemic antimuscarinic adverse events (dry mouth, constipation, central nervous system effects), those with conditions refractory to medical and behavioral treatments and

those who do not wish to have or are not candidates for an implantable surgical device or reconstructive surgery. Future studies of PTNS in combination with behavioral or pharmacotherapy are needed as PTNS does not preclude these interventions. Given that PTNS has been shown in rigorous clinical studies to be effective, durable and comparable to drug therapy in effectiveness, PTNS should be considered a viable treatment for OAB symptoms.

## CONCLUSIONS

This multicenter, double-blind, randomized, sham controlled trial provides level I clinical evidence that PTNS therapy is safe and effective in treating OAB symptoms. The compelling efficacy of PTNS as demonstrated in this trial, along with other recently published reports, should have a significant impact on the future clinical management of OAB.

## APPENDIX 1

### Additional Investigators from the SUMiT Trial

Nicholas Franco, Specialists in Urology, Naples, FL; David Glazier, Virginia Urology, Richmond, VA; Craig McCoy, Central Missouri Women's Healthcare, Marshall, MO; Lora Plaskon, Athena Urology, Issaquah, WA; Jason Bennett, Female Pelvic Health Medicine and Urogynecology Institute of Michigan, Grand Rapids, MI; Brian Murray, Capital Region Urological Surgeons, Albany, NY; Richard Lotenfoe, Urology Health Solutions, Celebration, FL; Jeffrey Ranta, Greenwich Urological Associates, Greenwich, CT; Judd Boczek, Center for Advanced Urology, White Plains, NY; Susan Kalota, Arizona Urological Specialists, Tucson, AZ; Neal Shore, Carolina Urological Research Center, Myrtle Beach, SC; Denise Elser, Illinois Urogynecology Ltd., Oak Lawn, IL; Naveen Kella, Urology of San Antonio, San Antonio, TX; Lewis Kritekman, North Fulton Urology, Roswell, GA; Harold Tsai, Florida Specialists in Urology, Ft. Myers, FL; Norman Zinner, Western Clinical Research, Torrance, CA; Peter Sand, Evanston Continence Center, Evanston, IL.

## APPENDIX 2

### Baseline Inclusion and Exclusion Criteria

#### Inclusion Criteria

- Women and men  $\geq 18$  years of age
- A score of  $\geq 4$  on the OAB-q short form for urgency
- Average urinary frequency of  $\geq 10$  voids per day
- Self-reported bladder symptoms  $\geq 3$  months
- Self-reported failed conservative care
- Discontinued all antimuscarinics for  $\geq 2$  weeks
- Capable of giving informed consent
- Ambulatory and able to use toilet independently without difficulty
- Capable and willing to follow all study-related procedures

#### Exclusion Criteria

- Pregnant or planning to become pregnant during study duration
- Neurogenic bladder
- Botox<sup>®</sup> use in bladder or pelvic floor muscles within past one year
- Pacemakers or implantable defibrillators
- Current urinary tract infection
- Current vaginal infection
- Use of Interstim<sup>®</sup>
- Use of Bion<sup>®</sup>
- Current use of TENS in pelvic region, back or legs
- Previous PTNS treatment
- Use of investigational drug/device therapy within past 4 weeks
- Participation in any clinical investigation involving or impacting gynecologic, urinary or renal function within past 4 weeks

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