Long-Term Durability of Percutaneous Tibial Nerve Stimulation for the Treatment of Overactive Bladder

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Abbreviations and Acronyms

GRA = global response assessment

OAB = overactive bladder

OAB-q = Overactive Bladder Questionnaire

OrBIT = Overactive Bladder Innovative Therapy

PTNS = percutaneous tibial nerve stimulation

SNS = sacral nerve stimulation

Submitted for publication June 20, 2009.

Supported by Uroplasty, Inc.

Study received institutional review board approval.

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† Financial interest and/or other relationship with Uroplasty, Pfizer, Watson, Astellas and Allergan.

‡ Financial interest and/or other relationship with Medtronic, Advanced Bionics, Boston Scientific, Allergan, Pfizer, Celgene and Trillium Therapeutics.

§ Financial interest and/or other relationship with Uroplasty, Astellas and Watson.

‖ Financial interest and/or other relationship with Uroplasty, Pfizer, Allergan, Tengion, Solace, Contura and Astellas.

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** Financial interest and/or other relationship with AMS, Medtronic, Uromedica, Uroplasty and QiG.

†† Financial interest and/or other relationship with C. R. Bard.

‡‡ Financial interest and/or other relationship with Medtronic, AMS, Novartis, Allergan, Astellas and Boston Scientific.

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Purpose: The Overactive Bladder Innovative Therapy Trial during phase 1 was a randomized trial demonstrating comparable effectiveness of percutaneous tibial nerve stimulation and extended-release tolterodine during 12 weeks of therapy for frequency, nocturia, urgency, voided volume and urge incontinence episodes. In this second phase of the Overactive Bladder Innovative Therapy Trial we assessed the sustained therapeutic efficacy of percutaneous tibial nerve stimulation in subjects with overactive bladder during 1 year.

Materials and Methods: After 12 weeks subjects randomized to weekly percutaneous tibial nerve stimulation with Urgent® PC were offered an additional 9 months of treatment with assessments at 6 and 12 months from baseline. Outcome measures included voiding diary data, overactive bladder questionnaires, global response assessments and safety assessments.

Results: A total of 33 percutaneous tibial nerve stimulation responders continued therapy with 32 and 25 subjects completing 6 and 12 months of therapy, respectively. Subjects received a mean of 12.1 treatments during an average of 263 days, with a mean of 21 days (median 17) between treatments. Subject global response assessments showed sustained improvement from 12 weeks at 6 and 12 months, with 94% and 96% of responders, respectively. At 12 months mean improvements from baseline included a frequency of 2.8 voids daily ($p < 0.001$), urge incontinence of 1.6 episodes daily ($p < 0.001$), nocturia with 0.8 voids ($p < 0.05$) and a voided volume of 39 cc ($p < 0.05$). Overactive bladder questionnaire symptom severity was significantly improved from 12 weeks to 12 months ($p < 0.01$) as well as from 6 to 12 months ($p < 0.01$). No serious adverse events occurred.

Conclusions: Statistically significant overactive bladder symptom improvement achieved with 12 weekly percutaneous tibial nerve stimulation treatments demonstrates excellent durability through 12 months. The durability of response demonstrates the effectiveness of percutaneous tibial nerve stimulation as a viable, long-term therapy for overactive bladder.

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

OVERACTIVE bladder is a symptom syndrome defined as urinary urgency with or without urge incontinence, usually associated with urinary frequency and nocturia (sleep disturbing voiding).[1] With a prevalence of approximately 16% of the adult U.S. population patients may be profoundly affected by OAB with significant disability including reduced quality of life and mobility,

0022-5347/10/1831-0234/0
THE JOURNAL OF UROLOGY®

Vol. 183, 234-240, January 2010
Printed in U.S.A.
DOI:10.1016/j.juro.2009.08.160

along with social relationship and sexual function deterioration, and sleep deprivation.[2,3] This chronic condition requires lifelong therapy to control symptoms with the therapeutic goal of restoring quality of life while balancing efficacy and side effects. Early therapy involves conservative measures including dietary controls, fluid modification, bladder training and pelvic floor muscle rehabilitation. The mainstay of treatment is pharmacotherapy with the effectiveness of antimuscarinic agents well documented in the clinical literature.[3] Patient adherence rates with medication decrease during 12 months of therapy for many reasons including intolerable side effects or lack of sufficient symptom relief.[4] Recent research reports adherence rates during 12 months in 45,576 patients with OAB on drug therapy are low with a 32% average proportion of days covered.[5]

Neuromodulation therapy targets specific nerves in the sacral plexus that control the pelvic floor and bladder function. Sacral nerve stimulation with an implantable device has demonstrated the efficacy of neuromodulation to control OAB symptoms.[6] Despite its effectiveness the therapeutic impact of sacral nerve stimulation has been limited in clinical practice due to several factors including invasiveness, associated costs, and its limitations in older adult patients and those who are frail or who have several medical comorbidities.[7]

Several single and multicenter studies have demonstrated the efficacy, safety and positive impact on urodynamic parameters of PTNS targeting the sacral plexus from an accessible, minimally invasive entry point into the nervous system via the posterior tibial nerve.[8–12] This office based, neuromodulation therapy can be used for the treatment of OAB symptoms in women and men.

The first phase of the OrBIT Trial entered 100 subjects with OAB between June 2006 and September 2008 in an institutional review board approved, multicenter, nonblinded, randomized, controlled trial comparing the effectiveness of a series of 12 weekly, 30-minute office based PTNS treatments using Urgent PC and 12 weeks of 4 mg daily extended-release tolterodine tartrate (Detrol® LA). Of the 44 subjects undergoing PTNS and the 43 on tolterodine who completed 12 weeks of therapy, similar results from voiding diaries were reported in reducing OAB symptoms of urgency, urge incontinence, nocturia and frequency. The GRA demonstrated a statistically significant improvement or cure over baseline in OAB symptoms in 79.5% of the PTNS group vs 54.8% of the tolterodine group ($p = 0.01$).[12,13] In the second phase of the OrBIT Trial, reported here, we assessed the sustained effectiveness of PTNS therapy offered at individualized intervals during 1 year in subjects who finished an initial course of 12 consecutive weekly sessions.

MATERIALS AND METHODS

OrBIT subjects who finished an initial course of 12 consecutive weekly PTNS treatments were offered ongoing sessions of therapy for an additional 9 months to monitor improvement in frequency, nocturia, urgency, urge incontinence episodes and voided volume. Subjects were required to be OAB drug-free throughout the study. Subjects were reimbursed for clinical trial associated expenses including time and travel. Under the supervision of the investigator the subjects selected treatment intervals allowing them to control OAB symptoms at an acceptable level. Sound clinical judgment was used to extend or shorten the treatment interval based on treatment efficacy and patient wishes in care decisions. The individual treatment sessions were 30 minutes in duration using a 34 gauge needle electrode inserted approximately 5 cm cephalad to the medial malleolus and slightly posterior to the tibia. When connected to the Urgent PC stimulator a current level of 0.5 to 9 mA at 20 Hz was selected based on patient sensory and motor response (fig. 1).

An evaluation of OAB symptom control was completed at 6 and 12 months for comparison to baseline and the initial OrBIT 12-week evaluation. Assessments included an independent analysis of 2-day voiding diaries for the mean change in voids per 24 hours, number of nocturnal voids, volume voided, moderate to severe urgency episodes using the Indevus Urgency Severity Scale[14] and improvement in OAB-q scales.[15] Additional comparisons included investigator and subject GRA ratings of OAB symptoms between 12 weeks, and 6 and 12 months.

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 using SAS® version 9.2. Mean values were analyzed for significant change using a 2-sided paired t test and median values were analyzed using a Wilcoxon signed rank test with $p < 0.05$ considered statistically significant. No corrections for multiple comparisons were made.

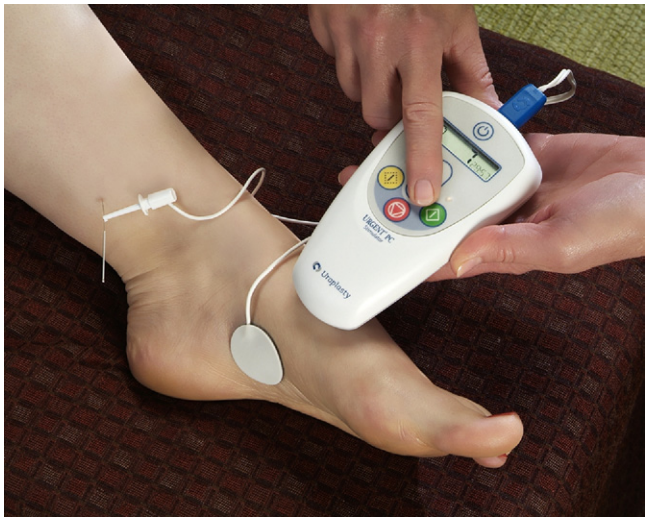

Figure 1. Urgent PC system