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UROLOGY



A Closed-Loop Wearable Tibial Neuromodulation System for Overactive Bladder and Urgency Urinary Incontinence

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A Multicenter Study Evaluating the FREquency of Use and Efficacy of a Novel Closed-Loop Wearable Tibial Neuromodulation System for Overactive Bladder and Urgency Urinary Incontinence (FREEOAB)

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OBJECTIVE	To evaluate the effectiveness and safety of a novel wearable neuromodulation system in-
	corporating embedded electromyographic evaluation, representing the first closed-loop wearable
	therapy for bladder control.
METHODS	This 12-week, multicenter, open-label, single-arm study of subjects with overactive bladder assessed response of bladder diary parameters and quality of life (QOL) metrics. Subjects used the transcutaneous tibial neuromodulation system, either once or three times weekly, with evaluations at weeks 1, 4, 8, and 12. Enrolled subjects (N = 96) were assessed for changes in urinary frequency, urgency, and urgency urinary incontinence episodes, and QOL changes using various questionnaires.
RESULTS	In the intent-to-treat population (N = 96, mean age 60.8 ± 13.0 years, 88.5% female), significant reductions in 3-day diary parameters were observed for daily voids, incontinence, and urgency episodes at 12 weeks. QOL improvements exceeded the minimal clinically important difference for all QOL questionnaires. Long-term results remained robust at 12 months. Device-related adverse events were mild and there were no device-related serious adverse events. Mean therapy compliance at 12 weeks was 88.5% . High satisfaction rates were reported for the device overall.
CONCLUSION	The Avation device demonstrates promising efficacy in treating adults with overactive bladder and urge urinary incontinence. At 12 weeks, both diary parameters and QOL indicators showed significant improvement and remained robust at 12 months. The device had a favorable safety profile with high compliance and patient satisfaction. This novel, closed-loop wearable tibial neuromodulation system represents a significant advancement in bladder control therapy, of- fering a noninvasive, patient-centered alternative with improved accessibility and ease of use. UROLOGY xx: xxx–xxx, xxxx. © 2023 Elsevier Inc. All rights reserved.

he International Continence Society (ICS) defines overactive bladder (OAB) as a syndrome characterized by urgency, with or without

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urgency incontinence, usually accompanied by frequency and nocturia, in the absence of other obvious pathology.¹ It has long been recognized that OAB, in general, and urinary incontinence, in particular, present a substantial burden for patients, impacting multiple areas of daily life and imposing severe medical, social, psychological, and sexual consequences.² In guidelines addressing the management of OAB, a tiered methodology is recommended, beginning with behavioral modifications and advancing to pharmacological treatments as warranted. Should conservative strategies prove inadequate, the guidelines advocate for the consideration of thirdline therapeutic options, encompassing neuromodulation

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or onabotulinumtoxinA injections, though reserving surgical intervention for refractory cases resistant to more conservative approaches.²

In spite of the distress experienced by OAB patients, treatment adherence remains low, attributable to multiple obstacles, including temporal and financial limitations, adverse drug reactions, therapy fatigue, and apprehension toward invasive interventions.³ Advancements toward decreased complexity and invasiveness and greater affordability may bridge the gap between patient need and treatment availability.

A new category of wearable transcutaneous tibial neuromodulation has emerged for adults with symptoms of OAB, providing a noninvasive, low-risk treatment option that is self-administered. Compared to other OAB interventions, closed-loop wearable tibial neuromodulation may present fewer side effects, reduce complexity, increase compliance, and lower costs, making it an attractive alternative in the management of OAB.⁴ Nevertheless, similar to other neuromodulation therapies employed for OAB management, transcutaneous tibial neuromodulation systems have thus far utilized an "openloop" configuration, contingent on interpretation of sensory or motor responses to ascertain appropriate nerve stimulation, which may pose a hindrance to the effective implementation of home-based therapeutic interventions. In contrast, closed-loop systems utilizing wearable sensors are used in multiple other areas, including Parkinsonism, multiple sclerosis, sleep medicine, pain, cardiology, and epilepsy.⁵ A closed-loop system provides objective confirmation of tibial nerve activation and a sensor-based algorithm that monitors neuromodulation output to enable automatic adjustments during therapy. Aiming to refine this treatment modality, the present investigation assesses the effectiveness and safety of a novel wearable neuromodulation system (Avation Medical, Inc) that incorporates embedded sensors for electromyographic (EMG) evaluation, providing the first

noninvasive closed-loop wearable therapy for bladder control.

METHODS

Study Overview

This multicenter, open-label, single-arm 12-week study evaluated changes from baseline in OAB symptoms as measured by bladder diaries and quality of life (QoL) instruments through 12 weeks of therapy. Institutional Review Board approval was obtained by each participating site.

Inclusion in the study required adult subjects to have been diagnosed or have symptoms of OAB for \geq 3 months, with an average of \geq 10 daily voids on a 3-day bladder diary. Each subject had to have a detectable electromyography (EMG) signal with the system, tolerate a 30-minute therapy session, and agree to remain either drug-naive, or stable on any OAB medication regimen.

This study was comprised of two phases. In phase I, subjects were asked to use the device for 1-3 thirty-minute sessions per week for 12 weeks. Subjects returned to the clinic or had a remote visit after 1, 4, 8, and 12 weeks. Remote visits were utilized due to the COVID-19 pandemic, facilitated by a HIPAA-compliant cloud database. Upon completion of phase I, subjects were given the opportunity to continue treatment with the system beyond the initial 12 weeks, provided they were compliant with therapy and data collection. Subjects signed a new informed consent and continued to complete bladder diaries prior to each phase II visit. Phase II efficacy results were analyzed after all subjects completing their 6-month and 12-month visits. During phase II patients tapered therapy to only two 30-minute sessions per month.

Device Description

The Avation device (Fig. 1) is a wearable, noninvasive bladder control therapy utilizing transcutaneous tibial neuromodulation to treat patients with OAB with or without urgency urinary incontinence. The device uses a proprietary EMG analysis algorithm to monitor neuromodulation energy to the tibial nerve via biosensor electrodes strategically placed within the garment, detecting muscle contractions of the dorsal foot. As a true closed-loop control system, the device objectively confirms activation of the tibial nerve and continually monitors the EMG response to adjust neuromodulation energy parameters during therapy to ensure optimal therapeutic output.

Therapy is prescribed by a clinician after establishing an upper and lower boundary for the neuromodulation energy, with the lower boundary being driven by detection of the patient's EMG signal (an indication of nerve activation) and the upper limit being a comfortable limit of stimulation. During therapy, neuromodulation output will automatically adjust based on the amplitude required to maintain nerve activation. Neuromodulation output can also be manually adjusted by the patient, but only within a range set by the clinician.

The device is comprised of a controller with rechargeable battery, a wearable garment, gel cushions (which aid in energy transmission and comfort), and accessories. The digital components include a mobile app that allows patients to control and monitor therapy sessions.

Enrollment and Disposition

Subjects who met all eligibility and screening criteria were enrolled in the study at one of eight study centers in the United States. The screening procedure required a 3-day bladder diary and confirmation of activation of the tibial nerve (as confirmed by an EMG signal). There were 159 subjects consented; following screening, a total of 96 subjects were enrolled, with most exclusions (59/63, 93.6%) due to inadequate symptom severity or other inclusion/exclusion criteria. The remaining four patients (4/63) were excluded due to inadequate EMG signal. Enrollment in phase I began in January of 2021, and phase II 12-month follow-ups were completed in June of 2023. Subject disposition is provided in Figure 2.

Outcome Measures

Subjects who met eligibility criteria and received therapy were analyzed for changes in urinary frequency (UF), urinary urgency (UU), and urge urinary incontinence (UUI) episodes per day from baseline.

QoL changes were also evaluated using the Overactive Bladder Quality of Life Questionnaire (OAB-q), the Incontinence Quality of Life Questionnaire (I-QOL), and the Patients' Global Impression of Change (PGIC). Safety was evaluated through adverse events (AE) related to the device, personalization procedure, and therapy (all considered devicerelated AEs). All device-related AEs were reported for subjects who received Avation device therapy. As the device was cloudconnected, actual compliance to therapy was also evaluated.

The purpose of this study was to evaluate the clinical efficacy, subject compliance, safety, and subject satisfaction of the use of the device after 12 weeks of use. Reduction in average daily diary symptoms from baseline was calculated for each subject after 12 weeks and was summarized for all subjects. A power analysis was conducted using mean percent improvement in daily voids relative to an upper normal limit of eight voids per day with a total of 80 evaluable subjects yielding a 95.6% power.

Statistical Analyses

All effectiveness and safety data are summarized descriptively, using population proportion or mean with 95% confidence intervals. At individual time points, the one-sample t test was

performed at significance level P < .05 to assess the mean percent improvements.

Phase I analysis included the Intent-to-Treat (ITT) population: all subjects enrolled in the study, regardless of whether they completed phase I (N = 96). Supporting analysis was conducted, which included those subjects with diary data from both baseline and week 12, as well as those who failed to provide data for week 12, and those who withdrew from the study early. For those who withdrew early or were otherwise missing endpoint data, the Last Observation Carried Forward method was used to impute the missing data. To assess efficacy over time, subjects were evaluated either in person at the clinic or via a remote visit (via phone/video conferencing), after 1 week \pm 2 days, 4 weeks \pm 4 days, 8 weeks \pm 4 days, and 12 weeks \pm 4 days.

Phase II analysis includes the long-term population: all subjects who entered phase II of the study (N = 50) and completed their 6-month (N = 47) and 12-month (N = 39) follow-up visits.

RESULTS

Baseline Characteristics

The ITT study population (Table 1) demonstrates a mean age of 60.8 ± 13.0 years at the time of enrollment with the majority female (85/96,88.5%). The study population was representative of patients seeking care for OAB, particularly those seeking care for UUI.⁶

Baseline severity of OAB symptoms in the ITT group, measured by events recorded in a 3-day bladder diary, was influenced by study inclusion criteria requiring a minimum average of 10 voids/day over the 3-day diary period. Mean UF events (13.4 ± 4.2) per day, mean UU episodes (6.9 ± 5.8) per day, and mean UUI episodes (4.7 ± 4.1) per day, were consistent with a substantial symptom burden.

Phase I 12-Week Diary Parameters

Comparison of 3-day diary parameters between baseline and 12-week diaries demonstrated significant reductions in each domain. Voiding events in 89 (94.7%) subjects reporting UF showed a mean reduction of 2.84 \pm 2.4 (*P* < .0001) from baseline. Incontinence episodes in 76 (80.8%) subjects were reduced by 1.91 \pm 3.1 (*P* < .0001), and urgency episodes in 74 (78.7%) subjects decreased by 3.09 \pm 3.9 (*P* < .0001) (Fig. 3). In terms of patients with diary parameters that returned to normal at 12 weeks, 25.8% [16.7, 34.9] of patients returned to \leq 8 voids/day, 23.7% [14.1, 33.1] of patients reported no daily leaks, and 25.7% [15.7, 35.7] of subjects reported no daily urgency episodes at the 12-week visit.

Quality of Life

In evaluating changes in QOL with the OAB-q questionnaire, a Minimal Clinically Important Difference (MCID) of 10 points was utilized.⁷ Changes in the OAB-q health related quality of life (HRQL) domains (coping, concern/worry, sleep, and social interaction) all exceeded the MCID, with most domains at least twice the MCID. The mean change in I-QoL in 86/94 (91.5%) of patients with baseline and 12-week QoL data was 14.6, exceeding the MCID of 6.3 points.⁸ PGIC (Question 1 only) demonstrated a mean change of 1.9, indicating a general perception of positive change across all aspects of their QOL.



Figure 2. Subject disposition flow chart. (Color version available online.)

Phase II Long-term Response Rates

Subjects who completed the 12-week phase and met criteria were provided with the opportunity to continue treatment beyond the initial 12-week assessment. A total of 50 patients elected to enroll in continued therapy, with 47 (94%) and 39 (78%) subjects completing therapy for 6 and 12-month analyses, respectively. Improvement in diary parameters persisted at 6-month with mean reductions in UF events of 2.67 \pm 2.5 (P < .0001), of UUI episodes of 2.13 ± 3.0 (P < .0001), and of UU episodes of 3.97 ± 5.2 (P < .0001). Improvement in diary parameters (Fig. 3) remained robust across all symptoms at 12 months with mean reductions in UF events of 1.85 ± 2.8 (P < .0001), of UUI episodes of 1.29 ± 3.9 (P = .0556), and of UU episodes of 2.84 ± 4.9 (P = .0040). Durability of therapy persisted in long-term follow-up despite the requirement that frequency of therapy was gradually reduced to twice per month after the first 12 weeks.

Safety and Usability

There were 12 device-related AE with none determined to be severe. Most device-related AEs were considered anticipated. All related AE were able to be resolved with adjustment of the stimulation parameters or replacement of the component parts.

the number of completed therapy sessions in 12 weeks divided

by the number of expected therapy sessions in 12 weeks. As

therapy data was uploaded to a HIPAA-compliant cloud,

compliance is actual and not patient-reported. Mean therapy

compliance at 12 weeks for the ITT safety population (N = 96)

was 88.5%. Patients were asked to rate satisfaction with the

device on a scale from 0 to 4 with scores greater than or equal

to 2 indicating satisfaction. With 87 (90.6%) subjects re-

sponding, 90.8% reported satisfaction with the garment and the

app, 93.1% reported ease of fitting therapy into their routine,

In this study, the Avation device demonstrated pro-

mising therapeutic efficacy for patients with OAB, par-

ticularly in those suffering from UUI. The study

population, predominantly female and representative of

Compliance was calculated as (maximum limited to 100%)

None required additional treatment.

and 97.7% found the system easy to use.

COMMENT

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Table 1.	Demographics	of ITT	efficacy	population
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Demographics	ITT Population (N = 96)
Sex (N (%))	
Female	85 (88.5%)
Male	11 (11.5%)
Ethnicity (N (%))	
Hispanic/Latino	11 (11.5%)
Not Hispanic/Latino	84 (87.5%)
Other	1 (1.0%)
Race (N (%))	
White/Caucasian	77 (80.2%)
Black/African American	10 (10.4%)
Asian	3 (3.1%)
Other	6 (6.2%)
Age (y) (mean ± SD)	60.8 ± 13.0
Height (cm) (mean ± SD)	164 ± 9.11
Weight (kg) (mean ± SD)	83.7 ± 26.6
Daily symptom severity (mean \pm SD)	
Voids (89/94)	13.4 ± 4.2
Urgency incontinence (76/94)	4.7 ± 4.1
Urgency episodes (74/94)	6.9 ± 5.9

ITT, Intent-to-Treat.

patients seeking care for OAB and UUI, exhibited a substantial symptom burden at baseline. Improvements in diary parameters indicated that the majority of patients experienced meaningful symptom reduction in one or more symptom domains, with a smaller proportion of patients achieving normalized diary parameters at 12 weeks. Furthermore, the device's impact on QOL was notable, with all domains surpassing the MCID. Phase II long-term improvements remained robust at 12 months, even with a reduction in the frequency of therapy to just two times per month. Furthermore, the therapy demonstrated a favorable safety profile with no severe devicerelated AE reported. Compliance and satisfaction rates were high among patients, who found the system easy to use and integrate into their daily routines.

Transcutaneous neuromodulation of the tibial nerve has long garnered interest for the treatment of OAB and urgency incontinence due to its noninvasive nature and fewer side effects compared to traditional pharmacological interventions.⁹ More recently, it has emerged as a promising, patient-centered alternative to existing therapies, with the potential to significantly expand therapy options and access to care. In a recent systematic review conducted by Sayner et al, 13 randomized controlled trials were assessed, with all but one indicating that transcutaneous tibial neuromodulation is an effective treatment option for OAB. Notably, those studies reported low dropout rates and a minimal number of AE, further supporting the safety and tolerability of wearable tibial neuromodulation as a therapeutic intervention.¹⁰

In this investigation, mean reductions in UF events of 2.8 from baseline, and mean reductions in UUI events of 1.91 at 12 weeks signify a clinically meaningful impact for the majority of patients receiving treatment. It may be useful to compare this to the well-established therapy of percutaneous tibial nerve stimulation (PTNS), where a mean reduction of 1.7 UF events per day and 2.4 UUI episodes per day were observed by Kobashi et al using the NURO system. However, those participants were drug



Figure 3. Changes in HRQL and subscales at 12 weeks. For symptom severity lower scores indicate improvement. For all other subscales, higher scores indicate improvement. Minimal Clinically Important Difference = 10-point change. (Color version available online.)

naïve and had a baseline UF and UUI rates of 11.5 and 3.5 episodes/day, respectively, compared to our study's population, many of whom had prior medication therapy and mean UF and UUI rates of 13.4 and 4.7 episodes/ day, respectively.¹¹ Moreover, UF, UU, and UUI episodes all experienced significant reductions at 12 weeks in our study population. These reductions can also be compared to previous studies of transcutaneous tibial neuromodulation where the therapy demonstrated decreases in daily episodes of voiding (1.6), urgency (2.2), and incontinence (0.8), although subjects in that trial exhibited lower baseline symptom severity than seen in the present study.¹² The improvements in diary parameters in our study are also akin to those seen in previous PTNS trials, with frequency reductions ranging from 1.7 to 2.7 voids/day and urgency incontinence reductions of 1.3-2.4 episodes per day.^{11,13,14}

OAB is a chronic condition that often necessitates lifelong therapy. Consequently, it is crucial to assess OAB treatments for long-term efficacy, tolerability, and adherence to therapy.¹⁵ Percutaneous tibial therapy typically begins with weekly sessions followed by a transition to less frequent maintenance therapy. This trial's design mirrored the PTNS paradigm. In clinical trials, 55%-80% of patients receiving initial PTNS treatment progressed to maintenance therapy,¹⁵ while real-world studies report 42%-50% progression.¹⁶⁻¹⁸ In our cohort, 50/88 patients (56.8%) advanced to the long-term trial, with 59/88 (67%) meeting the eligibility criteria and 50/ 59 (84.7%) of those eligible opting to participate. At the 12-month follow-up, 39/50 subjects (78%) completed the trial, a significantly higher rate than the 39.5% reported by Du et al for maintenance PTNS at the same time point.¹⁷ Finally, our study population demonstrated persistent improvement in diary parameters at 12 months, with a mean decrease of 1.85 UF events and 1.29 UUI episodes per day. These results are somewhat lower than those of the STEP study by Peters et al, which reported mean reductions of 3.3 voids/day and 3.0 incontinence episodes/day at 3 years.¹⁹

A key advantage of transcutaneous wearable tibial neuromodulation lies in its ability to be self-administered at home, potentially promoting wider availability and greater therapy adherence. However, previous devices intended to be used at home, necessitated precise electrode placement and monitoring of sensory or motor responses to ensure adequate target nerve stimulation, with individual anatomical variations posing challenges and limiting therapy accessibility.^{12,20-24} Moreover, nerve activation demands a minimal stimulation threshold; as the distance between the stimulation source and target increases, a higher current is required, increasing the risk of discomfort.²⁵ The Avation device addresses these concerns by integrating the stimulation source into various-sized garments designed to accommodate a wide range of anatomical features and facilitate accurate electrode placement. Importantly, the system includes an EMG sensor and proprietary algorithm,

which not only confirms successful nerve stimulation but also individualizes therapy by continuously adjusting the stimulatory output during each treatment session. Consequently, the Avation device represents the first noninvasive closed-loop tibial neuromodulation system currently available to treat bladder conditions. Finally, with at-home use, frequency of therapy can be determined by the physician and the patient, allowing therapy to be personalized and creating the ability to use the system more frequently for no additional cost.

CONCLUSION

The Avation device has shown promising therapeutic efficacy in treating the symptoms of urinary incontinence and UU caused by OAB. A significant reduction in symptom burden was observed in all diary parameters at 12 weeks. Notably, improvements remained robust out to 12 months, even with reduced frequency of therapy. The device exhibited a favorable safety profile with no severe device-related AE. High compliance and satisfaction rates were observed among patients, indicating the system's ease of use and integration into daily routines.

Wearable tibial neuromodulation has garnered interest as a noninvasive, patient-centered alternative to existing therapies, expanding treatment options and access to care. The novel, closed-loop design of the Avation device, which calibrates to the patient's EMG signal to create a personalized therapeutic range, objectively confirm nerve activation, and automatically adjust to patient movements, enables successful nerve activation and individualized therapy in the home environment. It provides a safe and effective therapy and significantly reduces barriers to patient compliance, representing a significant advancement in therapy for symptoms of OAB.

Data availability

The authors elect not to share data.

Declaration of Competing Interest

Colin Goudelocke Study Investigator Funded by Sponsor (Avation). Jennifer Sobol Study Investigator Funded by Sponsor (Avation). Denise Poulos Study Investigator Funded by Sponsor (Avation). Ekene Enemchukwu Study Investigator Funded by Sponsor (Avation). Stanley Zaslau Study Investigator Funded by Sponsor (Avation). Rohit Dhir Study Investigator Funded by Sponsor (Avation).

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