Noninvasive neuromodulation reduces symptoms of restless legs syndrome

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Study Objectives: Restless legs syndrome (RLS) is a common neurological disorder characterized by an uncontrollable nocturnal urge to move the legs and often associated with chronic sleep disturbances. The most common treatments for RLS are medications that can have debilitating side effects. Here, we evaluated a novel alternative modality of RLS treatment, noninvasive bilateral electrical stimulation of the common peroneal nerve.

Methods: To assess the impact of this noninvasive peripheral nerve stimulation (NPNS) approach to RLS symptomatology, we conducted a multisite randomized crossover study comparing NPNS to sham. RLS patients with moderate-to-severe RLS (n = 37) self-administered NPNS and sham nightly for 14 days per treatment in randomized order.

Results: NPNS resulted in a reduction in RLS severity of 6.81 points on the International RLS Rating Scale relative to 3.38 for sham (P < .01) and a 66% clinically significant responder rate on the Clinical Global Impressions-Improvement scale compared to 17% for sham (P < .01). Subgroup analysis indicated that medication-resistant and medication-naïve participants both exhibited similarly robust responses. There were no moderate or serious device-related adverse events.

Conclusions: These results suggest that NPNS could be a promising alternative to pharmacological therapies for RLS and could provide a solution for medication-resistant RLS patients and for medication-naïve RLS patients who are unwilling or unable to take medication.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Noninvasive Peripheral Nerve Stimulation for Restless Legs Syndrome; URL: https://clinicaltrials.gov/ct2/show/NCT04700683; Identifier: NCT04700683.

Keywords: restless legs syndrome, neurological disorder, sleep disorder, neuromodulation, peripheral nerve stimulation, bioelectronic


INTRODUCTION

Restless legs syndrome (RLS)—also known as Willis-Ekbom disease—is a neurological condition and sleep disorder that affects the ability to fall and stay asleep. RLS is characterized by an uncontrollable and distressing urge, often associated with uncomfortable and irritating sensations, to move the legs and often other body parts; becomes increasingly severe in the evenings and night; and can be temporarily relieved by voluntary leg movements such as walking.1 When RLS patients stop moving and attempt to go to sleep, symptom severity typically increases, thereby disrupting sleep. Ten percent of the adult population in the United States has RLS and 2% to 3% suffer from clinically relevant RLS, wherein symptoms occur more than 3 nights per week, significantly disrupt sleep, and reduce quality of life.2 The sleep disturbances associated with RLS have daytime consequences of depressed mood, irritability, forgetfulness, difficulty learning, and lack of motivation,3,4 and long-term serious health risks that include heart failure, hypertension, and diabetes mellitus.5 Psychological distress from RLS increases the risk of self-harm and suicide.6

The standard of care for RLS is dominated by dopamine agonist medications that become progressively less effective over time, induce chronic exacerbation of RLS symptoms, and are associated with debilitating side-effects.7,8 Whereas dopamine agonists have become by far the most commonly used first line of treatment due to their immediate efficacy at relieving RLS symptoms, these medications often induce augmentation, paradoxical worsening of RLS symptoms, and accelerated progression of RLS.7–10 Long-term studies have demonstrated that as many as 50% to 70% of RLS patients using dopamine agonists develop augmentation over the first 10 years of use.10
As a result, a large subset of medication-resistant RLS patients continue to suffer with clinically severe RLS despite taking dopaminergic medications. Although off-label opioids may provide relief for medication-resistant RLS, opioids are associated with well-established risks, including addiction and overdose, and there is increasing concern among patients and clinicians due to the ongoing opioid epidemic. Additionally, a large proportion of medication-naive RLS patients suffer with moderate or severe RLS symptoms because they are unwilling to risk the long-term outcomes associated with RLS medications. As a result of these shortcomings in the current standard of care, patients with RLS continue to experience substantial quality of life reductions.

Neurostimulation is a promising potential treatment for RLS. Neurostimulation has been established as a safe and effective modality of treatment for neurological conditions including chronic pain, epilepsy, tremor, and cluster headache and for sleep conditions including obstructive sleep apnea. Neurostimulation can be administered invasively via an implanted device or noninvasively via transdermal stimulation. Preliminary data suggest that invasive spinal cord stimulator implants could be effective at relieving RLS symptoms, indicating that neurostimulation could be a promising modality of treatment. However, the surgical costs and risks associated with spinal cord stimulation make it unlikely that this would become a common treatment for RLS patients. A nonimplanted transdermal neurostimulation approach could circumvent these limitations.

Here, we tested the effects of a novel nonimplanted transdermal neurostimulation approach—noninvasive peripheral nerve stimulation (NPNS)—on the severity of RLS symptoms. The NPNS system tested here consisted of wearable devices that were positioned bilaterally over the common peroneal nerve of each leg. When activated by the RLS patient each night, the NPNS system transmits electrical stimulation for 30 minutes. The common peroneal nerve innervates the lower legs and feet, the parts of the body associated with the distressing sensations and urge to move for RLS patients. This NPNS system was designed to minimize the distracting paresthesia sometimes associated with neurostimulation, phantom sensations that can feel like pinpricks and interfere with sleep onset.

**METHODS**

**Study protocol**

This randomized, participant-blinded, crossover study was conducted at 3 clinical sites in the United States. The protocol and informed consent were approved by a central institutional review board (IRB) and site-specific IRB as appropriate. All participants provided written informed consent prior to participation. Each participant was assigned to 2 weeks of active...
NPNS (“NPNS”) and 2 weeks of sham NPNS (“sham”) in randomized order (Figure 1); treatment was self-administered by participants at home. Participants were required to complete a 30-minute stimulation session at or immediately prior to bedtime each night and were given the option to self administer up to 3 additional 30-minute sessions per day as needed depending on symptom timing and severity.

Randomization and blinding
Participants were randomized to receive either an active-to-sham or sham-to-active treatment order prior to screening and consent and were not informed of their assignment. Sham mode was designed to minimize unblinding \(^{22,23}\); sham and active devices were identical in appearance, weight, visual feedback, and instructions for use. Research staff were left unblinded but were provided with standardized scripts designed to reduce unintentional bias. No participants with prior experience with any, may be temporary or continuous, and that all of these experiences were natural responses. Active stimulation consisted of a ~30-second ramp-up to the titrated intensity value at the start of stimulation, ~30 minutes at the titrated intensity, and a 10-second ramp-down at the end of stimulation. Sham stimulation consisted of the same ~30-second ramp-up to the titrated intensity value, followed immediately by a 10-second ramp-down, and 0 mA output for the remainder of the 30-minute session. This transient stimulation approach is an established method for reliably blinding sham-controlled noninvasive neurostimulation studies involving transcutaneous electric nerve stimulation and transcranial direct current stimulation devices.\(^{22,24,25}\)

Efficacy outcome measures
Efficacy was evaluated with 4 participant-rated outcome measures: IRLS (International RLS Study Group Rating Scale), Clinical Global Impressions-Improvement (CGI-I), summary
Numerical Rating Scale (NRS), and Daily NRS. The IRLS scale consists of 10 questions, each of which are scored from 0 to 4, such that the total IRLS score ranges from 0 (no RLS symptoms) to 40 (most severe possible RLS symptoms), to rate RLS symptoms for the previous 7 days. The IRLS was administered at study entry (baseline) and for week 2 of both interventions (NPNS and sham). The CGI-I is a 7-point scale, wherein the responder rate is defined as the proportion of “Very much improved” or “Much improved” responses, each of which are typically classified as clinically significant improvement. Participants completed the CGI-I after both interventions (NPNS and sham), rating RLS improvement during week 2 of each intervention relative to study entry. The CGI-I was added as an endpoint after the first 8 participants had completed the study and thus was administered to all of the final 29 participants. The Summary NRS and Daily NRS were patient ratings of acute RLS symptom severity on an 11-point numerical rating scale of the type commonly used to assess pain, where higher values represent more severe symptoms. For the Summary NRS, participants retrospectively rated the average nightly RLS symptoms for the 14 nights of in-home use for the time points “Before” (30 minutes before), “During” (10–30 minutes), and “After” (no time interval defined) each 30-minute prebedtime stimulation session. For the Daily NRS, participants completed the same scale on a daily basis each morning, rating their RLS symptoms Before (30 minutes before), During (5–30 minutes), and After (30 minutes after) their prebedtime 30-minute stimulation session for the night before.

Safety outcome measures
Safety was evaluated by assessing the frequency and severity of device-related adverse events. Adverse events were classified as device-related if they had a clear temporal relationship to device usage and/or were an anticipated outcome associated with noninvasive electrical stimulation.

Suggested immobilization test procedure
To evaluate acute response to NPNS in a controlled procedure, the 60-minute suggested immobilization test (SIT) procedure was administered at baseline with no treatment and after each 2-week intervention. For the SIT procedures after each intervention, the stimulation mode from the previous intervention (NPNS or sham) was administered for 60 minutes, throughout the SIT procedure. Each SIT procedure was conducted between the hours of 7 PM and 9 PM according to a modified protocol that required participants to maintain a stationary seated position with legs outstretched but allowed leg movements as needed to relieve RLS symptoms. Participants completed the 11-point NRS of acute RLS symptom severity at the beginning of the SIT (t = 0) and every 10 minutes thereafter.

Statistical analysis
For the efficacy outcome measures, a hierarchical test procedure (fixed-sequence procedure) was applied in the following order as specified in the protocol: IRLS, Daily NRS, Summary NRS, and CGI-I. Hierarchically ordered hypotheses were tested in sequence at a .05 significance level until first nonrejection. Once a hypothesis was not rejected, no further testing was performed. For the Daily NRS and Summary NRS, a .025 significance level was used for each of the 2 time points (During and After) to account for continued multiplicity and hierarchical testing if either of the 2 null hypotheses was rejected. The Last Observation Carried Forward method was used to impute missing data points for participants who withdrew during or after active NPNS (n = 2). Mean reduction in IRLS relative to study entry during NPNS and sham was compared using a 2-tailed matched-pairs t test. Mean reductions in NRS relative to the Before time point were compared using separate 2-tailed matched-pairs t tests. For CGI-I, the difference in responder rate to NPNS and sham was compared using a continuity-corrected paired proportions McNemar’s test. For safety outcome measures, a continuity-corrected McNemar’s paired proportions test was employed with a .05 significance level. For the NRS administered during the SIT procedure, a 2-way repeated-measures analysis of variance was used to evaluate statistical significance across the 6, 10-minute intervals. For the SIT tests that were terminated early due to intolerable RLS symptoms, data from the final segment before termination were imputed for the remaining data points. For IRLS, subgroup analysis was performed using 2-tailed matched-pairs t tests and analysis of order dependency was performed using a 2-tailed unpaired t test. For CGI-I, subgroup analysis was performed using continuity-corrected paired proportions McNemar’s tests.

RESULTS

Participant disposition
Out of 43 enrolled participants, 39 began the first intervention of the crossover and 35 completed both interventions (Figure 1). There was no difference in the number of participants who withdrew or were removed during NPNS (n = 2) compared to sham (n = 2). The modified intention-to-treat efficacy analysis population (n = 37) included all participants who began the NPNS phase, thereby excluding participants who withdrew during sham preceding NPNS (n = 2).

Participant characteristics
The average IRLS score at enrollment was 24.0. In total, 14 participants were naïve to prescription RLS medication (medication-naïve), 4 had previously discontinued RLS medication(s), and 21 had moderate-to-severe symptoms despite a stable RLS medication regimen (medication-resistant). Most medication-resistant participants were resistant to dopamine agonists (n = 16), which are the most common first-line medications for RLS and are associated with a high rate of augmentation. RLS medication profiles and demographics were similar for participants who received NPNS or sham first (Table 1). The timing of subject-reported bedtimes during the treatment period—and thus the timing of the primary session of stimulation—varied among subjects with a mean of 11:04 PM, standard deviation of 75 minutes, 90% bounds of 9 PM to 1 AM, and range of 6:45 PM to 4 AM.

Safety results
No moderate or severe device-related adverse events (AEs) were reported. All AEs—whether device-related or not—were
mild (grade 1) and resolved without medical intervention or clinical sequelaes. Moreover, the proportion of participants experiencing device-related AEs was not significantly different between NPNS and sham (25.6% vs 14.0%, P < .01).

The most common device-related AEs were uncomfortable sensations during stimulation, skin irritation associated with removing the adhesive, or a transient (nightly) increase in RLS symptoms (Table 2). Reports of uncomfortable sensations during stimulation were more common during NPNS than sham (12% vs 0%, P < .05); this AE was typically resolved by retraining on device instructions, such as reducing stimulation intensity by 5% to 10%.

Efficacy results
Treatment with NPNS reduced RLS severity, as measured by the IRLS scale, a validated patient-report measure of RLS severity.26 NPNS resulted in a reduction of 6.81 points in IRLS

Table 1—Participant demographics and medication history.

<table>
<thead>
<tr>
<th></th>
<th>NPNS First (n = 21)</th>
<th>Sham First (n = 18)</th>
<th>Total (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>54.4 (10.7)</td>
<td>57.7 (14.5)</td>
<td>55.7 (12.4)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (48)</td>
<td>7 (44)</td>
<td>17 (46)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (52)</td>
<td>9 (56)</td>
<td>20 (54)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>17 (81)</td>
<td>14 (88)</td>
<td>31 (81)</td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>1 (5)</td>
<td>2 (13)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Native American</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Indian</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>IRLS score, mean (SD)</td>
<td>24.0 (4.0)</td>
<td>24.1 (3.8)</td>
<td>24.0 (3.9)</td>
</tr>
<tr>
<td>Age of onset, years, mean (SD)</td>
<td>30.7 (18.2)</td>
<td>39.1 (17.2)</td>
<td>34.4 (18.0)</td>
</tr>
<tr>
<td>Duration of symptoms, years, mean (SD)</td>
<td>23.5 (17.6)</td>
<td>17.8 (11.6)</td>
<td>20.9 (15.3)</td>
</tr>
<tr>
<td>Parent or sibling with RLS, n (%)</td>
<td>12 (57)</td>
<td>8 (53)</td>
<td>20 (56)</td>
</tr>
<tr>
<td>RLS medication history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication-naïve</td>
<td>7 (33)</td>
<td>7 (39)</td>
<td>14 (36)</td>
</tr>
<tr>
<td>Discontinued medication(s)</td>
<td>2 (10)</td>
<td>2 (11)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Medication-resistant</td>
<td>12 (57)</td>
<td>9 (50)</td>
<td>21 (54)</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>8 (38)</td>
<td>8 (44)</td>
<td>16 (41)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3 (14)</td>
<td>0 (0)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Opioids</td>
<td>0 (0)</td>
<td>2 (11)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

IRLS = International RLS Study Group rating scale, NPNS = noninvasive peripheral nerve stimulation, RLS = restless legs syndrome, SD = standard deviation.

Table 2—Summary of adverse events.

<table>
<thead>
<tr>
<th></th>
<th>NPNS (n = 43)</th>
<th>Sham (n = 43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>11 (25.6)</td>
<td>6 (14.0)</td>
<td>.18</td>
</tr>
<tr>
<td>Device-related</td>
<td>10 (23.3)</td>
<td>6 (14.0)</td>
<td>.27</td>
</tr>
<tr>
<td>Transient increase in RLS symptomsa</td>
<td>5 (11.6)</td>
<td>2 (4.7)</td>
<td>.24</td>
</tr>
<tr>
<td>Uncomfortable sensations during stimulationa</td>
<td>5 (11.6)</td>
<td>0 (0.0)</td>
<td>.02*</td>
</tr>
<tr>
<td>Skin irritationa</td>
<td>1 (2.3)</td>
<td>4 (9.3)</td>
<td>.17</td>
</tr>
<tr>
<td>Muscle fatigue</td>
<td>1 (2.3)</td>
<td>0 (0.0)</td>
<td>.31</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>1 (2.3)</td>
<td>0 (0.0)</td>
<td>.31</td>
</tr>
<tr>
<td>Gastrointestinal distress</td>
<td>1 (2.3)</td>
<td>0 (0.0)</td>
<td>.31</td>
</tr>
<tr>
<td>Flu</td>
<td>1 (2.3)</td>
<td>0 (0.0)</td>
<td>.31</td>
</tr>
</tbody>
</table>

Incidence of each adverse event (AE) category shown in terms of number (n) and percentage (in parentheses) of participants during NPNS and sham, where (*) denotes device-related AE category, P values denote comparisons between NPNS and sham and (*) denotes statistical significance at P < .05 on a continuity-corrected paired proportions McNemar’s test. NPNS = noninvasive peripheral nerve stimulation, RLS = restless legs syndrome.
during week 2 of device usage relative to baseline (study entry),
which was significantly greater than the reduction of 3.38 points
with sham (difference of 3.43, \(P < .01, n = 37\); Table 3) and also
greater than the minimally clinically significant reduction of 3.0
points on the IRLS.\(^{29}\)

NPNS also resulted in a statistically significant increase in
responder rate, the percentage of study participants with a
clinically significant response on the patient-rated CGI-Impression scale (CGI-I), as denoted by a response of “Very much improved” or “Much improved” RLS symptoms. The
CGI-I responder rate was 66% for NPNS and 17% for sham \((P < .01, n = 29, \text{Table 3}).\)

NPNS acutely reduced RLS severity as measured by patient-reported numerical rating scale (NRS) ratings of RLS symptom severity before, during, and after each 30-minute use of the stimulation device. Relative to before stimulation, NPNS reduced RLS symptoms during stimulation by 19.5% compared to 10.5% for sham \((P < .025; \text{Table 3})\) and reduced RLS symptoms after stimulation by 52.5% compared to 34.4% for sham \((P < .025; \text{Table 3})\), as measured by the daily-rated (“Daily”) NRS. On the retrospectively rated “Summary” NRS, NPNS relative
to sham significantly reduced RLS symptoms after but not
during stimulation \((P < .025; \text{Table 3})\). These results indicate
that NPNS acutely reduces RLS symptoms immediately fol-
lowing stimulation.

There was no evidence of order dependency between the first
and second interventions in the crossover. As illustrated in
Figure 3, NPNS led to a 6.62-point reduction when adminis-
tered first and a 7.06 point reduction when administered second
\((P < .82)\), and sham was associated with a 3.29 point reduction
when administered first and a 3.50 point reduction when admin-
istered second \((P < .91)\).

Subgroup analysis based on medication history
The responses of medication-resistant and medication-naïve
participants—as defined above—were analyzed via subgroup
analysis. Medication-resistant participants exhibited a statisti-
cally significant reduction in IRLS of 7.57 points with NPNS
compared to 3.85 points for sham, a difference of 3.72 points \((P < .01\); Table 4\), and exhibited a higher CGI-I responder rate of 67% for NPNS compared to 13% for sham \((P < .05\); Table 4\).

Medication-naive participants exhibited a reduction in IRLS of 7.08 points with NPNS compared to 2.50 points for sham, a difference of 4.58 points \((P < .06\); Table 4\) and a CGI-I responder rate of 64% for NPNS compared to 27% for sham \((P < .10\); Table 4\). The effect sizes for IRLS were 0.63 for medication-resistant participants and 0.60 for medication-naive participants (Cohen’s d) and 1.18 and 0.75 for medication-naive participants (Cohen’s h).

### Suggested immobilization test results

To further investigate the timing of patient response to stimulation, we employed the suggested immobilization test (SIT), a 60-minute procedure designed to exacerbate and measure RLS symptoms.\(^28\) As illustrated in Figure 4, NPNS reduced subjective NRS ratings of RLS discomfort relative to baseline \((P < .01\) and showed a strong but nonsignificant trend towards reducing NRS scores relative to sham \((P < .06\). There was no indication that the effects of NPNS weakened with time; on the contrary, the reduction in NRS persisted throughout the 60-minute procedure.

### DISCUSSION

These results indicate that NPNS has the potential to reduce or relieve RLS symptoms when used on a nightly basis. The reduction in RLS symptom severity in response to NPNS was clinically significant; the IRLS is a well-established metric of RLS severity and the observed reduction of 6.81 points was greater than the minimally clinically significant difference of 3.0 points.\(^29\) There was no evidence of a carryover effect following 2 weeks of NPNS usage; response during sham was equivalent regardless of whether sham preceded or followed active treatment (Figure 3). Further testing is needed to determine if a longer duration of NPNS usage could result in prolonged carryover effects.

Safety analysis indicated that NPNS was well tolerated during in-home and in-clinic use. This was expected based on results for noninvasive neurostimulation devices with similar electrical output characteristics. For example, transcutaneous electric nerve stimulation and functional noninvasive electrical neuromuscular stimulation devices have been categorized as nonsignificant risk by the U.S. Food & Drug Administration.

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**Table 4**—Comparison of IRLS and CGI-I results based on medication history.

<table>
<thead>
<tr>
<th></th>
<th>Mean Change in IRLS Score</th>
<th>CGI-I Responder Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>NPNS Mean (SEM)</td>
</tr>
<tr>
<td>All participants</td>
<td>36</td>
<td>-6.81 (0.94)</td>
</tr>
<tr>
<td>Medication-resistant</td>
<td>20</td>
<td>-7.57 (1.39)</td>
</tr>
<tr>
<td>Medication-naive</td>
<td>12</td>
<td>-7.08 (1.37)</td>
</tr>
</tbody>
</table>

Subgroup analysis comparing responses of medication-resistant and medication-naive participants. \(P\) values denote comparisons between NPNS and sham and (*) denotes statistical significance at \(P < .05\); 2-tailed matched-pairs \(t\) tests were used for IRLS, and a continuity-corrected paired proportions McNemar’s test was used for CGI-I. Mean change in IRLS during NPNS and sham is relative to baseline (study entry). CGI-I = Clinical Global Impressions-Improvement, IRLS = International RLS Study Group rating scale, NPNS = noninvasive peripheral nerve stimulation, SEM = standard error of the mean.
Our results suggest that the condition of RLS does not appear to confer any significant additional short-term safety risks. Although the long-term safety and tolerability of NPNS for RLS remains to be determined, neurostimulation therapies for other chronic conditions, eg, epilepsy, chronic pain, and obstructive sleep apnea, have been widely studied over periods as long as 10 years with reports of consistent safety and tolerability.16–18

Both medication-naive and medication-resistant RLS patients exhibited comparable reductions in RLS severity in response to NPNS, as measured by the IRLS and CGI-I. Therefore, both of these patient populations could potentially experience benefits from NPNS. Although medication-naive patients have the opportunity to choose among several FDA-approved medications, they may be hesitant to do so because of the well-characterized and potentially debilitating side effects of these medications.7–10 Medication-resistant RLS patients have fewer existing options; no FDA-approved treatments are labeled for medication-resistant RLS. There is a large and growing population of medication-resistant RLS patients, resulting from gradual augmentation to the most common first-line agents, dopamine agonists.9,10 Evidence from clinical practice suggests that carefully titrated doses of opioid medications may provide relief to this patient population,11 but opioids are not FDA-approved for RLS and many patients and clinicians are hesitant to resort to opioids due to the highly publicized long-term outcomes associated with misuse, dependency, and addiction. Therefore, NPNS could provide a viable alternative for many RLS patients who are not well managed by the current standard of care, most notably the medication-resistant RLS patients.

Our results suggest that relief of RLS symptoms begins during NPNS stimulation, persists during stimulation, and persists for at least a brief period of time afterwards. Results from the Daily and Summary NRS rating scales indicate that when NPNS stimulation is administered for 30 minutes, RLS symptom reduction starts during NPNS stimulation (Table 3, During time-point) and persists after NPNS stimulation is turned off (Table 3, After time-point). Results from the SIT procedure indicate that when NPNS stimulation is administered continually for 60 minutes, RLS symptom relief persists throughout stimulation (Figure 4). Together, these data point to a mechanism of symptom relief that rapidly develops within the first 30 minutes of stimulation, persists during stimulation, and persists for at least a short period of time after stimulation.

Our instruction to use NPNS for 30 minutes at bedtime was designed to ensure tolerability and maximize clinical significance of any RLS symptom relief resulting from NPNS. We expected that 30 minutes of NPNS would be tolerable, because similar durations of neurostimulation have been well tolerated across a variety of indications and applications.32–34 Usage at bedtime was selected because the circadian timing of peak RLS symptoms tends to be in the late evening or night and we expected that bedtime use could reduce the pathological deficits in sleep initiation for the RLS patient population based on 2 assumptions. First, we assumed that symptom relief would be present primarily during stimulation, similar to the relief from voluntary leg movements and consistent with gate control theory.38 Second, we assumed that 30 minutes of RLS symptom relief would be sufficient to facilitate sleep initiation, since sleep onset latency in the healthy population (ie, in the absence of RLS symptoms) is 10 to 20 minutes.39 Consistent with this, prior research indicates that 30 minutes of treatment with a vibratory counter-stimulation device is sufficient to yield an improvement in subjective sleep quality.40 Contrary to the first assumption, we found that duration of RLS symptom relief extends beyond the duration of stimulation. This raises the possibility that a stimulation duration shorter than 30 minutes, applied at bedtime, could be sufficient to facilitate sleep initiation. We also found that the longer stimulation duration of 60 minutes employed during the SIT procedure (Figure 4) was well tolerated, and recent reports indicate that noninvasive neurostimulation can be well tolerated for 4 hours per night.41 This raises the possibility that a stimulation duration longer than 30 minutes could provide extended relief, which could help treat RLS patients who experience longer-duration symptoms throughout the afternoon and evening.

Another limitation to our approach is that the circadian timing of peak RLS symptoms varies considerably among RLS patients,35,36 and thus instructing all patients to use the device at bedtime may not be optimal. Instead, providing personalized instructions for timing of use based on circadian timing of symptom onset or peak symptoms could enhance the clinical significance of patient response to NPNS. Further investigation is needed to determine the optimal duration and timing of stimulation.

The stimulation parameters of this NPNS approach may also have contributed to its tolerability and efficacy when administered at bedtime. Stimulation parameters were designed and calibrated to transmit maximal stimulation intensity—thereby potentially increasing efficacy while allowing for comfortable self-administration without distracting paresthesia—thereby potentially increasing tolerability during bedtime usage. In contrast, alternative neurostimulation approaches such as spinal cord stimulation21 or transcutaneous electric nerve stimulation devices typically induce distracting paresthesia that could interfere with sleep onset and thus preclude bedtime usage.

The specific electrode positioning and putative nerve target of this NPNS approach may have contributed to its efficacy. Stimulation electrodes were positioned over the common peroneal nerve, which provides sensory and motor innervation to the lower legs and feet, the regions of the body most commonly associated with subjective RLS symptoms. Inspired by the gate control theory of pain,38 one plausible mechanism of action is that NPNS activates sensory nerve fibers in the peroneal nerve to suppress pathological neural signals originating in the peripheral nervous system at the level of the spinal cord. A similar mechanism could explain why walking, which activates proprioceptive nerve fibers in the legs, often results in short-lived relief of RLS symptoms.43 An alternative or complementary possibility is that NPNS suppresses pathological neural signals in the brain by transmitting signals through the ascending sensory pathways. Consistent with this possibility, recent literature suggests that the pathological basis of RLS may be located primarily in the brain instead of the peripheral nervous system.44 Further investigation will be needed to distinguish between these potential mechanisms.
Significant precautions were taken to ensure that subjects remained blinded to the assignment of sham or active treatment. In accordance with best practices for blinding medical device treatments, active and sham NPNS devices were visually and physically identical and provided identical visual feedback cues during operation. Neurostimulation devices are often associated with paresthesia, abnormal sensations localized to the skin around the site of active stimulation, which can be more noticeable with active stimulation than for sham stimulation. In accordance with specific best practices for blinding neurostimulation interventions, both active and sham modes included a transient ramp-up in stimulation intensity at the beginning of each stimulation session during which sensations were noticeable and a standardized script instructed participants that the nature and duration of sensations during stimulation, if any, may be temporary or continuous. Despite these precautions, one limitation of this study is that these paresthesias may have contributed to unblinding for some subjects.

The magnitude of the placebo response in clinical trials for RLS therapeutic interventions tends to be large but varies widely depending on study design and outcome measure. For the endpoint used here—mean reduction in IRLS—a meta-analysis indicates that the effect size (Cohen’s d) in published clinical trials varies from 0.04 to 2.67 and is the lowest for crossover trial designs and trials with relatively short durations. Consistent with this meta-analysis, the placebo effect size in this crossover study (0.58) was on the lower end of this range but was similar to the 2 other published studies with a crossover design, which reported placebo effect sizes of 0.04 (Adler et al) and 0.30 (Kushida et al) on the IRLS. The absence of drug washout in our study may have also contributed to the relatively low placebo response effect size. Clinical trials for RLS medications often require cessation of concurrent RLS medications shortly prior to the study, which—in the case of the commonly prescribed dopamine agonist medications—can lead to withdrawal that gradually subsides over weeks to months. Such a gradual reduction in withdrawal during a clinical study could boost the placebo response in a manner similar to regression to the mean. Most importantly, due to the variation in placebo response among RLS clinical trials, it is critical to show statistical superiority to sham, as we have shown here.

There are a few limitations related to the eligibility criteria for this study. First, this study enrolled patients with a varied medication history, including medication-naive, medication-resistant with concurrent medication, or medication-resistant without concurrent medication. Although the results in Table 4 suggest that there may be response similar to NPNS for medication-naive and medication-resistant RLS patients, the study was not powered for stratified analysis of these subgroups, and response may be lower for some medication histories or concurrent medications. Second, the study relied on patient-reported medical history information for screening and could have been strengthened by the following tests during screening: an overnight polysomnography test to rule out undiagnosed comorbid sleep disorders and assess periodic limb movements of sleep, nerve conduction tests to rule out iron-deficient anemia.

In conclusion, these results provide compelling preliminary evidence suggesting that NPNS has the potential to provide relief of RLS symptoms for both medication-resistant and medication-naive RLS patients. Further research will be needed to assess the longer-term efficacy and tolerability of NPNS in a larger patient population, to optimize the instructions for NPNS use, to assess the real-world effectiveness of this treatment modality, and to determine whether NPNS can improve sleep quality for patients with RLS.

**ABBREVIATIONS**

AE, adverse event
CGI-I, Clinical Global Impressions-Improvement
FDA, U.S. Food & Drug Administration
IRLS, International RLS Study Group rating scale
NPNS, noninvasive peripheral nerve stimulation
NRS, numerical rating scale
RLS, restless legs syndrome
SIT, suggested immobilization test

**REFERENCES**


Noninvasive neuromodulation reduces RLS symptoms


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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at Mark J. Buchfuhrer private practice, Downey, CA; Center for Health Sciences, SRI International, Menlo Park, CA; Sleep Medicine Specialists of California, San Ramon, CA; and Noctrix Health, Inc., Oakland, CA. Dr. Buchfuhrer is a consultant and scientific advisor for Noctrix Health, Inc.; Dr. Singh is a consultant for Noctrix Health, Inc.; Dr. Charlesworth, Dr. Raghunathan, and Ms. Kolotovska are currently employed by Noctrix Health, Inc. and have received financial support from NIH R44NS117294 for work unrelated to this study. The other authors report no conflicts of interest.