Targeted Pressure on Abductor Hallucis and Flexor Hallucis Brevis Muscles to Manage Moderate to Severe Primary Restless Legs Syndrome

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Video commentary from Dr Kuhn is available online.

Context: Restless legs syndrome (RLS) treatments have included medications with many adverse effects and limited utility. A noninvasive device would potentially have extensive use where RLS medications may not be appropriate, such as in pregnant or breastfeeding women, people with mild RLS, people who operate machinery or drive occupationally, people with severely impaired renal function, or people who are taking medications contraindicated with RLS medications.

Objective: To assess the efficacy and safety of a device that produces targeted pressure on the abductor hallucis and the flexor hallucis brevis muscles to reduce the symptoms of moderate to severe RLS, and to compare the current findings with findings from studies of ropinirole use in patients with primary RLS.

Methods: This 8-week single-arm, open-label, clinical trial with a repeated measures design was conducted between April 2009 and August 2012 in 2 offices in Erie, Pennsylvania. Adults with moderate to severe primary RLS were recruited for the study. Mean (SD) follow-up was 15.6 (6) months. Patients wore RLS devices (1 on each foot) for set periods intermittently throughout the course of the study. The primary end point was mean change in the International Restless Legs Syndrome Study Group (IRLSSG) Rating Scale from baseline to day 56, and the secondary measure was the Clinical Global Impression scale. A meta-analysis was used to compare the RLS device findings with the findings of 3 historic studies of ropinirole vs placebo. The demographics, disease severity, inclusion and exclusion criteria, and assessment tools were similar among the 4 studies.

Results: Thirty patients (22 women, 8 men; mean age, 51.5 years [range, 30-75 years]) participated in the study. Change in mean (SD) IRLSSG score was significantly greater for the RLS device (17.22 [6.16]; $P<.001$) compared with the ropinirole vs placebo findings (12 [0.86] vs 8.9 [0.86], respectively; $P<.05$). Sleep loss significantly decreased from 119.5 (61.6) minutes to 22.1 (31.1) minutes per night ($P<.001$). Global Improvement Scale scores indicated significantly greater improvement with the RLS device compared with ropinirole (27 of 30 [90%] vs 293 of 464 [63%], respectively; $P<.05$). Mild, transient adverse effects of the device (eg, pain, paresthesia) were reported, but these effects were relieved by loosening the straps. The RLS device demonstrated none of the adverse effects associated with current dopamine agonist therapy, such as augmentation, tolerance, rebound, somnolence, and nausea.

Conclusion: Producing targeted pressure on the abductor hallucis and flexor hallucis brevis muscles with an external RLS device reduced the symptoms of moderate to severe primary RLS without the adverse effects of medication therapy. (ClinicalTrials.gov number NCT02386423.)

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Restless legs syndrome (RLS), or Willis-Ekbom disease, is a neurologic disorder causing unpleasant sensations and an urge to move the legs when at rest. The sensations are relieved by movement. The loss of sleep associated with RLS can cause extreme fatigue, which may affect concentration and may in turn lead to anxiety and depression, resulting in a poor quality of life.[1]

The prevalence of RLS varies depending on geographic location, inclusion criteria, and other factors. In the United States, the prevalence ranges from 5% to 10%.[2] With the population estimated at 306 million, the number of people in the United States with RLS ranges from 15 to 30 million, and those with moderate to severe symptoms, 9 million. Restless legs syndrome disproportionally affects women[2]; the incidence in women is estimated to be twice as high as that in men. Although symptoms can manifest at any age, moderate to severe cases often manifest in people middle-aged or older, with symptoms increasing with increasing age.[2] In approximately 3% of people with RLS, the symptoms are so severe that they seek treatment.[3] Potent medications, such as opioids, central nervous system depressants, anticonvulsants, and dopamine agonists have been used to ease symptoms, each with adverse effects.[4,5] Reports on the efficacy of nonpharmacologic therapies, such as sequential compression devices, are emerging.[6]

An RLS device in the form of a foot wrap was designed to put adjustable targeted pressure on the abductor hallucis and the flexor hallucis brevis muscles in the foot (*Figure 1*). Anecdotal evidence suggested that pressure on these muscles reduced the symptoms of RLS. The device was cleared by the US Food and Drug Administration as a Class 1 device (the lowest risk category, because of the mild and transient adverse effects) in December 2013 to reduce the symptoms of RLS. The purpose of this study was to determine the efficacy and safety of this device in reducing the symptoms of moderate to severe RLS.

Methods

This study was approved by the Institutional Review Board of Saint Vincent Health Center in Erie, Pennsylvania. Three clinicians (2 podiatrists [including D.J.O.]; and 1 neurologist [J.P.S.]) explained the study to each patient and then obtained his or her informed consent. The investigators and participants were masked to all summary results and outcomes. All data were collected, stored, and summarized off-site. Because the patients applied and removed the device and the clinicians were monitoring the patients, masking the intervention to the patients and clinicians was not feasible.

Inclusion and Exclusion Criteria

Otherwise healthy adults between the ages of 18 and 75 years, in whom moderate to severe primary RLS was diagnosed, were recruited from Erie and the surrounding locations by newspaper, television, and radio ads; flyers in the waiting room; and by the clinicians themselves. Each patient was examined by a neurologist or 1 of the 2 podiatrists experienced in diagnosing RLS. Patients were screened using medical history, the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria,[7] and the IRLSSG Rating Scale, a validated survey with high interexaminer reliability.[8] Inclusion criteria included the following: (1) a total score of 15 or greater on the IRLSSG Rating Scale; (2) self-reported evening and nighttime symptoms with sleep impairment due to RLS; and (3) RLS for at least 6 months with symptoms at least 2 to 3 times per week. At least 12 and as many as 42 episodes of RLS per patient were anticipated during the study period.

Patients were excluded if they were pregnant or had any serious medical conditions, conditions that presented a safety concern, or conditions that affected efficacy assessment, such as taking medications known to affect RLS (eg, antidepressants). Disqualifying medical conditions included but were not limited to claudication; diabetes mellitus; fragile, thin skin; impaired wound healing; inability to sit still or remain motionless; injury

Figure 1.
This restless legs syndrome device is a foot wrap that puts adjustable and continuous targeted pressure on the abductor hallucis and the flexor hallucis brevis muscles on the medial and plantar aspect of the feet. An outer cloth wrap supports and holds the pressure pad in place. The cloth wrap is held in place by hook and loop straps, which allow application and retention of adjustable pressure.

to feet or legs; involuntary movements similar to a tic; movement problems; narcolepsy; nerve problems; nighttime discomfort not due to RLS; obstructive sleep apnea; parasomnias involving abnormal movements; Parkinson disease; poor circulation; secondary RLS; and sleep disorders. Patients taking medication for RLS must have discontinued treatment for at least 30 days before the start of the study.

Study Design and Intervention

This single-arm, open-label clinical trial with a repeated measures design was conducted between April 17, 2009, and August 12, 2012, in 2 office settings in Erie, Pennsylvania. We incorporated a unique trial design to circumvent the inherent problems with RLS studies (ie, extremely high placebo effect) and to keep the patients safe from adverse effects associated with medication therapy and a potential tripping hazard from a sham device. After data were collected and analyzed, results were compared with baseline and after periods without the device, as well as with results of a meta-analysis of 3 national and international studies that were similar in patient demographics, disease severity, inclusion and exclusion criteria, and assessment tools.[9-11]

Restless legs syndrome devices (restiffic, mediUSA) were administered, 1 on each foot, intermittently throughout the course of the study for set periods:

A: 1-week baseline period without the devices (days 1-7)
B: 3 weeks of initial testing with the devices (days 8-28)
C: 1-week without the devices (days 29-35)
D: 3 weeks of subsequent testing with the devices (days 36-56).

On day 8, patients were instructed on the application of the RLS device and checked by a study administrator to ensure that the devices were correctly applied. Patients were instructed to start with slight pressure for the first hour and, if their symptoms did not resolve, to increase pressure in small increments until symptoms were alleviated. They were told to watch for circulation problems; in case of pain, numbness, or tingling or if the foot or toes turned purple, immediate loosening or removal of the device was advised.

Patients were instructed to put the device on both feet after RLS symptoms occurred in the evening, when they were relaxing, or after they had gone to bed and only during periods B and D. The patients were instructed to remove the device after symptoms had resolved completely or in the morning, whichever came first. The time of day could vary depending on the occurrence of symptoms and the patients' work schedule (ie, first, second, or third shift). Patients were instructed to only wear the device when off their feet. Examples included going to bed, sleeping, lying down, sitting, reading, watching television, or riding in a vehicle or airplane.

Outcome Measures

The main and secondary outcome measures were the IRLSSG Rating Scale[8] and Clinical Global Improvement (CGI) Scale,[12] respectively. To be included in the final analysis, patients had to have completed at least 1 cycle of device wear (period B) and undergone at least 2 CGI evaluations to allow for comparisons.

IRLSSG Rating Scale Scores

Patients completed a series of 22 surveys: 3 times during period A; 8 times during period B; 3 times during period C; and 8 times during period D. Each survey had 10 questions, each rated by severity of symptoms as 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe). The scores were added to determine the severity of RLS: 1-10 (mild), 11-20 (moderate), 21-30 (severe), and 31-40 (very severe). Mean IRLSSG Scores were reported on the initial day and the final study day. The difference between the initial RLS device score and the final score for each patient and then the aggregate population was determined. Calculating mean scores on days 1 and 56 allowed direct comparisons with historic data[9-11] by periods at baseline without the device, during the initial test period with the device, after the initial test period without the device, and during the second test period with the device for both the individual patient and for the aggregate population.

Descriptive statistics were used to determine IRLSSG score means and SDs for each period. A paired *t* test, (α=.05) was used to determine significant differences among the groups. By calculating mean IRLSSG scores within each period, more data points were collected, decreasing variability over time (by survey days). Descriptive statistics were used to calculate the mean and SD IRLSSG score for each of the 22 survey days.

In addition, we identified studies on the use of ropinirole, a dopamine agonist, and placebo and their effects on RLS symptoms. Each ropinirole study[9-11] was examined to determine the initial, final, and change in mean IRLSSG scores for ropinirole and placebo. A meta-analysis (Meta-Analysis, Biostat) was used to combine IRLSSG scores of the 3 ropinirole and placebo arms. These studies were all sponsored by industry and had similar demographics, inclusion and exclusion criteria, disease severity, interventions, assessment tools, and outcomes. Therefore, the heterogeneity was very low, providing a high level of confidence that these studies could be combined.

The change in mean IRLSSG scores with the RLS device was compared with the change in mean IRLSSG scores for ropinirole and placebo by meta-analysis. By comparing the changes, the effects of different length of treatment, treatment timing, and end points were negated. A 2-sample *t* test (α=.05) was then used to determine differences among the RLS device, ropinirole, and placebo pill.

CGI Scale

The clinicians completed 4 CGI Scales,[12,13] 1 each on days 1, 29, 36, and 57. On the last day of the study (day 57), patients were interviewed by phone by a clinician who completed the final CGI and inquired about any adverse events. Descriptive statistics were used to analyze CGI Scale scores. The severity and improvement from baseline were compared with results at the end of the study. The number of responders (percentage of patients much improved or very much improved by study end) were also determined. The therapeutic effect ranged from 1 (unchanged or worse) to 4 (vast improvement). The adverse effect ranged from 1 (none) to 4 (outweigh therapeutic effect). A matrix of therapeutic effect vs adverse effect was created to determine the efficacy index. The efficacy index ranged from 0.25 (therapeutic effect: unchanged or worse; adverse effects: outweigh therapeutic benefit) to 4 (therapeutic effect: vast improvement or nearly complete remission of all symptoms; no adverse effects).

The RLS device CGI Scale scores were compared with the historic controls by χ^2 analysis (α=.05). Responders in the ropinirole studies were compared with responders in the RLS device study by χ^2 analysis (α=.05).[9-12] Of note, the efficacy index and severity were not reported in the historic controls, negating comparisons.

Safety

Adverse effects were monitored and documented by the clinicians during examinations at each visit. Also, all patient-reported problems were documented. All information on all adverse effects was collected and analyzed for severity and relation to RLS device and compared with the ropinirole studies using descriptive statistics.

Follow-up Survey

A survey comprising 17 questions (10 from the IRLSSG Rating Scale and 7 additional questions) was conducted by telephone and mail at a mean (SD) of 16.8 (6) months (range, 8.4-28.8 months) after study completion. Results of the initial survey were compared with the results of the final survey by *t* test (α=.05).

Statistical Analysis

Enrollment of at least 30 patients was used to account for dropouts and to ensure that 6 patients were included in the final analysis. PASS 11, a power analysis program by NCSS Statistical Software, was used to perform the power analysis, with α=.05 and a power of 90%. Assuming a mean difference of 10 to 15 from the beginning of the study to the end (actual difference, 17.2) and an SD of 5.3 (derived from the actual value at baseline), a sample size of 6 control and 6 test patients (single arm, 6 total) was calculated to be sufficient to provide 90% power to detect a difference of 10 to15 points between baseline (no device) and active treatment (device) on the IRLSSG rating scale, with a .05 significance level. This study was a modified intent-to-treat protocol. All patients were included, but some were excluded in the final analysis. To address missing data, a last observation carried forward method of accounting was used (ie, if a patient dropped out of the study before it ended, then the last observed score on the dependent variable was used for all subsequent missing observation points). A *P* value ≤.05 was considered statistically significant.

Results

Of 132 patients who were screened by phone, 47 were enrolled, 36 received the intervention, and 30 otherwise healthy adults (22 women and 8 men; mean age, 51.50 years [range 30-75 years]) were included in the final analysis (*Table 1* and *Figure 2*). No patients had been taking medication for RLS.

Outcomes

IRLSSG Rating Scale

The RLS device proved highly effective, with overall mean (SD) IRLSSG scores decreasing significantly, from severe 25.05 (5.33) on the initial study day to mild 7.83 (6.33) on the final study day, for a mean (SD) difference of 17.22 (6.16) (SD of the population [95% CI], 2.22 [14.92-19.52]; *P*<.001). Of note, the initial and final scores for each question were significantly different (*P*≤.05) (*Table 2* and *eTable 1*).

A statistically significant decrease was found in the mean (SD) severity of sleep disturbance, from 2.7 (0.8) (moderate) to 0.6 (0.7) (mild). At baseline, patients reported losing about 2 hours of sleep because of RLS, and on the final testing day, they reported losing 22 minutes of sleep (*P*<.001) (*eTable 1*).

When reported by periods, the IRLSSG scores decreased significantly from 24.7 (severe) to 9.2 (mild) or 2 levels of improvement by study end (*P*<.05) (*eTable 1*). Comparison of the results from each period disclosed that each period was significantly different from the other periods (A vs B, *P*<.001; A vs C, *P*<.001; A vs D, *P*<.001; B vs C, *P*=.012; B vs D, *P*=.011; C vs D, *P*<.001; A+C vs B+D, *P*<.001). The RLS device resulted in a statistically significant decrease in the IRLSSG scores; removal of the device caused a statistically significant increase. In the first 24 hours of application of the RLS device, the mean IRLSSG score decreased from 24.53 to 16.63, and the score continued to decrease during the second treatment period, demonstrating a residual effect. The intermittent application showed improvement with the device and worsening without it (*Figure 3*).

A statistically significant difference in change in mean IRLSSG scores was found between RLS device and ropinirole (*P*<.001), as well as the RLS device and placebo (*P*<.001) (*eTable 2* and *Figure 4*).[9-11] The device was approximately 1.44 times as effective as ropinirole and twice as effective as the placebo in reducing RLS symptoms. No differences were seen in the baseline IRLSSG scores for ropinirole, placebo, and RLS device (*P*>.05).

Table 1.
Patient Demographics and Mean (SD) IRLSSG Scores by Periods Wearing and Not Wearing the RLS Device[a]

Patient No.; Sex; Age, y	Without Device, A (Days 1-7)	With Device, B (Days 8-28)	Without Device, C (Days 29-35)	With Device, D (Days 36-56)	Decrease
001F37	25.67 (0.58)	16.00 (7.60)	20.33 (0.58)	13.75 (8.68)	11.92
002F34	27.00 (0)	21.25 (3.81)	13.00 (4.36)	NA	14.0
003F63	25.67 (3.06)	12.25 (1.83)	16.00 (3.46)	9.13 (3.64)	16.94
004M59	35.33 (2.08)	32.25 (8.38)	39.00 (1.73)	28.38 (12.57)	6.96
005F42	25.67 (0.58)	16.25 (2.31)	22.50 (0)	13.00 (0)	12.67
008M43	36.67 (0.58)	11.00 (0)	33.00 (0)	13.00 (0)	23.67
010F69	26.33 (1.15)	11.63 (5.80)	8.00 (0)	2.00 (0)	24.33
011F35	18.33 (1.15)	9.13 (3.76)	5.00 (4.36)	2.50 (1.69)	15.83
012F56	19.33 (0.29)	2.38 (2.33)	9.67 (1.15)	10.88 (1.36)	8.45
013M49	21.00 (0)	19.75 (1.16)	22.00 (0)	11.88 (1.77)	9.13
014F32	24.00 (1.73)	12.75 (4.40)	25.00 (0)	0	24.00
015F46	21.00 (9.54)	10.13 (8.56)	18.67 (3.79)	5.00 (4.63)	16.00
018F50	19.00 (2.00)	14.50 (0.53)	12.00 (0)	11.88 (0.35)	7.12
019F44	28.00 (0)	24.50 (1.60)	26.50 (0.50)	22.25 (0.71)	5.75
020F56	17.00 (0)	0	8.67 (8.50)	4.13 (5.30)	12.87
021F57	24.00 (0)	19.25 (4.80)	17.00 (0)	10.63 (3.34)	13.37
024F62	28.33 (1.15)	19.38 (5.32)	27.33 (0.58)	21.00 (4.87)	7.33
030F52	32.00 (2.00)	22.50 (5.73)	28.33 (1.15)	15.25 (1.98)	16.75
031F50	33.00 (0)	16.38 (3.96)	8.67 (7.51)	0	33.00
033M40	17.67 (0.58)	10.25 (0.46)	19.00 (0)	10.38 (1.06)	7.29
035F75	29.00 (0)	12.75 (7.13)	19.00 (12.7)	4.25 (2.38)	24.75
038M59	22.00 (0)	11.88 (3.31)	10.00 (0)	8.31 (2.52)	13.69
039F61	22.00 (3.61)	1.25 (2.05)	8.00 (3.46)	2.38 (1.06)	19.62
041F62	20.33 (5.77)	8.25 (7.46)	12.33 (1.15)	10.50 (3.96)	9.83
042F42	18.33 (0.58)	6.13 (3.36)	16.67 (1.15)	6.13 (3.68)	12.20
043M75	30.33 (2.08)	14.63 (6.80)	28.33 (1.53)	11.88 (1.25)	18.45
044M49	23.67 (2.89)	3.00 (0)	25.00 (0)	0	23.67
046F36	16.33 (4.93)	16.13 (5.25)	9.33 (4.04)	3.00 (3.21)	13.33
047F51	32.33 (0.58)	18.50 (7.63)	21.33 (2.31)	8.25 (4.50)	24.08
049M57	26.67 (1.15)	21.75 (3.54)	26.00 (2.00)	20.13 (2.23)	6.54
Total	**739.67**	**394.50**	**516.33**	**246.94**	**453.54**
Mean (SD)	24.66 (2.15)	13.60 (3.16)	18.44 (3.05)	9.15 (2.85)	15.51 (6.96)

[a] International Restless Legs Syndrome Study Group (IRLSSG) Rating Scale scores 0 (no symptoms); 1-10 (mild); 11-20 (moderate); 21-30 (severe); and 31-40 (very severe).

Abbreviation: NA, not available; RLS, restless legs syndrome.

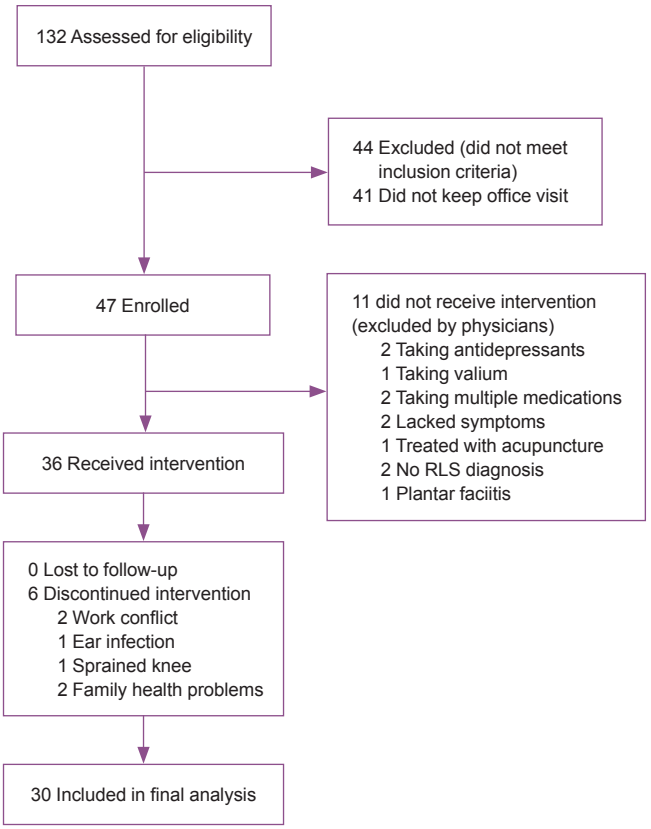

Figure. 2.
Flow diagram for the restless legs syndrome device clinical trial.

CGI Scale

This instrument comprises a severity scale, improvement scale, and efficacy index (adverse effects vs therapeutic efficacy). By clinician observation, 29 of 30 patients (97%) had a decrease in severity, and severity in 25 of 30 (83%) decreased 2 or more levels. All patients improved. Symptoms were "much improved" or "very much improved" in 27 of 30 patients (90%) by the end of the study. These patients were designated as responders.[9-11] A statistically significant increase in responders was found in the RLS device study compared with ropinirole and placebo studies (27 of 30 [90%] vs 293 of 464 [63%] vs 218 of 467 [47%], respectively; $P<.05$).

Eighteen of 30 patients (60%) scored an efficacy index of 4 (vast improvement, no adverse effects); 8 of 30 (27%) scored 3 (moderate improvement, no adverse effects); 2 of 30 (7%) scored 2 (minimal or slight improvement, no adverse effects); 1 of 30 (3%) scored 2 (vast improvement, adverse effects did not interfere with functioning) and 1 scored 1.5 (moderate improvement, adverse effects did not interfere with functioning).

Adverse Effects

Seven patients had adverse effects related to the device. These effects included pain (2), paresthesia (2), irritability (3), spasm (1), and a local complication of warm feet (1). All adverse effects resolved when the device was loosened. Other mild adverse effects reported resolved spontaneously.

Several severe and some potentially life-threatening adverse effects, including somnolence, worsening of symptoms, dosage augmentation, rebound, and nausea have been noted with dopamine agonist use.[9-11,14,15] The RLS device demonstrated none of the adverse effects associated with the current medications used for RLS. The adverse effects associated with medication may limit its usefulness in many patients, including those who drive or operate heavy equipment, those with mild RLS, and women who are breastfeeding.

Follow-up Survey

Seventeen of 30 patients (57%) responded to the follow-up survey (*Table 2)*. At long-term follow-up, the RLS device proved highly effective, decreasing mean IRLSSG scores from severe to mild. Fourteen respondents reported their symptoms were less; 2, the same; and 1, no answer. Eleven of the 17 respondents reported no problems wearing the device. Sixteen would recommend the device. Four patients reported complete remission of symptoms; 8 reported still wearing the device, but less frequently and for a shorter duration. Twelve respondents rated the device as either a 9 or 10 on a 10-point scale, with 10 being "best."

Table 2.
Ratings of RLS Symptoms at Baseline, on Final Study Day, and at Follow-up After Wearing the RLS Device[a,b]

Question	Baseline	Final	Follow-up[c]
1. Overall, how do you rate the discomfort in your legs due to RLS?	2.7 (0.7)	0.8 (0.7)	1.0 (0.87)
2. Overall, how would you rate the need to move around because of your RLS symptoms?	3.1 (0.8)	0.7 (0.7)	1.03 (1.10)
3. Overall, how much relief of your RLS discomfort do you get from moving around?	2.7 (0.8)	1.1 (1.2)	1.41 (1.18)
4. Overall, how severe is your sleep disturbance from your RLS symptoms?	2.7 (0.8)	0.6 (0.7)	0.79 (0.81)
5. How severe is your tiredness or sleepiness from your RLS symptoms?	2.4 (0.7)	0.5 (0.6)	0.76 (0.75)
6. Overall, how severe is your RLS as a whole?	2.8 (0.7)	0.8 (0.6)	0.97 (0.87)
7. How often do you get RLS symptoms?	3.0 (0.9)	1.5 (1.2)	1.29 (1.0)
8. When you have RLS symptoms, how severe are they on an average day?	2.4 (0.7)	0.9 (0.8)	1.12 (0.76)
9. Overall, how is the impact of your RLS symptoms on your ability to carry out your daily affairs, eg, carrying out a satisfactory family, home, social, or work life?	1.6 (0.7)	0.5 (0.6)	0.53 (0.80)
10. How severe is your mood disturbance from your RLS symptoms, eg, angry, depressed, sad, anxious, or irritable?	1.6 (0.9)	0.6 (0.7)	0.35 (0.61)
Total IRLSSG Score[d]	**25.1 (5.3)**	**7.8 (6.3)**	**9.26 (0.33)**

[a] Data are given as mean (SD).
[b] Ten questions were each scored as 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe).
[c] Seventeen of 30 patients (57%) responded to the follow-up survey, completed at a mean (SD) of 15.6 (6) months.
[d] IRLSSG scores: 0 (no symptoms);1-10 (mild), 11-20 (moderate), 21-30 (severe), and 31-40 (very severe).

Abbreviations: IRLSSG, International Restless Legs Syndrome Study Group; RLS, restless legs syndrome.

Discussion

Mechanism of Action

We theorize that patients with RLS have a mild dopamine dysfunction in the afferent nerve pathway that signals pain or irritation. The brain interprets the signals and instructs the muscles to contract. The contraction, in turn, produces pain or irritation, again signaling the brain to instruct continued or increased contraction, producing continued pain or irritation. Movement disrupts the contraction and produces temporary relief (*Figure 5*).

We believe that continued pressure on the abductor hallucis and flexor hallucis brevis muscles throughout the evening signals the brain to relax rather than contract the muscles, acting as a counter-stimulant. This theory represents a new and unique mechanism of action to suppress the symptoms of RLS. Pressure produced by the RLS device on the muscles may also stimulate a

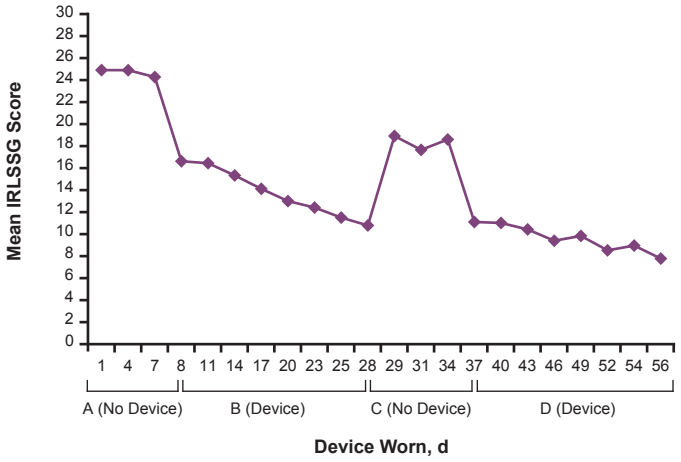

Figure 3.
Mean International Restless Legs Syndrome Study Group (IRLSSG) Rating Scale scores over time. Study Group (IRLSSG) Rating Scale scores: 0 (no symptoms); 1-10 (mild); 11-20 (moderate); 21-30 (severe); and 31-40 (very severe).

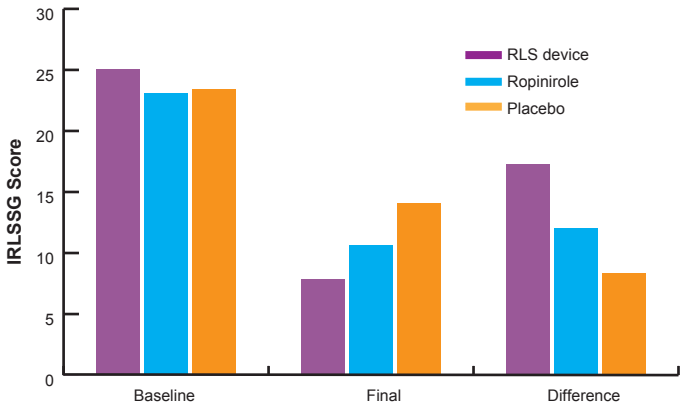

Figure 4.
Baseline and final International Restless Legs Syndrome Study Group Rating Scale scores in patients with restless legs syndrome (RLS) wearing the RLS device (N=30) or taking medication for RLS (ropinirole vs placebo; N=380,[9] N=284,[10] N=266[11]). Rating Scale scores: 0 (no symptoms); 1-10 (mild); 11-20 (moderate); 21-30 (severe); and 31-40 (very severe).

dopamine release, similar to massage therapy or acupressure. In a study of sequential compression devices that wrap the lower portion of the legs, Eliasson and Lettieri[6] reported a statistically significant decrease in IRLSSG scores. Their study, which was an uncontrolled prospective study using a convenience sample of adults, had a small sample size (N=9). However, findings such as these lend support to the theory that pressure on targeted regions causes the muscles to relax, decreasing RLS.

The RLS device in the current study exemplifies the underlying philosophy of the tenets of osteopathic medicine—the body is a unit and is capable of self-healing.[16] Pressure on the foot caused responses in the brain, which, in turn, relaxed the muscles in the leg, leading to a decrease in symptoms of moderate to severe RLS.

Ropinirole Safety

After ropinirole was marketed to larger numbers of patients, the safety profile changed. Somnolence (and falling asleep while driving), rebound, and compulsive behavior became problematic, resulting in several lawsuits.[9]

In many cases, prolonged medication use led to dosage tolerance, which required regular increases in the dose to manage symptoms.[14,15] Although tolerance can occur with several medications used to treat RLS, dopamine therapy is associated specifically with dosage augmentation.[17]

Placebo Effect

A large placebo response has been observed in RLS studies, ranging from 40% to 75% in some clinical RLS trials.[9-11,13,17] Fulda and Wetter[17] noted that "This unique responsiveness of RLS to both dopaminergic agents and opioids places it at the crossroad of the 2 systems implicated in the placebo response."[17] In control groups, endogenous upregulation of dopamine and opioids mediated by belief alone can obfuscate results.[18] In the 3 ropinirole studies, the placebo pill was 75% as effective as ropinirole.

True-negative controls are lacking in most RLS studies but are needed because of the extreme placebo response.[17,18] Excessive placebo response can confound results and, in some studies, obscure test/placebo differences when true differences exist.[18] If the RLS device responses were solely mediated by a placebo effect, the RLS devices' IRLSSG score would have improved no more than 8 points, as seen in the 3 ropinirole studies[9-11]; instead, it improved 17 points.

Limitations

When a meta-analysis is used, several opportunities for bias exist, particularly if studies are selected that prejudice the results toward a particular conclusion. Publication bias can occur when research underrepresents the population of completed studies. Bias can be minimized when the instruments of measure are standardized, measuring specific outcomes across studies.[20] Risk of bias in a review should be assessed regardless of variability. The low heterogeneity among the 4 studies we compared diminished publication bias.

The lack of a sham device or control was a limitation. Loosening the straps to produce a sham device control could have caused a potential tripping hazard. A study on ClinicalTrials.gov revealed that device studies using a sham were rare, representing 0.4% (65 of 15805) of all studies reported.[19] When practical considerations prevent running a sham control, the current standard of care or best medical therapy is commonly used, which in this case, was ropinirole.[19] Because ropinirole had been extensively studied, results of 3 of the largest national and international drug trials comprising 931 patients were used as a historic control for comparison with the RLS device.[9-11] Using historic controls spared the patients exposure to a myriad of adverse effects of ropinirole.

Future studies are needed using a modified device in controlled double-blinded conditions with the incorporation of true negative controls (no placebo device or medication). Magnetic resonance imaging studies and measurement of dopamine levels would also be helpful in elucidating the mechanism of action, but those measures were beyond the scope of the current study.

Conclusion

Targeted pressure on the abductor hallucis and the flexor hallucis brevis muscles with the RLS device was almost twice as effective as historic placebo medication and 1.4 times as effective as ropinirole in lowering IRLSSG scores, with none of the adverse effects associated with current medications for RLS.

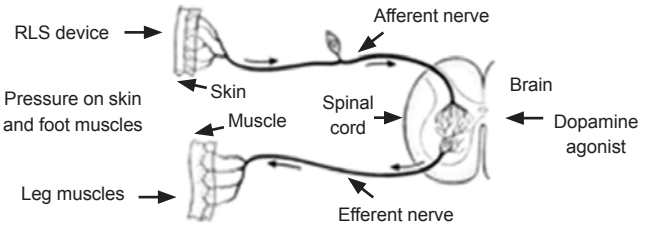

Figure 5.
Proposed mechanism of action. The restless legs syndrome device works on foot muscles, and the dopamine agonists target the brain. Both lead to the relaxation of leg muscles.

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Author Contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; all authors drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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eTable 1.
IRLSSG Scores in Patients With Moderate to Severe RLS at Baseline and After Periods of Wearing a Device (n=30)[a]

Outcome Measure	Baseline	Difference	Final
Mean (SD)	25.05 (5.33)	17.22 (6.16)	7.83 (6.33)
SD of the population (95% CI)	1.19 (23.14-26.96)	2.2 (14.92-19.52)	2.2 (5.53-10.07)
Mean (SE)	25.05 (0.97)	17.22 (1.12)	7.83 (1.56)

[a] International Restless Legs Syndrome Study Group (IRLSSG) Rating Scale scores: 1-10 (mild); 11-20 (moderate); 21-30 (severe); and 31-40 (very severe).

Abbreviation: RLS, restless legs syndrome.

eTable 2.
Adjusted Mean (SD) IRLSSG Scores in Patients With RLS Taking Ropinirole vs Placebo at Baseline and Study End[a]

	Ropinirole			Placebo		
Study	Baseline	Difference	Final	Baseline	Difference	Final
Bogan et al[9] (N=380)	22.0 (4.99) (n=187)	13.5 (1.2)	8.4 (7.32)	21.6 (4.79) (n=193)	9.8 (1.2)	11.9 (9.20
Trenkwalder et al[10] (N=284)	24.4 (5.75) (n=146)	11.04 (0.72)	13.5 (9.3)	25.2 (5.63) (n=138)	8.03 (0.74)	17.1 (9.4)
Walters et al[11] (N=266)	23.6 (5.9) (n=131)	11.2 (0.76)	12.7 (8.39)	24.8 (5.4) (n=135)	8.7 (0.75)	15.8 (9.59
Meta-Analysis						
Weighted mean (SD)	23.1 (5.4) (n=464)	12.0 (0.86)	10.62 (8 est)	23.4 (5.1) (n=466)	8.9 (0.86)	14.07 (9.07)
SD of the population (95% CI)	0.49 (22.61-23.59)	0.08 (11.92-12.08)	0.73 (9.89-11.35)	0.46 (22.94-23.86)	0.08 (8.9-.86)	0.82 (13.25-14.89)
Weighted mean (SE)	23.1 (0.25) (n=464)	12.0 (0.04)	10.62 (0.38)	23.4 (0.24) (n=466)	8.9 (0.04)	14.07 (0.42)

[a] International Restless Legs Syndrome Study Group (IRLSSG) Rating Scale scores: 1-10 (mild); 11-20 (moderate); 21-30 (severe); and 31-40 (very severe).

Abbreviation: RLS, restless legs syndrome.