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ORIGINAL RESEARCH

Sleep improvement for restless legs syndrome patients. Part 1: pooled analysis of two prospective, double-blind, sham-controlled, multi-center, randomized clinical studies of the effects of vibrating pads on RLS symptoms

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Purpose: Pooled data from two randomized, double-blind, prospective clinical trials were analyzed (i) to determine if vibratory stimulation can safely treat patients with moderately severe restless legs syndrome and (ii) to compare two types of shams.

Patients and methods: One hundred and fifty-eight patients with at least moderately severe primary restless legs syndrome (a score of 15 or greater on the International Restless Legs Syndrome Study Group rating scale) were enrolled at five investigational sites, between April 20, 2009 and February 12, 2010. Patients were randomly assigned to treatment with a vibrating pad or control (sound-producing or light-emitting sham pad). Patients and investigators were blinded to pad assignment type (treatment pad or sham pad). Efficacy was measured as a change in score from baseline to week 4, on the Medical Outcomes Study Sleep Problems Index II, the Johns Hopkins Restless Legs Syndrome Quality of Life summary scale, and the International Restless Legs Syndrome Study Group rating scale. Clinicians were asked to evaluate the effectiveness of the pad assignment and to guess whether treatment or sham therapy had been assigned. Adverse events related to vibrating pad assignment were tabulated.

Results: The Medical Outcomes Study Sleep Problems Index II scores improved significantly more for patients receiving a vibrating pad over those receiving a sham pad ($P \leq 0.02$) even when corrected for multiplicity ($P \leq 0.04$). Clinician evaluation favored patients assigned vibrating pads, and neither patients nor clinicians accurately guessed which pad was assigned. No significant difference in adverse event rates was observed between the vibrating and sham pad groups. Sound and light sham pads performed comparably with respect to safety and efficacy.

Conclusion: Four weeks of treatment with vibrating pads safely improved sleep in patients with restless legs syndrome and both shams functioned comparably.

Keywords: restless legs syndrome, vibration therapy, sham-controlled, double-blind, randomized clinical trial

Introduction

Restless legs syndrome (RLS) is diagnosed as (i) an urge to move the legs, which is (ii) usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; in which (iii) the sensations begin or worsen during periods of rest or inactivity, such as lying or sitting; which are (iv) partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; which are

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(v) worse or only occur in the evening or night; and which are (vi) not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.[1] Diagnostic criteria, consequently, include episodes occurring during the daytime when drowsy.[2]

With the single exception of frank mania, RLS patients with severe symptoms have the least amount of sleep of any sleep disorder.[3] Over half of patients with RLS report waking with symptoms three or more times per night on nights they experience an attack.[4] The sleep loss of RLS leads to a generalized decrease in quality of life similar to other forms of insomnia, such as sleep apnea.[4,5] RLS victims are more likely than people without RLS to be late to work, miss work, make errors at work, and miss social events because of sleepiness.[6]

During an RLS attack, the unpleasant sensations of RLS either prevent patients from falling asleep or awaken them after they have fallen asleep. These dysphoric sensations lead to leg movements, seemingly as an unconscious attempt to diminish the amplitude of the unpleasant tactile sensations. Patients seek relief by resorting to overwhelming or swamping afferent sensory inputs that appear to provide "counterstimulation" to the unpleasant sensations of RLS.[7,8] Such measures include walking about, stomping the feet, rubbing, squeezing or stroking the legs, taking hot showers or baths, or applying ointment, hot packs, or wraps to the legs.[9] However, even though these actions quickly diminish unpleasant limb sensations, they do so at the expense of sleep.

Distraction of attention from pain by counterstimulation is a well-known modulator of discomfort. Anyone who has wielded a hammer and hit his or her thumb has unconsciously employed a form of counterstimulation to decrease thumb pain. As soon as the hammer hits the thumb, one unconsciously starts shaking the hand with the thumb injury. Thus, instead of solely pain sensations reaching the brain from the crushed thumb, a host of nonpain sensations also enter the brain from the hand and diminish the perceived intensity of pain from the hammer blow. Other effective sensory pathways, such as light or sound, can also act as a counterstimulus to extremity pain.[8,10–13]

For the vast majority of patients with RLS, the extremities and the sensory pathways from the extremities to the brain seem normal. For most, the movement-demanding sensations of RLS appear to originate not in the legs, but in the brain. From this point of view, during an attack, these sensations are "mapped" or "projected" from the brain to either or both legs, and, much less commonly, to either or both arms. (In a related disorder, disturbing sensations originating in the brain are mapped to the genitals.[14]) Thus, the sensations of RLS are, in effect, somatic hallucinations. Amputees with phantom-limb syndrome experience similar phenomena during which somatic sensations arising in the brain are mapped or projected by the individual's brain to a limb that is not present. These sensations are not usually referred to as "hallucinations," but from this perspective, perhaps they should be. Furthermore, amputees may also experience RLS in the absent limb.[15] Phantom-limb pain has been treated with vibratory and transcutaneous electrical nerve stimulation (TENS).[16] Since there is such a wide range of touch sensations reaching the brain from the extremities and because all these stimuli ultimately reach the thalamus and cerebral cortex, it makes sense that the unpleasant, painful leg sensations of RLS are very diverse in character.

The use of vibratory stimulation (VS) as a treatment for pain was first published in 1964.[17] Treatment with TENS, a better-known modulator of pain, was described 10 years later.[18–21] VS delivers mechanical energy to the skin and deeper tissues, which excites specialized microscopic receptors or mechanical-electrical transducers that then initiate action potentials in one or more sensory nerves. When therapeutic vibration is applied to the site of pain, it can decrease the perception of pain at that site. More remarkably, when VS is applied to a site some distance from the site of pain, pain is still diminished, suggesting that VS pain relief involves the higher central nervous system.[22–25] A case report of successful treatment of a patient with RLS-like symptoms using VS, TENS, and a combination of the two modalities has been published.[26]

To improve sleep in patients with RLS symptoms, a simple source of counterstimulation – a vibrating pad that can reside in bed each night and be slid under the legs during an RLS attack – was developed and evaluated. Because the construction of a sham for a physical type of therapy is difficult, or at times impossible, two different shams were studied.

Materials and methods

Patient population

Eligible patients were those between 18 and 79 years of age experiencing at least moderately severe, primary RLS symptoms during at least 15 nights of the previous month. RLS symptoms were limited to the legs. RLS severity was defined as a score of 15 or more points on the International Restless Legs Syndrome Study Group rating scale (IRLS).[27–29]

Patients were either taking no medication for RLS symptom control or were on a constant dosage of an FDA-approved RLS drug, either ropinirole or pramipexole (dopamine agonists), throughout the course of the trials. Patients on any other RLS drug were excluded.

Patients with secondary RLS (eg, associated with renal failure, pregnancy, iron deficiency anemia); unprovoked daytime RLS symptoms; off-label medication use to treat RLS; a history of alcohol or drug abuse; another primary sleep disorder (eg, narcolepsy, sleep-disordered breathing); a movement disorder (eg, Parkinson disease, dyskinesia, or dystonia); a medical condition that could affect RLS (eg, diabetes, fibromyalgia, peripheral neuropathy, rheumatoid arthritis); an allergy to Lycra™ or polyurethane foam; a history of deep vein thrombosis and/or current treatment with anticoagulation medications; cellulitis or open sores of the legs; pregnancy; or a history of RLS device or drug trial within the past month, were excluded.

Study design

Patients were randomized to either treatment (vibration) pads (Symphony™, Sensory Medical Inc, San Clemente, CA, USA) or sham pads, in two trials designed to measure improvement in RLS symptoms. Patients and clinicians were blinded to assignment type (treatment versus sham), and, at the end of the trials, were asked to guess whether they had received treatment or a sham. The two studies were identical in every way (patient inclusion and exclusion criteria, treatment regimen, outcome measures, and follow-up schedules) except for the type of sham device (sound versus light). The two trials were NIH registered (ClinicalTrials.gov NCT00877916 and NCT01145651) and IRB approved (SMI-001-09030-01 and SMI-002-09115-01; Independent Review Consulting, 100 Tamal Plaza #158, Corte Madera, CA, USA). After signing their IRB-approved informed consents, patients were enrolled in SMI-001 between April 20, 2009 and July 9, 2009; enrollment for SMI-002 occurred from October 13, 2009 through February 12, 2010. Individual trial details have been published on the manufacturer's website.[30] The data from the two studies was analyzed across study variables to determine if it could be pooled. Pooled data was analyzed as arms of a single trial to allow comparison of the two sham types. The arms are identified as "Arm 1" and "Arm 2" throughout.

The vibrating pad consisted of six low voltage motors embedded in a cotton cloth-covered foam pad that was sized to fit the patient. Weights were attached to the motor shafts to make them vibrate. The degree of vibration was patient-modulated by a knob on the controller. When activated, the vibrating pads produced an audible hum that increased with increasing vibration. A photograph of a pad and its controller is shown in Figure 1.

Arm 1 – vibrating versus sound sham pads

Seventy-seven patients were randomly assigned either a vibrating pad or a sham pad in a 1:1 ratio. The sham pads were identical to the vibrating pads except that the sham pads did not vibrate. Instead, they generated a variable audible hum of the same loudness as the vibrating pads and were, therefore, referred to as "sound sham pads." Like the vibrating pads, patients could vary the loudness of sound in the sound sham pads by turning a knob on the controller.

Arm 2 – vibrating versus light sham pads

Eighty-one patients were randomly assigned to a vibrating pad or sham pad in a 2:1 (therapy to sham) ratio to allow greater accumulation of vibrating pad safety data. The sham pads were identical to the vibrating pads except that the sham pads did not vibrate. Instead, a light-emitting diode that was visible on the pad between the patient's legs was incorporated into the top of the sham pad. Diodes were used, so the light did not produce heat. These sham pads were referred to as "light sham pads." By turning a knob on the controller, patients could vary the intensity of light.

Intervention

Figure 2 demonstrates placement of a pad under a patient's calf. Patients were instructed to place and activate the pad under their legs for 35 minutes each night and during RLS attacks.

For both therapy and sham pads, a cycle of pad usage was 35 minutes. Patients controlled the pad vibration,

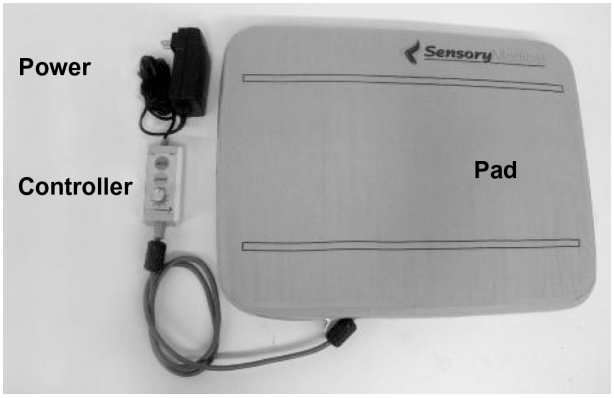

Figure 1 Photograph of a pad with its power source and controller.
Note: The two lines on the pad indicate where legs would be placed.

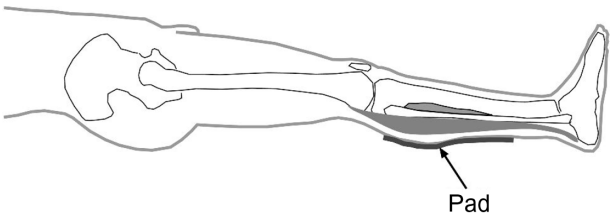

Figure 2 Drawing of a leg with a pad placed under the calf.

light or sound intensity for the first 30 minutes of the 35-minute cycle. During the last 5 minutes of a cycle, the final patient-determined level of vibration, sound, or light slowly diminished (the "cooldown") until the pad turned off. When desired, patients could initiate additional cycles. The cooldown feature was developed to allow the patient to fall back to sleep without having an abrupt change from "on" to "off" and without having to actively turn the pad off.

Double-blinding

Patient- and clinician-blinding were optimized by excluding any patient who had prior RLS treatment with vibration and by avoiding a crossover trial design.[31] Each arm used sealed envelopes by which pads were randomly and blindly assigned to patients from a master randomization table created prior to patient enrollment. Therapy and sham pads were sent to the clinical centers in unmarked boxes that were opened by each patient when he or she got home.

At the beginning of each study, patients were told that they would receive a pad that would emit different forms of energy: vibration, sound, or light. At the conclusion of the study, patients and clinicians independently "guessed" whether they had received a therapy (vibrating) or a sham pad. Comparison of the assigned pad to these guesses defined blinding success.

Outcome measures

Efficacy

Three efficacy variables were measured from baseline to week 4: (i) the Medical Outcomes Study Sleep Problems Index II (MOS-II); (ii) the Johns Hopkins Restless Legs Syndrome Quality of Life (RLS-QoL) summary scale; and (iii) the IRLS scale.

The MOS scale is a reliable and valid assessment of sleep in RLS patients that correlates with overall RLS quality-of-life and IRLS scores.[32] The MOS sleep inventory measures sleep disturbance in the following domains: sleep disturbance (four items), sleep adequacy (two items), sleep quantity (one item), somnolence (three items), snoring (one item), and shortness of breath (one item). Consisting of nine of the twelve MOS questions, the MOS-II scale is the most comprehensive scale in the sleep inventory. It measures sleep problems in the following domains: sleep disturbance, sleep adequacy, respiratory impairment, and somnolence. The MOS-II scale records sleep disturbance during the prior four weeks on a scale of 0 (no problems) to 100 (very disturbed sleep). Improvement on the MOS-II scale would be a decrease in score.

The RLS-QoL instrument is a reliable and valid assessment of quality of life for RLS patients.[29,32–34] It correlates with IRLS and MOS scores.[32] The full survey contains 18 questions in seven subscales. The largest subscale, the "summary score," is comprised of ten of the 18 RLS-QoL questions and was administered prior to pad assignment and at the end of week 4. A score of 0 on the summary scale indicates very poor quality of life; 100, very good. Improvement in an RLS-QoL scale would be an increase in score.

The IRLS scale measures RLS severity[27–29] and was administered as a requirement of entry into the study and at the end of weeks 1 through 4. The IRLS scale consists of ten questions, with each question having a potential score of 0 to 4. On a scale from 0 to 40, high summary IRLS scores indicate greater RLS severity; low scores indicate less severity. Improvement on the IRLS scale would be a decrease in score. The IRLS scale has been shown to correlate with MOS and RLS-QoL scores.[32]

In addition, clinicians examined each patient at the beginning and at the end of the 4-week trial and scored change in clinical status into three categories: "improved," "unimproved," and "uncertain."

Safety

Any adverse event that was related temporally to the use of a pad was reported and evaluated as mild, moderate, or severe, by an independent physician.

Comparison of shams

The effectiveness of sound and light shams as controls was determined by comparing the change in MOS-II scores from baseline and week 4, between the two shams.

Statistical analysis

Statistical analyses were performed with SAS software, version 9.3 (SAS® Institute Inc, Cary, NC, USA). A difference of $P \leq 0.05$ was considered statistically significant throughout. Because efficacy was measured with three correlated endpoints, the Westfall and Young step-down bootstrap and permutation procedures for three correlated endpoints

were used to correct for multiplicity.[35] This correction is a statistical "penalty" levied to control for Type I errors when more than one study endpoint exists.

Results

On average, pads were used 0.97 times per night over the course of the 4-week trial. No significant difference in pad usage was noted between the treated and control groups. Nightly sleep characteristics were not recorded. Monthly sleep was characterized with the MOS-II inventory.

Efficacy

Correlation among standardized instruments

Change in MOS-II, RLS-QoL, and IRLS scores from baseline were correlated (Table 1). All correlations were moderate in magnitude, statistically significant at the $P \leq 0.0001$ level, and comparable to published correlations.[32]

Standardized instruments

When changes in the MOS-II, RLS-QoL, and IRLS scales were simultaneously examined as a single outcome variable in a multivariate analysis of variance (MANOVA) approach, patients randomized to the vibrating pads had significantly better outcomes than did patients randomized to the sham pads ($P \leq 0.03$). Further analysis demonstrated that (i) responses on the IRLS scale were nearly indistinguishable between the treated and control populations; (ii) responses on the RLS-QoL scale favored vibrating pads over sham pads, but the difference was not significant; and (iii) MOS-II outcomes were significantly superior for patients assigned vibrating pads ($P \leq 0.02$) (Table 2). That the MOS-II scale showed superiority in these findings is not surprising, as the vibrating pad was designed to improve bedtime sleep and only the MOS-II inventory measures sleep improvement.

Patients assigned vibrating pads averaged a 13.3 point improvement (drop) in MOS-II scores compared with a 6.2 point drop for patients assigned sham pads, a statistically significant, 114% improvement over sham pads (*t*-test, $P \leq 0.02$, Figure 3).

Table 1 Correlation coefficients for efficacy variables

	Correlation coefficient	Count	*P*-value
IRLS change vs RLS-QoL change	–0.57	154	<0.0001
IRLS change vs MOS-II change	+0.64	153	<0.0001
RLS-QoL change vs MOS-II change	–0.55	153	<0.0001

Abbreviations: IRLS, International Restless Legs Syndrome Study Group rating scale; RLS-QoL, Restless Legs Syndrome Quality of Life scale, MOS-II, Medical Outcomes Study Sleep Problems Index II.

Table 2 Score changes from baseline by scale

	IRLS scores	RLS-QoL scores	MOS-II scores
Vibrating pad patients (SD)	–6.68 (7.28)	11.14 (17.98)	–13.29 (19.67)
Sham pad patients (SD)	–6.39 (7.50)	7.01 (15.52)	–6.20 (15.69)
(Vibration – sham) differences (95% CI)	–0.29 (–2.66 to 2.08)	4.13 (–1.33 to 9.59)	–7.09 (–12.92 to –0.27)
% superiority vibration over sham	4.5%	58.9%	114.4%
P-values	0.81	0.14	0.02

Abbreviations: IRLS, International Restless Legs Syndrome Study Group rating scale; RLS-QoL, Restless Legs Syndrome Quality of Life scale, MOS-II, Medical Outcomes Study Sleep Problems Index II; SD, standard deviation.

Because change from baseline for MOS-II scores was one of three correlated VS trial endpoints, a correction for multiplicity was computed using the Westfall and Young step-down bootstrap and permutation procedures for three correlated endpoints.[35] After the multiplicity adjustment was made, the difference between vibrating and sham pads remained significant at $P \leq 0.04$.

Clinical evaluation

Clinician evaluation (Figure 4) demonstrated that patient improvement was greater for patients assigned a vibrating pad. Patients were evaluated by clinician interview at the beginning and completion of the trial and scored as "clinically improved," "clinically unimproved," or "outcome uncertain." According to the clinician interviews, patients assigned vibrating pads improved more than did patients assigned sham pads (Chi-square, $P < 0.01$).

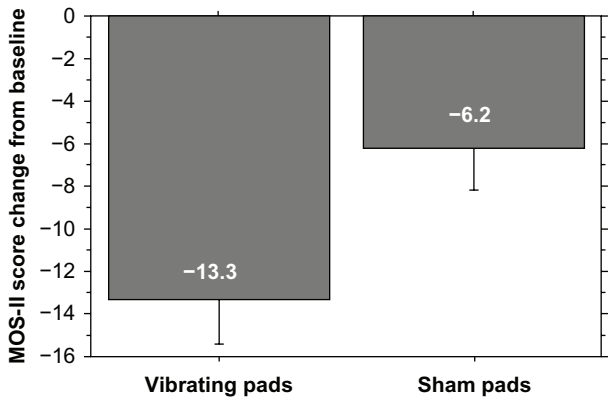

Figure 3 Bar graph showing greater sleep improvement in MOS-II scores from baseline for patients assigned a vibrating pad (±1 SEM bars).
Abbreviations: MOS-II, Medical Outcomes Study Sleep Problems Index II; SEM, standard error of the mean.

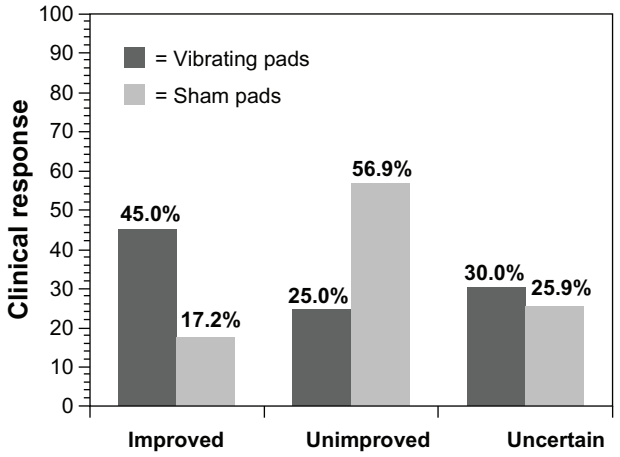

Figure 4 Bar graph showing greater clinical improvement for patients assigned vibrating pads.

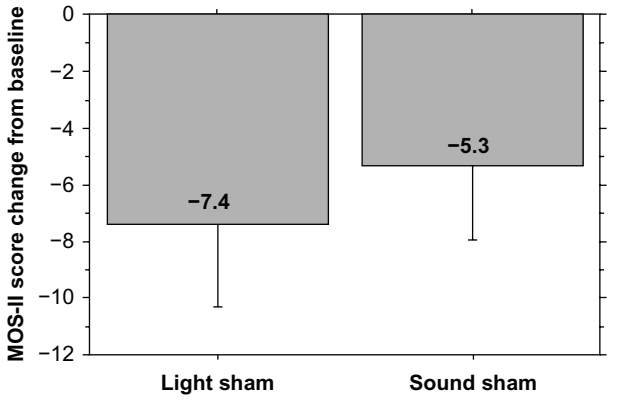

Figure 5 Bar graph showing comparable effects for sound and light sham pads (±1 SEM bars).
Abbreviations: MOS-II, Medical Outcomes Study Sleep Problems Index II; SEM, standard error of the mean.

Safety

In the sound sham arm, seven mild and one moderate adverse event occurred; five of the eight events were judged to be related to pad usage. Seven of the events occurred in patients assigned a vibrating pad, and one occurred in a patient assigned a sound sham pad. In the light sham arm, six mild, two moderate, and one severe event occurred; seven of the nine events were judged to be related to pad usage. The severe event (pneumonia that required hospitalization) was judged to be not related to pad usage. In both arms, adverse events occurred more frequently in patients assigned therapy pads than in patients assigned sham pads (80% versus 20%), but the difference was not significant ($P > 0.07$, Chi-square test). Events related to vibrating pad usage were primarily described in terms of temporary worsening of RLS symptoms. When pad use stopped, all adverse events connected to pad usage resolved quickly. None required medical intervention.

Sham comparison

Figure 5 demonstrates that as shams, sound and light pads functioned comparably, producing MOS-II change scores of –5.3 and –7.4, respectively ($P > 0.60$). Neither of the two shams significantly influenced change in MOS-II scores from baseline, and the difference in MOS-II change scores between the two shams (–2.0) was not significant ($P \geq 0.61$).

Methodology evaluation

Poolability

The data from the two trials was poolable and could be analyzed as two arms of a single trial because there was no significant difference across any measurable study variables, between the two arms, or between patients assigned vibrating or sham pads (Table 3) ($P > 0.05$ for all comparisons). The two arms and their five study sites used common study protocols, were adequately monitored to ensure protocol compliance, and gathered and validated data by the same mechanism. Treatment arm effect and treatment arm-treatment interaction effect on MOS-II change scores were not statistically significant (analysis of variance [ANOVA], $P > 0.69$ and $P > 0.28$, respectively). No statistically significant study site or study site-treatment interaction effects on sleep improvement were observed (ANOVA, $P > 0.20$ and $P > 0.046$, respectively).

Randomization

Randomization was successful. A 1:1 VS to sham randomization ratio was sought in Arm 1; a ratio of 1.03:1 was observed. A 2:1 ratio was sought in Arm 2, and a ratio of 1.8:1 was observed. Both observed ratios fell within their 95% confidence interval (CI). Table 3 demonstrates that across patient characteristics, no statistically significant difference was observed between patients assigned vibrating pads and patients assigned sham pads ($P > 0.05$ for all comparisons).

Double-blinding

Neither patients nor clinicians accurately guessed pad assignment. Pad assignment guess accuracy was 55.7% for patients and 57.6% for clinicians. Neither accuracy was greater than chance (Chi-square test, $P > 0.46$ and $P > 0.85$, respectively).

Comparable test completion rates between treatment and sham groups also indicate that patients were adequately blinded. One hundred fifty-eight patients took the baseline MOS test and 154 (97.5% compliance) completed the test

Table 3 Baseline patient characteristics

Patient characteristic	Arm 1 N = 77 (SD)	Arm 2 N = 81 (SD)	*P*-value**	Vibrating pad, N = 90 (SD)	Sham pad, N = 67 (SD)	*P*-value**
Age (yrs)	52.8 (15.4)	53.7 (14.6)	0.67	52.8 (14.8)	53.9 (15.1)	0.64
Height (inches)	66.0 (3.5)	66.4 (3.6)	0.52	66.2 (3.6)	66.2 (3.6)	0.94
Weight (lbs)	183.8 (41.4)	179.3 (42.1)	0.50	182.7 (39.1)	179.9 (45.1)	0.67
IRLS baseline score	24.7 (5.3)	23.8 (5.2)	0.28	24.5 (4.9)	23.9 (5.7)	0.47
MOS-II baseline score*	50.8 (15.8)	48.7 (16.5)	0.42	51.5 (15.3)	47.5 (17.2)	0.13
Age of onset (yrs)	32.8 (18.0)	34.6 (18.1)	0.55	33.4 (18.8)	34.2 (17.0)	0.78
Duration (yrs)	19.9 (15.6)	19.1 (17.0)	0.77	19.4 (16.7)	19.7 (15.8)	0.91
No current RLS drug use	57.1%	69.1%	0.18	65.9%	59.7%	0.50
Female gender	72.7%	63.0%	0.23	65.9%	70.2%	0.58
Only bedtime symptoms	79.2%	80.2%	0.99	23.1%	16.4%	0.30
Both legs affected	98.7%	100%	0.49	98.9%	100.0%	0.39

Notes: *In the general population, MOS-II scores average 25.8; **t-tests for continuous variables; Chi-square tests for dichotomous variables.
Abbreviations: IRLS, International Restless Legs Syndrome Study Group rating scale; MOS-II, Medical Outcomes Study Sleep Problems Index II; RLS, restless legs syndrome.

at week 4, with no significant difference between treatment or control groups (Chi-Square test, $P > 0.99$).

Sensitivity analyses

Potential covariates

Covariates did not significantly influence efficacy outcome. To determine if baseline study variables influenced MOS-II improvement scores, potential covariates were identified by correlation of change scores with all of the baseline study variables.[36] Three covariates that could have potentially influenced change in MOS-II scores from baseline were identified: (i) baseline MOS-II scores, (ii) age, and (iii) involvement of the thigh. Including these three variables as covariates, the least square means adjusted average improvements in MOS-II scores still favored vibration over sham treatment with −7.1 in the sham pad group and −12.6 in the VS group (ANCOVA, $P < 0.05$).

Missing values

There were one missing baseline and four missing final MOS-II scores, but this did not significantly affect efficacy outcome. Missing MOS values were imputed following Rubin's multiple imputation procedure.[37] Five imputations were performed. Each missing value was replaced with a set of plausible values that reflected the uncertainty of the value to impute, which resulted in a valid inference about the uncertainty of missing values.[38] Following replacement of missing scores with imputed ones, the change in MOS-II scores for the vibrating pad group was still significantly greater than for the sham group, −13.3 and −6.2, respectively, ($P \leq 0.02$).

Potential moderators

Pad assignment "guess" accuracy and RLS drug usage did not influence efficacy outcome. When used as independent variables in a two-way ANOVA, the vibrating pad group showed significant improvement ($P \leq 0.01$), while guess accuracy did not ($P > 0.48$). Similarly, with pad assignment and current RLS drug use as independent variables, MOS-II scores associated with vibrating pad assignment improved significantly ($P \leq 0.03$) but those associated with current RLS drug usage did not ($P > 0.69$). Patients experienced sleep improvement from treatment pad usage, whether on RLS drugs or not.

Discussion

Three physical RLS treatment modalities have been evaluated with the randomized clinical trial (RCT) design: leg compression,[39] leg heating,[40,41] and leg vibration. Compression therapy assumes that leg venous and/or lymphatic stasis (insufficiency) contributes to or causes RLS. Heat therapy was founded on the idea that leg tissue perfusion in RLS patients is deficient. However, neither of these treatments was designed for application during an RLS attack in bed at night. Both were designed for periodic, preemptory application. By contrast, vibration therapy was developed as a counterstimulus to RLS sensations, to be applied in bed at night during an RLS attack. Furthermore, the results of the studies involving leg compression or heat therapy were troubled with potentially faulty blinding for the patient and/or the investigator, which could have skewed interpretation.

Compression stockings

In a 35-patient study of pneumatic compression stocking treatment of RLS, treatment stockings were worn for an hour each day and inflated to a pressure of 40 cm of water every 5 seconds. Shams were only inflated to 3–4 cm of water.[39] Treatment was not coincident with RLS attacks. It was thought that periodic compression of the legs with

pneumatic pressure would diminish vascular stasis problems and later relieve RLS symptoms, while inadequate compression, the sham, would be of little benefit. Improvement in IRLS severity scale scores (the IRLS severity scale is a subscale of the IRLS instrument, consisting of six of the ten IRLS questions), quality of life scores, and analog sleep scale scores between baseline and week 4 were significantly greater for patients assigned therapy stockings. However, blinding effectiveness was not measured. In fact, the authors acknowledged, "… patients in the sham group may have been able to determine that they were receiving sub-therapeutic pressures."[39] Consistent with the possibility that blinding was not effective, compliance with stocking use was not equal for high- and low-pressure stockings. If patients knew which stocking was assigned and knew that investigators thought only higher-pressure stockings were therapeutic, then this trial failed to blind, and its results are difficult to interpret.

Heat lamps

Leg heat treatment with an array of near-infrared light emitting diodes (LED) bonded to flexible pads was compared with a treatment with identical pads that did not heat, in 37 RLS patients.[40] Three times a week, over 4 weeks, each leg was wrapped with a pad for half-hour treatments. Treatment was not coincident with RLS attacks. Patients were not told their pad assignment, but those receiving active treatments felt heat, while sham patients felt nothing. Treating clinicians were not blinded to pad assignments and could have inadvertently communicated their knowledge to patients during leg-heating sessions. IRLS scores were obtained prior to trial initiation and weekly thereafter. Comparison of change in IRLS scores from baseline to week 4 demonstrated a significant superiority of heat therapy over the sham. However, because blinding effectiveness was not measured, it is difficult to know what the trial demonstrated. By contrast, a similar open-label heat-source comparison[41] may not have demonstrated the effect of leg heating, as open-label placebo treatment has recently been shown to be effective.[42]

Vibrating pads

Vibrating pads were designed to provide counterstimulation during an RLS attack while a patient was in bed at night. The goal was to allow a patient to either fall asleep when an RLS attack occurred prior to sleep or to return to sleep when the attack woke the patient from sleep. Unlike the compression and heat studies, both the patients and physicians in this study were blinded to the treatment or sham exposure. Sham pads were constructed as controls yet may have acted as plausible treatments. To be plausible, it was thought that sham pads had to be physically indistinguishable from vibrating pads, have a sensory output that patients could control with a knob, and yet not be therapeutic. As shown, neither patients nor clinicians accurately guessed whether a treatment or sham pad was assigned. However, in the service of effective blinding, sham pads may have been effective counterstimuli for a minority of control patients.

These patients could have focused attention on light or sound, tuned light or sound to an intensity that they felt was comforting, and therefore diverted their attention away from RLS sensations. Seeing and hearing do not involve pathways of touch from the legs or the spinal cord. However, because in the brain, sight and sound are integrated with touch sensations from the legs, light or sound can act as a counterstimulus, which may have been the case in the VS trials. Consequently, for some patients, sound or light sham pads could have had primary therapeutic effects. If so, such effects would have biased the study against finding a difference between treatment and sham pad groups. The contribution of assignment belief (the patient's belief that he was receiving treatment) to the results is further explored in Part III of this series.[43]

Conclusion

This study demonstrated that RLS-related sleep problems, as measured on the MOS-II scale, decreased significantly more in patients treated with a vibrating pad than in patients treated with a sham after one month of therapy (Table 2). By clinician evaluation, 45.0% of patients assigned vibrating pads were improved compared with 17.2% of patients assigned sham pads. Sound and light shams performed comparably and may have exerted primary therapeutic effects on some patients (Part III).[43]

However, vibration therapy failed to significantly improve scores on the RLS-QoL or IRLS scales. It is possible that vibration is a general aid to sleep that has no specific or unique therapeutic benefit for RLS patients. A nonspecific sleep aid for RLS patients would not limit the clinical use of vibrating pads as a method of improving sleep for these patients, but it would limit the theory that vibration is a counterstimulus to RLS symptoms. Alternatively, 4 weeks of vibration treatment may not have been sufficient to elicit significant changes in the IRLS and RLS-QoL scales. Longer studies will be required to differentiate between these two alternative theories.

More adverse events were observed in patients assigned vibrating pads, but the difference was not statistically significant. All adverse events related to pad usage resolved

rapidly without medical intervention. Nighttime treatment of RLS-associated sleep problems with a vibrating pad appears to be safe and effective.

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