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REVIEW

Improving sleep for patients with restless legs syndrome. Part II: meta-analysis of vibration therapy and drugs approved by the FDA for treatment of restless legs syndrome

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Background: Vibratory stimulation pads have been shown to improve sleep in patients with restless legs syndrome (RLS) to a greater extent than sham therapy. The current gold standard of treatment is drugs approved by the US Food and Drug Administration (FDA) for use in RLS. The aim of this meta-analysis was to compare the efficacy and safety of vibratory stimulation pads, sham pads, and drugs approved by the FDA for use in RLS.

Methods: We searched the PubMed, Embase, and clinical trial websites to identify the relevant randomized, double-blind, and placebo-controlled or sham-controlled studies. Fifteen studies including a combined total of 3455 patients with at least moderately severe primary RLS met our search criteria. Efficacy was defined as the standardized mean difference in sleep improvement between treatment and controls. Safety was assessed by comparing the odds ratios of any adverse events and adverse events leading to study withdrawal between treatment and control subjects.

Results: Improvement in Medical Outcomes Study (MOS) sleep inventory scores from baseline was significantly greater in patients treated with vibratory stimulation pads than in those receiving sham pads (Hedges's g, standardized mean difference –0.39, $P \leq 0.02$). There was no difference in improvement in sleep scores between patients treated with vibratory stimulation pads (–0.39) and those receiving an approved RLS drug (–0.44, $P > 0.70$). The risk of any adverse event or withdrawal because of an adverse event was not significantly different between patients treated with vibratory stimulation pads and those assigned to sham pads (Mantel-Haenszel odds ratio 2.16 [$P > 0.14$] and 1.39 [$P > 0.80$], respectively). The odds ratios for patients reporting any adverse events and adverse events leading to withdrawal were not significantly different between patients treated with vibratory stimulation pads (2.16 and 1.39, respectively) and those who received approved RLS drugs (2.11 [$P > 0.89$] and 2.07 [$P > 0.82$], respectively, mixed-effects model).

Conclusion: For patients with moderately severe RLS, vibratory stimulation pads were more effective than sham pads for improving sleep, as effective as FDA-approved RLS drugs, and as safe as both sham pads and FDA-approved RLS drugs.

Keywords: meta-analysis, restless legs syndrome, sleep, vibration, counterstimulation, drug therapy

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Introduction

Restless legs syndrome (RLS) was first identified in 1685,[1–3] and is characterized by uncomfortable or irritating paresthesias, which result in an overwhelming urge to move the legs. These urges are relieved in part or in whole by movement, such as walking, but may resume soon after activity ceases.[4] RLS may also occur during the daytime and in the arms.[5] The sleep-robbing

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nature of RLS was objectively characterized in the 1970s when sleep laboratories were first developed.[6]

The etiology of primary RLS is incompletely understood. Familial aggregation studies suggest a genetic component.[7,8] RLS is most commonly attributed to reduced concentrations of iron in the brain[9] and faulty neurotransmitters, particularly in the serotonin, endogenous opioid, gamma-aminobutyric acid, and/or dopamine systems.[7,8,10–19] However, intravenous iron showed no significant benefit compared with placebo in a recent study.[20] Other theories include venous stasis in the lower extremities, peripheral neuropathy, and spinal cord dysfunction.[21]

Consistent with the wide range of postulated etiologies, many therapies have been tested.[12] The severity of RLS is reduced following exercise.[22] Patients with RLS have also reported varying levels of improvement with sclerotherapy for varicose veins,[21] pneumatic compression stockings to reduce lymphatic stasis,[15,23] and infrared light to increase perfusion of the legs.[16,24] Acupuncture has been evaluated as a treatment, but the evidence is insufficient to reach a conclusion about efficacy.[25] In addition to these therapies, off-label drugs, including benzodiazepines, narcotics, and nonopioid pain killers, have been used widely to treat RLS.[12]

Patients with RLS spontaneously use counterstimulation sensory inputs, such as leg shaking, walking, hot showers, or baths to relieve acute RLS symptoms,[26] but these activities are incompatible with sleep. Vibratory stimulation is a form of counterstimulation that is an established treatment modality for pain and discomfort and has been tested as a nondrug treatment and shown to decrease RLS symptoms compared with sham treatment (addressed in Part I of this three-part series).[27]

Objective

While there are a wide variety of potential RLS treatments available, drugs approved by the US Food and Drug Administration (FDA) are the current gold standard.[29,30] Four drugs are currently approved by the FDA for the treatment of RLS. These are ropinirole (Requip®, GlaxoSmithKline, Research Triangle Park, NC), pramipexole (Mirapex®, Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT), gabapentin enacarbil (Horizant®, GlaxoSmithKline, Mississauga, ON, Canada, and XenoPort Inc, Santa Clara, CA), and rotigotine (Neupro® transdermal system, UCB Group, Brussels, Belgium). Ropinirole, pramipexole, and rotigotine are dopamine agonists, and gabapentin enacarbil is a gamma-aminobutyric acid agonist.

We performed a meta-analysis to compare the efficacy and safety of a vibrating counterstimulatory device with that of a sham device and FDA-approved RLS drugs. This meta-analysis addressed two questions:

- Can night-time vibratory stimulation pads improve sleep outcomes more effectively and safely than sham pads?
- How do the safety and efficacy of vibratory stimulation compare with those of FDA-approved RLS drugs?

Materials and methods

PRISMA checklist

Randomized controlled trial reporting was assessed using the 27-item PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist[31] and flow diagram (Figure 1).[32,33] Two researchers, blinded to study details, independently searched the PubMed, Embase, and drug manufacturers' websites, as well as Google Scholar, clinicaltrials.gov, and FDA databases, and extracted data from trials that met our predefined criteria. The search strategy was limited to publications after 2000, restricted to the English language, and included the following terms used individually and in combination: "RLS", "restless legs syndrome", "pramipexole", "ropinirole", "gabapentin", "rotigotine", "Mirapex®", "Requip®", "Horizant®", "XenoPort Inc", "Neupro®", "placebo", "double-blind", "randomization", "vibration", "clinical trial", and "counterstimulation". All included trials were parallel, randomized, double-blind, and placebo-controlled or sham-controlled in patients with at least moderately severe primary RLS (severity score $\geq$ 15 on the International Restless Legs Syndrome Study Group rating scale [IRLS]). Patients in the included drug trials had to have had stable dosages during the final 4 weeks of the trial. Finally, the studies had to report changes in sleep difficulty scores or pre-treatment and post-treatment scores from the Medical Outcomes Study (MOS) sleep inventory.[34] Extracted from the selected investigations were first listed author, year of publication, study design, study duration, number of participants, mean ages of treatment and control groups, gender distribution, diagnostic criteria for RLS, type of RLS (ie, primary or secondary), study treatment (including drug doses and treatment schedules), proportion of patients who completed the study, mean change in MOS sleep difficulty scores with estimates of precision for treatment and placebo, and incidence of any adverse events and adverse events leading to withdrawal.

Statistical analysis

Heterogeneity testing

Heterogeneity of treatment effect was evaluated by the Cochran's Q test and I^2 statistic using Comprehensive Meta-Analysis version 2 software (Biostat Inc, Englewood, NJ).[35] To compensate for insensitivity in small samples, when P_Q was <0.10, the null hypothesis of homogeneity was rejected

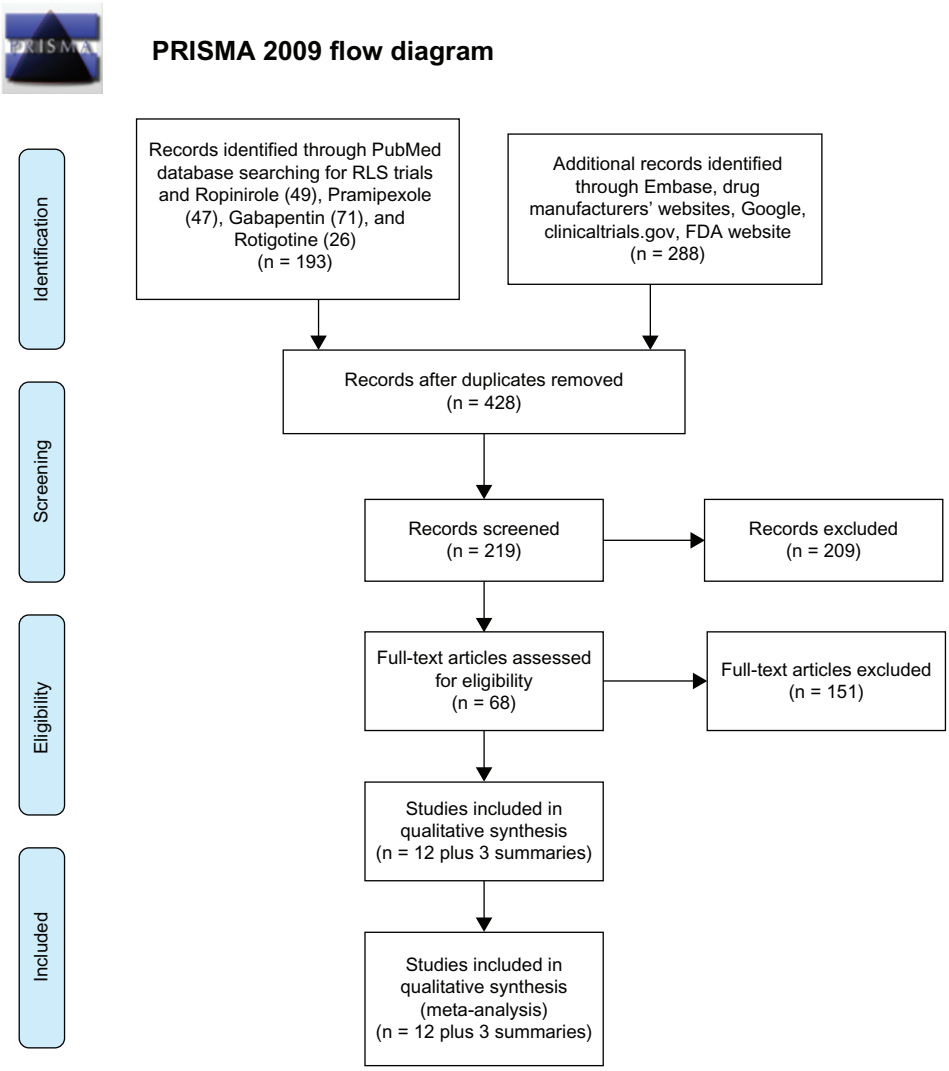

Figure 1 PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow chart.

and studies were considered to be heterogeneous. For all other tests, the alpha level was at $P \leq 0.05$. I^2 values range from 0% to 100%, with ≤25%, 50%, and ≥75% corresponding to low, medium, and high heterogeneity, respectively.[36] Differences between fixed-effect and random-effects models, the Tau^2 statistic, and visual inspection of forest plots were also used to evaluate heterogeneity.

Meta-analysis model

Outcome measures were compared using fixed-effect and random-effects statistical models. A random-effects model within subgroups and a fixed-effect model across subgroups (called a mixed-effects model) were used to combine trials and calculate subgroup statistics. Subgroups were compared indirectly using the $Q_{between\ groups}$ statistic, which is computationally equivalent to the Z-test and analysis of variance methods.[35] As a check of indirect comparisons, fixed-effect meta-regression comparisons were performed because they allow for heterogeneity not explained by subgrouping. Meta-regressions were also performed to evaluate the effects of potential covariates on efficacy and safety outcomes.[37]

Measurement of efficacy

Sleep improvement was measured using the MOS sleep inventory. Each patient's baseline MOS score was subtracted from his or her study completion score, creating within-subject change scores. Mean differences for changes in the subjects' scores were compared between patients assigned to vibratory stimulation pads and those assigned to sham pads. The between-group mean differences were then converted to standardized mean differences that were then corrected for small sample sizes using the Hedges's *g* statistic.[35] The standard error for the Hedges's *g* statistic was calculated as

the square root of the product of the square of Hedges's *g* correction factor (J^2) and the variance of the standardized mean difference (V_d).[35] Meta-analysis weighting was based on the inverse variance method.

The MOS inventory has been shown to be reliable and valid for measuring sleep disturbance in patients with RLS.[38] MOS scores correlate with overall quality of life and IRLS scores in patients with RLS.[39] The Medical Outcomes Study Sleep Problems Index II (MOS-II) scale is the most exhaustive measure of sleep difficulty in the MOS inventory and contains nine of the 12 inventory questions. The Medical Outcomes Study Sleep Disturbance Scale (SLPD4) is a subscale of the MOS-II scale, containing four inventory questions. Scores on the two scales are highly correlated ($r = 0.88$, $P < 0.01$[34] and $r = 0.91$, $P < 0.001$).[40] Based on a sample of 3053 subjects from the general population, scores on the SLPD4 scale demonstrated more variability than MOS-II scores.[34] Scores on both scales can range from 0 (no problems) to 100 (very disturbed sleep). Improvement in sleep score on both scales is a negative number, indicating a reduction in sleep difficulty, and the greater the negative number, the greater the improvement. Both scales measure sleep difficulty based on recall about sleep quality during the 4 weeks prior to taking the test. Average scores in the general population for the MOS-II were 25.8 and for the SLPD4 were 24.5.[40]

Measurement of safety

To adjust for the higher frequency of adverse events in studies comparing drugs with vibratory stimulation, differences in adverse events between treated and control RLS patients were compared using the Mantel-Haenszel odds ratio (OR) corrected for small samples.[41] Two measures of adverse events were evaluated, ie, occurrence of any adverse events and adverse events that led to study withdrawal. All available follow-up data were used to describe safety events.

Null hypotheses tested

Primary efficacy hypothesis

Efficacy of vibratory stimulation compared with shams [direct comparison]:

$$H_{01}: HS\Delta MC_{\text{in sleep problem scores}} = 0$$

Secondary efficacy hypothesis

Efficacy of vibratory stimulation compared with FDA-approved drugs [indirect subgroup comparison]:

H_{02}: $HS\Delta MC_{\text{in sleep problem scores}}$ for vibratory stimulation trials = $HS\Delta MC_{\text{in sleep problem scores}}$ for studies including drugs approved by the FDA for treatment of RLS.

Safety analyses

Safety of vibratory stimulation compared with sham devices [direct comparison]:

$$H_{03}: MHOR_{\text{any AE}} = 1.0.$$

$$H_{04}: MHOR_{\text{AE withdrawal}} = 1.0.$$

Safety of vibratory stimulation compared with drugs approved by the FDA for treatment of RLS [indirect subgroup comparison]:

H_{05}: $MHOR_{\text{any AE}}$ in vibratory stimulation trials = $MHOR_{\text{any AE}}$ in trials of drugs approved by the FDA for treatment of RLS.

H_{06}: $MHOR_{\text{AE withdrawal}}$ in vibratory stimulation trials = $MHOR_{\text{AE withdrawal}}$ in trials of drugs approved by the FDA for treatment of RLS.

where HSΔMC is the Hedges's *g* standardized difference in mean change between treatment and control groups, AE is adverse events, and MHOR is the Mantel-Haenszel OR between treatment and controls.

Results

Trial selection and flow diagram

Of 481 articles identified, 15 met our predefined selection criteria (Figure 1). All trials followed a similar protocol. As a result, patients met the "similarity assumption" for valid indirect subgroup comparisons.[42]

The vibratory stimulation trials were registered with the National Institutes of Health (ClinicalTrials.gov NCT00877916 and NCT01145651) and had institutional review board approval (SMI-001-09030-01 and SMI-002-09115-01; Independent Review Consulting, Corte Madera, CA). Both vibratory stimulation trials (abbreviated throughout as "SMI-001" and "SMI-002") used identical patient inclusion and exclusion criteria, outcome measures, and follow-up schedules, and differed only in the type of sham treatment used (see Part I of this report).[27]

The remaining 13 trials were comparisons of FDA-approved RLS drugs versus placebo. Summary data from 12 of these drug trials were obtained from the peer-reviewed articles, with some supplementary data from manufacturers' websites.[43–54] Data for the remaining trial was available only on the manufacturer's website.[55]

Description of selected trials

Table 1 summarizes the 15 selected trials, which were published between 2004 and 2012 and included 1810 patients

receiving investigational treatment and 1645 controls. All trials were randomized, concurrent, parallel, prospective, and double-blind, and included patients with at least moderately severe primary RLS.[43–58] Patients were between 18–79 years old, with symptoms limited to the legs.

Patients in the selected drug trials had at least 4 weeks of stable drug dosing during the final 4 weeks of each trial. Control pads used in the vibratory stimulation trials were identical in appearance to the vibratory stimulation pads but produced no vibration. In the two vibratory stimulation trials, patients on an FDA-approved RLS drug were permitted to continue treatment, but dose changes were not permitted during the course of the study. Of the 158 patients in the vibratory stimulation trials, 58 were taking either ropinirole or pramipexole. In the treatment arm, patients had been on their RLS drug for an average of 64.4 weeks and in the control arm for 66.5 weeks ($P > 0.93$). Additional characteristics of the patients receiving treatment with vibratory stimulation pads were reported in Part I of this project.[27]

Sensitivity analyses

Fixed-effect and random-effects statistical models were calculated for all analyses. No appreciable differences in results were observed, suggesting that they were not sensitive to this choice of model. Analysis of patient-level data for the effects of trial, study site, sham pad type, and patient characteristics demonstrated that the two vibratory stimulation trials were poolable and that the pooled results were not sensitive to potential covariates, possible moderators, or missing values (Part I).[27]

The trials differed in two categorical variables, ie, treatment type (vibratory stimulation versus FDA-approved RLS drugs) and MOS sleep difficulty scale (MOS-II versus SLPD4), and in six continuous variables, ie, trial duration (4–26 weeks), enrollment size (59–401 patients), patient age (range 49.3–59.4 years), percentage of females included (57.0–74.2), baseline IRLS scores (20.8–28.6), and baseline MOS sleep difficulty scores (48.7–65.2).

Sensitivity of the meta-analysis to these potential covariates was examined by meta-regression. Two covariates, ie, trial duration and baseline IRLS scores, exerted a statistically significant influence. Patients in longer trials or with higher baseline IRLS scores tended to drop out because of adverse events ($P \leq 0.01$ and $P \leq 0.04$, respectively, Table 2).

Outcomes efficacy

Figure 2 shows a fixed-effect meta-analysis of the 15 randomized controlled trials comparing Hedges's g standardized mean differences between treated patients and controls for each trial individually and grouped by vibratory stimulation and drug treatment. In all trials, sleep improvement was greater in the treatment groups. In two of the ten drug trials and in one of the two vibratory stimulation trials, superiority of treatment over the control was not statistically significant.

All 15 trials were homogeneous ($Q = 12.3$, $P_Q > 0.58$; $I^2 = 0.0\%$), including the two vibratory stimulation trials ($Q = 0.75$, $P_Q > 0.38$; $I^2 = 0.0\%$) and 13 drug trials ($Q = 11.4$, $P_Q > 0.49$, $I^2 = 0.0\%$). No significant difference was observed between the drug trials when grouped as ropinirole, pramipexole, rotigotine, or gabapentin trials ($Q_{\text{between groups}} = 2.61$, $P_Q > 0.46$). Based on the data in Figure 2, the H_{01} was rejected while the H_{02} was not. Sleep improvement was significantly greater for patients assigned vibratory stimulation pads as opposed to sham pads (Hedges's $g = -0.39$, confidence interval [CI] –0.71 to –0.06, $P \leq 0.02$) and was not significantly different from patients assigned drug treatment (Hedges's $g = -0.44$, CI –0.51 to –0.37, indirect subgroup comparison, mixed-effects model, $Q_{\text{between groups}} = 0.08$, $P_Q > 0.77$; meta-regression, $P > 0.78$).

Safety

The occurrence of any adverse events and adverse events leading to study withdrawal was substantially more frequent in drug trials than in the vibratory stimulation trials. For example, 78.4% of patients assigned an RLS drug experienced an adverse event compared with 16.5% of patients assigned to vibratory stimulation. The frequency of adverse events in the placebo arm was also high, being 65.4% compared with 9.0% for the sham arm of the vibratory stimulation trials. The Mantel-Haenszel OR compensated for these very large differences in frequencies of adverse events between the vibratory stimulation and drug trials. Figure 3 shows a fixed-effect meta-analysis of the 15 randomized controlled trials comparing the ORs of any adverse event for treated and control patients in each trial individually and grouped by vibratory stimulation and drug trials.

Prior to grouping, the 15 trials were homogeneous ($Q = 13.7$, $P_Q > 0.47$, $I^2 = 0.0\%$). When grouped by treatment type, the vibratory stimulation trials ($Q = 0.00$, $P_Q > 0.96$, $I^2 = 0.0\%$) and drug trials ($Q = 13.7$, $P_Q > 0.32$, $I^2 = 12.5\%$) remained homogeneous. As shown in Figure 3, H_{03} and H_{05} were not rejected. The odds of any adverse event for patients assigned to vibratory stimulation was not significantly greater than the odds for sham pads (OR 2.16, $P > 0.14$) or for FDA-approved drugs (OR 2.11, indirect subgroup comparison, mixed-effects model, $Q_{\text{between groups}} = 0.003$, $P_Q > 0.96$; meta-regression, $P > 0.95$).

Table 1 Trial characteristics

Trial (n)	Trial abbreviation	Reference	Treatment	Trial length (weeks)	Patients (n)		Patient age, mean (SD)		Females (n)		Baseline IRLS, mean (SD)		Sleep scale	Baseline sleep score, mean (SD)	
					Rx	C	Rx	C	Rx	C	Rx	C		Rx	C
1	SMI-001	57	Vibration	4	39	38	50.5 (15.5)	55.1 (15.0)	29	27	25.6 (5.4)	23.8 (5.0)	MOS-II	55.3 (14.1)	46.4 (16.4)
2	SMI-002	57	Vibration	4	52	29	54.5 (14.2)	52.4 (15.3)	31	20	23.7 (4.4)	24.0 (6.5)	MOS-II	48.6 (15.6)	48.9 (18.4)
3	Gaba Kushida et al	45	Gabapentin	12	113	108	52.0 (12.8)	50.2 (12.8)	67	65	23.1 (4.9)	22.6 (4.9)	SLPD4	50.4 (22.3)	50.7 (19.7)
4	Gaba Lee et al	49	Gabapentin	12	111	96	49.5 (12.7)	49.1 (12.2)	59	59	23.2 (5.3)	23.8 (4.6)	SLPD4	52.1 (22.9)	51.9 (23.2)
5	Prami Ferini-Strambi et al	46	Pramipexole	12	182	187	56.3 (12.4)	56.9 (13.0)	132	119	24.2 (5.2)	24.6 (5.7)	SLPD4	52.8 (20.5)	55.7 (22.3)
6	Ropi Kushida et al	51	Ropinirole	12	176	186	51.4 (13.8)	50.4 (13.1)	109	108	26.0 (4.7)	26.0 (4.3)	SLPD4	NR	NR
7	Ropi ROR104836	55	Ropinirole	26	196	205	56.5 (11.9)	56.1 (11.4)	123	130	27.7 (3.6)	27.5 (3.9)	MOS-II	NR	NR
8	Ropi Benes et al	47	Ropinirole	12	198	67	58.2 (11.4)	59.5 (11.3)	144	45	28.5 (4.5)	29.0 (4.6)	SLPD4	65.4 (17.9)	64.7 (19.7)
9	Ropi Allen et al	48	Ropinirole	12	29	30	55.4 (10.3)	53.3 (12.5)	17	17	NR	NR	SLPD4	NR	NR
10	Ropi Bogan et al	50	Ropinirole	12	187	193	52.2 (12.8)	52.4 (13.2)	109	123	20.0 (5.0)	21.6 (4.8)	MOS II	61.2 (21.6)	59.3 (21.9)
11	Ropi Trenkwalder et al	44	Ropinirole	12	146	138	54.0 (11.1)	56.2 (11.2)	88	91	24.4 (5.8)	25.2 (5.6)	SLPD4	NR	NR
12	Ropi Walters et al	43	Ropinirole	12	131	135	54.9 (10.9)	56.0 (11.3)	76	83	23.6 (5.9)	24.8 (5.4)	SLPD4	NR	NR
13	Rotig Trenkwalder et al	54	Rotigotine	26	109	114	57.3 (12.1)	59.7 (10.0)	82	80	28.2 (6.1)	28.1 (6.3)	MOS-II	NR	NR
14	Rotig Hening et al	53	Rotigotine	26	95	99	53.2 (12.2)	52.8 (12.3)	61	56	23.3 (4.6)	23.5 (5.1)	MOS-II	NR	NR
15	Rotig Oertel et al	52	Rotigotine	4	46	20	60.8 (9.4)	56.3 (9.8)	35	14	26.3 (6.4)	25.4 (6.3)	MOS-II	53.3 (19.9)	49.5 (20.8)

Abbreviations: NR, not recorded; Rx, investigational; C, control; IRLS, International Restless Legs Syndrome Study Group rating scale; n, number; SD, standard deviation; Gaba, gabapentin; Rotig, rotigotine; Prami, pramipexole; Ropi, ropinirole; MOS-II, Medical Outcomes Study Problems Index II; SLPD4, Medical Outcomes Study Sleep Disturbance Scale.

Table 2 Metaregression slopes with *P* values

Trial variables	Meta-analysis of outcome variables					
	Efficacy sleep improvement		Any adverse event		Adverse event leading to withdrawal	
	Slope	*P* value	Slope	*P* value	Slope	*P* value
Treatment (drug or VS)	0.047	>0.78	0.030	>0.95	–0.122	>0.92
MOS sleep scale (MOS-II or SLPD4)	0.080	>0.27	0.204	>0.27	0.115	>0.075
Trial duration (weeks)	0.004	>0.49	–0.005	>0.68	0.08	≤0.01
Total trial enrollment	<0.001	>0.31	<0.001	>0.96	<–0.001	>0.98
Average age, years	–0.003	>0.79	0.038	>0.21	0.045	>0.40
Percent females	–0.004	>0.58	0.028	>0.09	0.010	>0.72
Baseline IRLS	0.007	>0.65	0.064	>0.16	0.157	≤0.04
Baseline MOS	–0.005	>0.65	0.041	>0.10	0.034	>0.42

Abbreviations: VS, vibratory stimulation; MOS, Medical Outcomes Study; MOS-II, Medical Outcomes Study Sleep Problems Index II; SLPD4, Medical Outcomes Study Sleep Disturbance Scale; IRLS, International Restless Legs Syndrome Study Group rating scale.

Figure 4 shows a fixed-effect meta-analysis of the 15 randomized controlled trials presenting ORs for adverse events leading to patient withdrawal for each trial, both individually and for trials grouped by drug and vibratory stimulation. The 15 trials demonstrated medium heterogeneity prior to grouping ($Q = 28.0$, $P_Q > 0.02$; $I^2 = 50.0\%$). After grouping the vibratory stimulation trials were homogeneous ($Q = 0.05$, $P_Q > 0.83$; $I^2 = 0.0\%$) while the drug trials were moderately heterogeneous ($Q = 27.9$, $P_Q \leq 0.01$; $I^2 = 57.0\%$). Hypotheses H_{04} and H_{06} were not rejected. The odds of adverse events leading to study withdrawal for patients assigned to vibratory stimulation were not significantly greater than the odds for sham pads (OR 1.39, $P > 0.80$) or the odds for withdrawal while taking FDA-approved drugs (OR 2.07, indirect subgroup comparison, mixed-effects model, $Q_{\text{between groups}} = 0.05$, $P_Q > 0.82$; meta-regression, $P > 0.82$).

Discussion

This meta-analysis demonstrates that sleep improvement as a result of vibratory stimulation is not appreciably different in comparison with the improvement achieved by FDA-approved RLS drugs. Quantitatively, adverse events in this meta-analysis were similar for vibratory stimulation and drug treatment (Figures 3 and 4). However, the qualitative differences warrant examination.

Therapeutic vibrators and massagers have been available in the marketplace for a very long time, and they have not accumulated reports of long-term side effects. Because of

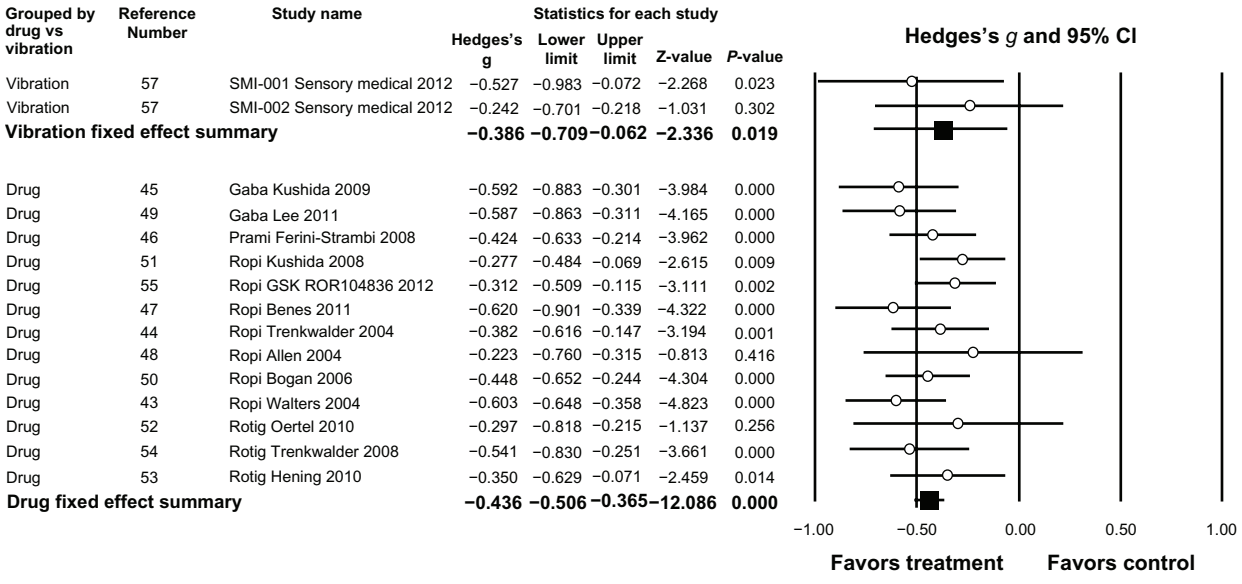

Figure 2 Forest plot of Hedges's *g* efficacy effect sizes for individual trials and for vibratory stimulation and drug trials.
Abbreviations: Gaba, gabapentin enacarbil; Prami, pramipexole; Ropi, Ropinirole; Rotig, Rotigotine; CI, confidence interval.

Group by drug vs vibration	Reference number	Study name	Statistics for each study				
			MH odds ratio	Lower limit	Upper limit	Z-value	P-value
Vibration	57	SMI-001 Sensory medical 2012	2.194	0.601	8.010	1.189	0.235
Vibration	57	SMI-002 Sensory medical 2012	2.100	0.406	10.851	0.885	0.376
Vibration fixed effect summary			**2.155**	**0.778**	**5.968**	**1.478**	**0.139**
Drug	45	Gaba Kushida 2009	1.628	0.852	3.108	1.475	0.140
Drug	49	Gaba Lee 2011	1.754	0.843	3.651	1.503	0.133
Drug	46	Prami Ferini-Strambi 2008	1.638	1.085	2.472	2.349	0.019
Drug	51	Ropi Kushida 2008	2.045	1.281	3.263	2.999	0.003
Drug	55	Ropi GSK ROR104836 2012	1.878	1.230	2.868	2.918	0.004
Drug	47	Ropi Benes 2011	2.963	1.675	5.241	3.732	0.000
Drug	44	Ropi Trenkwalder 2004	1.568	0.885	2.778	1.543	0.123
Drug	48	Ropi Allen 2004	4.203	1.035	17.069	2.008	0.045
Drug	50	Ropi Bogan 2006	3.042	1.836	5.041	4.319	0.000
Drug	43	Ropi Walters 2004	1.965	1.055	3.661	2.128	0.033
Drug	52	Rotig Oertel 2010	2.125	0.717	6.297	1.360	0.174
Drug	54	Rotig Trenkwalder 2008	5.469	2.458	12.166	4.165	0.000
Drug	53	Rotig Hening 2010	1.695	0.729	3.944	1.225	0.221
Drug fixed effect summary			**2.110**	**1.794**	**2.483**	**9.006**	**0.000**

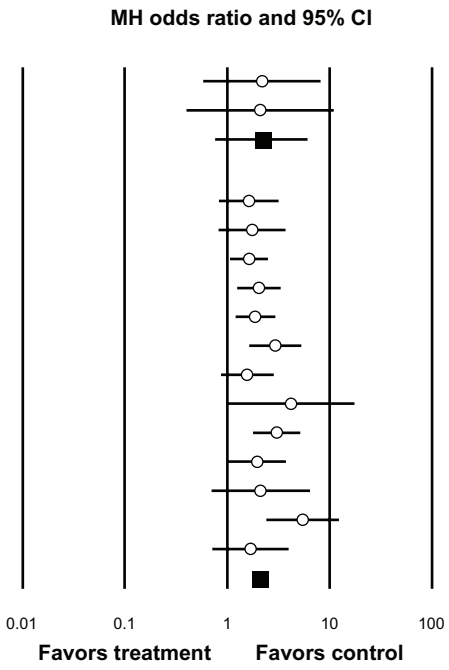

Figure 3 Forest plot of MH odds ratios for any adverse event for individual trials and for vibratory stimulation and drug trials.
Abbreviations: Gaba, gabapentin enacarbil; Prami, pramipexole; Ropi, Ropinirole; Rotig, Rotigotine; CI, confidence interval; MH, Mantel-Haenszel.

this safety record, the FDA has classified them as low-risk Class I medical devices. However, FDA-approved RLS drugs[59–61] may cause excessive drowsiness, perhaps without prior warning, as late as one year after initiation of treatment; impaired systemic regulation of blood pressure that could result in postural hypotension; worsening of symptoms in the morning hours (rebound) or earlier onset of symptoms (augmentation); spread of symptoms to other extremities; and intense, increased, or even uncontrollable urges, such as the urge to gamble or engage in sexual activity. Further-

Group by drug vs vibration	Reference number	Study name	Statistics for each study				
			MH odds ratio	Lower limit	Upper limit	Z-value	P-value
Vibration	57	SMI-001 Sensory medical 2012	0.975	0.019	50.367	−0.013	0.990
Vibration	57	SMI-002 Sensory medical 2012	1.718	0.068	43.548	0.328	0.743
Vibration fixed effect summary			**1.387**	**0.118**	**16.242**	**0.260**	**0.795**
Drug	45	Gaba Kushida 2009	3.398	0.909	12.702	1.818	0.069
Drug	49	Gaba Lee 2011	0.629	0.210	1.880	−0.831	0.406
Drug	46	Prami Ferini-Strambi 2008	1.101	0.538	2.252	0.264	0.792
Drug	51	Ropi RRL100013 2005	1.429	0.486	4.203	0.648	0.517
Drug	55	Ropi GSK ROR104836 2012	2.662	1.373	5.160	2.900	0.004
Drug	47	Ropi Benes 2011	1.993	0.787	5.045	1.455	0.146
Drug	44	Ropi Trenkwalder 2004	2.708	1.027	7.136	2.015	0.044
Drug	48	Ropi Allen 2004	3.190	0.125	81.250	0.702	0.482
Drug	50	Ropi Bogan 2006	0.635	0.204	1.978	−0.783	0.434
Drug	43	Ropi Walters 2004	0.838	0.336	2.094	−0.378	0.706
Drug	52	Rotig Oertel 2010	0.909	0.078	10.619	−0.076	0.939
Drug	54	Rotig Trenkwalder 2008	5.710	1.986	16.422	3.233	0.001
Drug	53	Rotig Hening 2010	9.885	2.997	32.610	3.762	0.000
Drug fixed effect summary			**2.070**	**1.589**	**2.697**	**5.390**	**0.000**

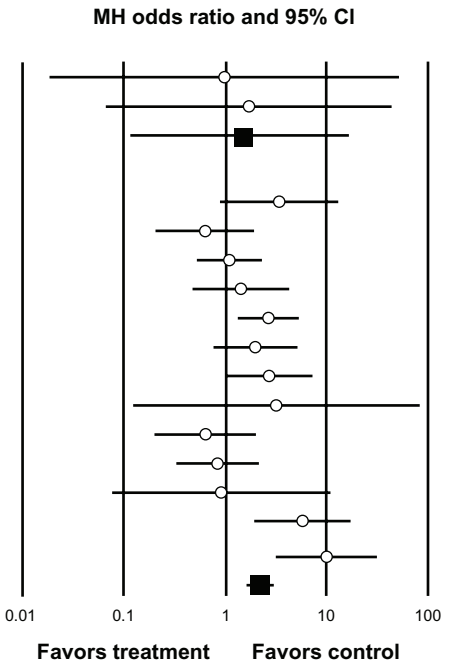

Figure 4 Forest plot of MH odds ratios for adverse events leading to study withdrawal for individual trials and for vibratory stimulation and drug trials.
Abbreviations: Gaba, gabapentin enacarbil; Prami, praipexole; Ropi, Ropinirole; Rotig, Rotigotine; CI, confidence interval; MH, Mantel-Haenszel.

more, adverse events on embryo-fetal development have been found in animals. FDA-approved RLS drugs cross the blood-brain barrier, change the basic chemistry of the central nervous system, and influence other organs as well. They are systemic treatments with systemic side effects, whereas vibration is a physical therapy with no known systemic side effects.

External validation

Standardized effect sizes can be sorted into three major categories, ie, "small" (≤0.3 range), "medium" (0.5 range), and "large" (≥0.8 range).[62] Published meta-analyses examining subjective and objective sleep measures have demonstrated that effect sizes for sleep improvement in RLS patients treated with drugs is in the medium range, which is comparable with the effect size for treatment with vibratory stimulation. In one meta-analysis of 1679 patients with RLS from six randomized controlled trials of ropinirole, Hansen et al demonstrated an overall Hedges's *g* standardized effect size for subjective sleep improvement on the MOS SLPD4 scale of –0.32 (95% CI –0.42 to –0.23, $P < 0.00001$).[63] In another meta-analysis of 22 dopamine agonist trials, Scholz et al integrated six different sleep inventories (including the MOS-II index) to measure subjective sleep improvement in 4592 patients.[64] In that study, the overall Hedges's *g* standardized sleep improvement effect size was –0.40 (95% CI –0.47 to –0.33, $P \leq 0.00001$). In a third meta-analysis, Scholz et al examined sleep laboratory data from 718 patients in nine parallel, randomized controlled trials that objectively measured sleep efficiency in RLS patients treated with dopamine agonists.[64] The overall Hedges's *g* standardized sleep efficiency effect size was –0.32 (95% CI –0.58 to –0.20). In these three published meta-analyses, no significant difference was detected between subjective and objective effect sizes (–0.32, –0.40, and –0.32) and vibratory stimulation (–0.39, Figure 2) using fixed-effect or random-effects models ($Q = 2.16$, $P_Q > 0.54$). The effect sizes of sleep improvement reported in our meta-analysis are comparable to the effect sizes observed in the other meta-analyses, which expands the generalizability of our findings.

Vibratory stimulation as an adjuvant to RLS drug therapy

Patients on FDA-approved RLS drugs may still have substantial RLS symptoms. Fifty-eight (36.7%) of 158 patients in the vibratory stimulation trials were taking an FDA-approved RLS drug. The average duration of drug treatment was 3.7 years (95% CI 2.7–4.7). There was no significant difference in sleep improvement following vibratory stimulation between patients taking RLS drugs and those not taking RLS drugs ($P > 0.51$). Despite long-term drug treatment, patients continued to have baseline IRLS scores ≥ 15 and an average baseline MOS-II score of 46.5. Clearly, there appears to be room for a complementary nondrug therapy in the treatment of RLS-related sleep disorders.

Treatment when treatment is needed

Finally, no currently available therapy, including drug treatment, can be used at the time of an RLS attack. Sclerotherapy, pneumatic compression stockings, infrared light, exercise, acupuncture, iron, and RLS drugs are all administered preemptively, at times other than the time of an attack, with the intention of preventing future attacks.[9,15,16,19–25] Vibratory stimulation is the only treatment that can be administered in bed, at the time of an RLS attack, and while an RLS patient is either trying to fall asleep or is trying to get back to sleep after being awakened by RLS symptoms.

RLS symptoms disturb at times other than bedtime. When RLS patients are quiet or find the motion of their legs restricted, symptoms may occur and make it difficult or impossible to sit quietly or relax during everyday activities. Portable vibrating devices tailored to daytime use might address RLS attacks in these settings.

Limitations

The trials included in our meta-analysis were of variable duration, ranging from 4 to 12 weeks. As mentioned earlier, standardized differences in mean sleep change scores from baseline between treated and control patients were not significantly influenced by trial duration (Table 2). This observation is consistent with the temporal response dynamics of RLS severity scores observed in the drug trials included in the meta-analysis data[43–55] and is exemplified by data from a 26-week pramipexole trial reported by Hogl et al (Figure 5),[65] which show consistent superiority of drug treatment over placebo beginning at the first week of treatment and extending to week 26. Thus, inclusion of trials of different duration in the current meta-analysis is justified because there is no meaningful change in the difference between treated and control subjects from week 1 to week 26. However, if a trial duration bias is present, the small, positive slope seen in the meta-regression of Hedges's *g* statistic for change in MOS scores (Table 2) suggests that the bias would be in favor of vibratory stimulation trials of shorter duration.

Significantly increased rates of trial withdrawal secondary to adverse events were observed as trial duration increased. Given that the vibratory stimulation trials were 4 weeks in

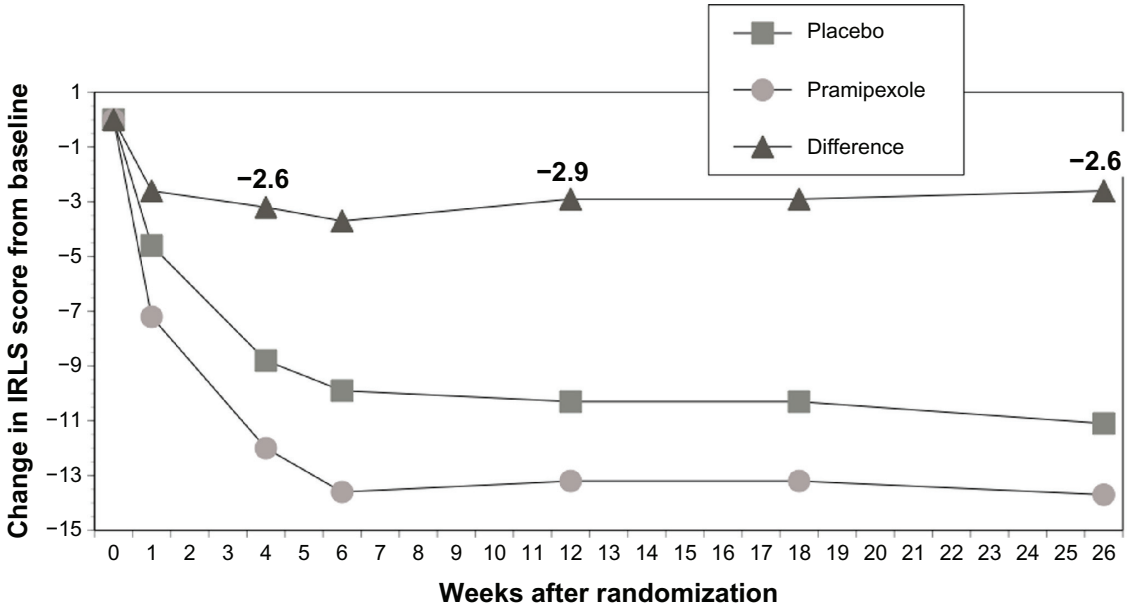

Figure 5 Stable differences between patients treated with pramipexole and placebo after week 4.
Abbreviation: IRLS, International Restless Legs Syndrome Study Group rating scale.

duration, their withdrawal rates because of adverse events would be expected to be lower than the withdrawal rates seen in the 12-week and 26-week trials. This represents a meta-analysis bias against drug trials of longer duration. Longer vibratory stimulation trials would be required to further examine the effects of trial duration.

Although inert pills and sham pads were designed not to have an influence in their respective trials, they may have introduced bias. In the two vibratory stimulation trials, sham pads were constructed to act as controls and yet be plausible treatments. To be plausible, sham pads had to be physically indistinguishable from vibratory stimulation pads and have a sensory output that patients could control with a knob and yet not be therapeutic. However, in the service of effective blinding, sham pads may have been effective counterstimuli for some 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 diverted their attention away from RLS sensations (Part III of this report).[66] Light can be an effective counterstimulus to extremity pain.[26] Similarly, sound has been demonstrated to modulate pain,[67–70] and has been used as a counterstimulus for patients with conditions such as tinnitus and auditory hallucinations.[71,72] Consequently, for some patients treated with sham pads, sound or light could have had primary therapeutic effects. If so, such effects would have biased the study against finding a difference between the treatment and sham pad groups.

Inert pills are commonly used as placebos in drug trials. However, in the case of RLS drugs, inert pills may have inflated the difference between treatment and control groups because RLS drugs produce a strong effect which is perceivable by patients, while inert pills do not. RLS drugs make many patients somnolent, often within an hour or so after ingestion. Comparison of crossover RLS drug trials with parallel trials demonstrates that patients can readily distinguish between an active RLS drug and an inert placebo.[73,74] Once distinguished, responses to outcome measures are distorted in favor of finding a difference between the drug and placebo. RLS drug trials might have been better blinded if they had used a short-acting soporific as their placebo (ie, one with drowsiness onset characteristics similar to those of RLS drugs).

Vibratory stimulation and pharmacologic treatments both had side effects that could have reduced efficacy. About 10% of patients found the vibration irritating. In a clinical setting, these patients would not be good candidates for treatment with vibratory stimulation. They could have been excluded from the two trials during screening, but to preserve blinding they were not. As a result, effect sizes for vibratory stimulation may have been muted by their inclusion. Similarly, the FDA-approved RLS drugs have many immediate unpleasant side effects (commonly headache and nausea), which could have deterred patients from continuing on drug therapy. To the extent that drug side effects compounded the disturbing symptoms of RLS, the effect sizes for drugs may also have been muted.

Conclusion

This meta-analysis shows that sleep improvement was greater in patients assigned to vibratory stimulation pads than in patients assigned to sham pads. Furthermore, sleep improvement with vibratory stimulation was comparable with

the improvement seen in FDA-approved RLS drug trials. No significant difference in adverse events was observed between vibratory stimulation pads and sham pads or between vibratory stimulation and FDA-approved drugs.

Disclosure

Financial support for the study was provided by Sensory Medical Inc, San Clemente, CA. The corresponding author is the Chief Executive Officer of Sensory Medical Inc and a minority shareholder. MJB is a consultant to and a minority shareholder in Sensory Medical Inc, and BK is an independent statistical consultant to Sensory Medical Inc.

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