Southern California RLS Support Group

St. Mary's Medical Center

1050 Linden Ave, Long Beach, CA 90813

5 October 2014

Sunday

1:00-3:00 PM

Conflict of Interest Statement

Fred Burbank, M.D.

is the

Chairman of the Board of Directors of

Sensory Medical, Inc

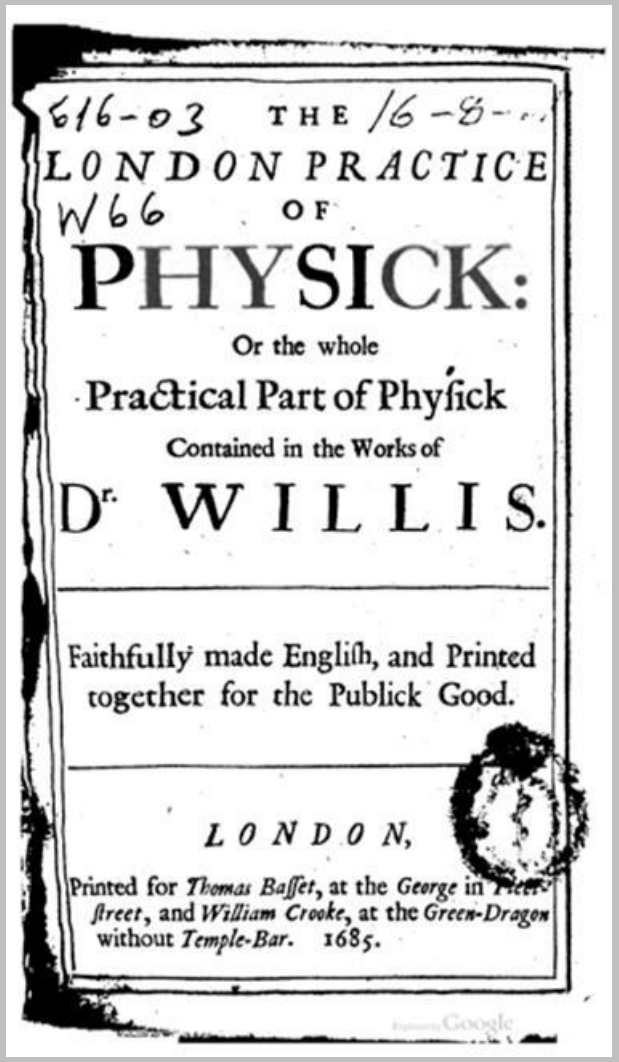
and an inventor of the Relaxis™ system described in this lecture

Counter-stimulation Treatment of Sleep Loss associated with RLS / Willis-Ekbom Disease

What is counter-stimulation?

Who were Willis and Ekbom?

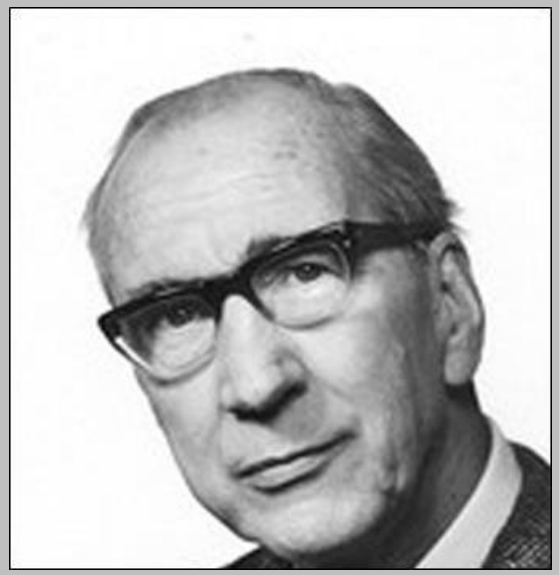
1685 Willis, T. The London practice of Physick. Instructions for curing the Watching evil. Published in London, by Bassett and Crooke; pp 402-407.



"Wherefore to some, when being abed they betake themselves to sleep, presently in the arms and legs, leapings and contractions on the tendons, and so great a restlessness and tossings of other members ensue, that the diseased are no more able to sleep, than if they were in a place of the greatest torture."

The symptoms are exclusively subjective and consist of peculiar … indefinable “crawling” sensation, developing only when the legs are still, mostly shortly after the patient retires for the night… The paresthesia is highly unpleasant, but real pain rarely occurs… The sensations are felt deep inside, never superficially in the skin…

To relieve the sensations, the patients move their legs continually or get up and walk about.



FROM THE NEUROLOGIC SERVICE OF THE SERAFIMER HOSPITAL, STOCKHOLM
HEAD: PROFESSOR NILS ANTONI

RESTLESS LEGS

A Clinical Study of a Hitherto Overlooked Disease in the Legs Characterized by Peculiar Paresthesia (»Anxietas Tibiarum»), Pain and Weakness and Occurring in two Main Forms, Asthenia Crurum Paraesthetica and Asthenia Crurum Dolorosa. A Short Review of Paresthesias in General

by

KARL-AXEL EKBOM

STOCKHOLM 1945

1945 Ekbom KA. Restless legs a clinical study. Acta Med Scand. 158, (Supplement)1-222.

Patients move to decrease RLS discomfort

Patients spontaneously seek counter-stimulation During an RLS Attack

"… 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."

Which of these activities compatible with sleep?

Mahowald MW. Restless legs syndrome: the CNS/iron connection. *J Lab Clin Med* 2006, 147:56-7.

Relaxis™ goal:

During an RLS attack

(1) you remain in bed,
(2) You focus on vibration, and
(3) you go to sleep or return to sleep.

YOU NEVER GET OUT OF BED

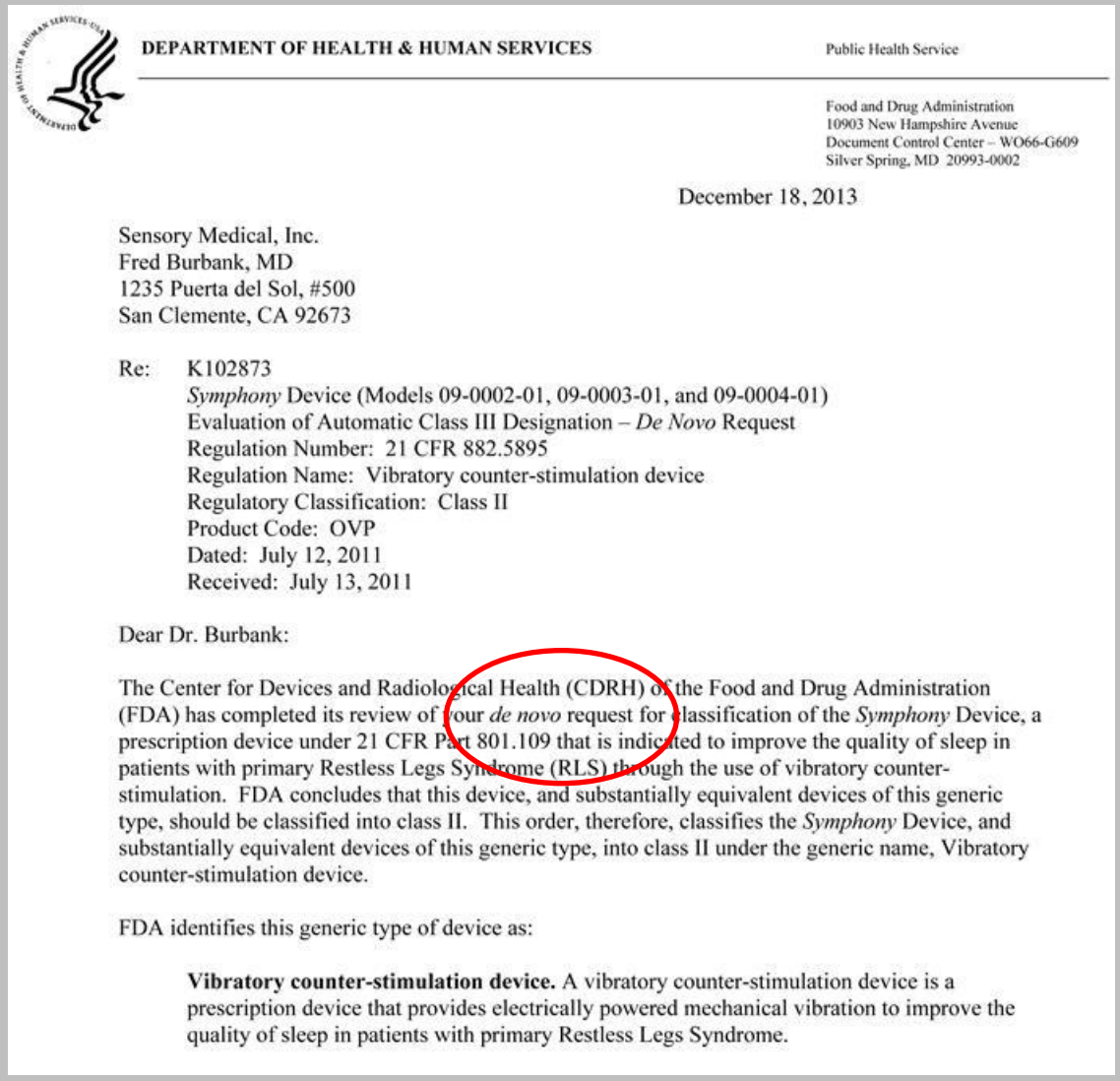
FDA – first counter-stimulation RLS device

Relaxis™

Counter-stimulation for Restless Legs Syndrome

INDICATIONS FOR USE:

"The purpose of the Relaxis™ device is to improve the quality of sleep in patients with primary Restless Legs Syndrome (RLS) through the use of vibratory counter-stimulation."



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

December 18, 2013

Sensory Medical, Inc.
Fred Burbank, MD
1235 Puerta del Sol, #500
San Clemente, CA 92673

Re: K102873
Symphony Device (Models 09-0002-01, 09-0003-01, and 09-0004-01)
Evaluation of Automatic Class III Designation – *De Novo* Request
Regulation Number: 21 CFR 882.5895
Regulation Name: Vibratory counter-stimulation device
Regulatory Classification: Class II
Product Code: OVP
Dated: July 12, 2011
Received: July 13, 2011

Dear Dr. Burbank:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your *de novo* request for classification of the *Symphony* Device, a prescription device under 21 CFR Part 801.109 that is indicated to improve the quality of sleep in patients with primary Restless Legs Syndrome (RLS) through the use of vibratory counter-stimulation. FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the *Symphony* Device, and substantially equivalent devices of this generic type, into class II under the generic name, Vibratory counter-stimulation device.

FDA identifies this generic type of device as:

Vibratory counter-stimulation device. A vibratory counter-stimulation device is a prescription device that provides electrically powered mechanical vibration to improve the quality of sleep in patients with primary Restless Legs Syndrome.

4 Relaxis Publications

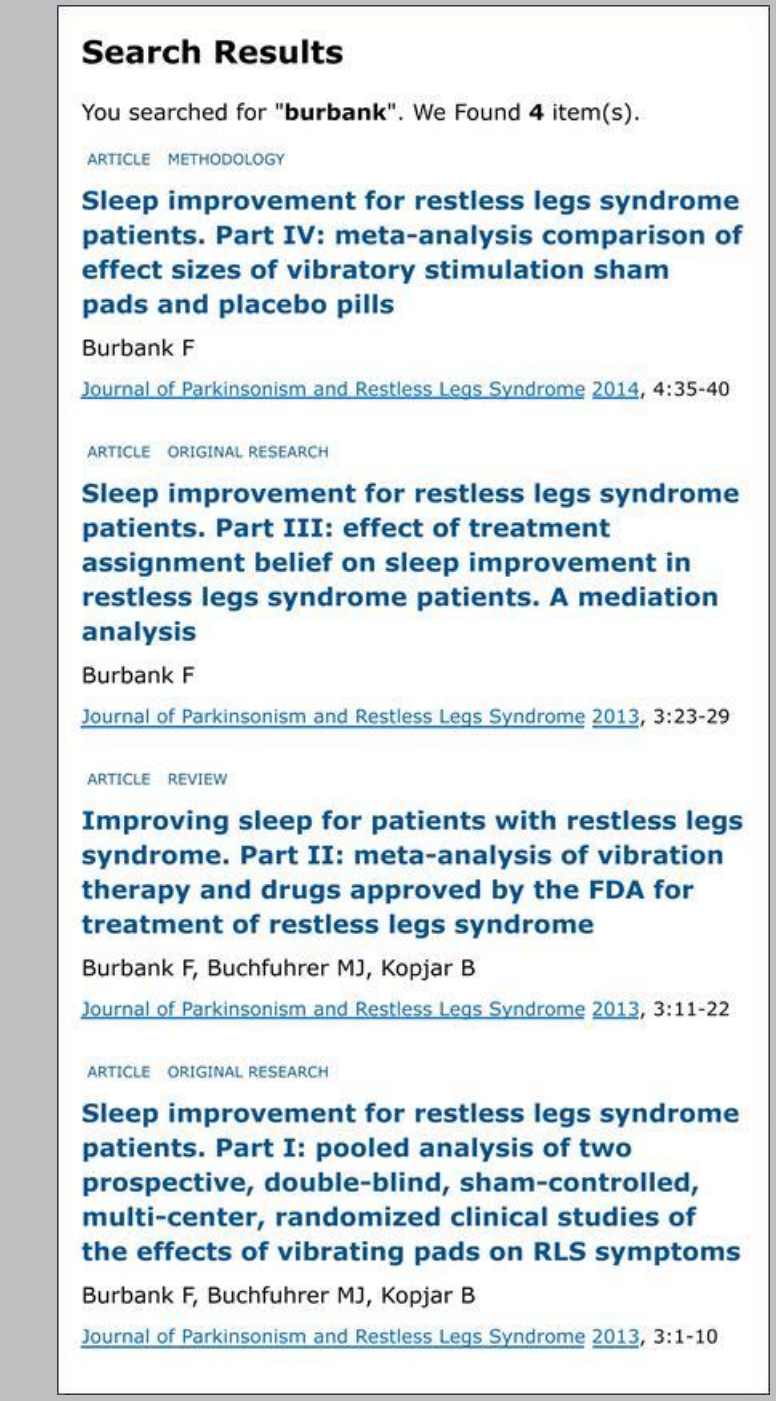
Free pdf downloads

Google “Dove Press.com”

at Dove Press

search “Burbank”

Note: Symphony™ = Relaxis™



Search Results

You searched for "**burbank**". We Found **4** item(s).

ARTICLE METHODOLOGY

Sleep improvement for restless legs syndrome patients. Part IV: meta-analysis comparison of effect sizes of vibratory stimulation sham pads and placebo pills

Burbank F

Journal of Parkinsonism and Restless Legs Syndrome 2014, 4:35-40

ARTICLE ORIGINAL RESEARCH

Sleep improvement for restless legs syndrome patients. Part III: effect of treatment assignment belief on sleep improvement in restless legs syndrome patients. A mediation analysis

Burbank F

Journal of Parkinsonism and Restless Legs Syndrome 2013, 3:23-29

ARTICLE 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

Burbank F, Buchfuhrer MJ, Kopjar B

Journal of Parkinsonism and Restless Legs Syndrome 2013, 3:11-22

ARTICLE ORIGINAL RESEARCH

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

Burbank F, Buchfuhrer MJ, Kopjar B

Journal of Parkinsonism and Restless Legs Syndrome 2013, 3:1-10

Part I

MOS-II Sleep Scale

>2x better Sleep Improvement than controls

Part II

Sleep improvement not significantly

different than FDA approved RLS Drugs

with

No Drug side-effects

Others are beginning to understand:

"External sensory input tends to reduce leg discomfort in patients suffering from restless legs syndrome."

NEW RESEARCH

SCIENTIFIC INVESTIGATIONS

JCSM
Journal of Clinical Sleep Medicine
http://dx.doi.org/10.5664/jcsm.3964

Effect of Sensory Stimuli on Restless Legs Syndrome: A Randomized Crossover Study

Anouk D. Rozeman, M.D.[1]; Truus Ottolini[1]; Diana C. Grootendorst, Ph.D.[2]; Oscar J.M. Vogels, M.D., Ph.D.[3]; Roselyne M. Rijsman, M.D., Ph.D.[1]

[1]Center for Sleep and Wake Disorders and [2]Landsteiner Institute, Medical Center Haaglanden, The Hague, The Netherlands; [3]Department of Neurophysiology, St. Antonius Hospital, Nieuwegein, The Netherlands

Study Objective: A variety of sensory stimuli relieve restless legs syndrome symptoms. Because systematic evaluations of sensory stimulation in restless legs syndrome are largely lacking, we performed a randomized crossover study to evaluate the effect of external sensory stimulation on restless legs syndrome symptoms.

Methods: Eighteen patients underwent 3 consecutive suggestive immobilization tests with the order of the following 3 conditions randomly assigned: no electrical stimulation (condition 1), tactile and proprioceptive sensory stimulation (condition 2), and tactile sensory stimulation only (condition 3). Restless legs syndrome symptoms were quantified by visual analog scales, and periodic leg movements during wake were measured.

Results: Baseline visual analogue scale score was 4.5 (range 0-60) in condition 1, 10.5 (range 0-96) in condition 2, and 8.5 in condition 3 (p = 0.21). There was a tendency towards a higher maximum visual analogue scale score and visual analogue scale score at the end of the suggested immobilization test in the conditions with tactile sensory stimulation, though not significant (p = 0.74 and p = 0.29, respectively). Fifteen patients suffered from periodic leg movements during wake. Median indices were 18 (range 0-145) in condition 1, 26 (range 0-190) in condition 2, and 49 (range 0-228) in condition 3 (p = 0.76).

Conclusions: We found a tendency towards less leg discomfort in the conditions in which an external sensory input was applied. This potential benefit of sensory stimuli on restless legs syndrome severity merits further investigation as this could open new ways towards a better pathophysiological understanding and non-pharmacological treatments.

Keywords: restless legs syndrome, suggestive immobilization test, periodic limb movement disorder

Citation: Rozeman AD, Ottolini T, Grootendorst DC, Vogels OJM, Rijsman RM. Effect of sensory stimuli on restless legs syndrome: a randomized crossover study. *J Clin Sleep Med* 2014;10(8):893-896.

Restless legs syndrome (RLS) is characterized by an urge to move combined with the occurrence of unpleasant or disabling sensory symptoms at rest. These symptoms begin or worsen during rest or inactivity and occur mostly during the evening or night. They are relieved by voluntary movement, at least as long as the activity continues.[1] Eighty to 90 percent of RLS patients also suffer from involuntary periodic limb movements during wake (PLMW) or sleep (PLMS).[1,2,3]

Clinical experience shows that, besides movement of the legs, a variety of sensory stimuli may relieve RLS symptoms. Cold showers, massaging of the legs, or a hot bath may lessen RLS symptoms.[4] One case study showed that a massage program reduced RLS complaints.[5] In addition, several studies report a positive effect on RLS symptoms with the use of external compression on the legs. Eliasion and Lettieri showed a positive effect on RLS severity and improvement of fatigue and daytime sleepiness with the use of sequential compression devices.[6,7] Moreover, Rajaram and colleagues reported a reduction in RLS symptoms in RLS patients that were treated with enhanced external counter pulsation (EECP) on the legs for congestive heart failure.[8] Nevertheless, a follow-up double-blind, placebo-controlled study showed no difference in reduction of RLS symptoms between the therapeutic EECP and placebo.[9]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Clinical experience shows that a variety of sensory stimuli may relieve RLS symptoms, though systematic evaluations of these phenomena are lacking. We performed a randomized crossover study to evaluate the effect of external sensory stimulation on restless legs syndrome symptoms.

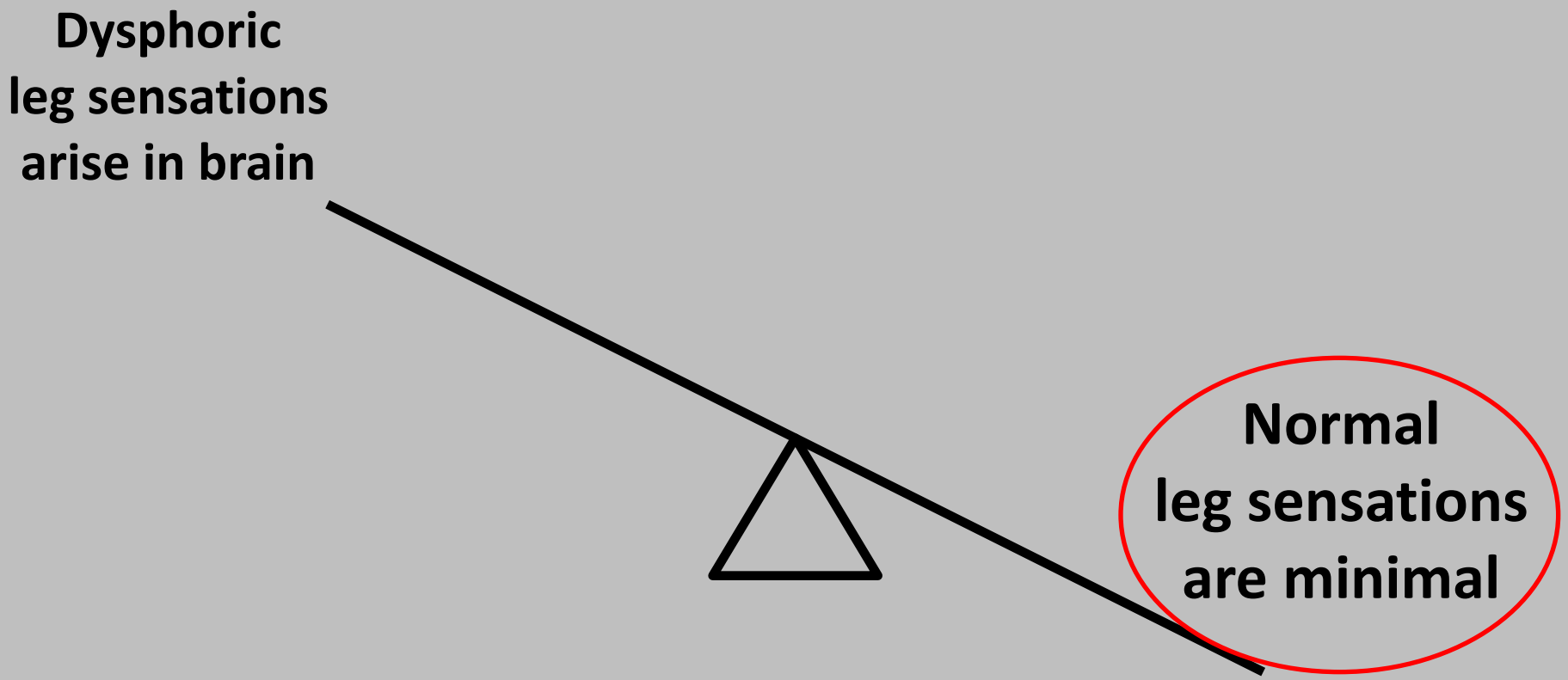
Study Impact: External sensory input tends to reduce leg discomfort in patients suffering from restless legs syndrome. This potential benefit could open new ways towards a better pathophysiological understanding and non-pharmacological treatments.

The positive effect of these local leg compression devices on RLS complaints may be attributed to an improved local circulation and decrease of subclinical local ischemia.[7,8] Nevertheless, one could also hypothesize that it is not the repetitive compression but repetitive sensory input on the legs that reduces the RLS symptoms.

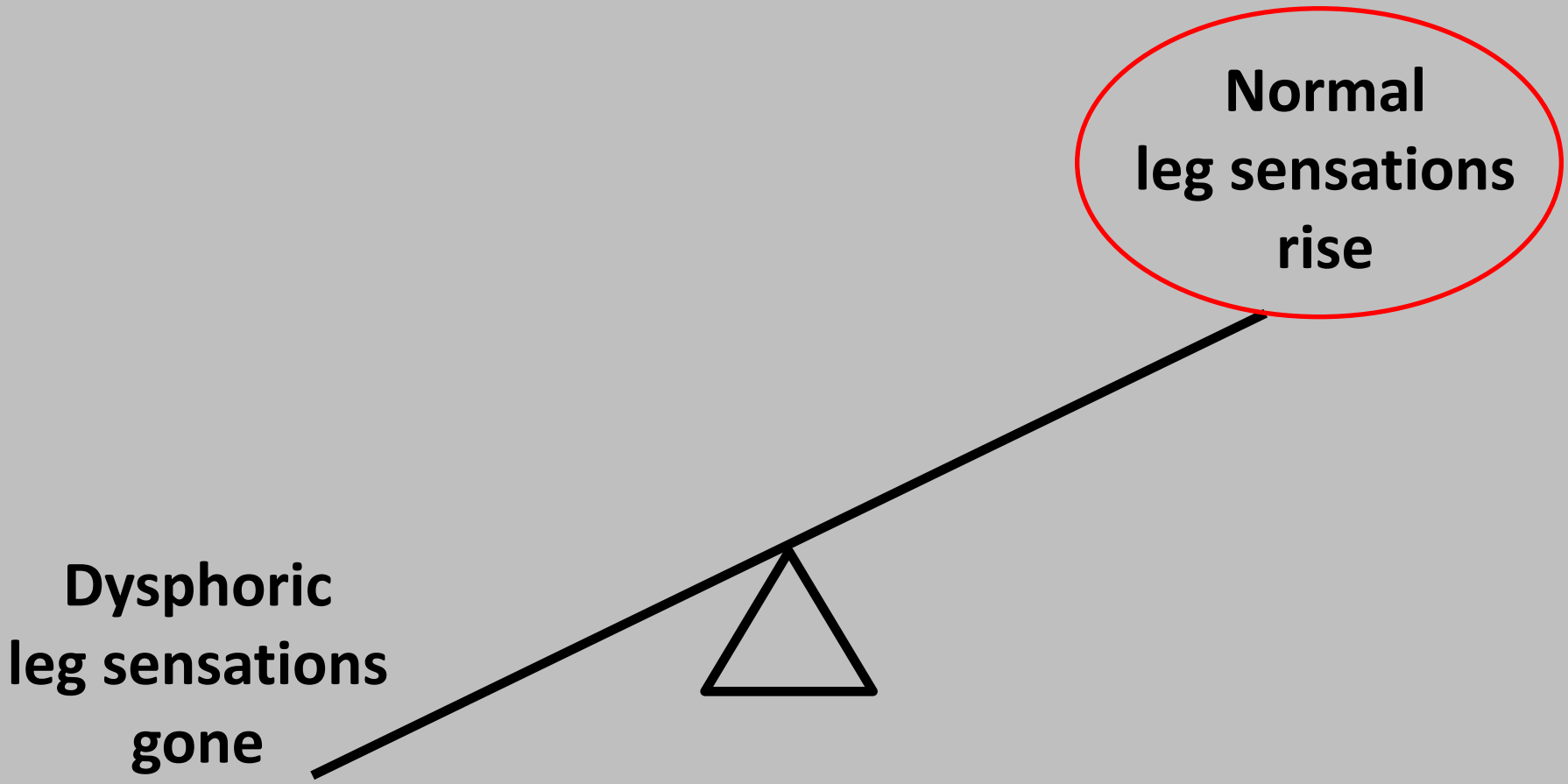
To objectify the phenomenon of sensory input reducing RLS complaints, we performed a randomized crossover study in

Without Relaxis

During an RLS attack:
in bed, sleepy or asleep



Standing and/or walking



But

Standing and walking, and the like, are

incompatible **with sleep**

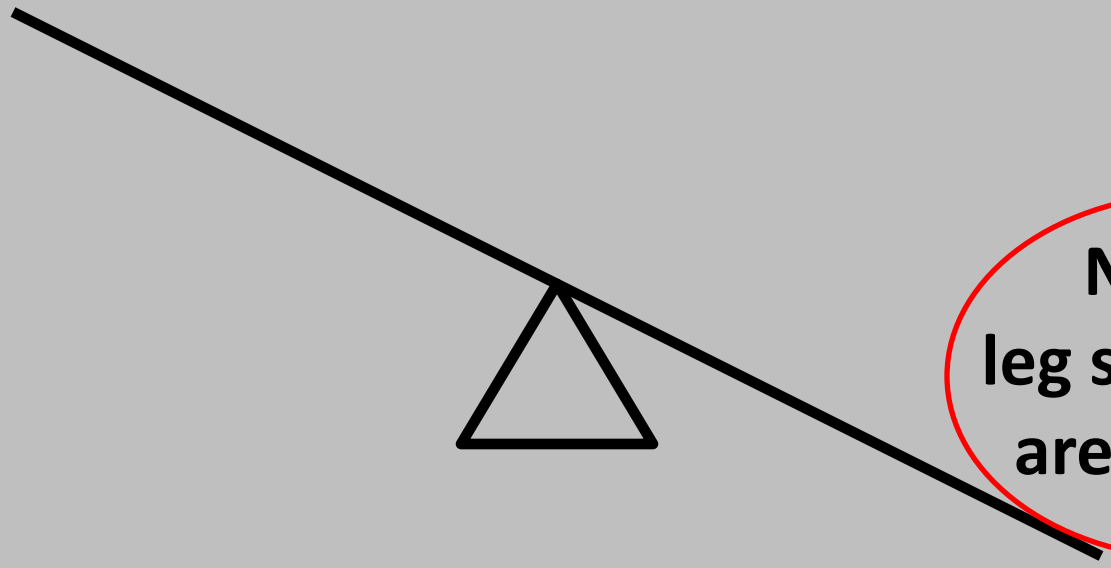
There you are. Standing, looking back at your bed. Decreased RLS sx but *now wide awake*. UGH!

With Relaxis

Vibrating counter-stimulation *is* compatible with sleep

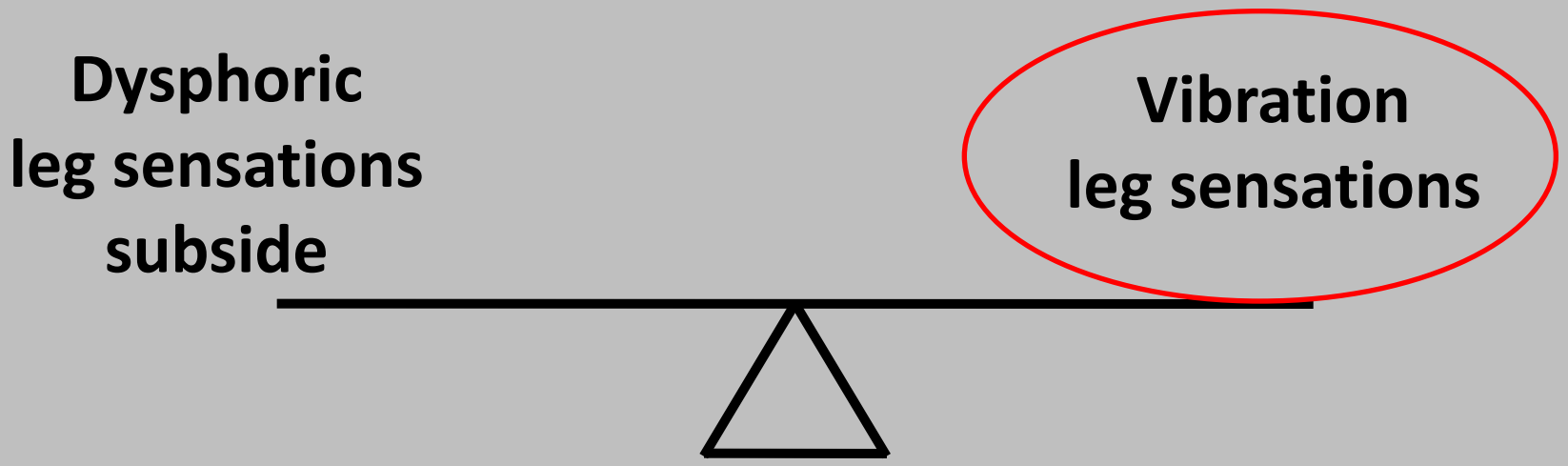
During an RLS attack:
in bed, sleepy or asleep

Dysphoric leg sensations arise in brain

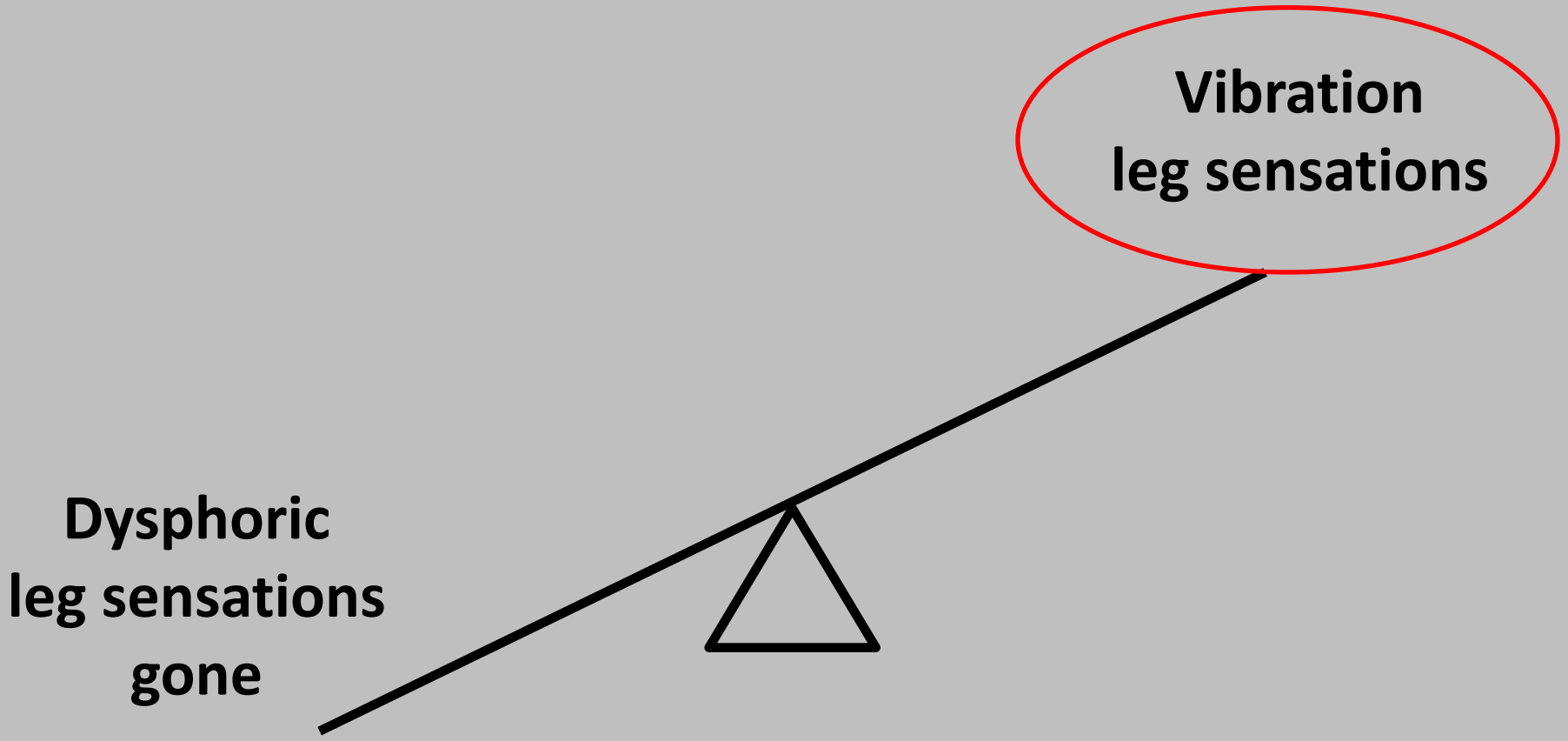


Normal leg sensations are minimal

Vibration during as RLS attack



Vibration = Real leg sensations



Vibration takes the place of standing and/or walking

If vibration is pleasant (90+ %) and slowly “ramped down” at the end of a cycle,

patients stay in bed & fall back to sleep

In Summary

We have conducted two multi-center, blinded, parallel, randomize, controlled trials to assess the safety and effectiveness of Relaxis.

The results of the studies show that Relaxis is effective in reducing sleep loss & = RLS drugs.

Relaxis will not work for some patients, primarily those who find the sensation of vibration uncomfortable.

Relaxis gives you control at the time of an RLS attack. With Relaxis drugs are not constantly circulating in your system.

We believe the trade-off between (i) the side effects and cost of RLS drugs and (ii) the Relaxis system makes Relaxis the first choice for RLS patients.

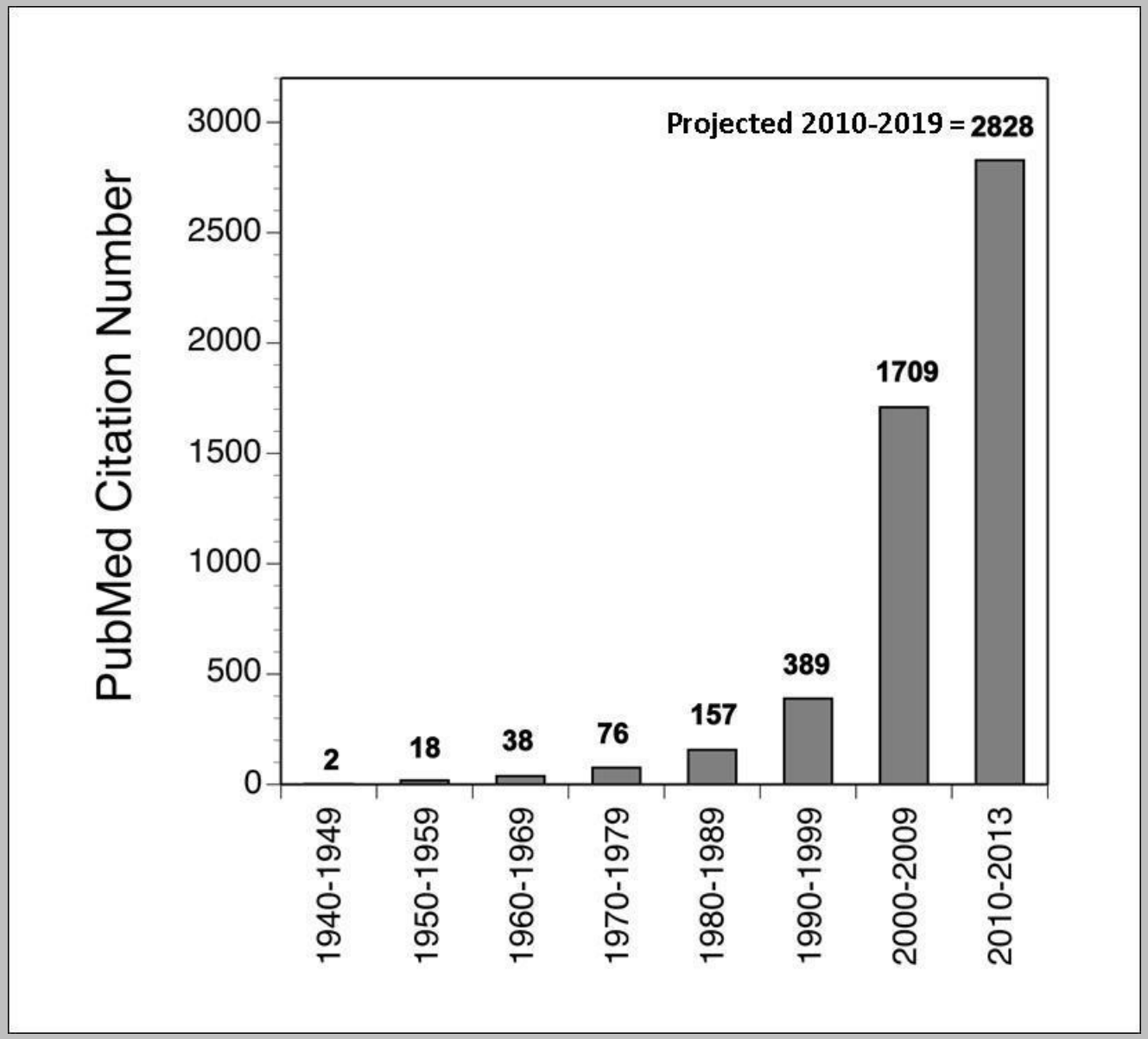
Where can I get a Relaxis?

- Relaxis is an FDA Cleared Type II Medical Device so it requires a doctor's prescription.
- Relaxis is the first and only FDA cleared device for RLS sleep loss, so we currently do not have insurance reimbursement (and won't for about 2 years).
- More information on www.sensorymedical.com
- Relaxis will be available in late October 2014.
- Contact your physician and ask about Relaxis.

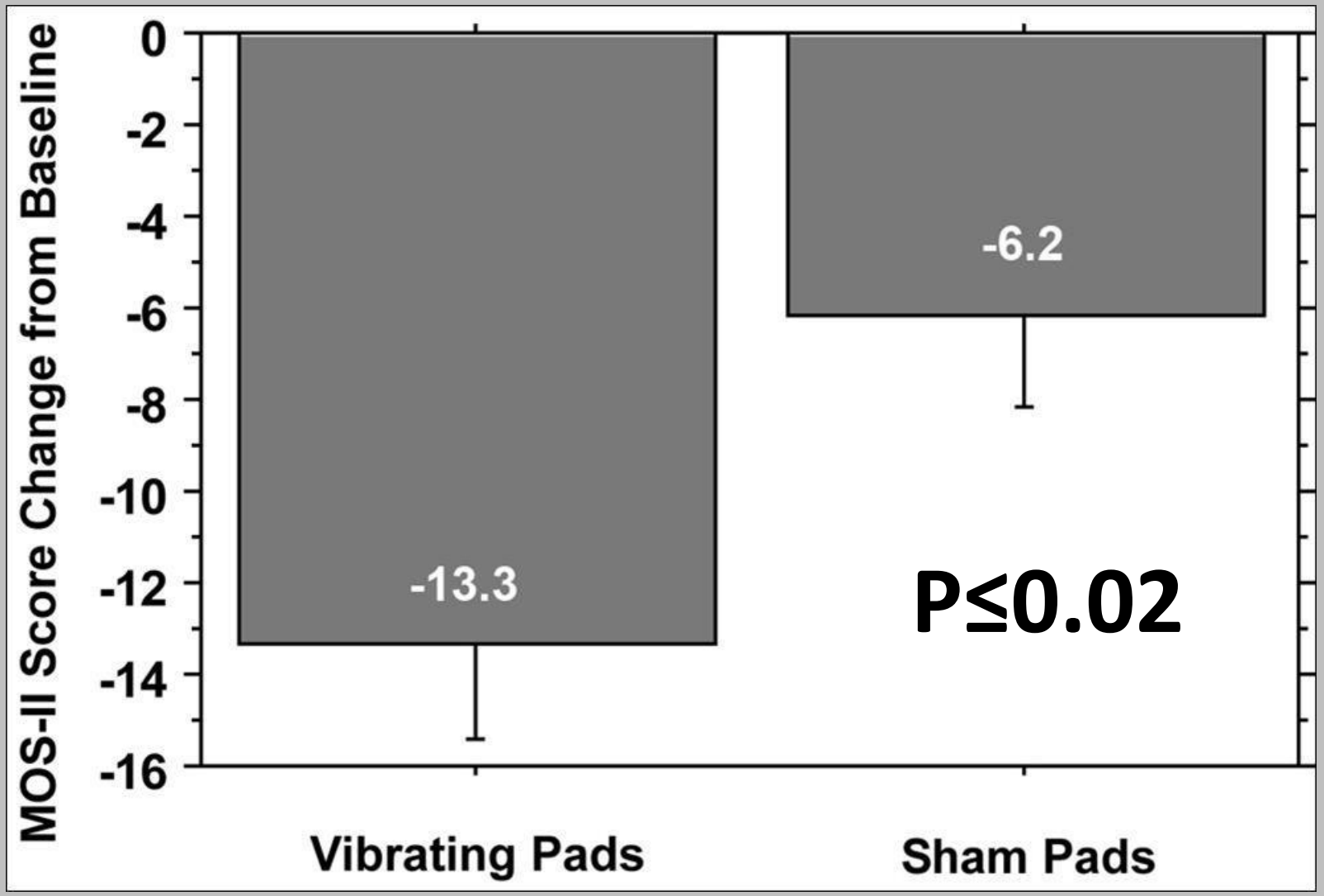
Relaxes can be your weapon against an RLS attack

THE END

Wide, growing interest in RLS

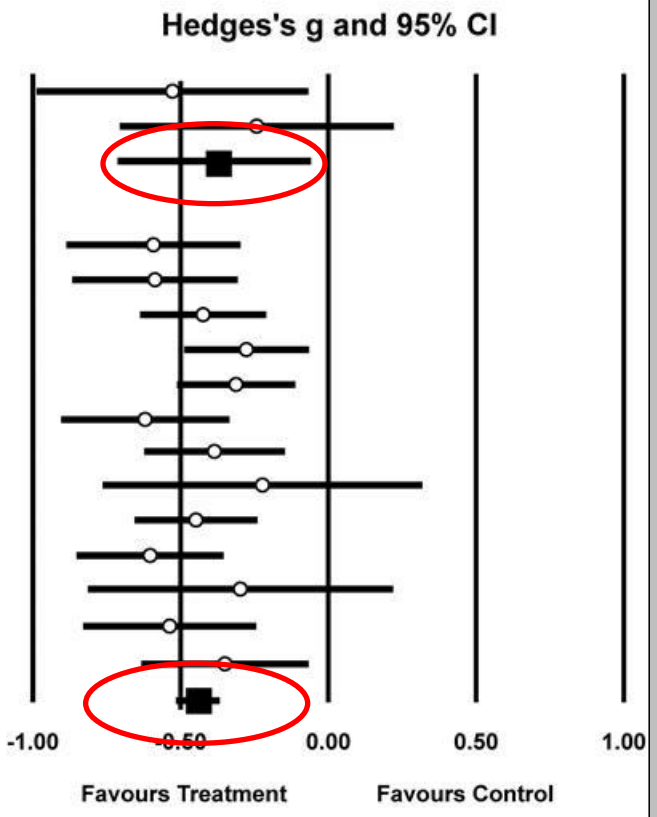


2x Sleep Improvement – MOS-II Sleep Scale



Sleep improvement not significantly different than FDA approved RLS Drugs

Grouped by Drug vs. Vibration	Reference Number		Statistics for each study				
			Hedges's g	Lower limit	Upper limit	Z-Value	p-Value
Vibration	57	SMI-001 Sensory Medical 2012	-0.527	-0.983	-0.072	-2.268	0.023
Vibration	57	SMI-002 Sensory Medical 2012	-0.242	-0.701	0.218	-1.031	0.302
Vibration Fixed Effect Summary			**-0.386**	**-0.709**	**-0.062**	**-2.336**	**0.019**
Drug	45	Gaba Kushida 2009	-0.592	-0.883	-0.301	-3.984	0.000
Drug	49	Gaba Lee 2011	-0.587	-0.863	-0.311	-4.165	0.000
Drug	46	Prami Ferini-Strambi 2008	-0.424	-0.633	-0.214	-3.962	0.000
Drug	51	Ropi Kushida 2008	-0.277	-0.484	-0.069	-2.615	0.009
Drug	55	Ropi GSK ROR104836 2012	-0.312	-0.509	-0.115	-3.111	0.002
Drug	47	Ropi Benes 2011	-0.620	-0.901	-0.339	-4.322	0.000
Drug	44	Ropi Trenkwalder 2004	-0.382	-0.616	-0.147	-3.194	0.001
Drug	48	Ropi Allen 2004	-0.223	-0.760	0.315	-0.813	0.416
Drug	50	Ropi Bogan 2006	-0.448	-0.652	-0.244	-4.304	0.000
Drug	43	Ropi Walters 2004	-0.603	-0.848	-0.358	-4.823	0.000
Drug	52	Rotig Oertel 2010	-0.297	-0.810	0.215	-1.137	0.256
Drug	54	Rotig Trenkwalder 2008	-0.541	-0.830	-0.251	-3.661	0.000
Drug	53	Rotig Hening 2010	-0.350	-0.629	-0.071	-2.459	0.014
Drug Fixed Effect Summary			**-0.436**	**-0.506**	**-0.365**	**-12.086**	**0.000**



Gaba = gabapentin enacarbil, Prami = Praipexole, Ropi = Ropinirole, Rotig = Rotigotine

Journal of Parkinsonism and Restless Legs Syndrome

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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

This article was published in the following Dove Press journal:
Journal of Parkinsonism and Restless Legs Syndrome
28 March 2013
Number of times this article has been viewed

Fred Burbank[1]
Mark J Buchfuhrer[2]
Branko Kopjar[3]

[1]Salt Creek International Women's Health Foundation, San Clemente, CA, USA; [2]Stanford University Center for Sleep Sciences, Downey, CA, USA; [3]Department of Health Services, University of Washington, Seattle, WA, USA

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

Correspondence: Fred Burbank
Salt Creek International Women's Health Foundation, 1235 Puerta del Sol, Suite 700, San Clemente, CA, 92673, USA
Tel +1 949 496 0026
Fax +1 949 492 0650
Email fburbank@cox.net

Journal of Parkinsonism and Restless Legs Syndrome

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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

This article was published in the following Dove Press journal:
Journal of Parkinsonism and Restless Legs Syndrome
29 March 2013
Number of times this article has been viewed

Fred Burbank[1]
Mark J Buchfuhrer[2]
Branko Kopjar[3]

[1]Salt Creek International Women's Health Foundation, San Clemente, CA, [2]Stanford University Center for Sleep Sciences, Downey, CA, [3]Department of Health Services, University of Washington, Seattle, WA, USA

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

Correspondence: Fred Burbank
Salt Creek International Women's Health Foundation, 1235 Puerta del Sol, Suite 700, San Clemente, CA, 92673, USA
Tel +1 949 496 0026
Fax +1 949 492 0650
Email fburbank@cox.net

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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ORIGINAL RESEARCH

Sleep improvement for restless legs syndrome patients. Part III: effect of treatment assignment belief on sleep improvement in restless legs syndrome patients. A mediation analysis

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Journal of Parkinsonism and Restless Legs Syndrome
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Number of times this article has been viewed

Fred Burbank

Director, Salt Creek International Women's Health Foundation, San Clemente, CA, USA

Purpose: Two parallel-design, randomized, sham-controlled clinical trials were conducted to study the safety and efficacy of vibratory stimulation (VS) on restless legs syndrome (RLS) patients (Part I of this series of articles). Pooled data from the two studies was retroactively analyzed to compare the relative effects of actual pad assignment with therapeutic pad assignment belief on sleep improvement for patients with RLS.

Patients and methods: One hundred fifty-eight patients with at least moderately severe RLS, as measured by a score of 15 points or greater on the International Restless Legs Syndrome Study Group rating scale (IRLS), were enrolled in the study. Patients were randomly assigned to treatment (patient-controlled vibration) or sham (patient-controlled sound or light-emitting) pads. Patients and clinicians were blinded to pad assignment. The pad was placed under the patient's legs while in bed at night and activated during an RLS episode. Improvements in Medical Outcomes Study Sleep Problems Index II (MOS-II) scores from baseline to week 4 were examined as a function of pad assignment (independent variable) and therapeutic pad assignment belief held by each patient (mediator variable) through mediation analysis.

Results: Therapeutic pad assignment belief influenced change in MOS-II scores more than actual pad assignment. Patients who believed they had been assigned a therapeutic pad had substantially greater sleep improvement than those who concluded the opposite. When a patient believed that a therapeutic pad had been assigned, sleep improvement was comparable in magnitude, independent of the type of pad assigned (vibrating or sham). Patients assigned vibrating pads believed that they had been assigned a therapeutic pad 2.6 times more frequently than patients assigned sham pads. Consequently, vibrating pads were more efficient at improving sleep than sham pads. Similarity of sleep improvement for those who believed that they had been assigned a therapeutic pad among vibrating, sound, and light pad patients suggests a common counterstimulation therapeutic mechanism of action within the brain.

Conclusion: Therapeutic pad assignment belief influenced improvement in MOS-II scores more strongly than actual pad assignment. Therapeutic pad assignment belief was more commonly associated with vibrating pads than sham pads. These results may have implications for the type of shams used in future device studies.

Keywords: restless legs syndrome, placebo effect, mediator variable, sleep, counterstimulation

Correspondence: Fred Burbank
Salt Creek International Women's Health Foundation, 1235 Puerta del Sol, Suite 700, San Clemente, CA, 92673, USA
Tel +1 949 496 0026
Fax +1 949 492 0650
Email fburbank@cox.net

Introduction

Vibration stimulation (VS) has been shown to improve sleep in patients suffering from restless legs syndrome (RLS) as measured by (1) the Medical Outcomes Study Sleep Problems Index II (MOS-II) scale and by (2) clinician evaluation (Part I).[1]

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METHODOLOGY

Sleep improvement for restless legs syndrome patients. Part IV: meta-analysis comparison of effect sizes of vibratory stimulation sham pads and placebo pills

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25 February 2014
Number of times this article has been viewed

Fred Burbank

Salt Creek International Women's Health Foundation, San Clemente, CA, USA

Purpose: To determine whether sham pads used as controls in randomized clinical trials of vibratory stimulation to treat patients with sleep loss associated with restless legs syndrome perform differently than placebo pills used in comparable restless legs syndrome drug trials.

Patients and methods: Sham pad effect sizes from 66 control patients in two randomized clinical trials of vibratory stimulation were compared with placebo responses from 1,024 control patients in 12 randomized clinical drug trials reporting subjective sleep measurement scales. Control patient responses were measured as the standardized difference in means corrected for correlation between beginning and ending scores and for small sample sizes.

Results: For parallel randomized clinical trials, sham effects in vibratory stimulation trials were not significantly different from placebo effects in drug trials (0.37 and 0.31, respectively, $Q_{\text{between subgroups}}=0.25$, $P_Q \geq 0.62$). Placebo effect sizes were significantly smaller in crossover drug trials than sham effect sizes in parallel vibratory stimulation trials (0.07 versus 0.37, respectively, $Q_{\text{between subgroups}}=4.59$, $P_Q \leq 0.03$) and placebo effect sizes in parallel drug trials (0.07 versus 0.31, respectively, $Q_{\text{between subgroups}}=5.50$, $P_Q \leq 0.02$).

Conclusion: For subjective sleep loss assessments in parallel trials, sham pads in vibratory stimulation trials performed similarly to placebo pills in drug trials. Trial design (parallel versus crossover) had a large influence on control effect sizes. Placebo pills in crossover drug trials had significantly smaller effect sizes than sham pads in parallel vibratory stimulation trials or placebo pills in parallel drug trials.

Keywords: sham effect, placebo effect, trial design, crossover study, parallel study, counterstimulation

Introduction

Background

Randomized clinical trials (RCTs) are nearly universally focused on the difference between an active treatment and an inactive or control treatment. If the active treatment effect size is large and the inactive effect size is small, the trial is a success. However, if the active treatment effect and the inactive treatment effect are both large, the trial is a failure. Clearly, the magnitude of the inactive or control treatment effect is of great importance in any RCT. In drug trials, control patients are given an inactive or a "placebo" pill that looks like the active pill but is pharmacologically inert. In physical medicine studies, control patients are exposed to a device that looks like, or is a "sham" of the physical treatment, but does not provide active treatment.

Correspondence: Fred Burbank
Salt Creek International Women's Health Foundation, 1235 Puerta del Sol, Suite 700, San Clemente, CA, 92673, USA
Tel +1 949 496 0026
Fax +1 949 492 0650
Email fburbank@cox.net