

# 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

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 counter-stimulation 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).<sup>1</sup>

Furthermore, it has been demonstrated that sleep improvement from vibration treatment was comparable to sleep improvement from US Food and Drug Administration (FDA)-approved RLS drugs (Part II).<sup>2</sup>

The current study is a mediation analysis of the pooled clinical trial data described in Parts I and II of this series of articles.<sup>1,2</sup> At the end of each of the two vibration trials, patients were asked whether they believed they had been assigned a therapeutic pad or a sham pad. Belief about pad assignment was a putative mediator variable.<sup>3,4</sup> Mediators are intervening variables that develop after treatment begins but before outcome assessment is complete. Examination of a mediator variable can help to understand the mechanism by which treatment affects outcome and may lead to the development of more effective treatments.<sup>5</sup> This mediation analysis will quantify the magnitude of the indirect effect of therapeutic pad assignment belief on sleep improvement.

## Materials and methods

### Double-blinding

Effective double-blinding is critical to understanding the role of therapeutic assignment belief on outcomes because patient-reported measurements such as the MOS-II sleep improvement scale are not objective measurements. In the two study arms described in Part I, patient and clinician blinding were optimized by excluding any patient who had prior RLS treatment with vibration and by not using a cross-over trial design.<sup>1,6</sup> Pads were randomly assigned to patients from a master randomization table created prior to patient enrollment. Pads were sent to the clinical centers in unmarked boxes opened by each patient when he or she got home.

### Efficacy variable

Change from baseline of RLS-related sleep disturbances was measured with the MOS-II scale.<sup>7,8</sup> The MOS-II scale has been shown to be reliable and valid for measuring sleep disturbance in RLS patients and proven to correlate with overall RLS quality-of-life scores and with RLS severity scores.<sup>9,10</sup>

### Mediator variable

At the completion of the study, patients were asked if they believed they had been assigned a therapeutic pad. Belief about pad assignment defined the putative mediator variable.

### Statistical analysis

The effects of actual pad assignment (the independent variable) and therapeutic pad assignment belief (the mediator variable)

on the MOS-II change score (the dependent variable) were evaluated using the mediation package in the statistical computing language R (The R Project for Statistical Computing, <http://www.r-project.org/>) developed by Imai, Keele, and Tingley.<sup>11,12</sup> Linear regression modeled pad assignment and therapeutic pad assignment belief. Individuals with missing data on the outcome or the belief variable were excluded from the model (5 out of 158 individuals). Probit regression was used to model therapeutic pad assignment belief compared to the actual pad assignment, based on the same set of data. These two models were then analyzed using the mediate function in the R mediation package to estimate the mediation effect, the direct effect, and the total effect of pad assignment on the outcome, along with parametric bootstrap confidence intervals based on 1000 simulations.

It should be noted that all mediation models are causal models. In the current study, therapeutic pad assignment belief is presumed to cause change in MOS-II scores and not vice versa. Mediation is not defined statistically; rather, statistics are used to evaluate a postulated mediation model.

A mediator variable can potentially account for none, some, or all of an observed relationship between an independent and a dependent variable. Full mediation occurs if inclusion of the mediation variable drops the direct relationship between the independent variable (actual pad assignment) and dependent variable (change in MOS-II scores) to zero. Partial mediation occurs when the mediating variable accounts for some, but not all, of the relationship between the independent variable and dependent variable. Partial mediation implies that in addition to a significant relationship between the mediator and the dependent variable, some direct relationship also exists between the independent and dependent variables.

Additional analyses were performed with SAS software version 9.3 (SAS Institute Inc, Cary, NC, USA). For all statistical tests, significance cut-off was at  $P \leq 0.05$ .

## Results

### Patient characteristics

One hundred fifty-eight RLS patients with at least moderately severe primary RLS were enrolled at five clinical sites. Patient characteristics (Table 1), randomization, test-taking compliance, blinding success, vibration safety, sham comparisons, and data poolability have been previously reported (Part I and Part II).<sup>1,2</sup>

### Double-blinding effectiveness

The results of Part I demonstrated that blinding success was adequate.<sup>1</sup> Neither patients nor clinicians accurately guessed

**Table 1** 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	52.8 (15.4)	53.7 (14.6)	0.67	52.8 (14.8)	53.9 (15.1)	0.64
Height	66.0 (3.5)	66.4 (3.6)	0.52	66.2 (3.6)	66.2 (3.6)	0.94
Weight	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 (years)	32.8 (18.0)	34.6 (18.1)	0.55	33.4 (18.8)	34.2 (17.0)	0.78
Duration (years)	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 Study Group rating scale; MOS-II, Medical Outcomes Study Sleep Problems Index II; RLS, Restless Legs Syndrome; SD, standard deviation.

pad assignment (guess accuracy was no greater than chance), and the completion rates for test-taking between the treatment and sham groups were comparable.

## Mediation analysis

One hundred fifty-seven (99.4%) of the enrolled patients contributed data to the mediation analysis, which separated the total effect of pad assignment on sleep improvement into two components:

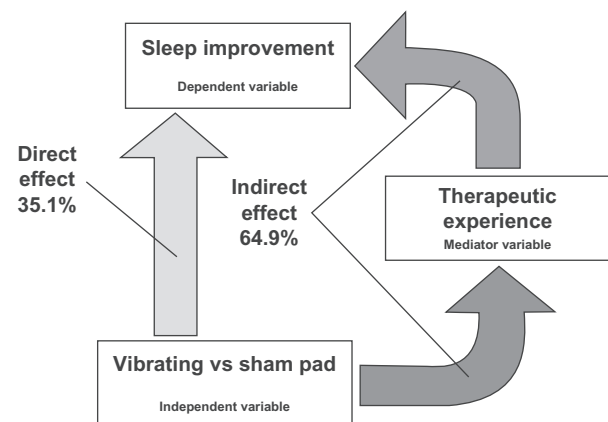
$$\text{Total effect} = \text{Direct effect} + \text{Mediation effect}$$

The analyses in Parts I and II focused entirely on total effect.<sup>1,2</sup> In Part I, total effect was calculated as the raw difference in MOS-II change scores between patients assigned vibrating pads and patients assigned sham pads. In Part II, total effect was calculated as a standardized difference between treatment and control (sham) groups and expressed as a Hedges's *g* statistic. In both analyses, assignment of a vibrating pad improved sleep significantly more than assignment of a sham pad.

Figure 1 and Table 2 summarize the mediation analysis. Total effect was significant at  $P \leq 0.05$ , which is consistent with the findings of Parts I and II.<sup>1,2</sup> The mediator variable, therapeutic pad assignment belief, caused 64.9% of the total effect ( $P \leq 0.001$ , Table 2). The effect size of the mediator variable was in the medium range (partial correlation coefficient product = 0.11).<sup>13</sup> Direct effect of actual pad assignment on MOS-II score improvement was 35.1% of total effect and was not statistically significant. However, it was not zero, implying that pad assignment belief was a partial mediator and that pad assignment had a separate, direct therapeutic effect on sleep improvement that was not mediated by pad assignment belief.

## Therapeutic effects were comparable for patients who believed they were assigned a therapeutic pad

When patients believed that they had been assigned a therapeutic pad – regardless of which pad was actually assigned – their sleep improvement was substantial (Figure 2). Most patients who believed that they had been assigned a therapeutic pad had actually been assigned one ( $N = 51$  [of 91], Figure 2). However, some of these patients had been assigned a sham pad ( $N = 15$  [of 66], Figure 2). When these two groups were compared, no significant difference was observed between either the vibrating or sham pad to improve MOS-II scores from baseline ( $-17.8$  and  $-19.5$ , respectively,  $P > 0.95$ , Figure 2). When a patient believed that a therapeutic pad had been assigned, comparable degrees of sleep improvement followed, independent of whether a treatment pad or a sham pad had been assigned.



**Figure 1** A diagram showing direct and indirect effects of vibrating pads on RLS sleep improvement.

**Abbreviation:** RLS, Restless Legs Syndrome.

**Table 2** Estimated mediation analysis effects on MOS-II scores\*

	<b>% total effect</b>	<b>Regression coefficient</b>	<b>95% confidence interval</b>	<b>99% confidence interval</b>	<b>99.9% confidence interval</b>
Mediation effect	<b>64.9</b>	<b>-4.74</b>	<b>-8.04, -2.25</b>	<b>-9.09, -1.67</b>	<b>-9.8, -0.99</b>
Direct effect	35.1	-2.56	-8.20, 3.20	-9.98, 5.15	-10.59, 6.21
Total effect	<b>100.0</b>	<b>-7.30</b>	<b>-12.99, -1.24</b>	-14.82, 0.42	-16.31, 1.51

**Note:** \*Effects that are significantly different from zero are shown in bold along with their bootstrap confidence intervals.

**Abbreviation:** MOS-II, Medical Outcomes Study Sleep Problems Index II.

Conversely, when patients did not believe that they had been assigned a therapeutic pad, they showed little improvement in MOS-II change scores (-5.1 and -1.2, respectively,  $P > 0.45$ , for patients assigned vibrating and sham pads).

### Vibrating pads were more efficient at creating the belief that a therapeutic pad had been assigned

Although assignment of either a vibrating pad or a sham pad could lead to the belief that a therapeutic pad had been assigned, they did not do so with equal efficiency. Fifty-four of the 91 patients (59.3%) assigned a vibrating pad believed that they had been assigned a therapeutic pad. Only 15 of the 66 patients (22.7%) [one missing data point] assigned a sham pad believed that they had been assigned a therapeutic pad. These differences were significant; vibrating pad recipients believed that they had been assigned a therapeutic pad 2.6 times more frequently (Figure 3,  $P < 0.0001$ , Chi-square test).

Therapeutic efficacy was significantly higher for vibrating pads than for sham pads. The mediated or indirect therapeutic

effect sequence for MOS-II score improvement appeared to be:

Sham pad assignment → 22.7% believed a therapeutic pad was assigned → 19.5 point sleep improvement on the MOS-II scale

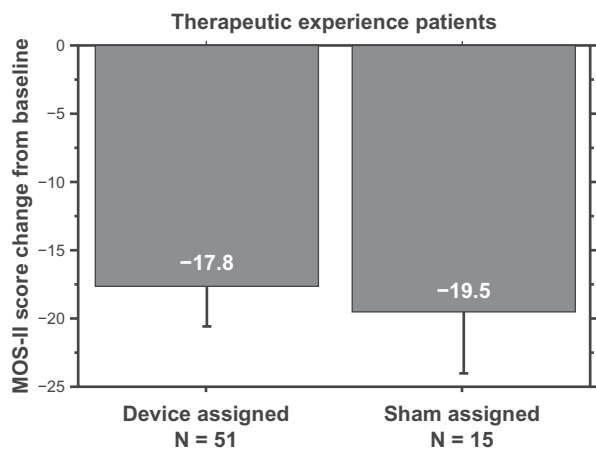
Vibrating pad assignment → 59.3% believed a therapeutic pad was assigned → 17.8 point improvement on the MOS-II scale

### Discussion

#### The randomized clinical trial (RCT) and placebo effect

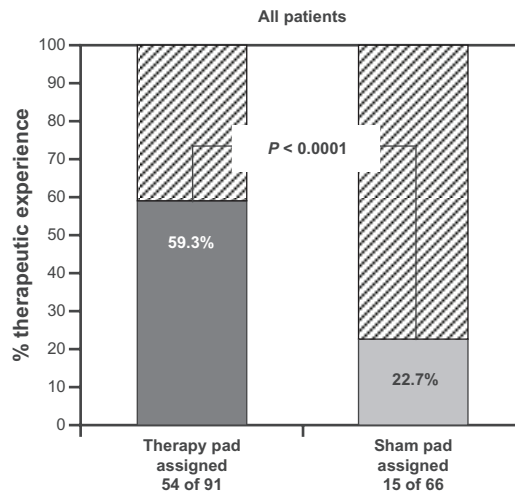
The RCT has become the gold standard of medical research<sup>14,15</sup> since it first appeared in the medical literature to describe a study of streptomycin treatment of pulmonary tuberculosis.<sup>16,17</sup> The RCT is composed of three elements: (1) random patient assignment to different groups, (2) blinding of investigators and patients as to which group each patient was assigned, and (3) comparison of the outcome of the groups by statistical inference computations.

In its simplest form, the RCT creates two identically diseased populations: one treated with an active drug,



**Figure 2** A bar graph showing no significant difference in improvement for patients assigned vibrating and sham pads in patients who believed that a therapeutic pad had been assigned ( $P > 0.05$ ).

**Abbreviation:** MOS-II, Medical Outcomes Study Sleep Problems Index II.



**Figure 3** A bar graph demonstrating 59.3% therapeutic pad assignment belief for patients assigned vibrating pads and 22.7% for those assigned sham pads.

procedure, or device and the other treated with an inert therapy (a “placebo” or a “sham,” depending on the setting). Ideally, a placebo would have no effect on the treatment outcome. When there is some degree of placebo influence, it is called a “placebo effect.” (From this point of view, the term placebo effect is an oxymoron since something that was chosen to have no effect had an effect. The complexity of the placebo effect in many trials has led to the need of additional definitions like “true” and “perceived” and “usual” and “enhanced” placebo effects<sup>18–20</sup>). When the effect is small, it is commonly treated like bothersome noise in an electronic circuit and ignored. However, when the effect is large, as in RLS treatment trials, it might be better termed a “therapeutic effect not attributable to active treatment” and investigated further. Moreover, placebo effect size is not static, it varies by culture, can increase over time, and in some settings may be related to the magnitude of active treatment effect.<sup>21–24</sup>

Placebo effect is not equal across different types of outcome variables. When the central nervous system has little or no control over the outcome variable, placebo effect is small. When the outcome variable measures a process that occurs within the brain – such as depression, anxiety, pain, or dysphoric leg sensations associated with RLS – placebo effect can be very large. A spectrum of placebo effect exists. Placebo effect appears to be smallest when a biochemical marker or an imaging study, such as glucose concentration or an x-ray (as in the streptomycin study), is the dependent variable; somewhat larger when a physiological parameter is measured, such as blood pressure or ventilation rate; larger still when outcomes are subjectively assessed by clinical observers; and largest when the endpoint is a patient-reported value, such as a number on a scale generated from a paper-and-pencil questionnaire like the MOS-II scale used in the current studies.<sup>24–26</sup> Fulda and Wetter even demonstrate differences in placebo effect across various scales that subjectively evaluate RLS.<sup>27</sup>

To be a success in an RCT, active treatment must be statistically superior to inert treatment. This requirement is based on two related assumptions: (1) that the putative inert treatment is truly inert and (2) when the active and placebo treatments have equal effects, both are considered ineffective instead of the opposite. For those unable to see that equal effects might represent trial success in one setting and trial failure in another, RCT methodology with its statistical complexity may have become more important than scientific understanding.<sup>a,28</sup> For example, Figures 2 and 3

demonstrated that patients who believed that they had been assigned a therapeutic pad were able to benefit from the counterstimulation generated by their pad and experienced decreased sleep problems – regardless of whether the assigned pad was a vibrating pad, a sound sham pad, or a light sham pad. For these patients, were their comparable responses to therapy and sham pads all placebo effect? Or, might they all have been therapeutic effects? Might it lead to better understanding to recognize sound or light as an effective counterstimuli for a minority of RLS patients than to dismiss their benefit as simply a placebo effect? For example, a pad with a choice of patient-controlled light, sound, or vibration might benefit a wider group of RLS patients than pads with only one of these three sensory counterstimuli.

Until somewhat recently, placebo effect was attributed to poorly defined patient personality characteristics, like gullibility, suggestibility, weakness, or mystification, rather than described as a true physiological phenomenon.<sup>29–32</sup> However, recent work has demonstrated that placebo effect is not the result of a faulty personality type, such as being a “placebo reactor.”<sup>32,29</sup> Rather, it appears to be based on brain opioid and dopamine receptor neurobiology.<sup>33–36</sup> From this point of view, does it matter if a vibrating pad, a humming pad, or a variable light pad elicited therapeutic neurobiology? It probably matters most how efficient a counterstimulus is.

Interestingly, like sham effect, the opiate and dopamine systems also appear to play a role in RLS brain pathology.<sup>37–43</sup> Perhaps RLS pathology and placebo effect reside at a crossroad in the brain.

We were unable to construct a “perfect sham,” one which could not be distinguished by patients from the vibrating pad and yet was not, in itself, therapeutic. In the construction of two shams, we erred on the side of building shams that led to effective blinding. But in the service of effective

<sup>a</sup>Many non-RLS physical treatment investigations have not appreciated the possibility of central nervous system, counterstimulus effects from their shams. For example, in a study of the effects of VS on neuropathic foot pain, patients assigned shams might have experienced unappreciated therapeutic counterstimulation effects.<sup>44</sup> In this study a vibrating foot pad that also produced light and an audible hum was compared to a sham foot pad that produced light and the hum. The authors assumed that the light and sound could have no possible therapeutic effect on foot pain. However, 8 of the 20 (40.0%) sham patients experienced “relaxation” from the “light and audible hum.” Two (10.0%) even experienced the sensation of “vibration” from just the “light and audible hum.” Sham patients had a 55.0% drop in pain scores; VS patients, 67.3%. The authors concluded that VS had no therapeutic benefit on foot pain because sham scores were statistically comparable to treatment scores. However, an equally plausible explanation was that both VS and light/sound counterstimulation decreased foot pain.

blinding, we constructed patient-controlled sound or light shams that appear to have been effective counterstimuli for a minority of patients. When we designed these sham pads, we speculated that neither sound nor light would be an effective counterstimulus during an RLS attack. We seem to have been wrong. For 15 of 66 (22.7%) patients, sham pads appeared to have been effective counterstimuli.

## Conclusion

For the purpose of developing vibration treatment, RLS attacks were conceptualized as sensory hallucinations projected from the brain to the legs during times of drowsiness or sleep (Part I).<sup>1</sup> A vibrating pad was constructed to treat RLS attacks by means of counterstimulation and was compared to non-vibrating, patient-controlled sound and light pads. Information collected at the completion of each study defined whether a patient believed that a therapeutic pad had been assigned.

As shown in Part I, randomization and double-blinding were effective, and all three pad types were safe.<sup>1</sup> By clinician evaluation, 45.0% of patients assigned vibrating pads were improved compared with 17.2% for patients assigned sham pads. As shown in Part II, the magnitude of sleep improvement in patients with moderately severe RLS was comparable to sleep improvement seen with FDA-approved drugs, whether subjectively measured by the patient-reported MOS sleep inventory scores (MOS-II and Medical Outcomes Study Sleep Disturbance Scale [SLPD4] inventories) or objectively by all-night polysomnography.<sup>2</sup> However, the wide range of worrisome side effects seen in RLS-drug treated patients were never observed in the two vibratory arms.

Actual pad assignment (the independent variable) and pad assignment belief (the mediator variable) both influenced improvement in MOS-II scores (Part I, Part II, and Part III; Figure 3); however, the mediator variable, pad assignment belief, was more influential.<sup>1,2</sup> Most patients (59.3%) who were assigned a vibrating pad believed they were assigned a therapeutic pad and improved substantially. However, a minority of patients (22.7%) who were assigned a sham pad believed they had been assigned a therapeutic pad and also experienced substantial sleep improvement. Devices designed to perform as shams appear to have exerted primary therapeutic effects in some RLS patients. These findings may have broader significance because of their implications for how to develop effective shams in future device studies. It appears that in order to minimize the impact of the mediator variable (treatment assignment belief), sham devices should not have patient-controlled sensory inputs that could skew results in favor of the sham.

## Disclosure

Financial support for the study was provided by Sensory Medical, Inc, San Clemente, CA, USA. The author is the Chief Executive Officer of Sensory Medical, Inc, and a minority shareholder. The author reports no other conflicts of interest.

## References

- Burbank F, Buchfuhrer MJ, Kopjar B. Sleep improvement for restless legs syndrome (RLS) 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. *Journal of Parkinsonism and Restless Legs Syndrome*. 2013;3:1–10.
- Burbank F, Buchfuhrer MJ, Kopjar B. Sleep improvement for restless legs syndrome (RLS) patients. Part II: Meta-analysis of vibration therapy and FDA-approved RLS drugs in the treatment of RLS. *Journal of Parkinsonism and Restless Legs Syndrome*. 2013;3:11–22.
- Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51(6):1173–1182.
- Kenny DA, Calsyn RJ, Morse GA, Klinkenberg WD, Winter JP, Trusty ML. Evaluation of treatment programs for persons with severe mental illness: moderator and mediator effects. *Eval Rev*. 2004;28(4):294–324.
- Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry*. 2002;59(10):877–883.
- Deyo RA, Walsh NE, Schoenfeld LS, Ramamurthy S. Can trials of physical treatments be blinded? The example of transcutaneous electrical nerve stimulation for chronic pain. *Am J Phys Med Rehabil*. 1990;69(1):6–10.
- Hays RD, Stewart AL. Sleep measures. In: Stewart AL, Ware JE, editors. *Measuring Functioning and Well-Being: The Medical Outcomes Study Approach*, 4th ed. Durham: Duke University Press; 1998: 235–259.
- Hays RD, Martin SA, Sesti AM, Spritzer KL. Psychometric properties of the Medical Outcomes Study Sleep measure. *Sleep Med*. 2005;6(1): 41–44.
- Abetz L, Arbuckle R, Allen RP, Mavraki E, Kirsch J. The reliability, validity and responsiveness of the Restless Legs Syndrome Quality of Life questionnaire (RLSQoL) in a trial population. *Health Qual Life Outcomes*. 2005;3:79.
- Allen RP, Kosinski M, Hill-Zabala CE, Calloway MO. Psychometric evaluation and tests of validity of the Medical Outcomes Study 12-item Sleep Scale (MOS sleep). *Sleep Med*. 2009;10(5):531–539.
- Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods*. 2010;15(4):309–334.
- Imai K, Keele L, Tingley D, Yamamoto T. Causal mediation analysis using R. *Lecture Notes in Statistics*. 2010;196:129–154.
- Shrout PE, Bolger N. Mediation in experimental and nonexperimental studies: new procedures and recommendations. *Psychol Methods*. 2002;7(4):422–445.
- Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. 2000;342(25):1887–1892.
- Evans D. Hierarchy of evidence: a framework for ranking evidence evaluating healthcare interventions. *J Clin Nurs*. 2003;12(1): 77–84.
- Forsetlund L, Chalmers I, Bjorndal A. When was random allocation first used to generate comparison groups in experiments to assess the effects of social interventions? *Economics of Innovation and New Technology*. 2007;16(5):371–384.
- Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *Br Med J*. 1948;2(4582):769–782.
- Ernst E, Resch KL. Concept of true and perceived placebo effects. *BMJ*. 1995;311(7004):551–553.

19. Kaptchuk TJ, Goldman P, Stone DA, Stason WB. Do medical devices have enhanced placebo effects? *J Clin Epidemiol*. 2000;53(8):786–792.
20. Ernst E. Placebo: new insights into an old enigma. *Drug Discov Today*. 2007;12(9–10):413–418.
21. Moerman DE. Cultural variations in the placebo effect: ulcers, anxiety, and blood pressure. *Med Anthropol Q*. 2000;14(1):51–72.
22. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002;287(14):1840–1847.
23. Walach H, Sadaghiani C, Dehm C, Bierman D. The therapeutic effect of clinical trials: understanding placebo response rates in clinical trials – a secondary analysis. *BMC Med Res Methodol*. 2005;5:26.
24. Meissner K, Distel H, Mitzdorf U. Evidence for placebo effects on physical but not on biochemical outcome parameters: a review of clinical trials. *BMC Med*. 2007;5:3.
25. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *J Intern Med*. 2004;256(2):91–100.
26. Wampold BE, Minami T, Tierney SC, Baskin TW, Bhati KS. The placebo is powerful: estimating placebo effects in medicine and psychotherapy from randomized clinical trials. *J Clin Psychol*. 2005;61(7):835–854.
27. Fulda S, Wetter TC. Where dopamine meets opioids: a meta-analysis of the placebo effect in restless legs syndrome treatment studies. *Brain*. 2008;131(Pt 4):902–917.
28. Lilienfeld AM, The Fielding H. Garrison Lecture: Ceteris paribus: the evolution of the clinical trial. *Bull Hist Med*. 1982;56(1):1–18.
29. Beecher HK, Keats AS, Mosteller F, Lasagna L. The effectiveness of oral analgesics (morphine, codeine, acetylsalicylic acid) and the problem of placebo “reactors” and “non-reactors”. *J Pharmacol Exp Ther*. 1953;109(4):393–400.
30. Doongaji DR, Vahia VN, Bharucha MP. On placebos, placebo responses and placebo responders. (A review of psychological, psychopharmacological and psychophysiological factors). I. Psychological factors. *J Postgrad Med*. 1978;24(2):91–97.
31. Doongaji DR, Vahia VN, Bharucha MP. On placebos, placebo responses and placebo responders. A review of psychological, psychopharmacological and psychophysiological factors. II. Psychopharmacological and psychophysiological factors. *J Postgrad Med*. 1978;24(3):147–157.
32. Pollo A, Benedetti F. The placebo response: neurobiological and clinical issues of neurological relevance. *Prog Brain Res*. 2009;175:283–294.
33. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia – imaging a shared neuronal network. *Science*. 2002;295(5560):1737–1740.
34. Kong J, Kaptchuk TJ, Polich G, Kirsch I, Gollub RL. Placebo analgesia: findings from brain imaging studies and emerging hypotheses. *Rev Neurosci*. 2007;18(3–4):173–190.
35. Oken BS. Placebo effects: clinical aspects and neurobiology. *Brain*. 2008;131(Pt 11):2812–2823.
36. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry*. 2008;65(2):220–231.
37. Walters AS, Ondo WG, Zhu W, Le W. Does the endogenous opiate system play a role in the Restless Legs Syndrome? A pilot post-mortem study. *J Neurol Sci*. 2009;279(1–2):62–65.
38. Walters AS. Review of receptor agonist and antagonist studies relevant to the opiate system in restless legs syndrome. *Sleep Med*. 2002;3(4):301–304.
39. Natarajan R. Review of periodic limb movement and restless leg syndrome. *J Postgrad Med*. 2010;56(2):157–162.
40. Salas RE, Gamaldo CE, Allen RP. Update in restless legs syndrome. *Curr Opin Neurol*. 2010;23(4):401–406.
41. Trenkwalder C, Paulus W. Restless legs syndrome: pathophysiology, clinical presentation and management. *Nat Rev Neurol*. 2010;6(6):337–346.
42. Zintzaras E, Kitsios GD, Papanthanasias AA, et al. Randomized trials of dopamine agonists in restless legs syndrome: a systematic review, quality assessment, and meta-analysis. *Clin Ther*. 2010;32(2):221–237.
43. Giummarra MJ, Bradshaw JL. The phantom of the night: restless legs syndrome in amputees. *Med Hypotheses*. 2010;74(6):968–972.
44. Paice JA, Shott S, Oldenburg FP, Zeller J, Swanson B. Efficacy of a vibratory stimulus for the relief of HIV-associated neuropathic pain. *Pain*. 2000;84(2–3):291–296.

## Journal of Parkinsonism & Restless Legs Syndrome

### Publish your work in this journal

Journal of Parkinsonism and Restless Legs Syndrome is an online, open access, peer-reviewed journal. The journal publishes review articles, historical reviews, original research articles, case reports, letters to the editor, clinical teaching cases, neuroradiology highlights, neuropathology highlights, neuropsychiatry highlights, autobiographies, conference

Submit your manuscript here: <http://www.dovepress.com/journal-of-parkinsonism--restless-legs-syndrome-journal>

proceedings, abstracts and book reviews. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Dovepress