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# Placebo and nocebo responses in restless legs syndrome

## A systematic review and meta-analysis

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### ABSTRACT

**Objective:** To estimate the placebo and nocebo responses in restless legs syndrome (RLS) and explore their determinants.

**Methods:** Databases were searched up to October 2015. Randomized, double-blind, placebo-controlled trials of patients with RLS were included if quantitative data were extractable in the placebo arm. Placebo response was defined as the within-group change from baseline, using any scale measuring RLS severity or disability. Nocebo response was defined as the proportion of patients experiencing adverse events in the placebo arm. Random-effects meta-analysis was used to pool data. Statistical heterogeneity was assessed with $I^2$ statistic. Several predetermined subgroup and sensitivity analysis were performed. PROSPERO registration number is CRD42015027992.

**Results:** We included 85 randomized controlled trials (5,046 participants). Pooled placebo response effect size was −1.41 (95% confidence interval [CI] −1.56 to −1.25, 64 trials, $I^2$ = 88.1%), corresponding to −6.58 points in the International RLS Study Group Scale (IRLS). Pooled nocebo response was 45.36% (95% CI 40.47%–50.29%, 72 trials; $I^2$ = 89.8%). The placebo and nocebo responses were greater in trials with longer duration, evaluating pharmacologic interventions and idiopathic RLS, and in industry-funded and unpublished studies. The placebo response was considerably smaller in objective as compared to subjective outcomes. In addition, the nocebo response increases proportionally with the placebo response, and has the same predictors.

**Conclusions:** The magnitude of the placebo response in RLS is above the threshold of minimal clinical important difference, and the frequency of adverse events is also considerable. These results are relevant to inform the design and interpretation of future clinical trials. ***Neurology*®** **2017;88:1–9**

### GLOSSARY

**CGI** = Clinical Global Impression improvement scale; **CI** = confidence interval; **ES** = effect size; **IRLSSG** = International RLS Study Group; **MCID** = minimal clinically important difference; **PGI** = Patient Global Impression improvement scale; **PLM** = periodic limb movements; **PLMI** = periodic limb movements index; **PLMSI** = periodic limb movements of sleep index; **RCT** = randomized controlled trial; **RLS** = restless legs syndrome.

Restless legs syndrome (RLS) is a chronic neurologic disorder[1] with negative effects on quality of life and sleep of patients and bed partners. RLS prevalence may reach up to 10% of the population.[2] The pathophysiology of RLS is not completely understood, and multiple abnormal processes in the central and peripheral nervous systems have been empirically studied. Furthermore, there seems to be a strong genetic susceptibility in affected patients.[3]

In addition to responses to opioid agents, and both dopaminergic and α-2-δ ligands, numerous trials have reported considerable improvements under placebo treament.[4]

Editorial, page XXX

Supplemental data at Neurology.org

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The key assumption regarding placebo, and the reason why we use it in clinical trials, is that it has no biological activity of interest. Therefore, any improvement seen in patients taking a placebo is deemed to result from the positive expectation of receiving an intervention. Since the work of Beecher,[5] a new line of research has emerged that brought the response to placebo to the forefront of interventional research.

Thus, we hypothesize that the placebo effect in RLS is relevant for trials' design and clinical interpretation of the findings, set out to quantify the magnitude of placebo and nocebo responses in RLS, and explore their determinants.

## METHODS

**Standard protocol approvals and registrations.** We report this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[6] The protocol was prospectively registered with PROSPERO (registration: CRD42015027992).

**Eligibility criteria.** We included double-blind randomized controlled trials (RCTs) with parallel or crossover design and at least one active treatment arm and a placebo arm. We excluded trials with an active run-in period before intervention with placebo. Patients required a diagnosis of RLS according to the International RLS Study Group (IRLSSG) criteria[1,7] or another specified method, if the study was conducted before the IRLSSG criteria publication. Studies were accepted regardless of RLS etiology, comorbid conditions, or age. We accepted any intervention categorized as placebo. Studies had to report quantitative data on at least one of the following outcomes, measured by validated instruments, within the placebo arm:

***Primary efficacy outcome.*** The primary efficacy outcome was placebo response, defined as the within-group change from baseline, using any rating scale measuring RLS severity or disability.

***Primary safety outcome.*** The primary safety outcome was nocebo response, defined as the proportion of patients experiencing adverse events in the placebo arm.

***Secondary efficacy outcomes.*** The secondary efficacy outcomes were change from baseline in the following endpoints: Clinical and Patient Global Impression improvement scales (CGI and PGI, respectively), quality of life, self-rated quality of sleep, daytime somnolence, sleep efficiency, and number of periodic limb movements (PLM) per hour of sleep or of time in bed (PLM of sleep index [PLMSI] and PLM index [PLMI], respectively). CGI, PGI, quality of life, self-rated quality of sleep, daytime somnolence, and sleep efficiency are subjective outcomes, while PLMSI and PLMI represent objective outcomes.

***Secondary safety outcomes.*** The secondary safety outcomes were proportion of withdrawals due to adverse events and proportion of patients experiencing augmentation, defined as "worsening of RLS symptoms, attributable to a specific therapeutic intervention for RLS."[1] For proposes of inclusiveness, other definitions were accepted.

No language, year of publication, or publication status restrictions were applied.

**Information sources.** We searched MEDLINE, EMBASE, and the Cochrane Register of Controlled Trials (CENTRAL) databases from inception to October 2015. Clinical trial registries (WHO International Clinical Trials Registry Platform and Clinicaltrials.gov) were also searched. Reference lists were cross-checked for additional citations.

**Search.** The search strategy combined variations of terms related to placebo and RLS. The Cochrane Highly Sensitive Search Strategy for identifying RCTs (2008 revision) was used for MEDLINE.[8] The search was restricted to human studies. All terms were searched as free text and controlled vocabulary. The complete search strategy for MEDLINE can be found in appendix e-1 at Neurology.org.

**Study selection.** Two reviewers independently screened titles and abstracts and analyzed full-text reports for potential inclusion. Disagreements were solved by consensus or by an independent party.

**Data collection process.** Two reviewers independently extracted individual study data onto a piloted form.

**Risk of bias in individual studies.** We used the Cochrane risk of bias tool to classify studies as being at low, high, or unclear risk of bias in the following domains: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.[8] Other sources of bias were considered, including funding, exclusive inclusion of special or enriched populations, and carryover effect in crossover trials. Two authors independently assessed risk of bias. Disagreements were solved by consensus or by a third party.

**Summary measures.** The placebo and nocebo data were derived from the last measured within-group response in the placebo arms of RCTs. Whenever possible, we retrieved and analyzed intention-to-treat data. The effect measure for continuous outcomes was effect size (ES). The ES was calculated as the quotient of the mean change from baseline divided by the SD at baseline, correcting for small-sample bias.[9] Negative changes indicate improvement in RLS severity, daytime somnolence, PLMSI, and PLMI, while positive differences indicate benefit in sleep quality, quality of life, and sleep efficiency. In case of insufficient reported data, we contacted authors as a first approach. In the lack of a positive response, absent mean changes from baseline and SDs were extracted from unpublished material. In some trials, SD was obtained from standard error or confidence intervals (CI). When such values were not reported, imputation methods were applied as described in appendix e-2. We also performed the analyses with the mean change from baseline and SD, using the natural units of the most commonly applied scale for each outcome. When a different scale was used, linear rescaling to the chosen instrument was conducted.[10] Dichotomous outcomes are reported as proportions. Heterogeneity between trial results was tested using a standard $\chi^2$ test and $I^2$ statistic was calculated for quantifying this inconsistency. We presented all results with 95% CI.

**Additional analyses.** The following predefined subgroup analyses were conducted to explore heterogeneity: time to last assessment (less than 6 weeks, 6–11 weeks, and 12 or more weeks), study intervention (pharmacologic vs nonpharmacologic intervention, route of administration of pharmacologic interventions), study population (idiopathic vs secondary RLS, naive vs previously treated patients), and published vs unpublished trials. In addition, to assess the influence of study quality on results, subgroup analyses of

studies with a low risk of bias vs those with unclear/high risk were performed. Predefined sensitivity analyses were conducted excluding studies where imputation methods were applied, and studies with crossover designs. The subgroup and sensitivity analyses were performed exclusively for the primary outcomes. Meta-regressions were performed for the primary efficacy outcome according to year of publication and to disease severity at baseline.[11]

Taking into consideration the findings of our meta-analysis regarding the pooled magnitude of the placebo response, we then performed sample size calculations for a hypothetical future equivalence trial that would be powered to detect differences in IRLS from placebo group of 5%, 10%, 15%, and 20% using $\alpha = 0.05$ and $\beta = 0.1$, in the R software.[12] Finally, we conducted a post hoc Pearson correlation analysis to investigate the relation between the placebo (primary efficacy effect) and the nocebo responses (primary safety effect), after establishing the normality of the data with a Shapiro-Francia W′ test for normal data.

## RESULTS

**Study selection and characteristics.** We included 85 RCTs (5,046 participants) (figure e-1), 65 with a parallel design, 5 tested nonpharmacologic procedures, and the remaining were pharmacologic trials, 65 of which with oral interventions. The most commonly studied drugs were ropinirole (n = 13), pramipexole (n = 12), rotigotine (n = 10), and gabapentin-enacarbil (n = 10). Five were performed exclusively in RLS secondary to end-stage renal disease under hemodialysis, and 70 exclusively enrolled patients with idiopathic RLS. Overall, the average age was 54.21 years, and 62.24% of patients were female. The mean IRLS score at baseline was 24.51 points. See table e-1 for characteristics of included studies and appendix e-3 for study references.

**Risk of bias within studies.** Twenty-five studies were deemed as having a low overall risk of bias (figure 1). The detailed risk of bias across studies can be found in figure e-2.

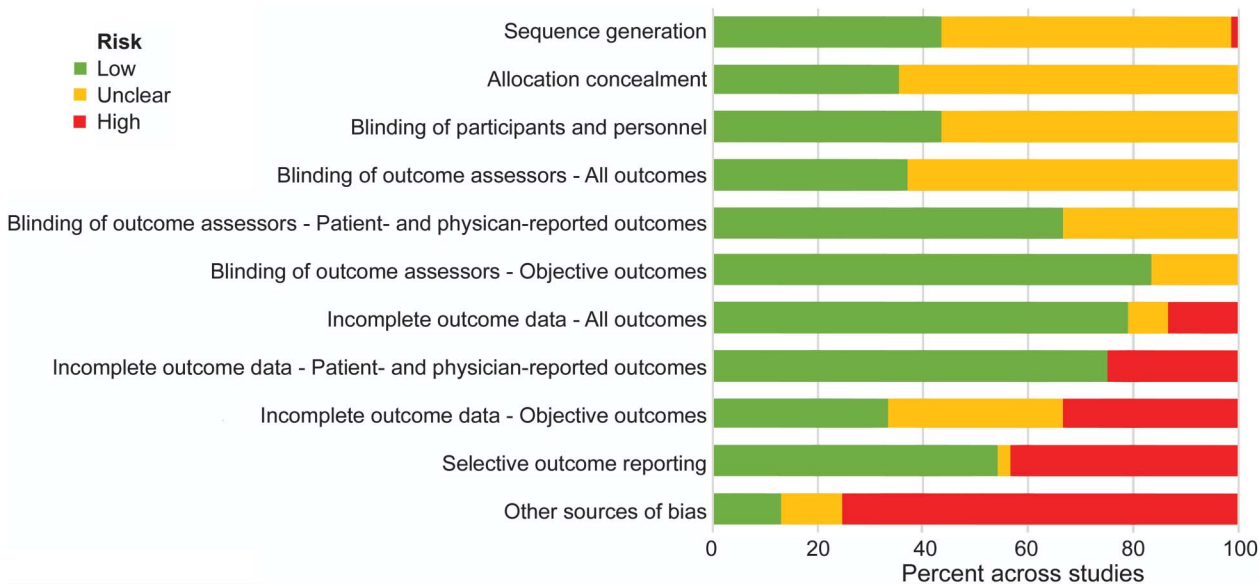
**Synthesis of results and additional analysis.** ***Primary efficacy outcome: Placebo response.*** Sixty-four studies reported a validated RLS severity assessment included in the primary efficacy outcome analysis, 62 of which used the IRLS. Among studies that did not use the IRLS, 2 used severity assessments that were eligible for inclusion and rescaled. The pooled ES was −1.41 (95% CI −1.56 to −1.25; figure 2), corresponding to a mean IRLS reduction of 6.58 points (95% CI 4.86–8.29). Statistical heterogeneity was very high ($I^2 = 88.1\%$).

Subgroup analysis revealed a greater improvement with placebo in studies with 12 or more weeks, studies with pharmacologic interventions, RCTs performed in idiopathic RLS, unpublished trials, and industry-supported studies (table e-2). Subgroup analyses of oral vs nonoral medications and low vs high/unclear overall and specific domain risk of bias did not reveal differences between groups.

No differences were observed in sensitivity analyses (table e-2) or in metaregressions for disease severity at baseline ($\beta = -0.05$; 95% CI −0.12 to 0.01) and year of publication ($\beta = -0.04$; 95% CI −0.09 to 0.01; figures e-3 and e-4, respectively). The predefined subgroup and sensitivity analyses were not able to adequately explain the considerable statistical heterogeneity we found (table e-2).

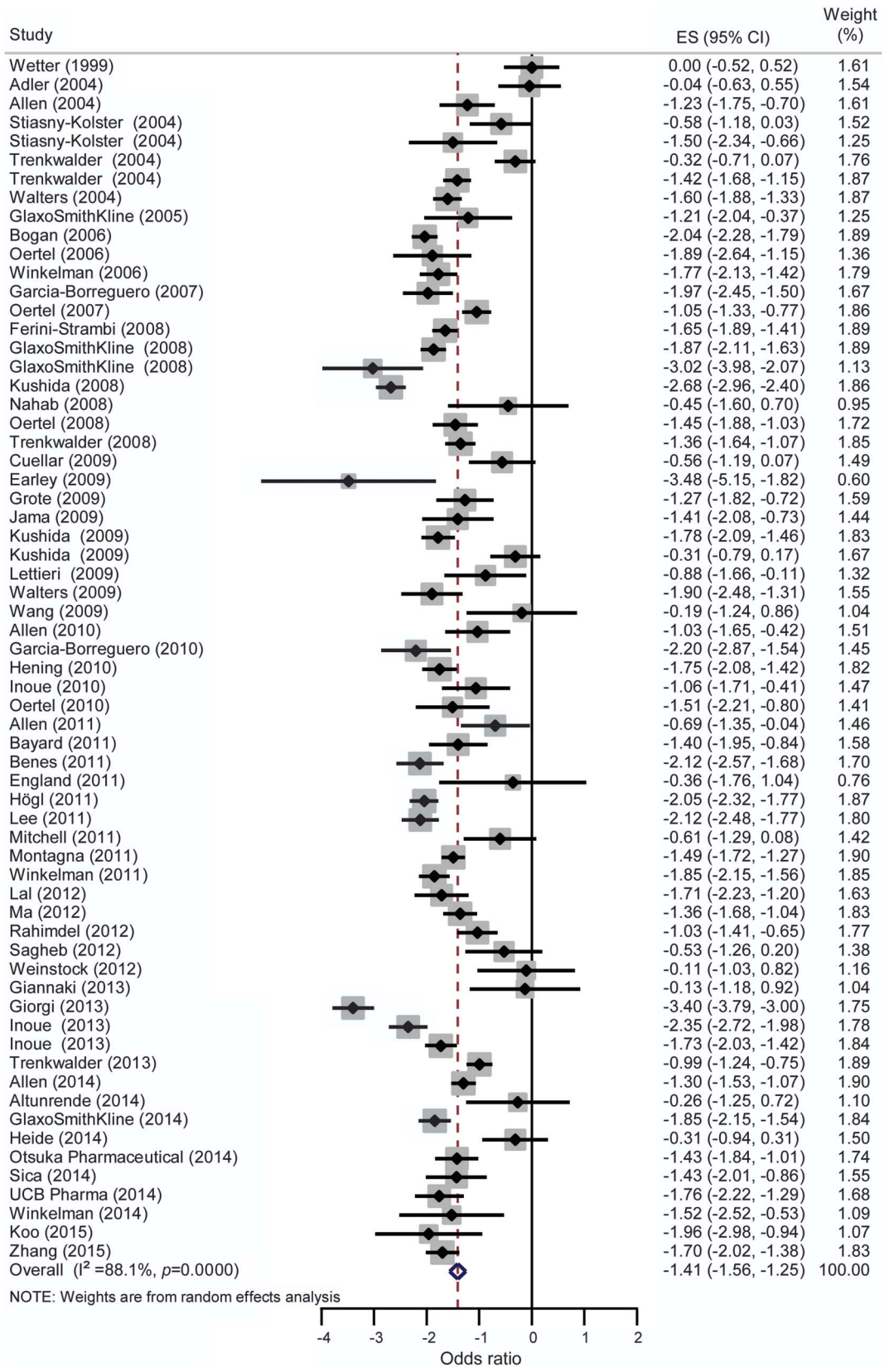
***Primary safety outcome: Nocebo response.*** Overall, 45.36% (95% CI 40.47%–50.29%, 72 trials; $I^2 = 89.8\%$) of patients experienced adverse events (figure 3). The proportion of patients experiencing any

**Figure 1** Risk of bias across domains




Each methodologic quality item is presented as percentages across included studies.

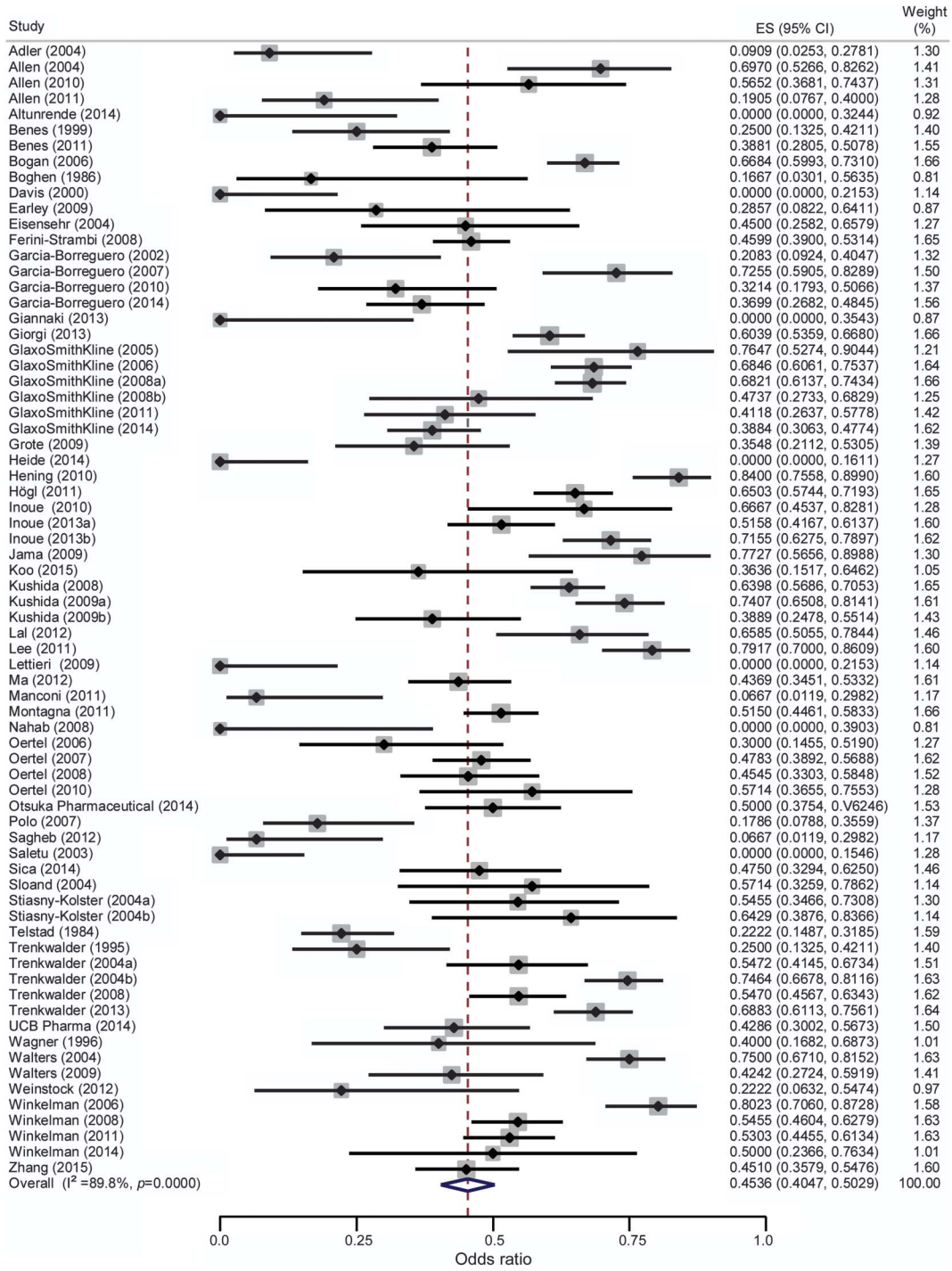
**Figure 2** Change from baseline in restless legs syndrome severity under placebo




CI = confidence interval; ES = effect size.

adverse events was greater in studies of 12 or more weeks, in pharmacologic studies, in idiopathic RLS, in unpublished trials, and in industry-funded trials (table e-2). Statistical heterogeneity was not explained by the predefined subgroup and sensitivity analysis (table e-2).

**Figure 3** Adverse events rate under placebo




CI = confidence interval; ES = effect size.

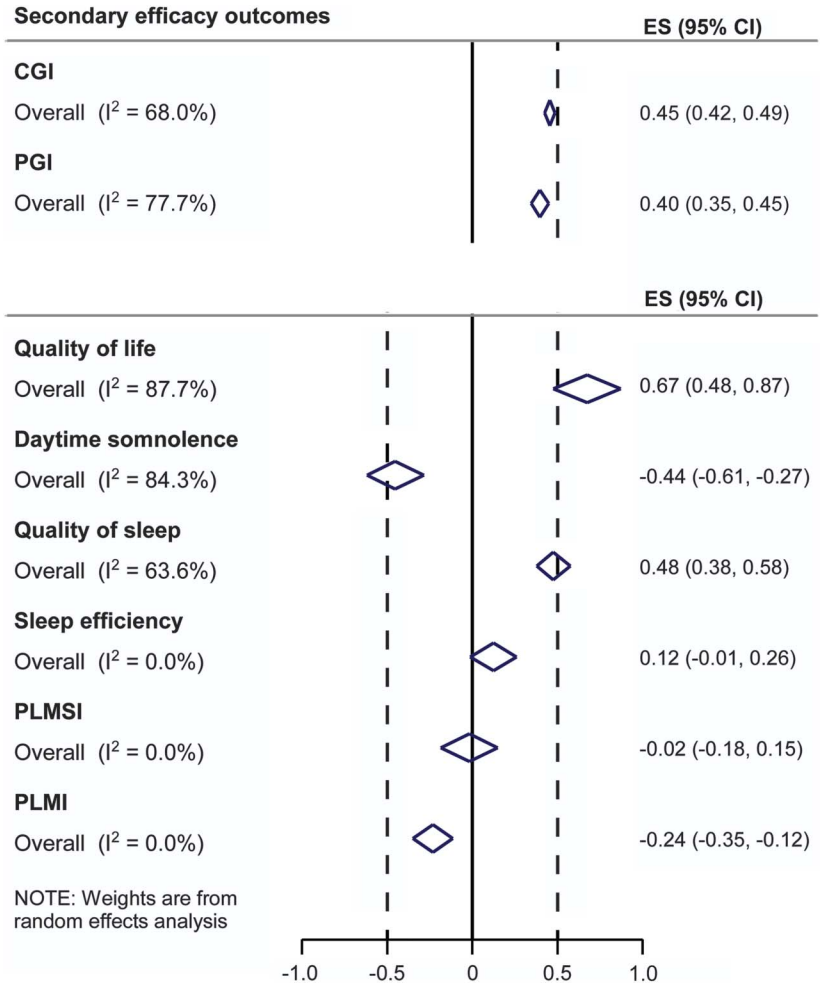
***Secondary efficacy outcomes.*** Seventeen studies reported both CGI and PGI; 24 only reported GCI and 3 others applied PGI. Overall, 45.46% of clinicians and 40.00% of patients reported a much improved or very much improved response under placebo (figure 4). Twenty-one studies reported quality of life assessments in an extractable manner, with overall quality of life improving under placebo (figure 4).

Thirty-one studies addressed daytime somnolence, having documented a reduction in daytime somnolence associated with placebo (figure 4).

Quality of sleep was rated in 35 studies. A significant improvement was found (figure 4).

Sleep efficiency, defined as the proportion of total sleep time during time in bed, was reported in 16 studies. PLMSI was reported in 14 studies and PLMI in 12 studies. Pooled ES for sleep efficiency was

**Figure 4** Change from baseline under placebo in secondary efficacy outcomes




Negative effect size (ES) changes indicate improvement in daytime somnolence, periodic limb movements of sleep index (PLMSI), and periodic limb movements index (PLMI), while positive differences illustrate benefit in Clinical Global Impression improvement scales (CGI), Patient Global Impression improvement scales (PGI), quality of sleep, quality of life, and sleep efficiency. CI = confidence interval.

nonsignificant (figure 4). Regarding PLM, an improvement was observed in PLMI, but not in PLMSI (figure 4).

***Secondary safety outcomes.*** A total of 208 (2.07%) withdrawals occurred due to adverse events in the placebo arm, among 81 studies (4,797 participants). Twenty-two studies reported augmentation in 13 of 1,863 participants, with no information from remaining trials.

***Sample size calculation.*** Table e-3 shows the estimated sample size required in an adequately powered future trial ($\alpha = 0.05$; $\beta = 0.10$) to detect a difference between treatment arms of 5%, 10%, 15%, and 15% in the IRLS, taking into consideration that on average patients under placebo treatment have an improvement of 6.58 points.

***Correlation analysis.*** The placebo and nocebo response were reported concomitantly in 46 RCT. The nocebo response increases proportionally with the placebo response ($r = 0.45$, $p = 0.0005$; figure 5).

**DISCUSSION** This systematic review and meta-analysis demonstrated a large response to placebo in RLS, with an average mean reduction in IRLS of 6.58 points. We additionally documented that many placebo-treated participants have adverse events (45.36%)—the nocebo response, and these responses change proportionally to one another.

Subgroup analyses showed that the placebo and nocebo responses vary in unison: both were increased in longer studies, in studies evaluating pharmacologic interventions and idiopathic forms of RLS, in industry-funded trials, and in unpublished trials.

All continuous self-rated outcomes (quality of life, sleep quality, and daytime somnolence) improved with placebo. However, the placebo response was small to nonexistent for objective outcomes (PLMI and PLMSI).

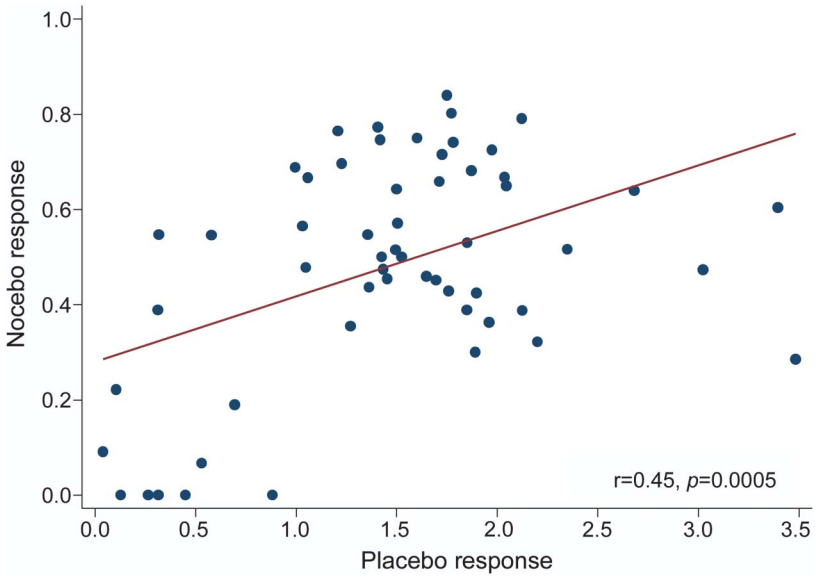
These findings imply that although people with RLS report considerable improvement with placebo, even in the most common clinical scale in usage—the IRLS—this is not accompanied by an actual improvement in the limb movements that more precisely characterize and define the condition.

Our findings are in accordance with a previous systematic review in RLS[4] that included a smaller number of trials (n = 36) and participants (n = 1,748), documenting substantial placebo responses in subjective outcomes, more evident in longer trials. The pattern is consistent with research in other areas,[13] such as in major depressive disorder,[14] though not, for example, in the case of Parkinson disease.[15] In contrast, an analysis of the predictors of placebo response in 6 RCTs, enrolling 883 participants, revealed greater placebo responses in more severe cases, and did not find differences concerning study duration.[16]

Our review quantified the change under placebo across several RLS outcomes, most of them showing improvement with placebo treatment. Two questions emerge: are those changes clinically relevant? Do they reflect a placebo effect?

For RLS severity, the first question could be answered when considering the minimal clinically important difference (MCID) for IRLS, i.e., the smallest change that patients perceive as important, using IRLS. Despite the absence of a consensual MCID for this scale, post hoc analyses of 2 trials included in this review[17,18] obtained a MCID of 5[19] and 6[20] points in IRLS. In addition, 15 of the 21 studies that used a MCID (used for sample size calculations in included trials) used a lower value than

**Figure 5** Correlation between the placebo and the nocebo response




The placebo response corresponds to the within-group change from baseline, using any rating scale measuring RLS severity or disability, and the nocebo response to the proportion of patients experiencing adverse events in the placebo arm. For the sake of interpretability, the placebo response scale was inverted. *r*, Pearson coefficient of correlation; *p*, *p* value.

the 6.58 points we found for our sample size calculations. The mean of minimal changes across these studies was 5.6 points. Thus, we can state that the placebo response found in this review exceeded the threshold for the MCID.

The answer to the second question is more complex, since we cannot identify to what extent our findings were affected by the natural course of RLS. Research evaluating placebo vs no treatment control groups in clinical trials, regardless of the condition, did not find that placebo interventions have clinically meaningful effects when compared with no treatment.[21] Only by including both no treatment and placebo arms in RCTs could we assess if our findings are indeed due to the placebo effect and not related to the natural course of the illness, patient–doctor relationship, or the expectation of being involved in a clinical trial, among many possible reasons.

In general, RLS is known to respond to dopaminergic stimuli.[17] Interestingly, studies in pain and Parkinson disease have shown that the placebo response maybe mediated by dopamine.[22,23] This could partially explain the magnitude of our results. That being said, there is also evidence of equally great responses where dopamine is not a major player, such as depression.[14]

In addition, dopamine plays a role in the brain reward systems and conditioning.[24] A certain number of participants included in our analysis may have been previously conditioned by an exposure to an efficacious intervention, and placebo interventions could have triggered some of these systems.

To our knowledge, our work is the largest systematic review evaluating the placebo response in RLS and the only one characterizing the nocebo response.

Our comprehensive search of the available evidence, using a far-reaching strategy and including clinical trial registries, allowed the inclusion of both published and unpublished RCTs. Four references generated by the search could not be retrieved[12,25–27] though these are unlikely to report a validated RLS severity assessment, having been published before IRLS validation. We assume these studies would not appreciably influence our primary outcomes.

Despite of the all-inclusiveness of our study, certain relevant data were generally not reported. Most included RCTs did not report separated results for naive and previously treated patients. An analysis of 2 RCTs found that pretreatment for RLS was associated with a smaller placebo response, in comparison to naive patients.[28] The authors postulate that previous treatment may contribute to conscious or unconscious unblinding of participants. Owing to insufficient reporting, we could not study this via a subgroup analysis, and therefore cannot corroborate such results.

Another field lacking data is RLS in children. Only one small trial could be included and it had the confounding factor of only including patients with attention-deficit/hyperactivity disorder, often misdiagnosed in children with RLS.[29]

As secondary RLS was an exclusion criterion in most of the included trials, this population was insufficiently addressed. Uremic RLS was notable for being poorly studied, as only 5 small trials (enrolling 62 participants overall) were included, meaning that extrapolation to this population should be done with care. We found no trials studying pregnant women with RLS or people with iron-deficient anemia.

Finally, few of the included studies reported augmentation (22 RCTs). Typically augmentation is regarded as a complication of long-term treatment, though it may occur at any time.[1] Underreporting may relate to selective reporting bias, and diminishes the quality of the evidence.

Regarding methodologic quality, many of the included studies had a risk of both selection and detection bias, and were at high risks of reporting bias, mainly for not reporting reasons for study discontinuation and incomplete data description, precluding the inclusion of one or more outcomes for analysis.

When contacting authors, we did not request data regarding naive/previously treated participants or

methodologic characteristics. Despite studying the nocebo response, we only accounted for global adverse events rates, regardless of their nature and of being intervention-related or not.

We performed sensitivity analyses for the primary efficacy outcome considering potential sources of bias. Pooling data from both phases of crossover trials could potentially be an issue,[8] though sensitivity analysis suggests it was not in our case. Similarly, imputation methods had no effect on our results.

The magnitudes of the placebo and nocebo responses in RLS are substantial, show similar patterns of variation, and change proportionally to one another. Indeed, the placebo response exceeds the threshold for clinical relevance, which is of great pertinence for planning future trials.

## AUTHOR CONTRIBUTIONS

Research project: Conception: J.J.F., R.M.F. Designing search strategies: F.B.R., G.S.D. Screening search results: G.S.D., M.A.S., R.C. Extracting data: M.A.S., R.C. Contacting authors for additional information: M.A.S. Judging risk of bias: G.S.D., M.A.S. Statistical analysis: Design: F.B.R., G.S.D., J.C., R.M.F. Execution: D.A., F.B.R. Review and critique: J.C., R.M.F. Manuscript: Writing of the first draft: M.A.S. Review and critique: F.B.R., G.S.D., J.C., J.J.F., R.C., R.M.F., T.M. Providing general advice on the review: C.T., J.C., J.J.F., R.M.F.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