Pharmacologic therapy for primary restless legs syndrome: a systematic review and meta-analysis

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CRD summary
Among individuals with primary restless legs syndrome with long-term high-moderate to very severe symptoms, dopamine agonists and alpha-2-delta ligands increased rates of response to treatment, reduced symptoms and improved sleep outcomes and disease-specific quality of life. Adverse events and associated treatment withdrawals were common. The conclusions of this well-conducted review are likely to be reliable.

Authors' objectives
To evaluate the efficacy, safety, and comparative effectiveness of pharmacological treatments for primary restless legs syndrome.

Searching
MEDLINE, EMBASE and Natural Standard were searched for studies in English up to June 2012. Trials registries, websites of regulatory agencies and the United States National Institute of Health RePORTER were consulted. Peer reviewers provided additional unidentified trials.

Study selection
Randomised controlled trials (RCTs) that evaluated pharmacologic interventions for primary restless legs syndrome versus placebo or active intervention were eligible for inclusion. Trials had to last a minimum of four weeks and had to report validated restless legs syndrome symptom or quality of life scale scores, clinician and patient global impact scale scores, or measures of sleep quality. Eligible interventions were limited to drugs approved for use for any condition in the USA.

The primary outcome was a clinically important response, defined as patients with at least 50% reduction in mean International Restless Legs (IRLS) symptom scores from baseline. Other outcomes were reported.

Mean age ranged from 49 to 60. Most participants were women and (where reported) nearly all were white. Restless legs syndrome duration ranged from about two to 23 years. Mean baseline IRLS score was high-moderate to severe (range from 20 to 29 out of 40). Between 22% and 81% of patients had received previous therapy.

Two reviewers screened the studies. Disagreements were resolved by discussion or with a third reviewer.

Assessment of study quality
Study quality was assessed using the Cochrane risk of bias tool. Overall strength of evidence for outcomes for each treatment comparison was assessed based on risk of bias, consistency, directness and precision of effect estimates.

It appeared that at least two reviewers assessed study quality and discrepancies in quality and strength of evidence ratings were resolved by discussion and consensus.

Data extraction
Outcomes data were extracted to calculate risk ratios (RRs) and mean differences. Data were extracted by one reviewer and checked by a second. Disagreements were resolved via discussion or with a third reviewer.

Methods of synthesis
Where possible, data were pooled in a random-effects meta-analysis to calculate risk ratios, weighted mean differences (WMD) or standardised mean differences (SMD) and corresponding 95% confidence intervals. Heterogeneity was assessed using $I^2$ and visual inspection of effect direction of the studies. The number needed to treat and number needed to harm were calculated. Publication bias was assessed using funnel plots and Egger's test.
Results of the review

Twenty-nine RCTs were included. The quality of the evidence was rated as high for most analyses.

**Dopamine agonists:** The rates of patients with a clinically important response were greater for patients who received dopamine agonist therapy compared with placebo (RR 1.60, 95% CI 1.38 to 1.86; seven trials; I²=49%). The rates of responders (much or very much improved) in the clinician-assessed global impression (CGI) scale was greater in the treatment group (RR 1.45, 95% CI 1.36 to 1.55; 15 trials).

Dopamine agonists were also associated with a small reduction in symptom severity compared with placebo (WMD -4.56 IRLS points, 95% CI -5.42 to -3.70; 14 trials; I²=46%), small-to-medium relative improvements in quality of life measures (SMD -0.37, 95% CI to -0.48 to -0.27; nine trials; I²=24%) and patient-reported sleep measures (SMD 0.38, 0.29 to 0.46; I²=0%).

Patients who received the intervention were associated with a higher risk of having at least one adverse event (including nausea, vomiting and somnolence) compared with placebo (RR 1.19, 95% CI 1.12 to 1.28; 16 trials; I²=57%) and a higher risk of withdrawals attributed to an adverse event (RR 1.37, 95% CI 1.03 to 1.82; 16 trials).

**Calcium channel alpha-2-delta ligands:** Calcium channel alpha-2-delta ligands were associated with an increased proportion of IRLS responders compared with placebo (RR 1.66, 95% CI 1.33 to 2.09; three trials; I²=0%). Response rates on the CGI scale were also significantly greater (RR 1.60, 95% CI 1.21 to 2.10; three trials). Mean change in IRLS score from baseline versus placebo was -4.26 points (95% CI -5.75 to -2.77; three trials; I²=0%). Patients who received treatment had a higher risk of having at least one adverse event compared with placebo (RR 1.17, 95% CI 1.00 to 1.36; five trials).

Further results were reported and these included analyses stratified by drug and number needed to treat.

**Authors’ conclusions**

Among individuals with primary restless legs syndrome and high-moderate to very severe symptoms of long duration, dopamine agonists and alpha-2-delta ligands increased rates of response to treatment, reduced symptom scores and improved patient-reported sleep outcomes, disease-specific quality of life and overall impact compared with placebo.

Adverse effects and treatment withdrawals due to adverse effects for dopamine agonists and alpha-2-delta ligands were common.

**CRD commentary**

The review question and selection criteria were clear. Several published and unpublished sources were searched.

Appropriate steps were taken to minimise risks of reviewer error and bias throughout the stages of the review. Quality of the evidence was assessed using appropriate tools and was rated as high for most analyses.

The choice of synthesis methods appeared appropriate. The clinical significance of effect estimates was addressed. As trial participants appeared to form a highly selected population, the authors raised concerns about the applicability of the results to the broader population of patients with the condition.

The conclusions of this well-conducted review are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that clinicians and patients should be aware of the large placebo response associated with pharmacologic treatment for restless legs syndrome.

**Research:** The authors stated that RCTs should be initiated to evaluate the benefits of off-label opioids, sedative hypnotics and tramadol for treatment of restless legs syndrome in individuals who were refractive to standard pharmacologic treatment. They stated that future trials required adequate blinding given the large placebo effect. Trials should investigate whether treatment benefits observed in short-term studies were maintained and whether therapies were tolerated in the long term. Additional recommendations for research were reported, including on the impact of patient characteristics on outcomes and the risk of augmentation associated with treatment (see Other Publications of Related Interest).
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