Levodopa for idiopathic restless legs syndrome: evidence-based review

CRD summary
The authors stated that short-term treatment with levodopa is effective and safe for restless legs syndrome, but evidence on long-term treatment is lacking. Given the wide variation in the primary studies, the poor reporting of methods and findings in the review, the use of unsuitable statistical methods and the questionable interpretation of safety data, these conclusions do not appear reliable.

Authors' objectives
To assess the efficacy and safety of levodopa for restless legs syndrome (RLS).

Searching
MEDLINE, EMBASE, LILACS, SciELO and the Cochrane Library were searched to January 2007; the search terms were reported. Theses indexed at the Biblioteca Regional Medicina/Panamerican Health Organization of the World Health Organization and the reference lists of studies retrieved were also screened.

Study selection
Randomised or quasi-randomised controlled trials of patients meeting any criteria for idiopathic RLS were eligible for inclusion. Studies of patients with secondary forms of RLS were excluded. The patients in the included studies were men and women with a mean age of 51 to 61 years. Eligible studies used levodopa as a treatment for RLS, and compared it with placebo, no intervention, or other pharmacological treatments. The interventions in the included studies (and usual daily dose) comprised levodopa (100 to 200 mg) with benserazide (25 to 50 mg) or carbidopa (25 to 500 mg) versus bromocriptine (2.5 mg), piribedil (40 mg), propoxyphene (100 to 200 mg), pergolide (0.125 mg), valproic acid (300 to 600 mg) or placebo. The interventions were in most cases given 0 to 3 hours before bedtime for periods ranging from 3 days to 3 weeks. Between the first and the comparison intervention there was generally a washout period of 0 to 7 days. Eligible studies measured the following outcomes: relief of RLS on a validated scale (primary outcome); sleep quality measured by subjective means or by polysomnography (PSG); subjective measures of quality of life; and treatment–related adverse events. In the included studies, measures of sleep quality and quality of life comprised a wide range of self-assessment tools (e.g. Clinical Global Impression Scale) and/or objective measures including physiological tests (e.g. PSG). The adverse events measured included augmentation (an abnormally severe pattern of RLS).

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The reviewers assessed validity by considering allocation concealment, blinding and attrition. The authors did not state how the validity assessment was performed.

Data extraction
For most outcomes, the p-values of differences between the two groups were reported in the text. Where data were suitable for pooling, risk ratios (RRs) were calculated for binary data and mean differences for continuous data, with associated 95% confidence intervals (CIs). Authors of primary studies were e-mailed for additional information.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The results of the primary studies were presented individually in the text, with a brief narrative synthesis in the 'Discussion' section. For two outcomes (PSG and adverse events), data were pooled to calculate summary RRs and
weighted mean differences (WMDs), with 95% CIs. A fixed-effect model was used and statistical heterogeneity was reported using the $\chi^2$ test and $I^2$ statistic.

Results of the review
Eight randomised controlled trials (RCTs; n=121) and one quasi-RCT (n=20) were included, all of double-blind crossover design.

The authors evaluated the studies as being of relatively good quality. However, all were small, only four had adequate allocation concealment and none described blinding of the outcome assessment. They were clinically heterogeneous with a variety of outcomes. It is unclear whether the washout periods between treatments were adequate.

Subjective measures of sleep quality and quality of life: 5 RCTs (n=61) reported statistically significant improvements in subjective measures of sleep quality compared with placebo (p≤0.05 where reported). The results for these outcomes in the other 3 RCTs and the quasi-RCT (n=80) were inconsistent.

PSG: a meta-analysis of data on eight PSG measures of sleep quality (5 RCTs, n=77) reported a statistically significant benefit associated with levodopa, compared with placebo, for periodic movements in sleep (PLMS) index (WMD –26.84, 95% CI: -36.41, -17.27, p<0.00001; 4 RCTs, n=64) and sleep latency (WMD -4.91, 95% CI: -9.69, -0.12, p=0.04; 4 RCTs, n=54). There was statistically significant heterogeneity for the PLMS outcome when using a fixed-effect model (p=0.006; $I^2=76\%$). No statistically significant difference between the groups was reported for another six PMS measures.

Adverse events: a meta-analysis of data on adverse events found a statistically significant benefit for the placebo group for the outcomes of augmentation (RR 9.09, 95% CI: 1.05, 30.51, p=0.04; 3 RCTs, n=48) and gastrointestinal symptoms (RR 2.78, 95% CI: 1.01, 7.67, p=0.05; 3 RCTs, n=58). No statistically significant difference between the groups was reported for the outcomes of headache, dry mouth and dizziness. Other results were reported in the review.

Authors' conclusions
Short-term treatment with levodopa is effective and safe for RLS but evidence on long-term treatment is lacking, particularly the phenomenon of augmentation.

CRD commentary
The review question was clear and the search was adequate. The inclusion criteria were wide, particularly with respect to the outcomes, and no details were provided about the outcome measures reported (e.g. whether a high score was desirable). This makes it difficult to interpret the results, or even to determine whether any studies reported the primary outcome. The authors did not report whether measures were taken to reduce the risk of reviewer error and bias in the study selection, validity assessment and data extraction processes, such as decisions being made independently by more than one reviewer. The narrative review was not always consistent with the tables. The statistical methods used to pool the studies were designed for parallel-group data and are unsuitable for crossover studies. Subgroups were pooled inappropriately and significant statistical heterogeneity, which was evident in the forest plot for PLMS, was not discussed. The authors’ conclusions about the safety of short-term levodopa are questionable in view of the increased risk of augmentation noted in the levodopa arms of 3 studies with durations of 3 days to 3 weeks. Given the wide variation in the primary studies, the poor reporting of methods and findings in the review, the use of unsuitable statistical methods and the questionable interpretation of the safety data, the authors’ conclusions do not appear reliable.

Implications of the review for practice and research
Practice: The authors stated that levodopa should be used to treat RLS on a short-term basis. Longer term treatment requires strict surveillance because of the potential risk of augmentation syndrome.

Research: The authors stated that well-designed RCTs with long-term follow up are needed to evaluate the safety and efficacy of long-term levodopa for RLS. Outcome measures should include relief of RLS using a validated scale and an assessment of augmentation.
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