Effect of non-ergot dopamine agonists on health-related quality of life of patients with restless legs syndrome

Talati R, Phung OJ, Mather J, Coleman CI

CRD summary
This review compared the effect of non-ergot dopamine agonists (NEDAs) with placebo on health-related quality of life of patients with restless legs syndrome and concluded that NEDAs yielded improved quality of life. This was a well-conducted review; despite uncertainty over the study selection process the findings are likely to reflect the available evidence.

Authors' objectives
To assess the effect of non-ergot dopamine agonists (NEDAs) on health-related quality of life of patients with restless legs syndrome.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions from inception to July 2008. Search terms were reported. References of retrieved studies were screened for additional studies.

Study selection
Randomised, double-blind, placebo-controlled trials that evaluated use of NEDAs in patients with restless legs syndrome and that reported health-related quality of life (HRQoL) using any restless legs syndrome disease-specific HRQoL instrument were eligible for inclusion. Withdrawal trials were excluded from the primary analysis. Drug regimens included in the included studies were: rotigotine (1.0 to 3.0mg/day); ropinirole (0.23 to 4.0mg/day); and pramipexole (0.25 to 0.75mg/day). Treatment duration ranged from six to 24 weeks. HRQoL instruments included Johns Hopkins specific restless legs syndrome-QoL Questionnaire and restless legs syndrome-QoL Questionnaire by Kohnen et al. Baseline International Restless Legs Syndrome scores ranged from 22.0 to 28.1 in the studies used for primary analysis; in most studies these reflected a disease severity score of severe.

The authors did not state how the studies were selected for the review.

Assessment of study quality
Trial quality was assessed using the Jadad scale of reported randomisation, blinding and withdrawals. Trials that scored less than 3 out of 5 were considered to be of low methodological quality. Quality of HRQoL data was assessed using an 11-item rating scale developed by Efficace et al. based upon the following criteria: a priori HRQoL hypothesis; rationale for using the specific HRQoL instrument; psychometric properties and validity of the instrument; adequacy of domains covered; instrument administration reporting; baseline compliance; assessment timing; documentation of missing data; presentation of results; and clinical significance. HRQoL was rated: probably robust (score 8 to 11); limited (score 5 to 7); and very limited (score 0 to 4).

Two reviewers independently assessed the quality of the included trials. Disagreements were resolved though consensus or through a third reviewer.

Data extraction
Two independent reviewers extracted adjusted mean change from baseline and variance for HRQoL data. Where necessary, pharmaceutical company websites, clinical trial registries and government agency websites were consulted for additional information. Disagreements were resolved by a third reviewer.

Methods of synthesis
HRQoL data were pooled using an inverse variance weighting approach as standardised mean differences (SMDs) and
95% confidence interval (CI). For trials that reported HRQoL data obtained using Johns Hopkins restless legs syndrome QoL questionnaire, adjusted mean difference data were pooled to calculate weighted mean difference (WMD) and 95% CI. A DerSimonian and Laird random-effects model was used to pool the data. Heterogeneity was assessed using the $I^2$ statistic. Sensitivity analysis were performed to assess the effect of inclusion of NEDA withdrawal trials and exclusion of less internally valid trials (Jadad score of <3 or Efficace HRQoL scores <5). Subgroup analyses were performed to assess the effect of each NEDA on HRQoL.

Publication bias was assessed using funnel plots and the Egger weighted regression statistic.

Results of the review
Seven trials (n=1,483) met all inclusion criteria. Jadad scores ranged from 3 to 5 (most studies scored 5). HRQoL data quality was considered to be limited in six studies and very limited in one study. Duration of follow-up ranged from 10 to 36 weeks. There was no evidence of publication bias.

Compared with placebo, patients with restless legs syndrome who took NEDAs had significantly improved HRQoL (SMD 0.20, 95% CI 0.10 to 0.30; seven studies); only ropinirole yielded significantly improved HRQoL (SMD 0.14, 95% CI 0.01 to 0.26; four studies).

Similar improvement with NEDAs compared with placebo were observed when trials that used Johns Hopkins restless legs syndrome QoL questionnaire were analysed (WMD 4.72, 95% CI 2.96 to 6.47; five studies). Both ropinirole (WMD 4.39, 95% CI 2.42 to 6.35; four studies) and pramipexole (WMD 6.00, 95% CI 2.11 to 9.89; one study) yielded significantly improved HRQoL when considered separately.

Significant heterogeneity was absent for these comparisons. The conclusions remained robust under sensitivity analysis.

Authors' conclusions
In patients with restless legs syndrome, use of NEDAs showed improved HRQoL compared with placebo. Since pooled effect sizes observed in this meta-analysis appeared to surpass accepted values for minimally important clinical differences, the improvements may be clinically relevant for the average studied patient.

CRD commentary
This review had clear inclusion criteria for study design, intervention and outcome. The authors searched some relevant sources without language restrictions. There was no indication that unpublished material was sought and some studies may have been missed. Publication bias was assessed and considered to be unlikely. Appropriate methods were used to minimise errors and bias during the review process for data extraction and validity assessment; it was unclear whether this was true for screening, which meant that reviewer error and bias could not be ruled out for study selection. Study quality was assessed using relevant criteria and the results were reported for each criteria; most studies were of good methodological quality (although none were scored probably robust on the HRQoL quality assessment scale). Heterogeneity between studies was investigated and the chosen method of synthesis appeared to be appropriate given the absence of statistical heterogeneity. As acknowledged by the authors, subgroup analyses provided limited data with which to compare groups and assess effectiveness because of the small number of studies included. This was a reasonably well-conducted review; despite uncertainty over the study selection process the findings are likely to reflect the available evidence.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies that evaluated long-term treatment of restless legs syndrome with NEDAs were required, along with head-to-head comparative trials and economic assessments.

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