Effect of nonergot dopamine agonists on symptoms of restless legs syndrome
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CRD summary
This well-conducted review assessed the effect of non-ergot dopamine agonists (NEDAs) in treatment of restless legs syndrome. It concluded that NEDAs may result in significant reductions in symptom severity in patients with moderate-to-severe restless legs syndrome, but many patients will discontinue their use due to adverse events. The conclusion appears to reflect the results and is likely to be reliable.

Authors' objectives
To assess the effect of non-ergot dopamine agonists (NEDAs) for treatment of restless legs syndrome

Searching
MEDLINE, EMBASE, CINAHL and Web of Science were searched from inception to July 2007 for relevant studies published in English. Search terms were reported. References of clinical trial reports were searched for further relevant details. Websites of the Food and Drug Administration (www.fda.gov), European Agency for the Evaluation of Medicinal Products (www.emea.eu.int) and four pharmaceutical companies that produced particular types of NEDA were searched.

Study selection
Eligible studies had to be placebo-controlled randomised controlled trials (RCTs) that assessed the effects of NEDAs in human populations with restless leg syndrome. Studies had to report either the percentage of responders to the medication (those assessed as much improved or very much improved on a Clinical Global Impression Improvement scale (CGI-I)) or adjusted mean change in International Restless Legs Symptoms study group scale (IRLS). Open label, cross-over and withdrawal studies were excluded.

NEDAs used included ropinirole, pramipexole, rotigotine and sumanirole; dose information was reported. Duration of follow-up ranged from one week to 12 weeks. Mean age of patients ranged from 51 to 76 years. All patients had similar disease severity. Most patients were female.

Study eligibility was assessed independently by two reviewers.

Assessment of study quality
Two reviewers assessed study quality independently using the Jadad scale to assign studies a score out of 5 based on assessment of randomisation, blinding and withdrawals and dropouts. Scores of less than 3 out of 5 were deemed low quality.

Data extraction
Two reviewers independently extracted data required to calculate risk ratios (RRs) with 95% confidence intervals (95% CIs) for the percentage of responders to medication as determined by the CGI-I scale and mean differences (MDs) with 95% CIs for adjusted mean change in IRLS scores. Risk differences were calculated. Safety and adverse event outcomes were also extracted, and risk ratios and 95% CIs calculated. Disagreements were resolved by consensus with a third reviewer.

Methods of synthesis
Risk ratios with 95% CIs and risk differences (RDs) with 95% CIs were pooled using a random-effects model for the patient responder outcome (assessed with the CGI-I scale). Number needed to treat (NNT) or number needed to harm (NNH) was calculated from risk differences. Mean differences in IRLS score from baseline were pooled as weighted mean differences (WMDs) with 95% CIs using a random-effects model.

Q and I² statistics were calculated to assess statistical heterogeneity.
The possibility and impact of publication bias was assessed by visual inspection of funnel plots, Egger's weighted regression statistics and the trim-and-fill method.

A number of sensitivity analyses were performed to assess the impact of type of NEDA, follow-up duration, publication bias (the effect of excluding unpublished but identified studies), intention-to-treat, Jadad score and use of fixed-effect model instead of random-effects model. The reviewers used meta-regression to assess whether the magnitude of impact depended on study duration.

**Results of the review**

Fourteen trials (n=3,197, range 41 to 381) were included in the analyses. All studies were prospective, randomised, double-blinded and placebo controlled. Jadad scores ranged from 3 to 5 out of five.

Pooled data from 13 trials favoured NEDAs over placebo using the CGI-I scale (RR 1.36, 95% CI 1.24 to 1.49, RD 0.18, 95% CI 0.13 to 0.23, NNT=6, 95% CI 5 to 8). Similarly pooled data from 10 trials favoured NEDAs over placebo using the IRLS score (WMD -4.93, 95% CI -6.42 to -3.43; score out of 40)

Withdrawal rates in NEDA arms were higher than in placebo arms (RR 1.35, 95% CI 1.00 to 1.81); this increase was statistically significantly greater in patients who took ropinirole but not other NEDAs. Overall NEDAs were associated with statistically significant increases in the adverse events of nausea, dizziness, somnolence and fatigue. Pramipexole was associated with a greater nausea risk. Ropinirole was associated with nausea, dizziness, somnolence and fatigue risk. Sunanatoine was associated with headache risk.

The review reported that visual inspection of funnel plots, the trim-and-fill method, and Egger's weighted regression all indicated low risk of publication bias.

Pooling results from each type of NEDA separately indicated that sumanirole was not statistically significantly different from placebo (RR 0.96, 95% CI 0.71 to 1.30). Sensitivity analyses for IRLS and CGI-I scores did not significantly alter the results. IRLS estimates based only on studies with shorter duration (less than 12 weeks) indicated a statistically substantially increased effects size; this relationship with duration was also seen in a random-effects meta-regression.

Heterogeneity was assessed to be statistically significant for the IRLS scores (Q test p<0.001, I²=69%) but not for CGI-I scores (Q test p<0.12, I²=33%).

**Authors' conclusions**

Three of the four NEDAs (pramipexole, ropinirole and rotigotine) when used in patients with moderate-to-severe restless legs syndrome resulted in significant reductions in symptom severity; a significant portion of patients discontinued use due to adverse events.

**CRD commentary**

This review addressed a clear review question supported by clear and appropriate study selection criteria. The search was comprehensive. The restriction to English-language publications only may have increased the risk of language bias. Formal assessment showed there was no evidence of publication bias. Most stages of the review process were undertaken in duplicate, which reduced potential for reviewer error and bias. Few primary study details were provided, which made the likely impact of clinical and patient heterogeneity on study outcomes harder to gauge and the review less transparent; however, some types of clinical heterogeneity were explored statistically within the subgroup analyses. Most studies had small sizes and short follow-up duration. A conventional approach was used to assess study quality, but only aggregate scores were presented. The methods of synthesis appeared comprehensive and appropriate and were clearly reported. The conclusion appears to reflect the results and is likely to be reliable.

**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 should be conducted to compare directly the efficacy of individual NEDAs against each other in patients with restless legs syndrome and include a longer follow-up period to assess the
longer-term effects; further research was needed to investigate the relationship between differences in the IRLS score and quality of life scores or clinical events to identify what magnitude of difference was statistically significant.

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