Meta-analysis of the efficacy and tolerability of pramipexole versus ropinirole in the treatment of restless legs syndrome

CRD summary
Pramipexole appeared to be more effective and better tolerated than ropinirole for treatment of restless legs syndrome, but should be confirmed in further trials. The authors’ cautious conclusions seemed appropriate, but should be considered in light of poorly reported methodology and a lack of quality assessment of the primary studies.

Authors’ objectives
To compare the efficacy and safety of pramipexole with ropinirole in the treatment of restless legs syndrome (RLS).

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched. No date or language limits were applied. Search terms were reported. Company trial registers for ropinirole were searched and pramipexole trials were provided by the manufacturer.

Study selection
Double-blind randomised controlled trials (RCTs) that compared pramipexole or ropinirole versus placebo were eligible for inclusion. Patients with idiopathic RLS were specified. Outcomes were required to include International Restless Legs Syndrome (IRLS) Study Group Rating Scale scores as the primary endpoint. Polysomnographic studies were included only for sensitivity analyses. The other most common outcome reported was the Clinical Global Impression improvement scale (CGI).

Pramipexole studies varied in dose of the active drug (0.125mg to 0.75mg). Most trials included multiple dosage arms. Mean age ranged from 49 to 56 years. Females made up 54% to 68% of the population. Follow-up lasted between six and 12 weeks.

Ropinirole studies were all two arm comparisons. Drug dosage was titrated from 0.25mg to 4mg. Mean age ranged from 52 to 56 years. Females made up 58 to 66% of the population. All studies reported 12-week follow-up.

The authors did not report how many reviewers performed the study selection.

Assessment of study quality
The authors did not report a validity assessment of the included studies.

Data extraction
Overall efficacy data were extracted as mean change in IRLS score with standard errors (SE). Safety and tolerability were assessed based on adverse events (nausea, headache, fatigue, somnolence, vomiting, dizziness, insomnia and nasopharyngitis). Numbers of patients for the dichotomous CGI and adverse events data were extracted and odds ratios (OR) calculated.

The authors did not report how many reviewers performed data extraction.

Methods of synthesis
Baseline differences were assessed using ANOVA for continuous outcomes and Cochran-Mantel-Haenszel tests for categorical variables. The analyses were considered in terms of direct and indirect comparisons. Weighted mean differences (WMD), odds ratios (OR) and number needed to treat (NNT) were calculated according to outcome type.

Direct analyses: An inverse-variance random effects meta-analysis was used to estimate the effect size and 95% confidence intervals (CI) for each drug versus placebo. Heterogeneity was assessed based on Forest plots, I² test and
Indirect analyses: A Bayesian approach was used to conduct indirect fixed-effect meta-analyses with placebo as the common comparator. Each drug was tested for non-inferiority based on an agreed non-inferiority margin (2.5 point difference for the IRLS score and 10% change for CGI responders) and then tested for superiority (hierarchical testing). Associated posterior probabilities and 95% credible intervals (CrI) were calculated.

Sensitivity analyses were used to explore the impact of study design and prior distributions.

Results of the review
Five trials were included in the main analyses: two of pramipexole (n=689) and three of ropinirole (n=931). Two polysomnographic studies (one of each drug) were included only in the sensitivity analyses (pramipexole n=109, ropinirole n=73). Sample sizes ranged from 266 to 380. All of the pramipexole studies had multiple arms. Heterogeneity for the pramipexole trials was noted to be moderate (range $I^2=26.8\%$ to 54.3%) for the outcomes IRLS score, withdrawals for any reason, withdrawals for adverse events and incidence of nausea or nasopharyngitis. All outcomes in the ropinirole trials were low heterogeneity except withdrawal due to adverse events ($I^2=54.1\%$).

Direct Comparisons:
For both drugs, there was a significantly greater change in IRLS scores for the active intervention compared with placebo (WMD for pramipexole -5.45, 95% CI -7.70 to -3.20 and WMD for ropinirole was -3.16, 95% CI -4.26 to -2.05).

Proportions of responders according to CGI rating were significantly higher for active interventions versus placebo (OR for pramipexole 2.98, 95% CI 2.08 to 4.26 and OR for ropinirole 1.99, 95% CI 1.52 to 2.60). Based on the CGI response data, for pramipexole NNT=4 (95% CI 3 to 5) and for ropinirole NNT=6 (95% CI 4 to 10).

Indirect comparisons:
Overall there was a greater change in IRLS scores for pramipexole patients versus ropinirole (mean change -2.33, CrI -4.23 to -0.41). The probability that pramipexole was non-inferior to ropinirole was 1 and that the treatment effect was clinically meaningful was 0.43. The odds ratio of being a responder according to CGI scores was 1.50 (95% CrI 0.97 to 2.32) in favour of pramipexole over ropinirole. The probabilities of non-inferiority and a clinically meaningful treatment effect were 0.99 and 0.92.

Tolerability/safety: Incidences of nausea, vomiting and dizziness were significantly increased when being treated with pramipexole compared with ropinirole (from the direct comparisons).

Sensitivity: Adding polysomnographic studies or varying prior distributions did not significantly alter the results.

Authors' conclusions
Differences in efficacy and tolerability favouring pramipexole over ropinirole for the treatment of restless legs syndrome can be observed and should be confirmed in head to head trials.

CRD commentary
This review addressed a clear question with explicit inclusion criteria. Reasonable searches without limits reduced the likelihood of publication and language biases. Both relevant companies were contacted. The authors did not report the methodological processes of study selection or data extraction, thus reviewer error and bias could not be excluded. Crucially no mention was made of validity assessment, so it was difficult to judge the reliability of the primary studies and their results although it appeared that sensitivity analyses were carried out on the basis of study size. Overall the analysis strategies appeared appropriate. The authors' cautious conclusions seemed appropriate, but should be considered in light of the potential methodological flaws in this review and the small amount of available evidence.

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

Research: The authors suggested that head to head trials of pramipexole and ropinirole were required, as was further research to explore factors such as treatment half life, dosage, titration period and effects on depression, quality of life and pain.

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