Rasagiline in Parkinson's disease: a review based on meta-analysis of clinical data

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CRD summary
The review concluded that rasagiline was efficacious for Parkinson's disease when compared with placebo but that the clinical significance of these data remained to be established. Despite some methodological and reporting limitations, these conclusions appear likely to be reliable.

Authors' objectives
To compare the efficacy of rasagiline versus placebo for improving symptoms of Parkinson's disease.

Searching
MEDLINE and Cochrane CENTRAL were searched (using the term “rasagiline”) for published studies up to April 2013. Reference lists of retrieved articles were examined to identify further studies.

Study selection
Trials of rasagiline for patients with Parkinson's disease were eligible providing they reported full descriptions on patient diagnosis, efficacy outcomes and duration and dosage of treatments. Trials that compared rasagiline with placebo, other anti-Parkinson drugs or different doses of rasagiline were eligible.

Most trials had durations of between 12 and 26 weeks; 1mg and 2mg were the most frequently studied doses. Patients in around one third of the studies also received levodopa. Outcome measures varied across studies.

The authors did not state how many reviewers selected studies.

Assessment of study quality
Study quality was evaluated using the Cochrane risk of bias tool. Each potential bias was ascribed a low, high or unclear judgement.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted mean difference data for Unified Parkinson Disease Rating Scale (UPDRS) and "off time" outcomes. Disagreements were resolved by a third reviewer.

Methods of synthesis
Meta-analyses were performed to calculate pooled mean differences with 95% confidence intervals. A random-effects model was used when significant heterogeneity was found and otherwise a fixed-effect model was used. Heterogeneity was assessed using the $I^2$ statistic. Studies unsuitable for meta-analysis were described individually.

Results of the review
Thirteen trials (around 3,600 patients, range six to 1,176) were included in the review. Several trials had associated publications of sub-studies. Three trials were non-randomised open studies, five trials used low risk methods for sequence generation and methods in six trials were unclear. Risk of biases due to inadequate blinding were generally low (except in the open studies). All trials had low risk of bias from incomplete outcome data but judgements on selective reporting were unclear for most trials.

Rasagiline monotherapy 1mg/day in early stages of the disease significantly reduced the UPDRS score when compared with placebo (mean difference -3.06, 95% CI -3.81 to -2.31; three studies; $I^2$=3%); a similar result was seen when pooling the same three studies for the 2mg/day data. Rasagiline also reduced the UPDRS score in trials with a delayed-start design (mean difference -0.89, 95% CI -1.78 to 0.00; $I^2$=0%; two studies) although there was significant heterogeneity of effect when the analyses were subgrouped by dose.
Compared with placebo, 1mg/day of rasagiline plus levodopa significantly reduced off-time (mean difference -0.93 hours, 95% CI -1.17 to -0.69; three studies; I²=0%). A smaller reduction was seen in the one study that used a dose of 0.5mg/day.

Authors’ conclusions
The review results confirmed the efficacy of rasagiline for Parkinson’s disease when compared with placebo but the clinical significance of these data remained to be established.

CRD commentary
The review addressed a clear question and was supported by reproducible eligibility criteria. Relevant studies may have been missed during the searches as the strategy seemed basic and only published studies were sought (it was unclear whether language restrictions were used). Duplicate processes were employed to reduce the risks of reviewer error and bias during data extraction but the authors did not report on whether such methods were used to select studies and assess study quality.

Risk of bias in the included studies was assessed appropriately, but the authors did not appear to make use of the bias judgements when interpreting their review results. However, it appeared that the large studies (on which the meta-analyses were mainly based) were unlikely to have been affected by bias. Trial details were provided, but were limited in terms of population parameters. Appropriate methods were used to pool data and to assess heterogeneity.

Notwithstanding some methodological and reporting limitations, the authors conclusions appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice other than to note the uncertainty surrounding the clinical significance of the review results.

Research: The authors stated a need for trials to compare rasagiline with other drugs used for Parkinson’s disease.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.