Indirect meta-analysis of randomised placebo-controlled clinical trials on rasagiline and selegiline in the symptomatic treatment of Parkinson's disease

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CRD summary
This review concluded that there were statistically and clinically significant benefits to rasagiline over selegiline for the treatment of Parkinson's disease, in terms of both efficacy and safety. There are concerns over the synthesis methods and the relatively small size and number of trials. The conclusions appear overly strong and may not be reliable.

Authors' objectives
To compare the efficacy and safety of rasagiline with selegiline in patients with Parkinson's disease.

Searching
Multiple databases including Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE were searched up to 2009. Search terms were reported. Congress proceedings, supplements, overviews, registries of regulatory agencies and references of relevant reviews and other publications were searched for additional studies.

Study selection
Randomised placebo controlled trials that assessed rasagiline (1mg/day) or selegiline as either monotherapy or adjunctive therapy in the treatment of Parkinson's disease were eligible for inclusion. Trials needed to have a parallel group design and a minimum duration of ten weeks. Studies needed to use clinically relevant scales such as the Unified Parkinson Disease rating Scale (UPDRS), the Columbia University Rating Scale (CURS) or the Schwab and England scale and to report safety and tolerability data. Discontinuation studies were excluded. UPDRS and CURS scores were the primary outcome; subscales of the UPDRS, the Schwab and England scale and daily off time were secondary outcomes.

Study durations ranged from three months to over 12 months. There was no additional information on participant or trial characteristics.

The authors did not state how many reviewers were involved in selecting the studies for the review.

Assessment of study quality
Studies were assessed for quality using the Jadad and Delphi scales which award up to a maximum of five and ten points respectively. The authors did not report how many reviewers carried out the assessment.

Data extraction
Data on baseline and post-treatment mean scores on efficacy scales were extracted and mean differences with 95% confidence intervals calculated. The first control examination data were used for the post-treatment measure. Rates of discontinuation and discontinuation due to adverse effects during the entire study duration were also extracted for the assessment of tolerability and safety.

The authors did not report how many reviewers were involved in data extraction.

Methods of synthesis
Trials were combined using a fixed-effect meta-analysis to compare drug therapy with placebo. The pooled estimates for each drug (rasagiline versus selegiline) were also compared. The statistical significance of these comparisons appeared to have been assessed using p-values but it was unclear which statistical test was used to generate these. Separate analyses were used for monotherapy trials and trials where the index drug was given in combination with other therapy. A combined analysis of all trials was also carried out. Heterogeneity was assessed using I². Where heterogeneity was such that I² was greater than 50%, outliers were identified using a funnel plot. Sensitivity analyses were conducted to explore the effect of excluding outliers on the pooled estimate. Risk differences for safety and tolerability outcomes were calculated for each treatment versus placebo and compared with each other; p values were
presented for the comparison. Intention-to-treat data were used in analyses.

**Results of the review**
Twenty-one RCTs were included in the review; six assessed rasagiline and 15 assessed selegiline. All of the rasagiline and nine of the selegiline trials were included in the efficacy analysis. Jadad scores ranged from 2 to 5; all except one study scored 3 or more. Delphi scores ranged from 4 to 10; all except one study scored at least 6 points.

In terms of UPDRS score, there were statistically significant effects favouring rasagiline monotherapy compared with placebo (SMD -0.528, 95% CI -0.650 to -0.407; three trials) and selegiline monotherapy versus placebo (SMD -0.328, 95% CI -0.451 to -0.205; four trials). The indirect comparison between rasagiline and selegiline showed a statistically significant difference favouring rasagiline. Sensitivity analyses showed similar results. Similar results were also found for the analysis of all trials. The analysis of adjunctive therapy studies was not considered meaningful due to the small number and short duration of studies available.

A statistically significant difference in UPDRS motor function favouring rasagiline monotherapy was found when compared indirectly with selegiline. Other outcomes (UPDRS activities of daily living, UPDRS mental, Schwab and England) were reported and there were no statistically significant differences in the indirect comparisons between the two drugs given as monotherapy. Daily time off could not be analysed. Results of all trials, including combination therapy were also reported.

The analyses of discontinuations of treatment due to non-compliance or loss to follow-up showed no significant difference between either of the treatments and placebo. Rates of discontinuation were numerically higher in the selegiline trials at 9.8% in both treatment and placebo arms, compared with rates of 2.9% (treatment) and 3.9% (placebo) in the rasagiline trials. This pattern was also seen for discontinuation due to adverse events. In this analysis, selegiline initially showed a higher rate of discontinuations than placebo but this result was not significant following a sensitivity analysis. Fifteen individual symptoms were documented in a minimum of four studies; results did not show statistical significance with the exception of dry mouth which was more common in rasagiline.

**Authors’ conclusions**
There was a statistically significant and clinically relevant advantage to rasagiline over selegiline in the primary endpoint. Rasagiline also showed advantages in tolerability and safety over selegiline.

**CRD commentary**
The review examined a clear question supported by specific inclusion criteria. An extensive search was conducted. The authors did not report using procedures to reduce reviewer bias or error at any stage of the review process. A validity assessment was conducted; the tools used assessed key criteria. However, only summary scores were reported; these indicated that most studies were of reasonable quality. The review sought and included only placebo controlled trials of each of the treatments assessed. Therefore all comparisons between rasagiline and selegiline were indirect. The methods used for the indirect comparisons were unclear; the authors did not provide a justification for not conducting a network meta-analysis. Evidence from indirect comparisons was more uncertain than evidence from direct comparisons because of the potential for systematic differences between the two sets of trials. This was particularly the case in this review where there was no information on the population and intervention characteristics of the included studies; the extent to which the patients receiving each treatment were comparable was unknown.

Although the conclusions reflected the results for the primary outcome, it was not clear if they represented the results of the safety and tolerability or secondary efficacy analyses. The primary efficacy conclusion that rasagiline was more effective than selegiline in reducing UPDRS score is uncertain due to the limitations of the synthesis methods and the relatively limited size and number of the trials. It is also unclear whether there are any differences between the treatments on other measures. The conclusions appear overly strong and may not be reliable.

It should be noted that the review was funded by the company which manufactures rasagiline and two of the authors had financial relationships with this company.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.
**Funding**
The review was funded by Lundbeck (the manufacturer of rasagiline); one of the authors is an employee of this company and a second is an advisor and consultant to Lundbeck and its partner company (TEVA).

**Bibliographic details**

**DOI**
10.1016/j.baga.2012.05.006

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Neuroprotective Agents; Parkinson Disease; Monoamine Oxidase Inhibitors; Selegiline; Humans

**AccessionNumber**
12013008870

**Date bibliographic record published**
15/03/2013

**Date abstract record published**
19/09/2013

**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.