Pharmacologic treatment of advanced Parkinson's disease: a meta-analysis of COMT inhibitors and MAO-B inhibitors

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CRD summary
The authors concluded that catechol-O-methyltransferase or monoamine oxidase type B inhibitors plus levodopa were superior to levodopa alone in reducing symptoms in patients with advanced Parkinson's disease, but they were associated with increased adverse events. There were some limitations to the review, but overall the authors' conclusions appeared to be supported by the evidence.

Authors' objectives
To compare catechol-O-methyltransferase (COMT) inhibitors or monoamine oxidase type B (MAO-B) inhibitors plus levodopa with levodopa alone in patients with Parkinson's disease.

Searching
MEDLINE, EMBASE, CINAHL, Web of Science and The Cochrane Library were searched from 1990 to October 2007. Search terms were reported. Reference lists of clinical trials and reviews were screened. Studies were included only if they were published in English.

Study selection
Randomised controlled trials (RCTs) that reported Unified Parkinson's Disease Rating Scale (UPDRS) scores (total, activities of daily living or motor) were eligible for inclusion. Although not explicitly stated in the inclusion criteria, it was clear that the review focused on comparisons of COMT or MAO-B plus levodopa versus levodopa alone in patients with Parkinson's disease.

Dose ranging studies, studies in patients with early-stage Parkinson's disease and studies that evaluated dopamine agonists were excluded.

The review also assessed: changes in on and off time (re-emergence of previously controlled symptoms towards the end of the dosing schedule) in hours per day; dose of levodopa; withdrawals due to adverse events; occurrence of dyskinesia; and overall mortality.

The included studies evaluated COMT inhibitors (entacapone and tolcapone) and MAO-B inhibitors (rasagiline and selegiline). Duration of treatment ranged from six weeks to five years. All included patients were already on levodopa. Mean age of patients ranged from 57 to 70 years. In all but one study, patients were predominantly male. Where reported, baseline total UPDRS scores ranged from 27.2 to 43.2 and mean duration of Parkinson's disease ranged from 3.0 to 10.1 years. One study was in patients with fluctuating and non-fluctuating disease.

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

Assessment of study quality
Two reviewers independently assessed validity using the five-point Jadad scale (considers randomisation, blinding and withdrawals). Studies that scored less than 3 were considered to be poor quality. Disagreements were resolved by consensus.

Data extraction
Adjusted mean changes in UPDR scores from baseline were extracted or calculated separately for treatment groups in order to calculate mean differences between groups. The number of prespecified adverse events was extracted to calculate odds ratios (ORs).
Two reviewers independently extracted data using a standardised tool. Disagreements were resolved by discussion or with the help of a third reviewer.

**Methods of synthesis**

Studies that evaluated COMT and MAO-B inhibitors were analysed separately. Pooled odds ratios and weighted mean differences (WMDs) with 95% confidence intervals (CI) were calculated using the random-effects DerSimonian and Laird model.

Heterogeneity was assessed using the Q statistic. Sensitivity analysis was performed using fixed-effect models to analyse effects of COMT and MAO-B on UPDRS total, ADL, motor scores and on and off time. It was not possible to evaluate the influence of study quality since all studies scored 3 or more on the Jadad scale and none were open-label. The possibility of publication bias was explored using funnel plots, Egger's test and the trim-and-fill method.

**Results of the review**

Thirteen RCTs were included (n reported as 3,775 patients in text and n=3,834 in tables). All studies scored 3 or more (maximum 5) on the Jadad scale. No studies were open-label.

**COMT inhibitors plus levodopa versus levodopa alone**

Nine RCTs, n=2,656 according to tables.

COMT inhibitors plus levodopa were associated with statistically significantly lower: UPDRS total scores (WMD -2.13, 95% CI -4.06 to -0.20; five RCTs, n=1,807 patients); UPDRS activities of daily living scores, (WMD -0.99, 95% CI -1.56 to -0.43; six RCTs, n=2,267 patients); and UPDRS motor scores (WMD -1.50, 95% CI -2.70 to -0.30; six RCTs, n=2,263 patients). Forest plots showed consistency of direction of treatment effect except for one study that included separate treatment comparisons for patients with fluctuating and non-fluctuating disease. Significant heterogeneity was found for UPDRS total (p=0.0007), UPDRS activities of daily living (p=0.03) and UPDRS motor scores (p=0.01).

COMT inhibitors plus levodopa were associated with a significantly greater risk of withdrawal due to adverse events (OR 1.67, 95% CI 1.28 to 2.16; eight RCTs) and dyskinesia (OR 1.69, 95% CI 1.30 to 2.18; nine RCTs).

There was no significant difference between treatments in mortality.

**MAO-B inhibitors plus levodopa versus levodopa alone**

Five RCTs, n=1,178 patients.

MAO-B inhibitors plus levodopa were associated with statistically significantly lower: UPDRS total scores (WMD -5.03, 95% CI -7.38 to -2.68; two RCTs, n=415 patients); UPDRS activities of daily living scores (WMD -1.48, 95% CI -2.13 to -0.83; three RCTs, n=855 patients); and UPDRS motor score (WMD -3.19, 95% CI -4.57 to -1.80; three RCTs, n=855 patients).

There was no significant difference between MAO-B inhibitors plus levodopa versus levodopa alone in withdrawals due to adverse events (five RCTs, n=1,178 patients) or mortality (three RCTs).

MAO-B inhibitors plus levodopa were associated with a significantly greater risk of dyskinesia (OR 1.84, 95% CI 1.17 to 2.89; two RCTs).

The authors stated in the discussion that MAO-B inhibitor studies were more homogeneous.

Changes in on and off time and effects of levodopa dose were reported in the review for both COMT and MAO-B inhibitors. Results were similar using a fixed-effect model for subgroup analyses.

Egger's test and trim-and-fill method suggested a low likelihood of publication bias.
Authors' conclusions
COMT or MAO-B inhibitors plus levodopa were superior to levodopa alone in reducing symptoms in patients with advanced Parkinson’s disease, particularly in patients with wearing-off phenomenon, but were associated with increased adverse events.

CRD commentary
The review question was clearly stated. Inclusion criteria were defined for study design and outcome. Although inclusion criteria for participants and intervention were not explicitly stated, criteria were clear from the text of the review. Several relevant sources were searched, but no attempts were made to minimise publication or language bias; publication bias was assessed and no convincing evidence found. Methods were used to minimise reviewer errors and bias in assessment of validity and extraction of data; it was unclear whether similar steps were taken in study selection. Only RCTs were included, validity was assessed and results were reported. Little information was provided about treatment regimens. Data were combined using meta-analysis. Heterogeneity was assessed and forest plots were examined to identify studies that may have accounted for heterogeneity. There appeared to be only limited discussion about reasons for the identified heterogeneity. The authors acknowledged the paucity of studies of MAO-B inhibitors. There were some limitations to the review, but overall the authors’ conclusions appeared to be supported by the evidence.

Implications of the review for practice and research
Practice: The authors stated that although the reductions in UPDRS scores were statistically significant, they did not meet the suggested criteria for clinical relevance.

Research: The authors stated that further research was required to evaluate criteria used to define a clinically important change in UPDRS score.

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