Dopamine agonists in the treatment of early Parkinson's disease: a meta-analysis

CRD summary
This review reported that dopamine agonist monotherapy was superior to placebo, but inferior to levodopa, for the early treatment of Parkinson's disease. Overall, dopamine agonists were associated with a greater incidence of adverse events compared with placebo, but fewer motor complications in comparison with levodopa. This appeared to be a well-conducted review and the authors' conclusions seem reliable.

Authors' objectives
To compare the efficacy and safety of monotherapy and adjunctive therapy with dopamine agonists for the early treatment of Parkinson's disease.

Searching
MEDLINE, EMBASE, CINHAL and the Web of Science were searched from 1990 to April 2007. Search terms were reported. In addition the Cochrane Library (Issue 2, 2007) was searched, along with the reference lists of clinical trials and reviews. Only published studies appear to have been eligible for inclusion in the review.

Study selection
Randomised controlled trials (RCTs) comparing the efficacy and safety of dopamine agonists in comparison with or in combination with levodopa, in patients with early Parkinson's disease, were eligible for inclusion in the review. Eligible trials had to report data using the unified Parkinson's disease rating scale (UPDRS) or report the incidence of wearing-off, dyskinesia, mortality, or withdrawal due to adverse effects. Trials that assessed a range of drug doses without providing cumulative data were excluded from the review.

Included trials compared dopamine agonists versus placebo, dopamine agonists versus levodopa, dopamine agonists versus levodopa/dopa-decarboxylase inhibitor, or dopamine agonists plus levodopa versus levodopa alone. Included dopamine agonists were bromocriptine, pramipexole, ropinirole, pergolide, lisuride, alpha-dihydroergocryptine, cabergoline, and piribedil. Mean treatment duration ranged from 2.3 to 60 months. The majority of included trials also allowed the use of concomitant medications, including most commonly anticholinergics and amantadine; 28% of trials allowed the use of levodopa. Where reported, the mean age of participants ranged from 57 to 69 years, the percentage of male participants ranged from 35 to 73% and the mean total baseline UPDRS score ranged from 24.4 to 38.4. The mean duration of follow-up ranged from seven to 53 months.

The authors did not state how papers were selected for review or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed the quality of the trials using the Jadad scale (randomisation, blinding and loss to follow-up). Each trial was awarded a score of up to 5 points; trials scoring below 3 points were considered to be low quality. Discrepancies were resolved through consensus or discussion with a third reviewer.

Data extraction
One reviewer extracted the trial data using a standardised form, which was checked for accuracy by a second reviewer. The mean change (and standard deviation) in UPDRS score was recorded from baseline and the difference between control and intervention groups calculated. Where mean differences were not reported separately for each study group, a pooled mean difference for the net change was calculated. Where mean differences for paired differences were not reported, they were calculated from the differences at baseline and at the end of follow-up, assuming a correlation coefficient of 0.5 and the presence of equal differences between the intervention and control groups throughout the duration of the trial. Event rates were recorded for dichotomous outcomes and used to calculate odds ratios (ORs) with 95% confidence intervals (CIs).
Methods of synthesis
Trials were grouped according to comparators and pooled using the random-effects method of DerSimonian and Laird. Weighted mean differences (WMDs), with 95% confidence intervals, were calculated for UPDRS scores, and pooled ORs, with 95% confidence intervals, were calculated for dichotomous outcomes. Additional analyses were performed excluding poorer quality trials (Jadad score less than 3 points) and using a fixed-effect analysis. Subgroup analyses examined the effects of non-ergot dopamine agonists versus ergot dopamine agonists, and pramipexole versus ropinirole. Statistical heterogeneity was assessed using the Q statistic and the I² statistic funnel plots, Egger's weighted regression statistics and the trim-and-fill method were used to assess the risk of publication bias.

Results of the review
Twenty-five RCTs (n=5,185 patients) were included in the review. Sample sizes ranged from 20 to 702 participants. Jadad scores ranged from 2 to 5 points, with 21 studies scoring at least 3 points (i.e. good quality).

Dopamine agonists versus placebo: In comparison with placebo, dopamine agonists were associated with a significantly greater reduction in activities of daily living (ADL) scores (WMD -1.64, 95% CI 2.65 to 0.62; six RCTs) and unified Parkinson's disease rating scale (UPDRS) motor scores (WMD -5.32, 95% CI -6.89 to -3.75; 10 RCTs), suggesting that dopamine agonists were superior. However, dopamine agonists were associated with a greater incidence of withdrawals due to adverse events (OR 2.49, 95% CI 1.69 to 3.65; nine RCTs). Both the analyses of ADL and UPDRS scores were associated with a statistically significant level of heterogeneity.

Dopamine agonists versus levodopa: In comparison with levodopa, dopamine agonists had a significantly higher ADL score (WMD 2.09, 95% CI 1.26 to 2.92; five RCTs) and a greater UPDRS motor score (WMD 4.69, 95% CI 3.76 to 5.61; seven RCTs), suggesting that dopamine agonists were inferior. The ADL analysis was associated with a significant level of statistical heterogeneity. Patients receiving dopamine agonists were also significantly less likely to experience wearing-off in comparison with those receiving levodopa (OR 0.52, 95% CI 0.40 to 0.66; six RCTs), but significantly more likely to withdraw due to adverse events (OR 2.46, 95% CI 1.44 to 4.20; nine RCTs).

Dopamine agonists plus levodopa versus levodopa alone (six RCTs): There were no statistically significant differences between the groups for wearing-off (three RCTs) and there were insufficient data to assess UPDRS scores. However, dopamine agonists plus levodopa were associated with a significantly higher level of withdrawals due to adverse events in comparison with levodopa alone (OR 4.0, 95% CI 1.50 to 10.64; four RCTs).

Other outcomes including the incidence of dyskinesia, mortality and specific adverse events were reported in the review. With respect to the main outcomes, the overall effects were similar in both the subgroup and sensitivity analyses. The risk of publication bias was judged to be low.

Authors' conclusions
Dopamine agonist monotherapy appeared to be superior to placebo, but inferior to levodopa. Overall, dopamine agonists were associated with a greater incidence of adverse events in comparison with placebo, but there were fewer motor complications in comparison with levodopa.

CRD commentary
This review answered a clear research question using well-defined criteria. It was unclear whether the literature searches included unpublished studies, but assessments suggested that there was a low risk of publication bias. The potential for language bias was unclear. Some attempts were made to reduce reviewer error and bias during the extraction of data, but it was unclear whether similar precautions were taken when selecting the trials for inclusion. Trial quality was assessed using appropriate criteria and steps were taken to reduce the risk of reviewer error and bias during the assessment.

Overall, the quality of the trials appeared to be good, suggesting that the data are reliable, although it should be noted that, in a number of cases, concomitant medications were allowed, which may have affected the findings. Appropriate statistical analyses were performed, taking into account both statistical and clinical differences between the trials. However, it should be noted that the review was funded by a pharmaceutical company and that one of the authors was employed by the same company, which may open the review up to potential bias.
This appeared to be a well-conducted review and authors’ conclusions seem to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that their review supported the initial use of dopamine agonist, followed by the subsequent addition of levodopa as required, or the use of levodopa initially, followed by the subsequent addition of dopamine agonist in lieu of increased levodopa doses, dependant on the circumstances of the individual patient.

**Research:** The authors stated that further studies are required to investigate the effects of combining dopamine agonists and levodopa versus higher doses of levodopa alone, in the treatment of early Parkinson's disease.

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