Systematic review of apomorphine infusion, levodopa infusion and deep brain stimulation in advanced Parkinson's disease
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CRD summary
The authors concluded that levodopa infusion and deep brain stimulation demonstrated significant functional benefits, with associated improvements in patient-rated quality of life. The absence of comparative studies meant that clinical judgement remained the primary tool in treatment choice. Poor reporting of the review process and uncertainties surrounding the included studies made the reliability of the authors' conclusions unclear.

Authors' objectives
To evaluate the effectiveness of apomorphine infusion, levodopa infusion and deep brain stimulation in patients with advanced Parkinson's disease.

Searching
PubMed and The Cochrane Library were searched to March 2009 for published English-language articles. Search dates were limited from February 2005 onwards for studies of deep brain stimulation and apomorphine infusion. Search terms were reported. Further studies were sought by electronic searching of general and specific medical journals and by scanning reference lists of reviews and clinical reports.

Study selection
All studies of patients with advanced Parkinson's disease presenting with motor fluctuations and/or dyskinesia uncontrollable by oral levodopa and dopamine agonist treatment and treated with continuous apomorphine infusion, levodopa infusion or deep brain stimulation were eligible for inclusion in the review. At least one arm of the study had to assess monotherapy. Non-RCT studies of deep brain stimulation had to include at least 40 patients. Studies were included only if they measured outcomes that related to motor complications, daily "off" time or Unified Parkinson's Disease Rating Scale (UPDRS) III motor examination score.

Included patients were generally younger than 70 years. Most patients had severe complications. Where reported, average duration of Parkinson's Disease ranged from 7.2 to 18 years. Just over half of the included studies assessed bilateral subthalamic nerve stimulation and just under half assessed levodopa infusion. None of the included randomised controlled trials (RCTs) directly compared the three treatment options. The outcomes assessed were UPDRS III (motor score), UPDRS II (activities of daily living), changes in daily "on" and "off" time (recorded in patient diaries), patient-rated quality of life (using the Parkinson's Disease Questionnaire) and adverse events. Endpoints were inconsistently reported.

The authors did not state how studies were selected.

Assessment of study quality
There was no formal validity assessment of the included studies other than consideration of randomisation method and allocation concealment in the RCTs.

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

Data extraction
Data were extracted on the outcomes of interest. Percentages were recorded for on and off times and adverse events. UPDRS scores were extracted for clinician-rated disability. PD39 summary index scores were collected for patient-rated quality of life.

The authors did not state how data were extracted.
Methods of synthesis
A narrative synthesis was presented, grouped by the outcomes of interest.

Results of the review
Twenty-seven studies were included in the review (n=1,405). Six RCTs were included (n=481, sample size range 10 to 255). Three RCTs assessed levodopa infusion (n=50) and three assessed deep brain stimulation (n=431). Randomisation and allocation concealment were reported to be adequately described on three RCTs. The other studies were uncontrolled studies. Follow-up across all studies ranged from six days to four years.

Outcomes related to motor complications:
In the three RCTs that assessed levodopa infusion, the percentages of a patient’s waking day in a functional on state ranged between 80% and 100% at the end of each study. In two RCTs that evaluated deep brain stimulation (surgery), positive functional outcomes were reported in terms of percentage increases in on times (66% and 138%). Statistically significant differences were reported for both RCTs in favour of surgery/immediate surgery compared to best medical therapy (p<0.001). The direction of findings was confirmed in uncontrolled studies. Three non-controlled apomorphine studies found a decrease in off time from baseline to the end of the studies.

The UPDRS motor score from one RCT of levodopa infusion showed an improvement from 25.5 at baseline to 14.5 at the end of the study (absolute change was not stated). Change in activities of daily living score was from 16 to 14.

Results from uncontrolled studies of levodopa infusion were inconclusive and those that assessed apomorphine infusion showed no effect. Two of the three RCTs of deep brain stimulation showed improvements in UPDRS motor scores (28% and 41%) and activities of daily living scores (69% and 39%); the third and largest RCT reported decreases in UPDRS (29%) and activities of daily living (24%) scores. Results from uncontrolled studies were inconclusive.

Patient-related quality of life:
One RCT of levodopa infusion showed a statistically significant (p<0.01) difference in median end of study Parkinson's Disease Questionnaire (PDQ) summary index score (25) compared to conventional treatment (35). One non-controlled levodopa study showed a statistically significant (p<0.005) improvement in the PDQ summary index score from 59.5 at baseline to 49.2 at end of study. Improvements of between 17% and 24% in PDQ summary score were reported for three RCTs of deep brain stimulation, two of which reported significantly better improvements for deep brain stimulation compared to conventional treatment (p=0.02 and p<0.01).

Adverse events and withdrawal rates were sparsely reported. Adverse events included administration site problems, dyskinesia, somnolence, hallucinations and nausea.

Cost information
Variable costs were reported for subthalamic nerve stimulation: 11,807 to 41,276 euros; £9,371 to £32,759; and US dollars $17,363 to $60,700.

Authors' conclusions
RCTs that compared levodopa infusion or deep brain stimulation with best medical management demonstrated significant functional benefits for these therapies, which appeared to correlate with improvements in patient-rated quality of life.

CRD commentary
The review question was clear and supported by potentially replicable inclusion criteria. The search strategy accessed some relevant sources, but the restriction to published English-language articles meant that language and publication biases could not be ruled out. There were no details of the review process and no formal validity assessment of included studies. The informal assessment was incomplete. These led to substantial concerns about the transparency and reliability of the review process and its findings. Study characteristics were reported in detail. The chosen method of synthesis appeared to be appropriate in light of the apparent clinical heterogeneity. Inconsistent reporting of endpoints made the interpretation of findings across studies difficult. Given the various potential methodological limitations, the
extent to which the authors' conclusions are reliable is uncertain.

The authors declared some financial interests with pharmaceutical sources, including the funders of editorial development for the review.

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

**Practice:** The authors stated that absence of direct comparative data meant that treatment for advanced Parkinson's Disease should be determined by clinical judgement and patient preference.

**Research:** The authors stated that well-designed clinical trials were needed that would ideally compare levodopa infusion, apomorphine infusion and deep brain stimulation directly. Future research should also consider the merits of adverse events and quality of life as primary outcome measures.

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