CRD summary
The authors concluded that only clozapine can be recommended for the treatment of drug-induced psychosis in patients with Parkinson's disease; olanzapine should not be used, nor should quetiapine until proven to be effective. This was generally a well-conducted review. However, it was based on very limited evidence and a more cautious conclusion may have been appropriate.

Authors' objectives
To evaluate the safety and efficacy of atypical antipsychotics for the treatment of dopamimetic psychosis in patients with Parkinson's disease.

Searching
MEDLINE, EMBASE, the Cochrane CENTRAL Register and ISI Web of Knowledge were searched from inception to 2005 using the reported search terms. No language restrictions were applied to full papers providing an English abstract was available; studies reported as abstracts were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that were at low or moderate risk of allocation concealment bias were eligible for inclusion in the review. Some studies were subsequently excluded if they were too small or if inappropriate statistics were used.

Specific interventions included in the review
Studies that evaluated atypical antipsychotic treatments were eligible for inclusion. The review evaluated clozapine, quetiapine and olanzapine compared with each other or placebo (mean drug doses were reported). The dopamimetic dosage was kept constant in all of the included studies. Treatment duration was 4 or 12 weeks.

Participants included in the review
Studies of patients with Parkinson's disease who developed dopamimetic psychosis were eligible for inclusion. The included patients were of both genders, with an average age of 71.4 years (range: 69.5 to 74).

Outcomes assessed in the review
Studies that assessed psychotic and motor symptoms using validated rating scales, adverse events, or withdrawals were eligible for inclusion. The most commonly used outcome measures included the Clinical Global Impression Severity Scale (CGI-S), the Unified Parkinson's Disease Rating Scale (UPDRS) for symptoms of Parkinson and the Mini-Mental State Examination (MMSE) for cognitive outcomes.

How were decisions on the relevance of primary studies made?
Five reviewers independently selected the studies and resolved any disagreements on inclusion through discussion.

Assessment of study quality
Studies were assessed for allocation concealment, blinding, follow-up and the reporting of data. The studies were classified as at low, moderate or high risk of bias based on the adequacy of allocation concealment. The authors did not state how the validity assessment was performed.

Data extraction
Two reviewers independently extracted the data. Where required, any disagreements were resolved through recourse to a third author. Changes in severity scores and the numbers of withdrawals were extracted from each study. Authors of abstracts were contacted for additional information.
Methods of synthesis

How were the studies combined?
Where possible, pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous data and pooled weighted mean differences (WMDs) or standardised mean differences (SMDs), along with 95% CIs, for continuous data. Fixed-effect models were used. Otherwise, the studies were combined in a narrative.

How were differences between studies investigated?
Heterogeneity was assessed using the I-squared statistic, taking 50% or more as indicative of high levels of heterogeneity.

Results of the review

Seven RCTs (n=419) were included. The sample size ranged from 31 to 87.

One study was judged to be at low risk of allocation concealment bias and six at moderate risk. All studies were described as randomised, but only two reported the randomisation method. Six reported double-blinding and one reported blinding of the rater only. All studies accounted for early withdrawals but only five reported reasons for withdrawal. Two studies reported intention-to-treat analysis and three reported complete analysis.

Clozapine versus placebo (2 trials, n=120): there was no significant difference between clozapine and placebo in the proportion of early withdrawals. Clozapine was associated with a significant improvement in the CGI (WMD -1.1, 95% CI: -1.24, -0.97) and UPDRS total and motor score (WMD -2.39, 95% CI: -3.58, -1.20 and WMD -1.74, 95% CI: -2.57, -0.92, respectively) compared with placebo. Both studies also reported a significant improvement in psychotic symptoms with clozapine compared with placebo when using different scales.

Clozapine versus quetiapine (1 trial, n=40 completed): there were no significant differences between clozapine and quetiapine for clinical efficacy, motor functioning, or adverse events.

Quetiapine versus placebo (2 trials, n=89): there were no significant differences between quetiapine and placebo in efficacy, safety, or the proportion of early withdrawals.

Olanzapine versus placebo (2 trials, n=170): olanzapine was associated with a significantly increased risk of early withdrawal (RR 2.11, 95% CI: 1.13, 3.92), particularly due to adverse events (RR 7.18, 95% CI: 1.76, 29.24), and a significant worsening of Parkinson's symptom (UPDRS, SMD 0.59, 95% CI: 0.40, 0.78). There was no significant difference between olanzapine and placebo in clinical efficacy or the MMSE.

Authors' conclusions

Evidence only supports the use of clozapine for the treatment of drug-induced psychosis in patients with Parkinson's disease; olanzapine should not be used, and quetiapine should not be used unless proven to be effective.

CRD commentary

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to locate unpublished studies. Methods were used to minimise reviewer error and bias in the selection of studies and extraction of data, but it is unclear whether similar steps were taken in the assessment of validity. The studies were appropriately grouped by the treatments compared and pooled. The included studies used a variety of severity scales to measure outcomes, and these were pooled where reported in more than one study. However, there were few included studies and these were small, with the largest having only 87 participants. Only 2 studies contributed to each pooled result, and one of the clozapine studies was allocated 95% of the weight in the main meta-analyses. This was generally a well-conducted review, but the evidence was limited and a more cautious conclusion may have been appropriate.

Implications of the review for practice and research

Practice: The authors stated that clozapine is associated rarely with agranulocytosis and treatment requires weekly
laboratory monitoring.

Research: The authors stated that further RCTs are required to evaluate quetiapine, other newer atypical antipsychotics (including ziprasidone and aripiprazole) and other drugs (including rivastigmine and ondansetron) for the treatment of drug-induced psychosis in patients with 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.