New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis

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CRD summary
This review assessed whether new-generation antipsychotic drugs cause fewer extra-pyramidal side effects (EPS) than low-potency conventional antipsychotics. The authors concluded that new-generation drugs might cause EPS equivalent to optimum doses of conventional treatments, and that these drugs might be more effective than conventional treatments. This was a well-conducted review which pointed to the need for further trials in this area.

Authors' objectives
To assess whether new-generation atypical antipsychotic drugs caused fewer extrapyramidal side-effects (EPS) than low-potency conventional antipsychotics.

Searching
The Cochrane Schizophrenia Group's Register of Trials was searched to March 2002. In addition, relevant journals and conference proceedings were handsearched, reference lists of relevant reviews were checked, and manufacturers of new-generation antipsychotics and authors of primary research articles were contacted. Further information on identified trials was requested from authors and manufacturers.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The duration of the included studies was between 4 and 12 weeks.

Specific interventions included in the review
Studies that compared new-generation antipsychotics (amisulpride, clozapine, olanzapine, quetiapine, remoxipride, risperidone, sertindole, ziprasidone or zotepine) with low-potency conventional antipsychotics (chlorpromazine, chlorprothixene, levomepromazine, melperone, mesoridazine, methotrimeprazine, perazine, pipamperone, promethazine, prothipendyl or thioridazine) were eligible for inclusion. Low-potency antipsychotics were defined as antipsychotics with potency less than or equivalent to chlorpromazine.

Participants included in the review
The inclusion criteria were not clearly specified, but patients with schizophrenia, schizoaffective disorders, schizophreniform disorders, delusional disorders and unclear diagnoses were included in the review. The majority of the patients (2,201 out of 2,320) had a diagnosis of schizophrenia.

Outcomes assessed in the review
The primary outcome eligible for inclusion in the review was the number of patients who experienced at least one EPS. Other outcomes included in the review were the number of patients with no clinically significant improvement, the number of patients who received anti-Parkinsonian medication at least once, and the number of patients who dropped out as a result of side-effects.

Assessment of study quality
Validity was assessed using the Jadad scale to assess randomisation, blinding and description of withdrawals. The
authors did not state how the studies were assessed for validity, or how many reviewers performed the validity assessment.

**Data extraction**

Two reviewers independently extracted all data. Only dichotomous data were included in the review; data from EPS-rating scales were excluded. Risk differences and 95% confidence intervals (CIs) were used as measures of effect size.

**Methods of synthesis**

**How were the studies combined?**

The studies were combined in meta-analyses. Weighted risk differences and 95% CIs were combined using a random-effects model. Numbers-needed-to-treat (NNT) were also calculated.

**How were differences between studies investigated?**

The studies were pooled according to the atypical antipsychotic used. Statistical heterogeneity was assessed using the chi-squared test. A dose-response plot was constructed to identify differences between studies resulting from differences in the dose of the low-potency conventional antipsychotics. Post-hoc meta-regressions were carried out to assess the impact of study quality, year of publication, or duration of the washout phase. A sensitivity analysis was conducted to assess the effect of excluding studies using non-chlorpromazine comparators, and especially those using remoxipride, from the analysis. Publication bias was assessed using the funnel plot method.

**Results of the review**

Thirty-one trials with 2,320 patients were included in the review.

Fifteen trials compared clozapine with chlorpromazine and 11 provided data on the number of patients with at least one EPS. The pooled estimate showed that fewer patients in the clozapine group experienced EPS (NNT 7, 95% CI: 4, 25, P=0.008). The pooled estimate also showed that more patients in the clozapine group achieved a clinically significant improvement (NNT 7, 95% CI: 4, 33, P=0.02).

Four trials compared olanzapine with chlorpromazine. Fewer patients in the olanzapine group experienced at least one EPS, but this was not statistically significant (P=0.07). More patients in the olanzapine group showed a clinically significant improvement (NNT 5, 95% CI: 2, 50, P=0.03).

One trial compared quetiapine with chlorpromazine. There was no significant difference in the number of patients experiencing EPS, but more patients in the quetiapine group experienced a clinically significant improvement (P=0.05).

Remoxipride was compared with chlorpromazine and thioridazine in 4 trials. There were no significant differences between the groups.

One trial compared risperidone with methotrimeprazine. Patients in the risperidone group showed a greater clinical improvement (NNT 3, 95% CI: 2, 100, P=0.04).

Zotepine was compared with chlorpromazine and perazine in 5 trials. There were no significant differences between the groups.

Dose of low-potency antipsychotic had a significant effect: the pooled risk difference (RD) for studies using doses lower than 600 mg/day chlorpromazine was not statistically significant (RD=-0.01, 95% CI: -0.03, 0.04, P=0.7), while that for studies with higher doses was statistically significant (RD -0.26, 95% CI: -0.37, -0.16; NNT 4, 95% CI: 3, 6, P<0.0001).

The meta-regression analysis showed no effect of study quality, washout phase, or year of publication on the outcomes.

The funnel plot analysis suggested that relevant unpublished studies that showed no benefit of new-generation drugs might not have been included in the review.
Authors’ conclusions
Optimum doses of low-potency conventional antipsychotics might not induce more EPS than new-generation drugs. The authors also concluded that new-generation drugs may have higher efficacy than the conventional treatments.

CRD commentary
The review question and the inclusion criteria were generally clear, with the exception of the participants eligible for inclusion in the review. The search was limited to one electronic database, although this is based on several other databases, and other search strategies were employed. Attempts to locate unpublished studies and to assess publication bias were made. The decision to use a meta-analysis was appropriate, and a thorough planned analysis to explore sources of heterogeneity was conducted. The authors’ conclusions were appropriately cautious given the limitations of the evidence base.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that well-designed trials to find the correct dose of low-potency antipsychotics are still justified. Further trials of the newer atypical antipsychotics, such as aripiprazole, sertindole and ziprasidone, are required to assess whether they are associated with lower incidence of EPS than low-potency conventional treatments.

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