A systematic review of atypical antipsychotic drugs in schizophrenia

CRD summary
This review assessed the safety and cost-effectiveness of ‘atypical’ antipsychotic drugs in patients with schizophrenia. The authors concluded that the evidence was limited and should be treated with caution. Generally, none of the eight drugs of interest were found to be more effective than the others, with one exception. The authors’ cautious conclusions are likely to be reliable.

Authors’ objectives
The main objectives were to assess the clinical effectiveness, safety and cost-effectiveness of ‘atypical’ antipsychotic drugs in schizophrenia in comparison with conventional antipsychotic drugs, placebo and other atypical antipsychotic drugs. The secondary objectives of the review were to investigate response in those with treatment-resistant schizophrenia, with predominantly negative symptoms or experiencing their first episode of schizophrenia.

Searching
The National Research Register and the meta Register of Controlled Trials were searched for relevant projects, and proceedings of major conferences were handsearched for relevant papers. A number of databases were searched from 1998 to April 2001. For searches of studies of side-effects, there was no limitation on the data. A detailed search strategy was provided in the review. In addition, the reference lists of all retrieved papers were checked for relevant studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and systematic reviews were included in the review. For data on safety, case-control studies that had a follow-up of more than 2 years, or had more than 2,000 participants, were included.

Specific interventions included in the review
Atypical antipsychotic drugs (amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine) were included in the review.

Participants included in the review
To be included in the review, the participants had to be diagnosed with schizophrenia using any method. Participants diagnosed with schizoaffective disorder, schizoaffective disorder or ‘psychotic illness’ were also included in the review, whereas those diagnosed with dementing illnesses, bipolar disorder, depression, or primary problems associated with substance abuse were excluded from the review.

Outcomes assessed in the review
The key outcomes assessed were death, morbidity, quality of life, social outcomes (e.g. employment), economic outcomes and leaving the study early.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed papers for inclusion. Any discrepancies were resolved by discussion or, if necessary, by a third reviewer.

Assessment of study quality
For RCTs, quality was assessed using the following criteria: adequacy of randomisation sequence generation, adequacy of allocation concealment, identification of cointerventions, reporting of eligibility criteria, adequacy of blinding, comparability of groups at baseline, attrition rate, adequacy of description of withdrawals, adequacy of intention-to-
treat analysis, appropriate dose of comparator drug, and adequate washout period. Studies of other designs were quality assessed using standard critical appraisal checklists, as reported by the Centre for Reviews and Dissemination (see Other Publications of Related Interest). It was not explicitly stated how many reviewers performed the quality assessment.

**Data extraction**
One reviewer extracted data from each study and a second reviewer checked the extraction. Any discrepancies were resolved by discussion or, if necessary, by a third reviewer. Where appropriate, a relative risk (RR) with 95% confidence interval (CI) was calculated for each study.

**Methods of synthesis**

**How were the studies combined?**
Where possible, the data were combined to create a pooled RR with 95% CI using a fixed-effect model. For continuous data, a weighted mean difference (WMD) with 95% CI was estimated. Publication bias was investigated using a funnel plot. For non-randomised studies, the main results were summarised in a narrative synthesis.

**How were differences between studies investigated?**
The authors investigated heterogeneity by visual inspection of the data, and by conducting chi-squared tests. Studies responsible for heterogeneity were summarised separately and possible reasons for differences were explored. Sensitivity analyses were used to investigate differences by certain participant characteristics, to assess the impact of including studies with more than 25% loss to follow-up and to assess the effect of using haloperidol as a comparator drug.

**Results of the review**
A total of 171 RCTs were included in the review, including 28 reporting commercial-in-confidence data. For safety data, 52 non-randomised studies were included in the review, including 7 reporting commercial-in-confidence data. The overall number of participants was not stated.

Generally, the evidence for new atypical antipsychotic drugs compared with older drugs was of poor quality, while the evidence for new atypical antipsychotic drugs compared with each other was limited.

In comparison with typical antipsychotic drugs, risperidone, amisulpride, zotepine, olanzapine and clozapine were more effective in relieving the overall symptoms of schizophrenia. There was no difference between typical antipsychotic drugs and quetiapine or sertindole in alleviating overall symptoms of psychosis.

With the exception of participants taking ziprasidone and zotepine, fewer participants taking atypical antipsychotic drugs left trials early compared with those in the typical drug groups.

All of the new atypical antipsychotic drugs appeared to cause fewer movement disorder side-effects than typical antipsychotic drugs.

The authors also reported on sedation, autonomic effects, gastrointestinal effects, weight gain, prolactin-related problems, and cardiotoxic effects for atypical versus typical antipsychotic drugs. Side-effects were also reported for atypical versus atypical antipsychotic drugs. Clozapine was more effective than typical antipsychotic drugs in those whose illnesses had not previously responded to treatment, and in improving negative symptoms in those whose illnesses were resistant to conventional treatment. In addition, zotepine seemed to be more effective on negative symptoms.

The authors provided more detailed results, but these were too lengthy to report in this abstract.

**Cost information**
The authors conducted an in-depth cost-effectiveness analysis, details of which were presented in the review.
Authors' conclusions
The authors concluded that the evidence was limited and should be treated with caution. In addition, based on attrition rates in trials, individuals with schizophrenia might have found that, with the exception of zotepine and ziprasidone, the new atypical antipsychotic drugs were more acceptable than typical comparators. None of the new atypical antipsychotic drugs were found to be more effective than the others, apart from clozapine, for those with treatment-resistant illness. All of the new atypical antipsychotic drugs had slightly different side-effect profiles, which may differ in importance for the patients and carers.

CRD commentary
The review question and inclusion and exclusion criteria were clearly presented. The search strategy was extensive and the presence of publication bias was assessed. The authors assessed and described the quality of each of the included studies, along with a detailed overview of the included studies. The authors took a number of steps to minimise bias in the review process. Given the strength of the evidence, the authors' cautious conclusions are appropriate.

Implications of the review for practice and research
Practice: The authors stated that any implications for practice are based on limited evidence. The authors made several recommendations. In general, some side-effects of the atypical antipsychotic drugs are not yet known and careful monitoring is important. For individuals with pre-existing cardiac or liver problems, these drugs should only be administered under close supervision. The side-effects of the various drugs examined in the review will have varying importance for those with schizophrenia and their carers.

Research: The authors stated that more long-term trials involving large sample sizes, less rigid inclusion criteria, and outcomes relevant to those with schizophrenia and their carers, are needed. They also stated that RCTs comparing atypical antipsychotic drugs with each other would be useful, particularly risperidone versus olanzapine and zotepine versus clozapine.

The authors also made several other recommendations.

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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.