Antipsychotic drugs and extrapyramidal side effects in first episode psychosis: a systematic review of head-head comparisons

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CRD summary
This review concluded that second generation antipsychotics offer an advantage over first generation drugs with respect to extrapyramidal adverse effects in patients with first episode psychosis, but the evidence largely related to comparisons with haloperidol. Despite limitations in reporting and synthesis, this conclusion seems reliable for haloperidol; limitations in the evidence base make its generalisability to other drugs uncertain.

Authors' objectives
To determine whether the risk of extrapyramidal adverse effects differed between antipsychotic drugs used in first episode psychosis.

Searching
The authors searched PubMed from inception to April 2011. The search was limited to publications in English. Limited search terms were reported. Additional studies were identified from the reference lists of papers in the primary search or known to the authors.

Study selection
Randomised controlled trials (RCTs) that compared two or more antipsychotic drugs and that enrolled patients diagnosed with schizophrenia or a related disorder were eligible for the review. Patients had to be undergoing a first episode of psychosis as defined by the trial investigators. Trials had to provide quantitative data on extrapyramidal symptoms (parkinsonism, akathisia, dyskinesia or dystonia) using a standard rating scale.

Included trials evaluated nine different drugs (most commonly haloperidol, risperidone and olanzapine) at various doses. All trials included at least one second generation antipsychotic. Most trials included patients with schizoaffective disorder or schizoaffectiveiform disorder as well as those with schizophrenia. Definitions of first episode psychosis varied, the most common criteria being a maximum age or maximum cumulative period of exposure to antipsychotic drugs.

The authors did not state how many reviewers were involved in study selection.

Assessment of study quality
The authors did not state that they assessed study quality.

Data extraction
The authors did not state how many reviewers extracted data for the review.

Methods of synthesis
A narrative synthesis was presented. Numbers of trials that reported a statistically significant difference were reported by comparison and outcome (vote counting). Differences between trials were discussed in the text and presented in tables.

Results of the review
Eleven RCTs with 2,734 participants (range 19 to 555) were included. Seven trials were described as double-blind, three as open-label and one was open but with blinded outcome assessment. Follow-up ranged from six weeks to over two years.

 Compared with one or more second generation drugs, haloperidol was associated with significantly higher rates and/or severity of parkinsonism (seven trials) and akathisia (six trials). Total drop-out rates because of adverse effects were higher with haloperidol in five trials; the other two trials reported no significant difference. Two out of four long-term trials (one year or more) found a higher risk of dyskinesia with haloperidol (compared with olanzapine or risperidone);
the other trials found no significant difference between haloperidol and comparators. Less severe extrapyramidal symptoms were reported in single trials with clozapine versus chlorpromazine and risperidone versus zuclopenthixol. There was little evidence of differences between second generation antipsychotics.

Authors’ conclusions
Second generation antipsychotics offer an advantage over first generation drugs with respect to extrapyramidal adverse effects in patients with first episode psychosis, but the evidence largely related to comparisons with haloperidol.

CRD commentary
The review addressed a clear question using relevant inclusion criteria. The search was limited in scope and restricted to English language publications, so it was possible that relevant trials could have been omitted. Publication bias was not assessed and could not be ruled out given the subject area of the review. Limited details of review methods were reported, so the risk of reviewer error or bias was unclear. Quality of the included trials was not formally assessed, although details of blinding were reported, which meant the risk of bias in trials was unclear.

The authors’ decision to present a narrative synthesis was reasonable, although the vote counting approach adopted meant that all trials were weighted equally regardless of sample size and quality. The limited quantitative data presented made it difficult to assess the clinical significance of the findings.

Despite these limitations, the authors’ main conclusion relating to haloperidol reflects the evidence presented and appears reliable. Limitations in the evidence base make its generalisability to other drugs uncertain.

Implications of the review for practice and research
Practice: The authors stated that in choosing an antipsychotic drug differences in extrapyramidal adverse effects should be considered alongside differences in risks of other adverse effects (not considered in the review). They also stated that the review findings supported recommendations that antipsychotic drug treatment in patients with first episode psychosis should start with a low dose.

Research: The authors stated that further RCTs that compared first and second generation antipsychotic drugs in patients with first episode psychosis were required. Trials should not use haloperidol as a comparator. The authors also stated that there was a need for more consistent assessment and reporting of extrapyramidal and other adverse effects.

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