Antipsychotics and abnormal liver function tests: systematic review

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CRD summary
The review concluded that liver function test abnormalities in patients receiving regular antipsychotics are common but generally mild and transient and that most of the research was of poor quality. The review had some methodological and reporting limitations that make the reliability of the authors’ conclusions uncertain.

Authors’ objectives
To assess the prevalence and pattern of liver function test (LFT) abnormalities associated with regular antipsychotics when taken by adults.

Searching
EMBASE, PsycINFO and MEDLINE were searched to January 2011 for studies in English; search terms were reported. Reference lists of relevant articles were examined to identify further studies.

Study selection
Cohort or cross-sectional studies of 10 or more adults (≥18 years) receiving regular antipsychotic medication were eligible for inclusion. Liver function tests (defined as five tests; specified in the review) had to be checked and results reported for all patients. Tests reference ranges had to be reported and abnormal results had to be presented for individual antipsychotics (not groups). Case studies or case series were eligible providing they were conducted in adults receiving antipsychotic medication.

The most frequently studied antipsychotic was clozapine with doses ranging from 75mg to 480mg; the other drugs studied were haloperidol, olanzapine, risperidone, quetiapine, perphenazine, perazine, aripiprazole and ziprasidone. Treatment durations ranged from one week to 36 months. Where reported, most patients were monitored weekly or fortnightly. Most patients had normal baseline LFT results.

Two reviewers independently screened abstracts, with disagreements resolved by discussion, although no details were reported for the full-paper screening process.

Assessment of study quality
The authors stated that study quality was evaluated by considering sample size, use of (previous antipsychotic) treatment wash-out periods and study design although more precise details of these criteria were not reported.

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

Data extraction
One reviewer extracted data relating to LFT abnormalities.

Methods of synthesis
A narrative synthesis was presented.

Results of the review
Ten group studies and 91 case studies/series were eligible. The authors reported that the 10 group studies comprised four chart reviews, four prospective naturalistic studies and two prospective safety and efficacy studies (one of which was a cross-over trial). Total sample size was unclear. Study quality was reported as being poor overall. Only two studies used a wash-out period.

The median percentage of patients with any abnormal LFT on any antipsychotic was 32% (range 5% to 78%). The median percentage of patients with clinically significant elevations was 4% (range 0% to 15%). Transaminase enzymes were the most commonly elevated.
Liver function test abnormalities generally arose within six weeks and were either stably persistent or resolved with continued treatment.

Case reports suggested that antipsychotics can be associated with severe hepatitis that was fatal in a small minority of cases. In the UK, chlorpromazine is the antipsychotic most commonly associated with severe hepatic injury.

**Authors' conclusions**
The liver function test abnormalities in patients receiving regular antipsychotics are common but generally mild and transient. Very rarely, a severe or fatal hepatic injury can emerge. Most of the research is of poor quality.

**CRD commentary**
The review addressed several clear questions. The eligibility criteria did not appear to allow clinical trials but one cross-over trial was included. The reasons behind the restrictions on study design were not stated so the possibility of relevant trial data being omitted from the review remains. Several relevant electronic databases were searched but the restriction to searching only for studies published in English means that some relevant studies may have been missed. It appeared that no searches were made to identify unpublished studies. Independent duplicate processes were used to reduce the risks of reviewer error and bias during initial study selection but no details were reported for the full-paper screening process and the quality assessment. Only one reviewer extracted data so the risks of error and bias affecting this process were not minimised.

It appeared that there was a basic assessment of study quality but few method details or results were reported and this made it difficult to evaluate the reliability of the evidence. Study details were provided except for the case series/case reports (these studies only constituted a minor part of the review results). Very few population characteristics were presented for individual studies. Use of a narrative synthesis appeared appropriate considering the variation present across studies, especially in the type and dose of antipsychotic.

The review had some methodological and reporting limitations that make the reliability of the authors' conclusions uncertain.

**Implications of the review for practice and research**
**Practice:** The authors stated that chlorpromazine should probably be avoided in patients with pre-existing liver disease.

**Research:** The authors stated that there was a need for future studies with antipsychotic-free psychiatric control groups and reporting of references ranges. They added that investigation of the interaction of antipsychotics and known risk factors for hepatic impairment would be beneficial, as would assessment of the links among antipsychotics, metabolic syndrome and LFT abnormalities.

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