Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review

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CRD summary
This review assessed the role of oral atypical antipsychotic drugs in the management of the behavioural and psychological symptoms of dementia. The authors concluded that the limited evidence suggests that there may be improved efficacy and adverse events compared with typical antipsychotics. The few short-term studies identified provided insufficient evidence to support the authors’ conclusions.

Authors' objectives
To review the role of oral atypical antipsychotic drugs in the management of the behavioural and psychological symptoms of dementia (BPSD).

Searching
MEDLINE, EMBASE and the Cochrane Library were searched up to September 2003; the search terms were reported. Reference lists were searched manually and experts in the field were contacted. Enzyme Commission numbers assigned to new substances were identified using the Chemical Abstracts Service registry.

Study selection
Study designs of evaluations included in the review
Only double-blind randomised controlled trials (RCTs) were eligible for the review. The included trials were of 6 to 12 weeks' duration.

Specific interventions included in the review
Studies of clozapine, risperidone, olanzapine, quetiapine, amisulpride, zotepine, sertindole, aripiprazole and ziprasidone were eligible for the review. The included studies compared risperidone and olanzapine with placebo or haloperidol. One study of intramuscular olanzapine was excluded. Fixed doses of 0.5, 1 or 2 mg of risperidone, or flexible dosing with a mean dose of 0.85 to 1.1 mg, were used. Olanzapine was used at a fixed dose of 5, 10 or 15 mg.

Participants included in the review
Studies of patients suffering from dementia were eligible. Most of the included studies were of patients living in institutions, most were elderly (mean age 82 years), and most had severe dementia (mean score on mini-mental state examination was 6.8 out of 30).

Outcomes assessed in the review
The inclusion criteria were not specified in terms of outcomes. The review assessed efficacy, safety and withdrawals. The included studies used a range of assessment tools to measure efficacy: the behavioural pathology in Alzheimer's disease rating scale (BEHAVE-AD), the Cohen-Mansfield agitation inventory (CMAI), the neuropsychiatric rating scale home version (NPI-NH), the brief psychiatric rating scale and the clinical global impressions scale. The included trials measured 'clinical response' in different ways.

How were decisions on the relevance of primary studies made?
Two specialists in geriatric medicine selected studies for inclusion in the review.

Assessment of study quality
The validity of the trials was assessed and scored using the Jadad scale, which considers the reporting and handling of randomisation, blinding and withdrawals. The review also assessed concealment of treatment allocation and follow-up.
Two reviewers independently scored the methodological quality of the studies.

**Data extraction**
Two reviewers independently recorded the data from each trial using a standardised form. The primary end points of each trial, as well as the most common and serious adverse events, were extracted.

**Methods of synthesis**
How were the studies combined?
The trials were combined in a narrative.

How were differences between studies investigated?
Study details and characteristics were presented in tabular format and any differences were discussed in the text.

**Results of the review**
Five RCTs (1,570 patients) were included in the review.

The trials were all sponsored by the pharmaceutical company manufacturing the drug. All of the trials were of reasonably good quality. Three RCTs used statistical analyses that took account of multiple comparisons.

Risperidone was studied in 4 trials, each of 12 weeks’ duration. All three comparisons with placebo found some beneficial effect of risperidone, although not always for the primary outcome. Two RCTs found no significant difference between risperidone and placebo in extrapyramidal effects; the third RCT did not report the statistical significance of the difference. One RCT found that risperidone increased serious adverse effects (including cerebrovascular events) compared with placebo: 17% versus 9%. No difference between risperidone and haloperidol (2 trials) was demonstrated, except for significant improvements with risperidone over haloperidol in the aggressiveness subscales of BEHAVE-AD and CMAI. Both RCTs found increased extrapyramidal symptoms with haloperidol.

Olanzapine at doses of 5 or 10 mg was superior to placebo, as assessed by the NPI-NH based response rate (1 RCT). The RCT found no statistically significant difference between treatments in extrapyramidal effects. Other adverse effects included somnolence and abnormal gait.

Most of the studies had high rates of withdrawal with active treatment and with placebo.

**Authors' conclusions**
Few RCTS have evaluated the use of atypical drugs for BPSD. The limited evidence suggests that there may be improved efficacy and adverse events compared with typical antipsychotics.

**CRD commentary**
The review addressed a specific research question, although the participants and outcomes were not well defined. The literature search was appropriate given that drug trials were sought. Attempts were made to locate unpublished studies but, as it was not stated whether any language restrictions were applied, the potential for language bias could not be assessed. Two reviewers independently selected the studies, assessed validity and extracted the data, thus reducing the potential for bias and errors. The quality of the included studies was good and sufficient detail of the primary studies was presented in the review. The narrative synthesis was appropriate given the varied outcome measures used across the small number of included studies.

Overall, the summary of results the authors presented appears reliable, although it must be remembered that the review's findings are based almost entirely on trials with risperidone, evidence from studies is limited and only short-term outcomes were assessed. Importantly, the authors' conclusions regarding possible improved efficacy of atypical over typical antipsychotic drugs are not supported by the evidence presented in the review.
Implications of the review for practice and research

Practice: The authors stated that further evidence is required before the use of atypical drugs for BPSD can be recommended.

Research: The authors stated that further research is required to identify non-pharmacological interventions for BPSD, and that future studies should have a longer duration of follow-up.

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Other publications of related interest

This additional published commentary may also be of interest. Hirsch C. Review: limited evidence supports the use of atypical antipsychotic drugs in behavioral and psychological symptoms of dementia. ACP J Club 2005;142:14-5.

Indexing Status

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