A systematic review of the efficacy and safety of atypical antipsychotics in patients with psychological and behavioral symptoms of dementia

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CRD summary
This review assessed the efficacy and safety of atypical antipsychotics in patients with psychological and behavioural symptoms of dementia. The authors concluded that clinicians require more information for making decisions. The evidence presented appears to support the conclusions, but poor reporting of review methods makes it difficult to confirm the robustness of these conclusions.

Authors' objectives
To assess the efficacy and safety of atypical antipsychotics in patients with psychological and behavioural symptoms of dementia.

Searching
The Cochrane Library (Issue 1, 2005), MEDLINE (1966 to March 2005), EMBASE (1980 to first quarter 2004) and PsycINFO (1985 to March 2004) were searched using the reported search terms. Reference lists and dossiers submitted by pharmaceutical companies were screened. The Food and Drugs Administration (FDA) website and the industry-sponsored Clinical Study Results Database were searched for unpublished studies and additional data. Studies published only as conference abstracts or posters were excluded.

Study selection

Study designs of evaluations included in the review
Controlled clinical trials (CCTs) were eligible for the assessment of effectiveness, while CCTs and observational studies were eligible for the assessment of long-term safety. All controlled studies included in the review were randomised. The duration of CCTs assessing efficacy and short-term safety ranged from 6 to 18 weeks, where reported.

Specific interventions included in the review
Inclusion criteria were not explicitly specified in terms of the interventions, but it was clear that the focus was on studies of atypical antipsychotics. The review compared atypical antipsychotics (olanzapine, risperidone, quetiapine and aripiprazole) with placebo, typical antipsychotics (haloperidol) and other atypical antipsychotics.

Participants included in the review
Inclusion criteria were not explicitly specified in terms of the participants, but it was clear that the focus was on patients with psychological and behavioural symptoms of dementia. Most of the primary studies included patients with Alzheimer's disease (AD) or vascular dementia and excluded patients with clinically significant medical comorbidities or did not provide information on medical co-morbidities.

Outcomes assessed in the review
Studies that assessed effectiveness and safety were eligible for inclusion. The included studies used a variety of methods to assess effectiveness and extrapyramidal symptoms (EPS): for effectiveness these included the Behavioral Pathology in Alzheimer's Disease Scale (BEHAVE-AD), the Neuropsychiatric Inventory: Nursing Home version (NPI-NH) and the Cohen-Mansfield Agitation Inventory (CMAI); for EPS these included the Simpson Angus Scale, Barnes Akathisia Scale, the Abnormal Involuntary Movement Scale and the Extrapyramidal Symptom Rating Scale (ESRS). The review assessed short-term and long-term adverse effects including cardiovascular adverse events (i.e. stroke and transient ischaemic attacks).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
The studies were assessed for randomisation, allocation concealment, blinding, baseline similarity of the treatment groups, maintenance of comparable groups, adequate reporting of drop-outs, attrition, crossover, adherence, contamination, losses to follow-up and the use of intention-to-treat analysis. Observational studies of adverse events were assessed for non-biased selection of patients, low losses to follow-up, non-biased and accurate ascertainment of events, and control for potential confounding factors. Studies with fatal methodological flaws were rated as poor quality, studies that met all validity criteria were rated good, and other studies were rated fair. Only studies rated fair or good were used in the assessment of the evidence.

The authors did not state how the validity assessment was performed.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Where possible, the percentage change from baseline was calculated for outcome scales and the statistical significance of treatment differences was noted.

Methods of synthesis
How were the studies combined?
The studies were grouped under the following headings and combined in a narrative: atypical antipsychotics versus placebo; atypical versus typical antipsychotics; atypical antipsychotics versus each other; and long-term safety. Efficacy and short-term safety outcomes were discussed separately.

How were differences between studies investigated?
Differences between the studies were discussed in the narrative synthesis, whilst additional differences were apparent from the tables.

Results of the review
Seven controlled trials (n=2,314) evaluated efficacy and short-term safety. Long-term safety was evaluated using data from one manufacturer-conducted review of data from placebo-controlled trials (n=3,486), one FDA report based on an analysis of 17 placebo-controlled trials, two observational studies, one retrospective cohort study (n=11,400) and one-case control study (n stated where possible).

Atypical antipsychotics versus placebo.
Olanzapine: two studies were identified. One good quality double-blind randomised controlled trials (RCT) reported a significantly greater improvement in NPI-NH Core Total at 6 weeks in patients taking 5 or 10 mg olanzapine compared with placebo but reported no difference between 15 mg olanzapine and placebo. One fair-quality double-blind RCT reported a significantly greater improvement in NPI-NH Psychosis Total score at 10 weeks in patients taking 7.5 mg olanzapine compared with placebo, but reported no difference between other doses of olanzapine (1.0, 2.5 and 5.0 mg) and placebo. It also reported a significantly greater improvement in the Clinical Global Impression of Change (CGI-C) in patients taking 2.5 mg olanzapine compared with placebo but not for other doses of olanzapine versus placebo.

Risperidone: two studies were identified. One fair-quality double-blind RCT reported a significantly greater improvement in BEHAVE-AD (most subscales of this scale) and the CMAI (total and aggressive subscales) in patients taking a final mean dose of 0.95 mg risperidone compared with placebo. One fair-quality RCT reported a significantly greater improvement in BEHAVE-AD in patients taking 1.0 and 2.0 mg risperidone compared with placebo, but reported no difference between 0.5 mg risperidone and placebo.

Quetiapine and aripiprazole: only limited evidence was found.

Short-term adverse effects.
There were generally no differences in EPS between olanzapine and risperidone compared with placebo. Exceptions
were an increase in the ESRS with risperidone 2 mg (one study) and a significantly higher rate of total withdrawals and withdrawals due to adverse events for 2 mg risperidone compared with placebo (one study). Withdrawal rates were high in all treatment groups including placebo (range: 20 to 42%).

Atypical versus typical antipsychotics.

Risperidone versus haloperidol: three studies were identified. Two fair-quality parallel-group trials reported no significant differences on the CMAI or BEHAVE-AD scales at 12 weeks between risperidone and haloperidol (0.5 to 2.0 mg for both drugs). One fair-quality crossover RCT that did not assess the carry-over effect reported significantly greater improvements on the CMAI, CGI-C, BEHAVE-AD scales at 8 weeks in patients taking risperidone (mean 0.80 mg) compared with haloperidol (mean 0.83 mg).

Short-term adverse events (three studies).

One study reported significant improvement in EPS in patients taking risperidone (mean dose 1.1 mg) compared with haloperidol (mean dose 1.2 mg). The second study reported improvements on some measures (ESRS total and parkinsonism subscales) for risperidone (mean 0.83 mg) compared with haloperidol (mean 0.80 mg) but not others (dyskinetic movement and dystonia subscales). The third study did not report comparative results. There were no significant differences between risperidone and haloperidol in total withdrawals or withdrawals due to adverse events.

Atypical antipsychotics versus each other.

Risperidone versus olanzapine: two studies were identified. Two small poor-quality studies reported no differences on any outcome (including withdrawal and withdrawal due to adverse events) between risperidone and olanzapine at 2 weeks and 2 months.

Long-term safety.

One manufacturer-conducted review of data from placebo-controlled trials reported that cardiovascular adverse events occurred in 1.3% (15 of 1,778) patients taking risperidone compared with 0.4% (2 of 478) taking placebo, and in 4% (29 of 764) patients taking olanzapine compared with 2% (7 of 466) taking placebo. The review authors stated that there was insufficient information available to assess the appropriateness of combining studies.

One FDA report based on an analysis of 17 placebo-controlled trials evaluating olanzapine, aripiprazole, risperidone and quetiapine reported an increased death rate with the atypical antipsychotic (1.6 to 1.7 times that of placebo).

Two observational studies reported no increase in the risk of stroke (one study) or ventricular arrhythmia or cardiac arrest (one study) associated with atypical antipsychotics. One good-quality retrospective cohort study reported no difference in the crude or adjusted stroke rate between patients given typical antipsychotics, risperidone and olanzapine. One fair-quality case-control study reported that the risk of hospitalisation for ventricular arrhythmia or cardiac arrest was significantly higher for users of typical antipsychotics compared with non-users, but there was no difference between users of atypical antipsychotics and non-users; the analysis was adjusted for risk factors.

Authors’ conclusions

Olanzapine and risperidone were more effective than placebo and short-term adverse events were similar for these drugs compared with placebo. Risperidone had similar efficacy to haloperidol but reduced EPS. There was insufficient evidence for other atypical antipsychotics. However, the studies were in highly selected populations and clinicians require more information about the benefits and potential harms of atypical antipsychotics.

CRD commentary

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design; the review question was appropriately broad with respect to the study design and outcomes. Several relevant sources were searched and attempts were made to locate unpublished studies, thereby reducing the possibility of publication bias. It was unclear whether any language limitations had been applied, thus the potential for language bias
could not be assessed. The methods used to select studies, assess validity and extract the data were not described, so it is not known any whether efforts were made to reduce reviewer errors and bias. Validity was assessed using defined criteria, the results of this assessment were reported, and only studies judged to be of higher quality were considered when evaluating the evidence.

The narrative synthesis was appropriate given the differences among the studies. However, it was unclear how the reviewers dealt with the reporting of multiple outcomes from individual studies, thus it is not possible to exclude the likelihood of selective reporting of the results in the review. The evidence presented appears to support the conclusions, but the lack of reporting of review methods make it difficult to confirm the robustness of these conclusions.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that additional data from existing trials and more complete reporting of results could provide information about the harms and benefits of atypical antipsychotics, including the effects of these drugs in patients with medical co-morbidities.

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