Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials

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CRD summary
This review assessed the risk of death associated with atypical antipsychotic drugs, compared with placebo, for patients with dementia. The authors concluded that there may be a small increase in the risk of death with such treatment, which should be considered in a wider medical context. This was a well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To determine whether atypical antipsychotic drug treatment for people with dementia resulted in an increase in mortality.

Searching
MEDLINE (1966 to April 2005) and the Cochrane Controlled Trials Register (Issue 1, 2005) were searched. In addition, the authors handsearched conference programmes, abstract books, conference proceedings, abstracts, poster presentations and slides from geriatric medicine, psychiatric, neurological and geriatric psychiatric professional society meetings since 1999. Pharmaceutical companies manufacturing atypical antipsychotics were also contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that were double-blind and placebo-controlled were eligible for inclusion. The trials were required to be of a parallel-group design.

Specific interventions included in the review
Comparisons of atypical antipsychotic drugs given orally and oral placebo were eligible for inclusion. The antipsychotic drugs included in the review were aripiprazole, olanzapine, quetiapine and risperidone.

Participants included in the review
Patients with Alzheimer's disease, vascular dementia, mixed dementia or primary dementia were eligible for inclusion. Eighty-seven per cent of the patients included had Alzheimer's disease, and 70% were female. The majority of the participants (78%) were in nursing homes; the remainder were out-patients.

Outcomes assessed in the review
The primary outcome assessed was mortality. The other outcome assessed in the review was drop-outs.

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 trials were required to be double-blind in order to be eligible for inclusion in the review. In addition, the studies were required to report methods of randomisation and the numbers of drop-outs. The assessment method formed part of the process by which papers were selected for the review, but the authors did not state who performed the validity assessment.

Data extraction
One reviewer extracted the data and a second reviewer checked them. Data were extracted on all-cause drop-outs and deaths occurring within the trial period or 30 days of its conclusion. Dosage groups were aggregated within trials. Odds ratios (ORs) and absolute risk differences were calculated for drop-outs and deaths.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a meta-analysis using a random-effects model (DerSimonian and Laird) for the outcome of drop-outs and a fixed-effect model (Mantel-Haenszel) for the outcome of deaths. In an additional ad hoc analysis, the death rates were divided by total drug or placebo exposure in patient-years, and relative risks (RRs) were calculated for each drug and analysed in a meta-analysis using a random-effects model. The authors stated that a funnel plot analysis was used to assess publication bias, but data for this were not shown.

How were differences between studies investigated?
Statistical heterogeneity between studies was investigated using chi-squared tests and the I-squared statistic, with a P-value of at least 0.20 or an I-squared value of at least 50% regarded as indicating significant heterogeneity. Sensitivity analyses were performed using the following subgroups: whether patients were required to have psychosis of dementia; out-patients versus nursing home patients; whether mean baseline cognitive severity measured on the Mini-Mental State examination was less than 10 or 10 or above.

**Results of the review**

Fifteen studies with 16 contrasts of antipsychotic drugs with placebo, and involving a total of 5,387 patients, were included in the review.

Death.
The pooled OR for all 15 trials was 1.54 (95% confidence interval, CI: 1.06, 2.23, P=0.02) in favour of placebo, with no significant heterogeneity among the studies.

In trials (n=3) using aripiprazole versus placebo, the risk difference was 0.01 (95% CI: -0.01, 0.03, P=0.20) in favour of placebo.

In trials (n=5) using olanzapine versus placebo, the risk difference was 0.01 (95% CI: -0.00, 0.07) in favour of placebo.

In trials (n=3) using quetiapine versus placebo, the risk difference was 0.02 (95% CI: -0.01, 0.05, P=0.22) in favour of placebo.

In trials (n=5) using risperidone, the risk difference was 0.01 (95% CI: -0.01, 0.02, P=0.33) in favour of placebo.

Drop-outs.
There was no significant difference in drop-outs between the drug and placebo groups, although there was significant heterogeneity among the trials and between drugs.

Other analyses.
The ad hoc analysis of death rates by length of exposure favoured placebo (pooled RR 1.65, 95% CI: 1.19, 2.29). The sensitivity analyses found no significant differences between groups.

**Authors’ conclusions**
Atypical antipsychotic drugs may be associated with a small increase in risk of death in comparison with placebo.

**CRD commentary**
The review question and the inclusion criteria were clear. The search was adequate and included unpublished material. The authors assessed publication bias but did not report whether they found any evidence of it. The use of language restrictions was not reported, so bias is unlikely to have been introduced in this way. The authors also did not report using methods to minimise bias and error when selecting studies for their review, and the validity assessment inherent in this process, although such methods were employed in the data extraction. The statistical analysis, which including meta-analysis, was appropriate and thorough. This was a well-conducted systematic review and the authors’ conclusions are likely to be reliable.

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

Practice: The authors stated that the small increased risk of death should be considered within the context of medical need for the drugs involved, evidence of their efficacy, medical co-morbidity, and the efficacy and safety of alternatives.

Research: The authors stated that individual patient analyses modelling survival and causes of death are required.

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**Other publications of related interest**

This additional published commentary may also be of interest. Hirsch C. Review: atypical antipsychotic drugs increase risk for death in dementia. ACP J Club 2006;144:36.

**Indexing Status**

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