Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence

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CRD summary
This review concluded that of the drugs used for treating neuropsychiatric symptoms of dementia, risperidone and olanzapine had the best evidence for efficacy although their effect sizes were modest and they increased the risk of stroke. This conclusion appears reasonable. However, there was only a small evidence base for most of the drugs considered in the review.

Authors’ objectives
To evaluate the efficacy of pharmacological agents used in the treatment of neuropsychiatric symptoms of dementia.

Searching
MEDLINE (from 1966 to July 2004) and the Cochrane Database of Systematic Reviews were searched for English language articles; the search terms were reported. The reference lists of relevant retrieved articles were also checked.

Study selection
Study designs of evaluations included in the review
Double-blind, placebo-controlled, randomised controlled trials (RCTs) and meta-analyses of RCTs were eligible for inclusion.

Specific interventions included in the review
Any drug therapy for patients with dementia was eligible for inclusion providing it was available for use and used widely in the USA. The studies included in the review involved:

typical antipsychotics (haloperidol, thioridazine, thiothixene, chlorpromazine, trifluoperazine, acetophenazine, perphenazine),
atypical antipsychotics (risperidone, olanzapine),
antidepressants (fluoxetine, trazodone, citalopram, sertraline),
mood stabilisers (carbamazepine, divalproex sodium, sodium valproate),
cholinesterase inhibitors (rivastigmine, donepezil, galantamine, metrifonate, tacrine, donepezil, velnacrine, physostigmine), and

memantine.

Participants included in the review
Participants with dementia (including Alzheimer disease, vascular dementia, mixed dementia, or dementia with Lewy bodies) were eligible for inclusion. The included studies considered a wide range of dementia types and levels of severity.

Outcomes assessed in the review
Studies reporting outcomes for neuropsychotic symptoms were eligible for inclusion. These symptoms included hallucinations, delusions, combativeness, verbal aggression, psychomotor agitation and wandering.

How were decisions on the relevance of primary studies made?
Two reviewers selected papers for inclusion.

**Assessment of study quality**
The authors stated that they extracted data relating to study quality, and comments relating to the quality of the individual studies were made within the text, but no specific criteria were described. Two reviewers independently extracted data on study quality. Any disagreements were resolved by discussion to consensus, or by the involvement of a third reviewer.

**Data extraction**
Two reviewers independently extracted the data from the studies. Any disagreements were resolved by discussion to consensus, or by the involvement of a third reviewer. Details of the study design and duration, drug name and dose, participant residence, type and severity of dementia, efficacy outcomes and adverse events, were extracted.

**Methods of synthesis**
How were the studies combined?
The studies were grouped according to drug type. For each group, details of the individual studies were tabulated and the studies were combined in a narrative.

How were differences between studies investigated?
Differences between the studies were apparent from the tables and were discussed within each narrative synthesis.

**Results of the review**
Twenty-five RCTs and 4 meta-analyses were included in the review. It is not clear whether there was any overlap of studies in the meta-analyses, and thus whether any RCTs were included twice. The breakdown according to drug type was:

- typical antipsychotics, 2 meta-analyses (covering 12 RCTs) and 2 further RCTs (1,237 participants);
- atypical antipsychotics, 6 RCTs (2,261 participants);
- antidepressants, 5 RCTs (429 participants);
- mood stabilisers, 5 RCTs (342 participants);
- cholinesterase inhibitors, 2 meta-analyses (covering 18 RCTs) and 6 further RCTs (8,764 participants);
- memantine, 2 RCTs (656 participants).

**Typical antipsychotics.**
A meta-analysis of 7 RCTs concluded that antipsychotics (haloperidol, thioridazine, thiothixene, chlorpromazine, trifluoperazine, acetophenazine) were beneficial in 18% of patients and found no difference in efficacy between the drugs on neuropsychiatric symptoms. Another meta-analysis concluded that haloperidol (1.2 to 3.5 mg/day) reduced aggression but was associated with adverse effects. One study reported an effect of thioridazine on agitation, but the trial was of a poor quality. Another trial found perphenazine to have had no benefit.

**Atypical antipsychotics.**
Four of the 6 RCTs reported a significant beneficial effect. In these studies, doses of 5 to 10 mg/day olanzapine or 1.0 mg/day risperidone had modest effects on neuropsychiatric symptoms in patients with Alzheimer disease or vascular dementia. Several of the studies also reported a greater incidence of adverse events, including stroke, in groups receiving atypical antipsychotics.
Antidepressants.

A trial of citalopram found a small significant improvement in some neuropsychiatric symptoms. Trials of sertraline, fluoxetine and trazodone detected no significant effects on neuropsychiatric symptoms.

Mood stabilisers.

Three RCTs found that valproate was ineffective for treating neuropsychiatric symptoms and that it also caused adverse events. Carbamazide was beneficial in one trial and ineffective in another.

Cholinesterase inhibitors. One meta-analysis reported a statistically significant improvement in one neuropsychiatric symptom measure. However, this might have been due to the inclusion of trials on metrifonate, which had not been approved for use in the USA on account of its toxicity. Two studies reported a very small improvement with galantamine. Donepezil was found to be beneficial in 2 studies and ineffective in two others, including the longest trial of cholinesterase inhibitors. A trial of rivastigmine found no beneficial effect.

Memantine.

One trial found no significant effect on neuropsychiatric symptoms, while the other did not demonstrate an effect of clear clinical significance.

Authors' conclusions

Of the drugs used for treating neuropsychiatric symptoms in dementia, the antipsychotics risperidone and olanzapine had the best evidence of efficacy, but the effect sizes were only modest and they may increase the risk of stroke.

CRD commentary

The review question and inclusion criteria were broad but clear. The search was limited to English language articles and unpublished data were not sought, thus relevant articles might have been missed. Two reviewers selected articles for inclusion and extracted the data, which should have minimised the introduction of bias and errors during these processes. Details of a quality assessment were not described, although there was some consideration of study quality within the text of the review. The narrative synthesis of the studies was appropriate considering the heterogeneity of the studies identified. The individual study were presented in sufficient detail to investigate heterogeneity. The authors' conclusions appear reasonable given the evidence presented on risperidone and olanzapine, although for most individual drugs considered in the review, the evidence base was too small for conclusions to be drawn about the treatment of neuropsychiatric symptoms of dementia.

Implications of the review for practice and research

Practice: The authors stated that non-pharmacological interventions should be attempted before using drugs to treat neuropsychiatric symptoms. They also provided an algorithm for the management of neuropsychiatric symptoms in dementia, which incorporated evidence from the review.

Research: The authors stated that more trials aimed specifically at treating patients with neuropsychiatric symptoms should be performed.

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Other publications of related interest
This additional published commentary may also be of interest. Ryder KM, Shorr RI. Review: Atypical antipsychotic drugs modestly improve neuropsychiatric symptoms of dementia. ACP J Club 2005;143:14.

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