

# Review: pharmacotherapy provides minimal improvements in the neuropsychiatric symptoms of dementia

Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA* 2005;293:596–608.



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## Q How effective are pharmacological treatments for the neuropsychiatric symptoms of dementia?

### METHODS

**Design:** Systematic review.

**Data sources:** MEDLINE (1966 to July 2004), Cochrane Database of Systematic Reviews, plus hand search of reference lists.

**Study selection and analysis:** The review included placebo controlled, double blind randomised controlled trials (RCTs) of drug therapy for the neuropsychiatric symptoms of dementia, and meta-analyses of such RCTs. Studies of drugs not available in the US or no longer in clinical use and studies of depressive symptoms alone were excluded.

**Outcomes:** Neuropsychiatric symptoms.

### MAIN RESULTS

Atypical antipsychotics: six RCTs, all of risperidone or olanzapine, met inclusion criteria. Four RCTs (1380 people) found that antipsychotic treatment improved neuropsychiatric symptoms compared with placebo (see <http://www.ebmentalhealth.com/supplemental> for table). However, improvements were often small, and risperidone and olanzapine have been reported to increase cerebrovascular events in people with dementia. Typical antipsychotics: two meta-analyses met inclusion criteria. One meta-analysis (seven RCTs; 252 people) found that typical antipsychotics reduced neuropsychiatric symptoms more than placebo (standardised effect size 0.18;  $p = 0.004$ ). The second meta-analysis (five RCTs; 573 people) found that haloperidol reduced aggression compared with placebo, but did not improve behavioural symptoms overall, and increased withdrawal due to adverse events (OR 2.5, 95% CI 1.2 to 5.2). Cholinesterase inhibitors: two meta-analyses and six additional RCTs met inclusion criteria. The larger meta-analysis (16 RCTs; 5529 people) found a small improvement in Neuropsychiatric Inventory score with cholinesterase inhibitors (six RCTs; score range 0 to 120; mean improvement 1.72, 95% CI 0.87 to 2.57). However, this benefit was influenced by RCTs of metrifonate, which is not approved in the USA due to side effects. Cholinesterase inhibitors did not improve Alzheimer disease assessment scale non-cognitive score compared with placebo (score range 0 to 50; mean difference 0.03; 95% CI 0.00 to 0.05). Other treatments: RCTs failed to show consistent evidence of benefit of antidepressants (five RCTs), mood stabilisers (five RCTs), memantine (two RCTs), or benzodiazepines (one RCT) for the neuropsychiatric symptoms of dementia.

### CONCLUSIONS

Current evidence suggests that the most effective drug treatments for the neuropsychiatric symptoms of dementia are olanzapine and risperidone. However, the absolute benefits are small, and should be balanced against an increased risk of cerebrovascular adverse events.

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### Commentary

Behavioural disturbances and psychotic symptoms are commonly associated with dementia. They are associated with excess morbidity and mortality, decrease the quality of life of people with dementia, and distress their caregivers. From their systematic review of pharmacological agents used to treat these symptoms, Sink *et al* concluded that “pharmacological therapies are not particularly effective” and that the best evidence supports the use of risperidone or olanzapine. However, they warn that their use is associated with an increased risk of cerebrovascular events. In April 2005, shortly after the publication of this review, the US Federal Drug Administration issued a warning that second generation (atypical) antipsychotics are associated with increased mortality in people with dementia and behavioural disturbances or psychotic symptoms (relative risk compared with placebo: 1.6–1.7). As this warning is based on the analysis of data mostly from unpublished randomised controlled trials (RCTs), one expects that if these RCTs had been included in the review, the risk/benefit of atypical antipsychotics would have been even less favourable.

Facing this evidence, what is a clinician to do? Many will be tempted to use medications from other classes. However, the review by Sink *et al* reminds us that first generation (typical) antipsychotics (for example, haloperidol) have been found to have only modest efficacy and are associated with significant adverse effects (probably also including an increased mortality). Valproate has not been found to be effective in patients with dementia and behavioural disturbances. While there is limited and conflicting evidence supporting the use of carbamazepine or specific serotonin reuptake inhibitors (SSRIs),<sup>1</sup> they can also be associated with serious adverse effects in the elderly (for example, haematological toxicity and drug/drug interaction for carbamazepine; falls, hyponatremia, or bleeding for SSRIs). Several studies suggest a modest statistical—but not necessarily clinical—benefit of cognitive enhancers (that is, cholinesterase inhibitors and memantine); given their effect on cognition, these drugs may be better at preventing the onset of behavioural disturbances than at treating them once they are present.

Future studies may help to pinpoint the role of specific drugs or classes of drugs for specific target symptoms<sup>2</sup> or for specific subgroups of people with dementia and behavioural disturbances or psychotic symptoms.<sup>3</sup> In the meantime, clinicians need to remember that the high rate of placebo response observed in RCTs suggests that behavioural disturbances or psychosis in people with dementia can be treated with increased clinical attention (that is, identification and management of comorbidities, frequent visits, increased interaction with clinical staff). Currently, when medications are used, atypical antipsychotics probably remain the drugs of choice, but prescribers and families need to be aware that these medications may be associated with significant adverse events, including death.

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