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COCHRANE CORNER

Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia: a Cochrane Review[†]

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[†] This review is the abstract of a Cochrane Review previously published in the *Cochrane Database of Systematic Reviews*, 2021, Issue 12: CD013304, doi: 10.1002/14651858.CD013304.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the *Cochrane Database of Systematic Reviews* should be consulted for the most recent version of the review.

We thank the Cochrane Dementia and Cognitive Improvement Group for their support in publishing this review.

See Round the Corner in this issue.

Background

Typical and atypical antipsychotics are widely used to treat agitation and psychosis in dementia. However, whether or not they are beneficial is uncertain. Some trials have yielded negative results and effectiveness may be outweighed by harms.

Objectives

To assess the efficacy and safety of antipsychotics for the treatment of agitation and psychosis in people with Alzheimer's disease and vascular dementia.

Search methods

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group's register, MEDLINE (Ovid Sp), Embase (Ovid SP), PsycINFO (Ovid SP), CINAHL (EBSCOhost), Web of Science Core Collection (ISI Web of Science), LILACS (BIREME), ClinicalTrials.gov and the World Health Organization's meta-register, and the International Clinical Trials Registry Portal on 7 January 2021. Two review authors independently screened the title and abstract of the hits, and two review authors assessed the full text of studies that got through this screening.

Selection criteria

We included randomised, placebo-controlled, parallel-arm trials comparing the effects of antipsychotics and placebo for the treatment of agitation or psychosis in people with dementia due to Alzheimer's disease or vascular dementia, or both, irrespective of age, severity of cognitive impairment, and setting. (The majority of) participants had to have clinically significant agitation (including aggression) or psychosis or both at baseline. We excluded studies about antipsychotics that are no longer available in the USA or EU, or that are used for emergency short-term sedation. We also excluded head-to-head trials and antipsychotic withdrawal trials.

Data collection and analysis

The primary outcomes were (1) reduction in agitation or psychosis in participants with agitation or psychosis, respectively at baseline, and (2) the number of participants with adverse events: somnolence, extrapyramidal symptoms, any adverse event, any serious adverse event (SAE), and death.

Two review authors independently extracted the necessary data and assessed risk of bias with the Cochrane risk of bias tool. We calculated the pooled effect on agitation and psychosis for typical and atypical antipsychotics separately, and the pooled risk of adverse effects independent of the target symptom (agitation or psychosis). We used RevMan Web for the analyses.

Main results

The search yielded 8233 separate hits. After assessing the full-text of 35 studies, we included 24 trials that met the eligibility criteria. Six trials tested a typical antipsychotic, four for agitation and two for psychosis. Twenty trials tested an atypical antipsychotic, eight for agitation and 12 for psychosis. Two trials tested both drug types. Seventeen of 26 comparisons were performed in patients with Alzheimer's disease specifically. The other nine comparisons also included patients with vascular dementia or mixed dementia. Together, the studies included 6090 participants (12–652 per study). The trials were performed in institutionalised, hospitalised and community-dwelling patients, or a combination of those.

For typical antipsychotics (e.g. haloperidol, thiothixene), we are uncertain whether these drugs improve agitation compared with placebo (standardised mean difference (SMD) –0.36, 95% confidence interval (CI) –0.57 to –0.15, 4 studies, $n = 361$); very low-certainty evidence, but typical antipsychotics may improve psychosis slightly (SMD –0.29, 95% CI –0.55 to –0.03, 2 studies, $n = 240$; low-certainty evidence) compared with placebo. These drugs probably increase the risk of somnolence (risk ratio (RR) 2.62, 95% CI 1.51–4.56, 3 studies, $n = 466$; moderate-certainty evidence) and increase extrapyramidal symptoms (RR 2.26, 95% CI 1.58–3.23, 3 studies, $n = 467$; high-certainty) evidence. There was no evidence regarding the risk of any adverse event. The risks of SAEs (RR 1.32, 95% CI 0.65–2.66, 1 study, $n = 193$) and death (RR 1.46, 95% CI 0.54–4.00, 6 studies, $n = 578$) may be increased slightly, but these estimates were very imprecise, and the certainty was low. The effect estimates for haloperidol from five trials were in line with those of the drug class.

Atypical antipsychotics (e.g. risperidone, olanzapine, aripiprazole, quetiapine) probably reduce agitation slightly (SMD –0.21, 95% CI –0.30 to –0.12, 7 studies, $n = 1971$; moderate-certainty evidence), but probably have a negligible effect on psychosis (SMD –0.11, 95% CI –0.18 to –0.03, 12 studies, $n = 3364$; moderate-certainty evidence). These drugs increase the risk of somnolence (RR 1.93, 95% CI 1.57–2.39, 13 studies, $n = 3878$; high-certainty evidence) and are probably also associated with slightly increased risk of extrapyramidal symptoms (RR 1.39, 95% CI 1.14–1.68, 15 studies, $n = 4180$; moderate-certainty evidence), serious adverse events (RR 1.32, 95% CI 1.09–1.61, 15 studies, $n = 4316$; moderate-certainty evidence) and death (RR 1.36, 95% CI 0.90–2.05, 17 studies, $n = 5032$; moderate-certainty evidence), although the latter estimate was imprecise. The drugs probably have a negligible effect on the risk of any adverse event (RR 1.05, 95% CI 1.02–1.09, 11 studies, $n = 2785$; moderate-certainty evidence). The findings from seven trials for risperidone were in line with those for the drug class.

Authors' conclusions

There is some evidence that typical antipsychotics might decrease agitation and psychosis slightly in patients with dementia. Atypical antipsychotics reduce agitation in dementia slightly, but their effect on psychosis in dementia is negligible. The apparent effectiveness of the drugs seen in daily practice may be explained by a favourable natural course of the symptoms, as observed in the placebo groups. Both drug classes increase the risk of somnolence and other adverse events. If antipsychotics are considered for sedation in patients with severe and dangerous symptoms, this should be discussed openly with the patient and legal representative.