Dementia medications and risk of falls, syncope, and related adverse events: Meta-analysis of randomized controlled trials
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CRD summary
This review concluded that cholinesterase inhibitors may increase risks of syncope, with no effect on other accidental injuries in cognitively impaired older adults. Memantine may have a favourable effect on fracture, with no effects on other events. These conclusions are likely to be reliable, but should be interpreted with some caution due to a lack of details on study quality.

Authors' objectives
To evaluate the effect of cholinesterase inhibitors (ChEIs) and memantine on the risk of falls, syncope and related events, defined as fracture and accidental injury.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to July 2009 without language restrictions. Search terms were reported. Unpublished data were sought by screening reference lists of relevant reviews, pharmaceutical clinical trial registries and medical and safety review documents of the United States Food and Drug Administration new drug application online.

Study selection
Parallel group randomised controlled trials (RCTs) that compared any ChEI or memantine to placebo in patients with Alzheimer's disease, vascular dementia, mixed dementia, Parkinson's disease with dementia, dementia with Lewy body, frontotemporal dementia or mild cognitive impairment were eligible for inclusion. Studies had to report data on falls and syncope or related adverse events.

Included studies assessed donepezil, galantamine, rivastigmine, tacrine and memantine. Mean age ranged from 69 to 86 years. Fifteen to 67% of participants were men, mean mini mental state examine (MMSE) scores ranged from 6 to 27. Most patients had a diagnosis of Alzheimer's disease or vascular dementia; patients with mixed dementia were included. Cognitive impairment was mild to moderate in most studies. Five studies were conducted in nursing home residents.

At least two reviewers assessed studies for inclusion; disagreements were resolved through consensus.

Assessment of study quality
Studies were assessed for methodological quality based on criteria of rigorousness of monitoring and quality of reporting of adverse events data, sequence generation, allocation concealment, blinding of participants and outcome assessors.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted data to calculate odds ratios (ORs) together with 95% confidence intervals (CIs). Where any cell contained zero, 0.5 was added to all cells of the 2x2 table. When more than one dose or formulation was used doses were combined into a single group and compared with placebo. Disagreements were resolved through consensus.

Methods of synthesis
Summary odds ratios and 95% CIs were estimated using a random-effects model. Heterogeneity was assessed using Q and $I^2$ statistics. The effects of dementia type, dementia severity, residential status, individual quality criteria and duration of follow-up were investigated using subgroup meta-analysis and meta-regression analysis. Sensitivity analyses restricted analyses to studies with complete follow-up, studies with at least 500 patients and exclusion of each study at a time from the analysis. Publication bias was assessed graphically using funnel plots and statistically using the Begg and
Results of the review
ChEIs (40 studies, 9,882 participants): There was no significant difference between ChEIs and placebo for falls (OR 0.88, 95% CI 0.74 to 1.04; 13 RCTs), fracture (OR 1.39, 95% CI 0.75 to 2.56; eight RCTs) and accidental injury (OR 1.13, 95% CI 0.87 to 1.45; 19 RCTs). There were significantly increased odds of syncope associated with ChEIs (OR 1.53, 95% CI 1.02 to 2.30; 13 RCTs).

The only subgroup analysis to show differences between groups was for syncope where the risk differed according to cognitive impairment (p=0.05) with higher odds ratios for studies of patients with Alzheimer's disease (OR 1.90, 95% CI 1.14 to 3.15) and mild cognitive impairment (OR 3.99, 95% CI 0.44 to 35.9). There was heterogeneity among studies of accidental injury (I²=55%) but not for studies of other outcomes (I²=0%).

Memantine (14 studies, 3,584 participants): There was no significant difference between memantine and placebo for falls (OR 0.92, 95% CI 0.72 to 1.18; nine RCTs), syncope (OR 1.04, 95% CI 0.36 to 3.04; four RCTs) and accidental injury (OR 0.80, 95% CI 0.56 to 1.12; seven RCTs). Significantly reduced odds of fracture were associated with memantine (OR 0.21, 95% CI 0.05 to 0.85; three RCTs).

Results did not differ according to subgroups. There was little heterogeneity for any of the analyses (I²=0 to 6%).

None of the sensitivity analyses showed significant results. There was no evidence of publication bias.

Authors' conclusions
ChEIs may increase the risk of syncope, with no effect on falls, fracture and accidental injury in cognitively impaired older adults. Memantine may have a favourable effect on fracture, with no effects on other events.

CRD commentary
The review addressed a focused question. Inclusion criteria were clearly defined. The literature search was appropriate and included steps to locate both published and unpublished data. It appeared that appropriate steps were taken to reduce reviewer error when selecting studies and extracting data; it was unclear whether such steps were employed when assessing study quality. Study quality was reported to have been assessed using appropriate criteria; the results of the assessment were not reported. A formal meta-analysis was conducted using appropriate methods and included detailed subgroup and sensitivity analyses.

The authors conclusions are supported by the data and are likely to be reliable, but should be interpreted with some caution due to the lack of details on study quality.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated a need for further research to confirm the reduction in fractures observed for memantine. They also stated that fall-related adverse events should be routinely included in trial reports of older adults with cognitive impairment and that high-quality observational research was warranted to evaluate the effect of these agents on fall-related adverse events in a more representative population.

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