Review: Cholinesterase inhibitors do not reduce progression to dementia from mild cognitive impairment

Russ TC, Morling JR. ***Cholinesterase inhibitors for mild cognitive impairment.*** *Cochrane Database Syst Rev. 2012;(9):CD009132.*

Clinical impact ratings: GM ★★★★★★☆ MH ★★★★★★☆ G ★★★★★☆☆ N ★★★★★★☆

Question

In adults with mild cognitive impairment, what are the efficacy and safety of cholinesterase inhibitors (ChEIs)?

Review scope

Included studies compared ChEIs (donepezil, rivastigmine, galantamine, or tacrine) with placebo for ≥ 1 month in adults with mild cognitive impairment (as defined by each study but including subjective memory complaint and relatively preserved daily functioning). Primary outcomes were progression to dementia, which included Alzheimer disease (National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria); vascular dementia (consensus criteria); and Lewy body dementia (consensus criteria) assessed at 12, 24, and 36 months; or dementia syndrome (*Diagnostic and Statistical Manual of Mental Disorders, 4th edition*, or World Health Organization International Statistical Classification of Diseases and Related Health Problems, 10th revision); and adverse events. Secondary outcomes included mortality.

Review methods

Cochrane Dementia and Cognitive Improvement Group Specialised Register (ALOIS), which includes search results from MEDLINE, EMBASE/Excerpta Medica, CINAHL, PsycINFO, LILACS, trial registers, Cochrane Central Register of Controlled Trials, and gray literature; and reference lists were searched for double-blind, randomized, controlled trials (RCTs). 9 RCTs (n = 5149, age range 45 to 90 y, follow-up range 16 wk to 3 y) met selection criteria. All RCTs had adequate randomization, blinding, and intention-to-treat analysis; 8 were funded by pharmaceutical manufacturers. Donepezil was studied in 3 RCTs, galantamine in 4, and rivastigmine in 2.

Cholinesterase inhibitors (ChEIs) vs placebo in adults with mild cognitive impairment*

Outcomes	Number of trials (n)	Weighted event rates		At 16 wk to 3 y	
		ChEIs	Placebo	RRR (95% CI)	NNT (CI)
Dementia at 1 y	3 (2560)	7.6%	12%	31% (0 to 53)	NS
Dementia at 2 y	2 (2048)	12%	18%	33% (17 to 45)	17 (12 to 34)
Dementia at 3 y	2 (1530)	20%	24%	16% (–2 to 30)	NS
Serious adverse events	6 (4207)	19%	19%	3% (–10 to 14)	NS
				RRI (CI)	NNH (CI)
Any adverse event	6 (4207)	89%	82%	9% (2 to 16)	15 (10 to 50)
Diarrhea	7 (4761)	29%	18%	110% (30 to 239)	10 (7 to 15)
Nausea	7 (4761)	22%	9.1%	197% (157 to 242)	8 (5 to 34)
Mortality	7 (4719)	3.3%	3.3%	8% (–46 to 21)	NS

**NS = not significant; other abbreviations defined in Glossary. Weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from control event rates and risk ratios in article using a random-effects model.*

Main results

The main results are in the Table.

Conclusion

In adults with mild cognitive impairment, cholinesterase inhibitors do not differ from placebo for progression to dementia at 1 and 3 years but increase nonserious adverse events.

Source of funding: No external funding.

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Commentary

The results of the review by Russ and Morling come as no surprise since a previous meta-analysis showed that ChEIs had limited, if any, effect on mild cognitive impairment (1). Clinicians continue to debate whether significant improvements in cognitive function in mild to moderate Alzheimer dementia with ChEIs translate into clinical significance because many studies have short treatment periods (usually 6 mo) (1). Russ and Morling assessed the efficacy, safety, and tolerability of ChEIs for mild cognitive impairment in adults and found no strong evidence of a beneficial effect on progression to dementia at 1, 2, or 3 years. However, conversion to dementia from mild cognitive impairment is a long process, and the longest duration of any trial included in the review was 3 years. Further, definitions of mild cognitive impairment varied between studies, which limits the validity of the comparisons, and loss to follow-up potentially introduced selection bias. Although the studies were done over a range of periods and reported a variety of outcomes, the ChEI group had more adverse events but did not differ for serious adverse events or deaths. As expected, gastrointestinal side effects were more common with ChEIs; cardiac problems did not differ between groups, but arrhythmias were not reported separately.

The cost-effectiveness of ChEIs for mild cognitive impairment is undetermined and an important concern in view of their limited efficacy. Insufficient information exists on the economic impact and burden of mild cognitive impairment, which limits the ability to model the cost-effectiveness of potential interventions for the condition.

Currently, no convincing evidence shows that ChEIs have a beneficial effect on progression to dementia in patients with mild cognitive impairment. There is no basis at present for recommending ChEIs for such patients.

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Reference

1. **Birks J.** Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006;(1):CD005593.