Review: Cholinesterase inhibitors may be effective in Alzheimer disease

Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. **Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials.** BMJ. 2005;331:321-7.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Geriatrics ★★★★★★★ Neurology ★★★★★★☆

QUESTION

In patients with Alzheimer disease (AD), does treatment with cholinesterase inhibitors (donepezil, rivastigmine, or galantamine) improve clinical outcomes?

METHODS

Data sources: MEDLINE (1989 to November 2004), EMBASE/Excerpta Medica (1989 to November 2004), the Cochrane Database of Systematic reviews, and bibliographies of relevant studies.

Study selection and assessment: Randomized controlled trials (RCTs) (published in any language) that compared cholinesterase inhibitors (donepezil, rivastigmine, or galantamine) with placebo in patients with AD. Studies that did not examine clinical outcomes or focused on vascular dementia were excluded. Study quality was assessed using a checklist of methodological criteria that included use of intention-to-treat analysis, numbers analyzed, sample size calculations, stratification, and blinding.

OUTCOMES

Measures of clinical outcome included Alzheimer's Disease Assessment–Cognitive Subscale, Clinician's Interview Based Impression of Change scale plus caregiver input, Clinical Global Impression of Change, Progressive Deterioration Scale, neuropsychiatric inventory, time to reach clinically evident functional decline, entry to institutional care, and the Gottfries-Brane-Steen scale.

MAIN RESULTS

12 RCTs of donepezil (n = 4125), 5 of rivastigmine (n = 1967), and 5 of galantamine (n = 2939) met the selection criteria. Duration of treatment varied between 6 weeks and 3 years. A summary of the results is in the Table. Adverse effects commonly associated with donepezil, rivastigmine, and galantamine included nausea, vomiting, diarrhea, and weight loss. ≥ 3 methodological shortcomings were identified in all studies.

CONCLUSION

A limited and methodologically flawed evidence base suggests that treatment with cholinesterase inhibitors (donepezil, rivastigmine, or galantamine) marginally improves clinical outcomes in Alzheimer disease.

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Cholinesterase inhibitors (donepezil, rivastigmine, or galantamine) vs placebo in Alzheimer disease at 6 weeks to 3 years*

Outcomes	Number of RCTs	Summary of findings
ADAS–cog	14	Differences between means ranged from 1.5 to 3.9 points in favor of cholinesterase inhibitors (12 RCTs)
CIBIC–plus	12	Differences between means ranged from 0.26 to 0.54 points in favor of cholinesterase inhibitors (5 RCTs)
Benefit on the CIBIC plus	11	More patients in ≥ 1 treatment group than in the placebo group derived benefit from the treatment (5 RCTs)
Time to clinically evident functional decline	1	Donepezil extended median time to clinically evident functional decline by 5 mo compared with placebo
Entry to institutional care	1	Groups did not differ
Neuropsychiatric inventory	2	A negative effect of withdrawal of donepezil (1 RCT)
Gottfries-Brane-Steen scale	1	Donepezil and placebo groups did not differ
CGIC scale	3	Difference favored donepezil (1 RCT)
Progressive Deterioration Scale	2	Difference favored rivastigmine (1 RCT)

*ADAS–cog = Alzheimer's Disease Assessment–cognitive subscale; CIBIC–plus = Clinician's Interview Based Impression of Change scale plus caregiver input; CGIC = Clinical Global Impression of Change; RCT = randomized controlled trial.

COMMENTARY

The current consensus on cholinesterase inhibitors in the treatment of AD is that they probably have a small positive effect on cognitive function, and possibly behavior, in some patients, but the clinical significance of the effect may be marginal. Kaduszkiewicz and colleagues have identified dozens of methodological flaws in previously reported RCTs of donepezil, rivastigmine, and galantamine and call this consensus into question. They describe most flaws accurately but sometimes mischaracterize them or overstate their significance. For example, they fault studies for "excluding" patients after randomization when these "exclusions" may represent withdrawal of consent by participants before baseline measurements were taken, a justifiable reason for not including them in the analysis that is not likely to introduce bias. The authors also criticize studies for reporting > 1 outcome without statistical correction for multiple comparisons, but many RCT methodologists do not seem to share this concern.

The authors, however, correctly highlight the potentially serious bias that could result from the absence of final outcome measures on most patients who are withdrawn. RCT methodologists continue to look for the optimal approach to imputing values to deal with this common dilemma. Cochrane reviewers of cholinesterase inhibitor trials (1–3) explored the potential effects of this bias and convincingly concluded that the likely magnitude of the bias does not invalidate the findings of these studies.

So with this review we have an exhaustive catalogue of minor, mostly unimportant flaws that do not come close to rocking the boat on the current consensus. Clinicians still must struggle with how to identify responders to cholinesterase inhibitors, how long to treat, and whether a trial of medication is cost-effective.

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