

Review: Donepezil, metrifonate, rivastigmine, and *Ginkgo biloba* are more effective than placebo in Alzheimer disease

Wolfson C, Moride Y, Perrault A, et al. Drug treatments for Alzheimer's disease. I. A comparative analysis of clinical trials. Ottawa, Ontario: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2000 May.

QUESTION

Which drugs are most effective for adults with Alzheimer disease (AD)?

DATA SOURCES

Studies were identified by searching MEDLINE, CINAHL, Applied Science and Technology, Core Biomedical Collection, Core Biomedical Collection III, PsycINFO, HealthSTAR, the Cochrane Library, references of review articles, and personal files.

STUDY SELECTION

Randomized controlled trials (RCTs) were selected if they were full reports published from 1986 to 1999 on drugs that were on the market or in phase III clinical trials; had a quality score ≥ 5 on the 8-item Jadad scale (maximum score 8); and used the U.S. National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria to diagnose AD.

DATA EXTRACTION

Data were extracted on RCT methods and duration, patients, type of drug, completion rates, adverse effects, and outcomes.

MAIN RESULTS

26 RCTs met the selection criteria. *Donepezil*: 4 RCTs compared donepezil with placebo for 12 weeks (2 RCTs) or 24

weeks (2 RCTs). A benefit on the Alzheimer Disease Assessment–cognitive subscale (ADAS-cog) was seen for donepezil, 5 mg/d, in 4 RCTs (difference in mean change from baseline scores 1.5 to 3.2); 10 mg/d, in 3 RCTs (difference in mean change from baseline scores 2.9 to 3.1); and 3 mg/d, in 1 RCT (difference in mean change from baseline scores 2.1). *Metrifonate*: 6 RCTs compared metrifonate with placebo. The double-blind phase ranged from 6 to 26 weeks. All but 1 RCT had a 2-phase dosing strategy, with a loading dose followed by maintenance doses to achieve a predetermined minimum level of acetylcholinesterase inhibition (30% to 70%). All studies reported a benefit for metrifonate over placebo on the ADAS-cog. The difference in mean change from baseline scores in 5 RCTs ranged from 1.5 (95% CI 0.2 to 2.8) to 2.9 (CI 1.6 to 4.3). *Rivastigmine*: 2 RCTs compared low-dose (1 to 4 mg/d) and high-dose (6 to 12 mg/d) rivastigmine with placebo for 26 weeks. 1 RCT ($n = 699$) showed a benefit in cognition and global functioning for both rivastigmine groups (mean score difference in decline on the ADAS-cog 3.8, 95% CI 2.6 to 4.9 for high-dose rivastigmine). In the other RCT ($n = 725$), a benefit was seen for the high-dose group (difference in mean change

from baseline scores on the ADAS-cog 1.6) but not for the low-dose group. *Ginkgo biloba*: 3 RCTs compared *Ginkgo biloba* with placebo for 12 weeks ($n = 20$), 24 weeks ($n = 222$), and 1 year ($n = 309$). Doses were 240 mg/d in 2 RCTs and 120 mg/d in 1 RCT. A benefit was seen on the ADAS-cog in 1 RCT (difference in mean change from baseline score 1.7, CI 0.2 to 3.2) and on the Syndrom-Kurz test in 2 RCTs. Studies did not show a clear benefit in cognitive or global outcomes for propentofylline (2 RCTs), lecithin (1 RCT), linopirdine (1 RCT), vitamin E (1 RCT), or selegiline (7 RCTs).

CONCLUSIONS

In adults with Alzheimer disease, donepezil, metrifonate, rivastigmine, and *Ginkgo biloba* are better than placebo for cognitive performance. No benefit was seen for vitamin E, lecithin, linopirdine, selegiline, and propentofylline.

Source of funding: Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

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COMMENTARY

Wolfson and colleagues have prepared a comprehensive and rigorous review of the published RCTs of treatments for AD. Differences in methods, including design and reporting strategies, precluded a meta-analysis. Many of the reviewed studies were designed to meet the research criteria for drug licensing: investigation of efficacy in treatment of cognitive impairment in dementia and drug safety. Studies included in the review were of short duration; some studies had potential for bias from high drop-out rates, and some studies had participants who were unlike usual patients with comorbid disorder.

This abstract only reports on the outcome of cognitive function. The review itself highlights some of the problems with the measurements of other outcomes. The abstracted treatment effects are differences in points on the ADAS-cog scale (range 0 to 70 points). Average treatment effects of cholinesterase inhibitors were 1.5 to 3.8 points. Somewhat smaller effects were recorded for *Ginkgo biloba*. Although these effects were statistically significant, clinical importance is not clear. Some people respond better than others, but the characteristics of those who respond well are not known.

From these data we can advise patients that some evidence exists to support the short-term use of donepezil, metrifonate, and rivastigmine. Clinical discussion should consider the lack of data on longer-term use, including the consequences of withdrawing the treatment and its potential for side effects.

We also want to know how these treatments affect the psychiatric and behavioral aspects of AD as well as the cognitive ones. The recently published RCT of galantamine provides data on response in all 3 types of symptoms in dementia (1). In addition to treatment effects on cognitive function, significant benefits for noncognitive symptoms may exist. Much of the research so far has been on patients with mild-to-moderate dementia. An important issue, therefore, is whether these treatments are effective in more severe dementia.

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Reference

1. Tariot PN, Solomon PR, Morris JC, et al. Neurology. 2000;54:2269-76.