Review: Donepezil improves cognitive and functional outcomes in vascular cognitive impairment

Malouf R, Birks J. **Donepezil for vascular cognitive impairment.** Cochrane Database Syst Rev. 2004;(1):CD004395.

QUESTION

In patients with vascular cognitive impairment, does donepezil improve cognitive and functional outcomes?

METHODS

Data sources: Cochrane Dementia and Cognitive Improvement Group Specialized Register, which included citations obtained from 24 databases. The Eisai Inc. drug company was contacted for unpublished studies.

Study selection and assessment: Randomized, placebo-controlled trials of donepezil in patients with vascular cognitive impairment or vascular or mixed dementia. Methodological quality was assessed using Cochrane Collaboration guidelines for allocation concealment.

Outcomes: Cognitive function, global assessment, activities of daily living, and adverse effects.

MAIN RESULTS

2 multicenter trials (n = 1219, mean age 75 y, 58% men) with identical protocols from the Donepezil Study Group met the inclusion criteria. 99% of patients had concomitant disease and were taking other medications. Patients were allocated to 5 or 10 mg/d of donepezil or placebo. Patients who received donepezil had greater improvements in cognitive function at 12 and 24 weeks than did patients who received placebo (24-wk data in Table). 10 mg of donepezil showed more improvement than placebo on the Clinical Dementia Rating scale (Table). 5 or 10 mg of donepezil was better than placebo for improving activities of daily living (Table). Donepezil 10 mg was associated with more adverse events than placebo (odds ratio 1.95, 95% CI 1.20 to 3.15); no difference was seen between the lower dose of donepezil and placebo.

CONCLUSION

In patients with vascular cognitive impairment, donepezil improves cognitive and functional outcomes.

Source of funding: No external funding.

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Donepezil (Don), 5 or 10 mg/d vs placebo for vascular cognitive impairment at 24 weeks*

Outcomes	Scale	Comparisons	Weighted mean difference (95% CI)
Cognitive function	ADAS-Cog	Don-5 vs placebo	–1.66 (–2.45 to –0.87)
		Don-10 vs placebo	–2.21 (–3.07 to –1.35)
	MMSE	Don-5 vs placebo	0.83 (0.38 to 1.29)
		Don-10 vs placebo	1.08 (0.62 to 1.55)
Activities of daily living	ADFACS	Don-5 vs placebo	–0.97 (–1.80 to –0.14)
		Don-10 vs placebo	–0.95 (–1.79 to –0.11)
	IADL	Don-5 vs placebo	–0.81 (–1.45 to –0.16)
		Don-10 vs placebo	–0.85 (–1.48 to –0.21)
Global assessment	CDR-SB	Don-10 vs placebo	–0.46 (–0.72 to –0.20)

	Weighted event rates		RBI (CI)	NNT (CI)
	Don-5	Placebo		
CIBIC-Plus (clinical improvement score ≤ 3)	37%	27%	35% (10 to 67)	10 (7 to 34)

*ADAS-Cog = Alzheimer's Disease Assessment Scale cognitive subscale; MMSE = Mini-Mental State Examination; ADFACS = Alzheimer's Disease Functional Assessment and Change Scale; IADL = Instrumental Activity of Daily Living; CDR-SB = sum of the boxes of the Clinical Dementia Rating; CIBIC-Plus = Clinician's Interview-Based Impression of Change-Plus caregiver input. Other abbreviations defined in Glossary; weighted event rates, RBI, NNT, and CI calculated from data in article using a fixed-effects model.

COMMENTARY

The diagnosis of vascular dementia (VaD) continues to challenge clinicians (1). It is clear, however, that Alzheimer disease (AD) and cerebrovascular disease (CVD) frequently coexist in patients with dementia (2). "Pure" VaD may be rare, and AD with CVD ("mixed dementia") may be more prevalent than once believed. VaD and AD share common risk factors. It is possible that the cholinergic deficit seen in AD might also contribute to VaD.

Cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, target this cholinergic deficit and have been shown to improve cognitive and functional measures in patients with AD. This class of drugs has been widely adopted to manage symptoms of AD. Rivastigmine and galantamine may also have benefits in VaD. A trial of galantamine showed effectiveness in patients with VaD and AD with CVD (3).

The review by Malouf and Birks suggests that donepezil may have benefits in "pure" VaD (i.e., without coexistent AD), and previous trials with other cholinesterase inhibitors suggest this may be a class effect. Some important caveats, however, are warranted. First, the benefits seen with donepezil are statistically significant but modest. For example, the weighted mean difference in MMSE scores with donepezil 10 mg/d compared with placebo was 1.08 points; the minimal clinically important difference for the MMSE has been estimated to be 3.72 points (4). Second, withdrawals because of adverse events were twice as common in the donepezil 10-mg group as in the placebo group.

This review suggests that donepezil may have benefits over 24 weeks in patients with VaD of mild-to-moderate severity. Optimal dosing and duration of treatment are unknown. The role of cholinesterase inhibitors in the setting of VaD and AD with CVD remains uncertain and requires further study. Clinicians should remember to manage vascular risk factors in this patient population (5).

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