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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

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DRUGS for ALZHEIMER's DISEASE

Three acetylcholinesterase inhibitors (AChE-I) are licensed for Alzheimer's Disease (AD) in Canada: donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl). In 2004 memantine (Ebixa), a neuro-receptor antagonist, was conditionally approved.

What treatment outcomes are important to patients and caregivers?

Relevant goals for community-living patients with dementia include:

- avoiding or delaying institutionalization;
- preserving activities of daily living (ADL) and cognitive functions such as reading and writing, ability to hold conversations, enjoy TV, radio, or music;
- improving the patient and caregiver(s)' quality of life;
- avoiding adverse drug effects, hospitalization, and extra costs or doctor visits.

What does AChE-I treatment achieve? Results of double blind RCTs

Donepezil - One trial measured institutionalization

AD2000 trial: This randomized controlled trial (RCT) of donepezil vs. placebo studied clinically suspected mild to moderate AD in 565 patients: donepezil (n=282), placebo (n=283); median age 75, baseline median Mini Mental Status Exam (MMSE) score 19 (30-pt scale).[1] 292 patients completed 60 weeks, and 111 completed 114 weeks of treatment, making this the longest RCT for AD. The authors reported: *"Donepezil did not reduce the relative risk of entering institutional care: RR 0.97 [95% CI 0.72-1.30; p=0.8] nor the combined risk of progression of disability or institutionalization: RR 0.96 [95% CI 0.74-1.24; p=0.7]. No significant differences were seen between donepezil and placebo in behavioural and psychological symptoms, carer psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths, or between 5 mg/d and 10 mg/d doses of donepezil."*

Eleven additional published trials provide evidence that donepezil 5-10 mg/d improves test scores assessing cognition and clinical impressions over 3-12 months, versus placebo:

- mean difference in MMSE of ~ 1 point (30-pt scale);
- 2-3 point mean difference in the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog), a 70-pt scale;
- mean difference of ~ 0.5 on a 7-pt scale, a clinical observer's interview-based impression of change with caregiver input (CIBIC+), where a 1-pt change represents minimal improvement.[2-12]

Cholinergic effects such as diarrhea [absolute risk increase (ARI)=12%; number needed to harm (NNH)=8] and nausea [ARI=5%, NNH=20] are the most frequent adverse effects.[7] Meta-analysis of 9 RCTs reporting serious adverse events (SAE) indicates a trend to increased SAE with donepezil 10 mg/d: 150/1345 (11.2%) vs. placebo 123/1317 (9.3%), RR 1.22 [0.97-1.52].[TI, unpublished]

Rivastigmine and Galantamine Similar magnitude of effect on scores

Rivastigmine: 5 published 3-6 month placebo-controlled RCTs of rivastigmine 6-12 mg/d in mild to moderate AD found changes similar to those observed with donepezil.[13-17] In a meta-analysis vs. placebo:

- mean ADAS-cog differed by ≤ 2.1 points;
- Progressive Disability Scale differed by ≤ 2.2 points (100-pt scale);
- CIBIC+ "improved" in ≤ 7% of patients.[18]

Nausea [ARI=17%, NNH=6] and vomiting [ARI=14%, NNH=7] were the most frequent adverse effects, and 1/6 to 1/5 of patients lost > 7% of body weight.

Galantamine: 5 published 6-12 month RCTs found that galantamine at 16-24 mg/d changed ADAS-cog by ~ 3.4 points.[19-23] However, galantamine led to more withdrawals due to adverse effects [ARI=7.5%, NNH=13] and caused cholinergic adverse effects in up to 20% of patients (e.g. NNH=5 for nausea at 24 mg/d).

What do trial results mean for patients?

The clinical relevance of this degree of difference on cognitive, ADL and clinical impression scales has not been established. In AD2000, a mean 0.8-pt improvement in MMSE was observed but disability

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and institutionalization were unaffected.[1] A meta-analysis of 16 RCTs summarized findings for AChE-I vs. placebo:

- 9% more patients experience improvement on CIBIC+ or a similar scale [number needed to treat (NNT)=12];
- 8% more patients experience adverse effects [NNH=12].[24]

AChE-I trial reports tend to exaggerate beneficial effects and underestimate adverse effects. This is due to incomplete follow-up and the bias introduced by more early withdrawals from the active-treatment groups in a progressively deteriorating disease. A systematic review concludes that, *"Because of flawed methods and small clinical benefits, the scientific basis for recommendations of cholinesterase inhibitors for the treatment of Alzheimer's disease is questionable."*[25]

Is one AChE-I better for AD?

No double-blind RCT compares donepezil, galantamine or rivastigmine with one another. Three open-label or partially blinded trials each claim that the sponsor's drug did better than the comparator.[26-28]

New evidence about prevention of AD

Mild cognitive impairment may precede diagnosis of AD. In a recent trial involving patients with mild cognitive impairment, progression to AD occurred in 16% of patients per year.[29] Placebo (n=259) was compared with donepezil 10 mg/d (n=253) or vitamin E 2000 IU/d (n=257) in patients whose baseline mean MMSE was 27 and average age was 73. Over 3 years, neither active treatment prevented progression to AD. Donepezil caused more adverse effects, including diarrhea [ARI=10.1%, NNH=10], muscle cramps [ARI=14.4%, NNH=7], insomnia [ARI=8.9%, NNH=11], nausea [ARI=6.5%, NNH=15], and abnormal dreams [ARI=5.2%, NNH=19]. Mortality did not differ between groups. Total serious adverse events were not reported.

Two large unpublished RCTs of galantamine 8-12 mg b.i.d. (combined n=2057) also found no effect on progression to AD, nor on a modified test of cognition at 1 or 2 years. However, combined analysis showed higher mortality in the galantamine groups (galantamine = 13/1026, placebo = 2/1022; hazard ratio = 4.86 [1.76-13.4],[30] prompting a Health Canada safety warning.
http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/reminyl_pa-ap_e.html

Can AChE-I therapy be discontinued?

The AD2000 trial observed at least 167 patients who discontinued donepezil or placebo under double-blinded conditions. There was no evidence of adverse effects from treatment discontinuation.[1]

Memantine

Memantine is licensed for moderate to severe AD. Two double blind RCTs (n=252; n=340) compared memantine 20 mg/d with placebo over a 24-28 week period.[31,32] In a third RCT (n=403) in patients already taking donepezil, addition of memantine 20 mg/d was compared with placebo.[33] None of these trials reports a difference in mortality, serious morbidity, time-to-institutionalization, or clinically significant functional advantages. Mean CIBIC+ scores did not differ[31] or improved by 0.25-0.3 points[32,33] with memantine use (1-pt difference = minimal improvement). A 100-point Severe Impairment Battery (SIB) scale assessing cognitive performance differed by 6.1 points ($p<0.001$) in one placebo-controlled trial,[31] but was unaffected in a second larger trial.[32] With memantine + donepezil vs. donepezil alone, although a significant difference in SIB scores was reported, the two treatment arms differed more at baseline (by 2 points) than at study termination (by 1.4 points).[33] ADL was unaffected or differed by 1.4 or 2.1 points out of a possible 54 points.[31-33] Memantine did not increase the rate of withdrawals in total or due to adverse effects.

Drug costs

Drugs for Alzheimer's disease

Drug Name	Brand Name	Daily Dose	Daily Cost
donepezil	Aricept ®	5-10 mg	$4.90
galantamine	Reminyl®	16-24 mg	$2.64-$5.28
rivastigmine	Exelon®	6-12 mg	$2.56-$5.12
memantine	Ebixa®	20 mg	$4.92

Conclusions

- **Donepezil has not been demonstrated to improve outcomes of importance to patients and caregivers (e.g. institutionalization or disability). Rivastigmine and galantamine have not been studied for these outcomes.**
- AChE-I cause gastrointestinal, muscular, and other adverse effects and likely increase serious adverse events.
- There is no evidence that stopping AChE-I treatment is harmful.
- In advanced AD, memantine has not been demonstrated to improve outcomes of importance to patients and caregivers.

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For a full list of references see the electronic version of this letter on the TI web site: www.ti.ubc.ca/pages/letter56.htm

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This Therapeutics Letter was submitted for review to 50 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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