

Drugs for Alzheimer's Disease

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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 (AD 2000) measured institutionalization. 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 5mg/day and 10mg/day doses of donepezil."

Eleven additional published trials provide evidence that donepezil 5-10mg/day 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-point scale;
- mean difference of ~0.5 on a 7-point 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 10mg/day: 150/1345 (11.2%) vs. placebo 123/1317 (9.3%), RR 1.22 [0.97-1.52].^{TI, unpublished}

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

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Rivastigmine and Galantamine - Magnitude of effect on assessment scores similar to donepezil.

UW Medicine Drug Costs

Drug Name & Daily Dose	Monthly Patient Charge
donepezil (Aricept) 5 - 10mg/day	\$162.65
galantamine (Reminyl) 6 - 12mg/day	\$44.65 - 85.10
memantine (Ebixa) 20mg/day	\$164.45
rivastigmine (Exelon) 16 - 24mg/day	Non-formulary

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

Can AChE-I therapy be discontinued? The AD2000 trial observed at least 167 patients who discontinued donepezil or placebo under doubleblinded conditions. There was no evidence of adverse effects from treatment discontinuation.¹

- mean ADAS-cog differed by ≤ 2.1 points;
- Progressive Disability Scale differed by ≤ 2.2 points (100-point scale);
- CIBIC+ "improved" in $\leq 7\%$ 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 16–24mg/day 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 24mg/day).

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-point improvement in MMSE was observed but disability 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

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 10mg/day (n=253) or vitamin E 2000 IU/day (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 8–12mg 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. See: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisoriesavis/public/reminyl_pa-ap_e.html

Memantine. Memantine is licensed for moderate to severe AD. Two double blind RCTs (n=252; n=340) compared memantine 20mg/day with placebo over a 24–28 week period.^{31,32} In a third RCT (n=403) in patients already taking donepezil, addition of memantine 20mg/day 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 differ³¹ or improved by 0.25–0.3 points^{32,33} with memantine use (1-point 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

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The Therapeutics Initiative was established in 1994 by the Department of Pharmacology and Therapeutics in cooperation with the Department of Family Practice at the University of British Columbia to provide up-to-date, evidence based, practical information on rational drug therapy. The Initiative is independent and at arm's length from government, pharmaceutical industry and other vested interest groups. For other Therapeutics Letter topics visit www.ti.ubc.ca/.

NPSG Standard 8A:

Implement a process for obtaining and documenting a complete list of the patient's current medications upon the patient's admission to the organization and with the involvement of the patient. This process includes a comparison of the medications the organization provides to those on the list.

NPSG Standard 8B:

A complete list of the patient's medications is communicated to the next provider of service when it refers or transfers a patient to another setting, service, practitioner or level of care within or outside the organization.

Impetus behind medication reconciliation: Prevent adverse drug events.

JCAHO Deadline for UW Medicine Implementation: January 1, 2006

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.

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.

(References available upon request.)

Medication Reconciliation

National Patient Safety Goal (NPSG) 8: Accurately and completely reconcile medications across the continuum of care.

Medication errors are one of the leading causes of injury to hospital patients, and chart reviews reveal that the majority of medication errors occur at the initial points of contact with a patient in which a caregiver is admitting the patient to the hospital or transferring the patient within the hospital or to another health care provider.¹ Experience across organizations has shown that poor communication of medical information at transition points is responsible for as many as 50% of all medication errors in the hospital and up to 20% of adverse drug events.² Medication Reconciliation is defined as a formal process of comparing a complete and accurate list of each patient's current home medications (name, dosage, frequency, and route) against the physician's admission, transfer, and/or discharge orders, with discrepancies brought to the attention of the prescriber for correction. The Medication Reconciliation process involves three steps:

- Verification (collection of medication history);
- Clarification (ensuring that the medications and doses are appropriate); and
- Reconciliation (documentation of changes in the orders).

Medication reconciling has been demonstrated to be a powerful strategy to reduce medication errors as patients move from one level of care to another.³⁻⁵ A successful reconciling process also reduces work and re-work associated with the management of medication orders. After implementation, nursing time at admission was reduced by over 20 minutes per patient.⁶ The amount of time that pharmacists were involved in discharge was reduced by over 40 minutes.⁶ Ensuring accuracy of a patient's current medications list at each instance of care is fundamental to providing safe and efficient health care.

Changes to patient medication lists can occur at any point in time and can be authorized and documented by a health care provider or initiated by patients and never documented. For example, a patient's medication list can change after hospital discharge because of an order by the patient's regular or on-call physician, or the patient could have customized their own medications because of side effects, cost considerations, misunderstanding, or other reasons. It is imperative for health care providers to recognize that the historical record, and especially the directions printed on the vials of prescription vials from home, may not always be an accurate reflection of how the patient is currently taking their medicines. As a result, health care organizations must use a team approach and many different resources, such as the historical record, an interview with the patient and/or family, or a discussion with the patient's regular pharmacist or physician, to gain an

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Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form & Strength	Therapeutic Classification	Use	Usual Adult Starting Dose*
Perflutren (Optison)	Injection, albumin microspheres: 3mL	Diagnostic aid	Cardiac imaging	0.5-1mL
	Note: Added to Formulary restricted to use for portable (bedside) exams or for patients who have a history of severe back pain associated with the administration of Definity [®] . Optison [®] will be stocked at HMC only.			

* Refer to product labeling for full prescribing information.

Medication Reconciliation, National Patient Safety Goal 8 (continued)

NPSG 8 is applicable to: prescription medications; sample medications; herbal remedies; vitamins; nutraceuticals; OTC drugs; vaccines; diagnostic and contrast agents used on or administered to persons to diagnose, treat, or prevent disease or other abnormal conditions; radioactive medications; respiratory therapy treatments; parenteral nutrition; blood derivatives; IV solutions (plain, with electrolytes and/or drugs).

accurate list of the medications the patient is taking. Today, few hospitals have processes in place that are adequate to reconcile patient's medications when entering the institution or transferring through or out of the organization.

Beginning January 1, 2006, however, JCAHO surveyors will look for evidence of consistent implementation of the requirements of NPSG 8. Less than 100% compliance will result in a requirement for improvement. It is the actual performance of the goals and their requirements (not the documentation) that surveyors will be evaluating. To come into compliance with NPSG 8, UW Medicine is in the process of developing and trialing a standardized system for creating and maintaining an accurate list of patient medications. In the new system, a medication reconciliation form will be used as a template for gathering information about patient's current medications. Once initiated, whenever a patient moves from one setting, service, practitioner, or level of care within or outside UW Medicine, the complete and current list of that patient's medications—as obtained on admission or entry and updated during that episode of care—will be communicated to the next provider of service for comparison (reconciliation) with the medications to be provided in/by the new setting, service, practitioner, or level of care. In this way, the patient medication list will more accurately reflect changes that occurred or were detected during the most current episode of care.

(References available upon request)

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drug therapy topics