Drugs for Dementia

Stephen H. Pasternak, MD, CM/ PhD, FRCPC

Presented at the Drug Therapy Day, Sponsored by the Division of Clinical Pharmacology, The Department of Medicine, Schulich School of Medicine, The University of Western Ontario, London, Ontario

Alzheimer's disease is the most common cause of dementia in adults; currently there are 500,000 Canadians with this disease. With the aging population, this number is predicted to rise to over one million by 2038.

Currently there are four medications approved in Canada for the treatment of Alzheimer's disease. None of these medications are believed to significantly alter the underlying pathophysiology (the Amyloid Cascade Hypothesis); instead, they treat symptomatic changes in neurotransmitter levels. Cholinesterase inhibitors (CIs) such as donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl), act primarily by preventing the breakdown of the neurotransmitter acetylcholine in the synapse. Memantine (Ebixa) reduces the toxic effects of glutamate over-secretion by blocking NMDA (glutamate) channels.

Cholinesterase Inhibitors

The effectiveness of CIs in Alzheimer's disease is modest but has been well established in clinical trials. Patients typically gain several (one to three) points on dementia rating scales (*i.e.*, the 30 point Mini-Mental State Examination [MMSE] or the 70 point Alzheimer's Disease Assessment Scale - Cognitive [ADAS-Cog]) and are usually stabilized for nine months to one year. CIs can also improve anxiety, mood, alertness, and social interaction and function; this is often more important to families than the gain of a few points on an MMSE. Newer medications (rivastigmine and galantamine) have theoretical pharmacological advantages, but practical differences are small. About 25% of patients do not respond to any given CI, but they may still respond instead to a different CI.

Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, act primarily by preventing the breakdown of the neurotransmitter acetylcholine in the synapse.

The main contraindications of CIs are cardiac conduction block, except for right bundle branch block (RBBB), and bradycardia/syncope. Serious adverse reactions are rare, but side effects of nausea, vomiting, and diarrhea are common. These are usually mild and

Table 1
Medications in Dementia

	Starting Dose	Minimal Effective Dose	Increase By	Usual Recommended Dose
Donepezil (Aricept)	5 mg	5 mg	5 mg after four to six weeks	10 mg
Galantamine Extended Release (Reminyl ER)	8 mg	16 mg	8 mg per month	14 to 24 mg
Rivastigmine (Exelon)	1.5 mg b.i.d.	3 mg b.i.d.	1.5 mg b.i.d. each month	3 to 6 mg b.i.d.
Rivastigmine Patch	Patch 5	Patch 5	After one month to Patch 10	Patch 10
Memantine (Ebixa)	5 mg q.a.m.	5 mg b.i.d.	5 mg per week	10 mg b.i.d.

transient, but can be debilitating. In general, side effects mostly occur with rivastigmine, to a lesser extent with galantamine, and least with donepezil. However, tolerance to any CI is variable and unpredictable, and patients who do not tolerate one medication often tolerate another. Rivastigmine is also available in patch form, which has much better tolerability, but unfortunately is not covered by ODB in Ontario.

CIs are started at low doses and titrated upwards each month to avoid side effects (Table 1). In Ontario, these drugs are paid for under Limited Use Codes for patients with an MMSE between 10 and 26. Limited Use Code 347 is used to fund a three month trial. If the medication is tolerated and the MMSE does not drop after this time, further use is authorized using Limited Use Code 348. If it is not tolerated, the medication should be discontinued, and another can be tried.

CIs have also been shown in clinical trials to be useful in treatment of vascular dementia (galantamine), Lewy body and Parkinson's dementia (rivastigmine), and in severe Alzheimer's dementia (donepezil). They may also be possibly useful in treating Mild Cognitive Impairment, where memory impairment is not sufficient to diagnose dementia. Because Alzheimer's disease can coexist with and mimic other dementias, it is often reasonable to try a three month trial of medication in many dementia settings.

Memantine

Memantine (Ebixa) is a relatively new drug in Canada for moderate to severe Alzheimer's disease (MMSE 5 to 15). In clinical trials, memantine has shown beneficial effects both alone and as an add-on to donepezil. In practice, efficacy of memantine varies considerably from patient to patient. Memantine may also reduce aggression and anxiety; this may be its best use. Overall, memantine is well tolerated, and lacks the GI and cardiac toxicity of the cholinesterase inhibitors. The most common serious side effect is worsening confusion. Since this medication is not covered by ODB in Ontario, I use a three

Table 2

Criteria for the Diagnosis of Alzheimer's Disease

- Memory impairment and at least one other cognitive function (*i.e.*, aphasia, apraxia, agnosia, executive function)
- Substantial impairment in social or occupational functioning
- Decline from a previous level
- Insidious onset, gradual worsening
- No other disease/not a delirium

month trial prior to committing patients to an expensive course of treatment.

Disease Progression

These medications probably do not alter the underlying pathology of Alzheimer's disease, therefore, all patients will eventually decline. When this happens, some authors propose switching CIs. However, there is usually a delay before the new agent reaches therapeutic threshold, with the attending risk of cognitive decline. Thus, my own practice is to raise the dose of cholinesterase inhibitor (when using rivastigmine or galantamine) or to add memantine.

Some authors recommend stopping CIs once there is "no further benefit." However, there is no definite way to determine this point. In clinical trials, patients declined following CI withdrawal. There are also numerous anecdotal reports of patients who "crashed" following CI withdrawal and failed to regain benefit when it was restarted. Therefore, stopping a CI should probably be done carefully (with monitoring), in conjunction with family wishes, when other medical problems intervene and/or when a patient is not capable of meaningful interactions.

In summary, the current medications for dementia have proven benefits; however, they have a small effect size, and variable efficacy and tolerance. I use a three month trial, using the MMSE in conjunction with clinical impression, to assess a patient's response to these medications. We anxiously await the arrival of better disease-modifying treatments, but these are likely several years away.

See Also: Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia. <http://www.cccdtd.ca/>

Take-home Message

Cholinesterase Inhibitors and Memantine have:

- Proven benefit in clinical trials
- Small effect size (not wonder drugs)
- Variable efficacy
- Variable tolerability, especially during titration

Use three month trial to test efficacy and tolerance.

Dr. Pasternak is a Neurologist, and Director of the Cognitive Neurology and Alzheimer's Disease Research Center, St. Joseph's Health Care Center, London, Ontario. He is also part of the Molecular Brain Research Group of the Robarts Research Institute and Department of Clinical Neurological Sciences, Schulich School of Medicine, the University of Western Ontario, London, Ontario.