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Cholinesterase inhibitors

Data gathered through the Alzheimer's Drug Therapy Initiative is expected to help assess various aspects of cholinesterase inhibitor use in BC.

ABSTRACT: Cholinesterase inhibitors are the most common medications used for the symptomatic treatment of Alzheimer disease. Data from published clinical trials have shown benefits for cognitive, behavioral, and functional outcomes. While the overall effect size identified in the trials is small, clinical response varies and individual patients may experience significant benefits. Cholinesterase inhibitors are generally well tolerated, but patients must be carefully monitored for adverse events. Given the difficulty of predicting which patients with Alzheimer disease are most likely to benefit, a trial of treatment with cholinesterase inhibitors should be considered in the absence of any contraindications.

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Current estimates indicate that the prevalence of dementia will more than double over the next 30 years. By 2030, there will be more than 1 million Canadians with dementia. The majority of individuals with dementia will have Alzheimer disease (AD),[1] a situation requiring physicians to understand the use of cholinesterase inhibitors for treatment of symptoms.

Pharmacology

Cholinergic transmission in the brain is an essential component of cognitive function. Pharmacological studies demonstrate that administration of drugs with anticholinergic properties are associated with worsening of memory and other cognitive function.[2] In Alzheimer disease, atrophy of the nuclei in the cells in key areas of the brain, such as the basal forebrain, leads to a demonstrable decrease in cholinergic function.[3,4] Researchers postulate that deficiencies in the cholinergic pathways of the brain are responsible for many of the cognitive and behavioral changes observed in AD.[5,6] While direct replacement of acetylcholine may not be feasible because of the associated intolerable side effects, drug therapies have been developed that focus on enhancing acetylcholine through other mechanisms as a means to improve symptoms associated with AD. Of these drugs, cholinesterase inhibitors (ChEIs) are probably the most studied. ChEIs act to increase cholinergic transmission through the inhibition of enzymes (cholinesterases) that act to break down acetylcholine. Effectively, the administration of ChEIs results in an increase in the number of acetylcholine molecules that are available to interact with the postsynaptic acetylcholine receptors, which results in an increase in central nervous system acetylcholine activity.

Currently, three ChEIs are prescribed in Canada: donepezil (Aricept), galantamine (Reminyl), and rivastigmine (Exelon) (**Table 1**). The main mechanism of action for each of these agents is inhibition of acetylcholinesterase activity. Galantamine is also

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reported to be an allosteric modulator of nicotinic acetylcholine receptors, while rivastigmine is identified as a pseudo-irreversible inhibitor of butyrylcholinesterase as well.[7] The clinical implication of these additional mechanisms of actions has not been definitively determined. Donepezil and galantamine are both metabolized by the cytochrome P-450 system, while rivastigmine is hydrolyzed by cholinesterases themselves. Each of these ChEIs is available in oral form. Rivastigmine is also available in a transdermal patch.

Table 1. Pharmacological characteristics of cholinesterase inhibitors.

Drug	Mechanism of action	Half-life	Protein-binding capacity	Metabolism
Donepezil	Selective reversible noncompetitive inhibitor of AChE*	58–90 hours	96%	CYP 2D6, CYP 3A4‡
Rivastigmine	Pseudo-irreversible inhibitor of AChE and BChE†	2 hours	40%	Non-hepatic, metabolized by AChE and BChE
Galantamine	Reversible inhibitor of AChE, presynaptic modulator of nicotinic AChE	5–7 hours	18%	CYP 2D6, CYP 3A4

*AChE = acetylcholinesterase
†BChE = butyrylcholinesterase
‡CYP = cytochrome P-450
Adapted from Hsiung GYR, Loy-English I[7]

Table 2. Dosage schedule for cholinesterase inhibitors.

Drug	Starting dose	Titration period	Dose increase	Maximum dose
Donepezil	5 mg	4–6 weeks	5 mg increase	10 mg
Rivastigmine	1.5 mg b.i.d.	2–4 weeks	1.5 mg b.i.d. increments	6 mg b.i.d.
Rivastigmine transdermal patch	4.6 mg/24 h	2–4 weeks	One-step increase to 9.5 mg/24 h	9.5 mg/24 h
Galantamine ER	8 mg	4–6 weeks	8 mg increments	24 mg

Adapted from Hsiung GYR, Loy-English I[7]

Efficacy and safety

ChEIs for the treatment of AD have been the subject of several systematic reviews and meta-analyses.[8-11] In the reported trials, the typical duration of the study period was 3 to 6 months. The results from the studies suggest that there is a statistically significant, albeit clinically modest, improvement in cognitive performance in subjects with mild to moderate Alzheimer disease. The trials involving ChEIs for AD also report statistically significant benefits on global clinical ratings for activities of daily living when compared with placebo.[12-14] Assessments of behavioral and psychological symptoms in AD have been included as outcomes in many of the studies. A modest improvement in symptoms is noted in the trials that include behavioral symptoms as a primary outcome of interest.[15] Overall, there appears to be a positive correlation between measurable improvement and target doses of medication treatment: that is, higher doses of donepezil (10 mg versus 5 mg) are associated with marginal benefits over lower doses, while higher doses of both galantamine (≥16 mg daily versus lower dose daily) and rivastigmine (≥6 mg daily versus < 6 mg daily) are more beneficial than lower doses. Few studies have directly compared the efficacy and safety of the different cholinesterase inhibitors with each other,[16] and thus there is no consensus regarding whether one particular ChEI is superior to the others in treating symptoms of mild to moderate AD. Donepezil, rivastigmine, and galantamine are all approved for symptomatic treatment of mild to moderate AD,[17-19] while donepezil is also approved by Health Canada for patients with severe AD.[17] See **Table 2** for a dosage schedule for ChEIs.

Adverse events associated with the use of ChEIs typically result from an increase in central and peripheral concentrations of acetylcholine. Adverse events with frequency rates greater than the rates for placebo include nausea, vomiting, diarrhea, anorexia, weight loss, dizziness, bradycardia, myalgias, and insomnia. These problems are generally felt to be mild to moderate in severity; however, since bradyarrhythmia may potentiate parasympathetic output, treating patients with this condition should proceed with caution. In randomized controlled trials, all cholinesterase inhibitors are associated with an increased likelihood of trial drop-out, adverse events, trial withdrawals due to adverse events, and greater rates of nausea, vomiting, and diarrhea when compared with placebo.[12-15] A meta-analysis found that patients were significantly more likely to withdraw from the drug (18%) than from the placebo (8%) (OR 2.32, 95% CI 1.95–2.76, $P < .00001$).[11] Relatively few studies directly compare different cholinesterase inhibitors regarding the rates of adverse events. Transdermal rivastigmine is better tolerated than comparable doses of the oral formulation,[14] while there is no difference in adverse event rate for

extended-release galantamine when compared with twice-daily immediate-release formulation.[13] Rates of adverse events are greater with higher doses of donepezil, galantamine, and rivastigmine when compared with lower doses of the same medication. In an effort to minimize the occurrence of adverse events, it is generally recommended that ChEIs be initiated at a low dose and titrated up slowly, as tolerated, over weeks or months to the target-dose range.

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Most published randomized, blinded clinical trials assessing the use of ChEIs for symptomatic treatment of Alzheimer disease lasted up to 6 months. Longer open-label studies have reported and these suggest that the beneficial effects resulting from the use of ChEIs may persist over several years. The interpretation of the results from open-label studies must, however, be approached with a degree of caution, as the potential for bias in the results is high.[20] Given the lack of compelling evidence from clinical trials, deciding when to discontinue the use of a cholinesterase inhibitor because of lack of efficacy is generally based upon patient and caregiver input, in conjunction with the clinical judgment of the prescriber.

ChEI use in BC

In British Columbia, the Alzheimer's Drug Therapy Initiative (ADTI) was introduced in 2007. Currently, the ADTI is funded to run through to March 2012. This province-wide program consists of a dementia education component as well as an assessment component for medication use. The Dementia Education Strategy is a program of conferences, public forums, and literature that focuses on sharing information and experience among physicians, health care professionals, and the public regarding dementia. The ADTI also provides financial coverage for ChEIs to eligible patients with AD. In order to qualify for ADTI coverage, a patient must also be registered with the provincial Fair Pharmacare program.[21] The ADTI uses a prior authorization procedure. To enroll, a patient must be a resident of British Columbia with a diagnosis of AD and a standardized Mini-Mental State Exam score of 10 to 26 and a Global Deterioration Scale score of 4 to 6. Once enrolled in the program, continued eligibility for coverage requires a reassessment every 6 to 7 months. The ADTI research program is currently collecting data that will be used to assess various aspects of ChEI use, including user characteristics, cost, efficacy and effectiveness, caregiver impact, and longer-term outcomes of indeterminate responders. The data gathered through the ADTI will provide further information about the use of ChEIs in a real-world setting. Three years after its launch, the ADTI medication program has registered approximately 12 500 individuals, which represents about 50% of all BC residents with a diagnosis of mild to moderate AD.

In addition to exploring the use of cholinesterase inhibitors to treat mild to moderate AD, researchers have explored using ChEIs to treat other conditions that affect cognitive function. Donepezil is reported to have cognitive, behavioral, and functional benefits for patients with moderate to severe AD.[12,22,23] ChEIs have also demonstrated cognitive benefits for patients with vascular dementia.[24] Galantamine has been studied for patients with "mixed dementia" (AD plus vascular dementia).[25] For individuals who do not meet the criteria for dementia, but who are felt to be experiencing mild cognitive impairment, insufficient evidence exists to support ChEI use to delay the progression of their condition.[26,27] Rivastigmine is associated with improvements in cognition and functioning in Parkinson disease dementia, and it may improve behavioral symptoms associated with dementia with Lewy bodies.[28,29]

Other therapies

Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist that is believed to decrease excitotoxicity associated with glutamate in the central nervous system. The efficacy of memantine for treating moderate to severe Alzheimer dementia has been evaluated in several trials.[30,31] Overall, memantine is associated with

statistically significant global improvement, as well as improvement of cognitive and functional symptoms in individuals with moderate to severe AD. Memantine may be prescribed as monotherapy or in combination with ChEIs.

To date, no specific therapies have been proven effective in altering the underlying disease process associated with AD; however, research that investigates various other treatments is ongoing. Medications that target amyloid or tau protein are being explored. Other therapies that actively or passively stimulate the immune system to prevent or treat AD are also being investigated. Ultimately, if treatment can alter the underlying pathological changes occurring in the brains of patients with AD, a cure for Alzheimer disease may be achievable.

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Summary

While many new disease-modifying treatments are under investigation, cholinesterase inhibitors are currently the most commonly used medications for the symptomatic treatment of Alzheimer disease. ChEIs may offer some stabilization of symptoms, which ultimately could provide patients with better quality of life in their remaining years. Statistically significant effects are reported in the published clinical trials for cognitive, behavioral, and functional outcomes. While the effect size identified in the trials is small, there may be a more clinically significant response in certain subgroups.[20] Given the difficulty of predicting which patients with AD are most likely to benefit, a trial of treatment with ChEIs should be considered in the absence of any contraindications.

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Competing interests

Dr Hsiung has been a site investigator for clinical trials sponsored by Baxter, Bristol-Myers Squibb, Elan, Janssen, and Pfizer. Dr Lee has received honoraria for speaking and participating on advisory boards for Janssen-Ortho, Novartis, and Pfizer. Drs Hsiung and Lee are co-investigators in the Alzheimer's Drug Therapy Initiative funded by the BC Ministry of Health. However, all inferences, opinions, and conclusions drawn in this publication are those of the authors and do not reflect the opinions or policies of the BC Ministry of Health.

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