abstract

In the past decade, there have been numerous advances in our understanding of the molecular biology and pathogenesis of Alzheimer disease (AD). Although to date no pharmacological treatments have been shown to alter the pathology of AD, several medications have been proven to offer symptomatic improvement and to delay the progression of cognitive, behavioural and functional deficits. This article reviews the currently available medications for management of cognitive symptoms in AD, as well as other promising drugs that are under investigation.

Key words: *Alzheimer disease, management, cholinesterase inhibitors, donepezil, memantine.*

Pharmacological Management of Alzheimer Disease: An Update

Ging-Yuek Robin Hsiung, MD, MHSc, FRCPC and Howard Feldman, MD, FRCPC, Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, BC.

Introduction

An estimated 8% of the Canadian population over age 65 suffers from dementia, of which 60–70% is caused by Alzheimer disease (AD). The incidence of dementia doubles for every five years of increased age between 65 and 85 years.[1] The management of dementia is a significant burden to our health care system, with an estimated annual cost of $3.9 billion in 1991.[2] Epidemiologic studies suggest that if the symptoms of dementia can be delayed by just two years, prevalence will decrease by 25%, with significant savings to the long-term care of these individuals. Appropriate management of symptoms of dementia not only improves the quality of life of the patient, but also decreases the burden on their caregivers and may substantially delay the need for nursing home placement.

Cholinesterase Inhibitors

Since the late 1970s, it has been shown that cholinergic transmission is an important mediator in memory and other cognitive functions.[3] An important feature of AD pathology is the deficit in central cholinergic transmission caused by degeneration of the basal forebrain nuclei as well as progressive loss of nicotinic receptors in the cerebral cortex.[4] Based on this "cholinergic hypothesis", most of the initial drug developments were aimed to increase central nervous system acetylcholine levels, one of the main neurotransmitters that is deficient in AD.

Cholinesterase inhibitors (ChEIs) act by reducing the degradation of acetylcholine in the synaptic cleft and, consequently, increasing the availability of acetylcholine molecules to act on postsynaptic receptors. ChEIs are the only approved treatment for AD in Canada at present. The four agents that belong to this class are tacrine, donepezil, galantamine and rivastigmine. However, tacrine has a short half-life and high risk of hepatotoxicity; it is no longer available in Canada since the approval of the second generation ChEIs.

Although donepezil, galantamine and rivastigmine are all ChEIs, they differ in their pharmacology and pharmacokinetics. Donepezil is a highly selective, non-competitive inhibitor of acetylcholinesterase. It is metabolized in the liver via the cytochrome P450 system with extensive first-pass metabolism. It has a long half-life and is given once daily. Galantamine is a selective reversible acetylcholinesterase inhibitor as well as a positive allosteric modulator of nicotinic receptors. It is also metabolized via the cytochrome P450 in the liver. It has a half-life of 5–7 hours and requires twice a day dosing. Rivastigmine is a slowly reversible (pseudo-irreversible) inhibitor of both acetylcholinesterase and butyrylcholinesterase. It is hydrolyzed and eliminated through the kidneys without liver metabolism. It has a short half-life and also requires twice a day dosing.

Systematic reviews[5-7] and a recent meta-analysis of all the ChEIs clinical trials data[8] confirm the modest but significant therapeutic effect on the symptoms of mild to moderate AD. The treatment effect in the short term (six months) is similar for all three ChEIs on global measures and cognitive rating scales. One study also demonstrated efficacy of donepezil in moderate to severe stages of AD,[9] while another study suggested its benefits may last for one year or more.[10] Patients may show improvement or sta-

bilization on alertness and attention, as well as improvements in memory, language and activities of daily living. Furthermore, behavioural disturbances such as agitation and aggressiveness may be reduced.

To date, no direct head-to-head randomized double-blind trials have been done to compare the ChEIs; therefore, choice of ChEIs mainly depends on ease of administration, tolerability profile and familiarity of the drug by the treating physician (Table). When a patient is intolerant to one, a switch to an alternative ChEI is warranted. The issue of switching ChEI is controversial when there is an apparent lack of benefit after an adequate trial (six months). Limited data suggest that switching to another ChEI may offer some benefits in 10–50% of patients. Side effects of the ChEIs are usually related to their peripheral cholinergic effects, such as nausea, vomiting, diarrhea and bradycardia. Slowing the titration schedule and taking the medication on a full stomach often minimize these adverse effects. There is no data to support using different ChEIs together, which will likely increase the risk of potential side effects.

Medications for Management of Alzheimer Disease with Class 1 Evidence Demonstrating Efficacy

Drug	Starting Dose	Titration Interval	Dose Increase Per Titration	Target Dose	Main Side Effects
Donepezil (Aricept)	5mg q.i.d.	46 weeks	5mg	10mg q.i.d.	GI upset, sleep disturbances
Galantamine (Reminyl)	4mg b.i.d.	46 weeks	4mg b.i.d.	12mg b.i.d.	GI upset
Rivastigmine (Exelon)	1.5mg b.i.d.	4 weeks	1.5mg b.i.d.	6mg b.i.d.	GI upset, weight loss
Memantine	5mg q.i.d.	4 weeks	5mg	10mg b.i.d.	Hallucinations, dizziness, headache
Vitamin E	400–1000 IU q.i.d.	14 weeks	400–1000 IU	1000 IU b.i.d.	Diarrhea, coagulation disorder

Memantine

Activation of NMDA-receptors mediates calcium influx into neurons, which is thought to be involved in long-term potentiation, a cellular process that underlies learning and memory.[11] However, excess intracellular calcium accumulation in neurons is believed to be toxic to cells and results in neuronal death. Memantine is a non-competitive NMDA antagonist with moderate affinity at the phencyclidine site, and it has been hypothesized to protect neurons from glutamate-mediated excitotoxic damage while preserving the normal physiologic activation of the NMDA receptor.

Two randomized double-blinded placebo-controlled trials demonstrated efficacy of memantine in improving cognitive and functional measures in advanced AD patients.[12,13] Preliminary report of another randomized controlled trial combining donepezil and memantine in treatment of moderate to severe AD also showed significant improvement on both global measures and assessment of cognition.[14] Based on these findings, memantine has now been approved in Europe and the U.S. for management of moderate to severe AD. No decision on its approval in Canada has been announced yet. It also may have beneficial effects as monotherapy or combination therapy in earlier stages of AD, but further data is needed before evidence-based recommendations can be made (Table). Potential side effects include headache, nausea, agitation, dizziness, hallucinations and lowered seizure threshold. Other NMDA antagonists such as amantadine, ketamine, and dextromethorphan should not be used concurrently.

Antioxidants

Preclinical data suggests that free radical formation may be involved in aging and in the pathophysiology of AD. *In vitro* studies have shown that presence of Aβ, the precursor peptide that forms amyloid plaques, increases oxidative stress, while Aβ toxicity can be attenuated by antioxidants. However, clinical data is limited. A single large placebo-controlled randomized clinical trial comparing vitamin E 1000 IU b.i.d. and selegiline 5mg b.i.d. in patients with moderate to severe AD suggested that vitamin E might delay nursing home placement, functional decline and/or death by about 25% compared to the placebo group, although no significant effect on cognition was found.[15] Nonetheless, vitamin E has been widely adopted as standard therapy because of its low cost and minimal side effects (Table). The main concern with its use is risk of coagulation disorders, especially at doses higher than 1000 IU per day. Caution must be exercised in patients using concurrent antiplatelet therapy or warfarin.

Anti-inflammatory Agents

Several lines of evidence have suggested that abnormal activity of immune function is associated with AD. Mediators of acute inflammation, including complements and cytokines such as interleukin-1 and interleukin-6, have been found to be increased in brains of patients with AD. Large epidemiological studies also have suggested that use of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of developing AD by 30–70% in healthy older subjects.[16] However, double-blinded, placebo-controlled trials using COX-2 inhibitors and corticosteroids have not demonstrated any significant positive effects.[17] It is possible that COX-1 inhibition, independent of COX-2 effects, may delay AD progression. Conversely, it is also possible that

although NSAIDs may prevent or slow very early steps of AD pathogenesis in clinically normal patients, they do not stop the cascade of biologic events that occur after the disease process has established. Further studies are in progress to address these questions. At present, there is insufficient evidence to recommend the use of NSAIDs, COX-2 inhibitors or other anti-inflammatory drugs in primary or secondary prevention of AD.

Estrogens

The beneficial effects of estrogen were suggested by observational studies demonstrating an inverse relationship between estrogen dose and duration of dementia.[18,19] Further studies suggested that estrogen may have neurotrophic and neuroprotective effects, and may improve cognitive function.[20] However, placebo-controlled trials using conjugated equine estrogen to treat women with AD have been negative; in fact, the active group showed mild worsening of cognitive function and more complications such as deep vein thrombosis.[21] Therefore, estrogen cannot be recommended for management of AD at present.

Ginkgo Biloba

The extract of the leaves and seeds of the *Ginkgo biloba* tree has been claimed to increase circulation, enhance blood flow to the brain and improve concentration and memory, and has been used by herbalists in treatment of AD, vascular dementia, intermittent claudication and tinnitus of vascular origin. It is believed to function as a neuroprotective agent, an antioxidant, a free-radical scavenger, a membrane stabilizer, a vasodilator and an inhibitor of platelet-activating factor. A Cochrane systematic review of 33 trials concluded that ginkgo appears to be safe and shows some evidence of improvement in cognition and social functioning. However, results from three larger recent trials are inconclusive.[22]

The main adverse effect with ginkgo is mediated by its inhibition of platelet-activating factor; therefore, concurrent use of warfarin, aspirin or other antiplatelet agents is relatively contraindicated. A number of serious complications such as intracerebral hemorrhage, subarachnoid hemorrhage and subdural hematoma have been reported in the literature. The doses used in these studies for treatment of AD range from 60–80mg b.i.d. to t.i.d. However, as an herbal product its manufacturing process does not have to meet any specific guidelines; therefore, the active ingredients may vary from one preparation to another. Based on the current available evidence, it cannot be recommended as a standard therapy for dementia. Further large-scale randomized controlled trials are being conducted, including a primary prevention of dementia study.

Cholesterol-lowering Agents

Genetic studies indicated that inheritance of the allele ε4 of apolipoprotein E (ApoE), a protein involved in cholesterol transport and distribution, is a major risk factor for developing late-onset AD. ApoE ε4 is associated with a slight increase of serum cholesterol, and epidemiological studies have shown that elevated serum cholesterol levels are correlated with increased susceptibility to AD.[23,24] In addition, molecular studies suggest that elevated cholesterol may have a direct role in the deposition of amyloid fibrils and Aβ aggregation. These findings have led to the hypothesis that lowering brain cholesterol may decrease the risk of developing AD. There is not enough evidence to recommend use of cholesterol-lowering agents for management of AD at the moment, but randomized controlled trials are being conducted with results expected in the next few years.

Other Promising Agents Under Investigation

In addition to the above medications, a number of new agents have shown promise in the preclinical stages and are moving on to clinical trials. Molecular genetics studies showed that metabolism of Aβ is linked to proteolytic processing of the amyloid precursor protein (APP) by a series of proteases known as secretases. Stimulation of α-secretase or inhibition of β- and γ-secretases are correlated with decreased amyloid production in the brain in animal models. Compounds that modify secretase activities have already been developed and are entering phase 1 clinical trials. Another protein that is involved in γ-secretase function is presenilin. Presenilin interacts with glycogen synthase kinase-3b (GSK-3b), and both molecules are required for γ-secretase activity. Recent studies with animal models showed that lithium, a GSK-3 inhibitor, can block the production of Aβ by interfering with APP cleavage at the γ-secretase step, and reduce the accumulation of Aβ in the brain.[25] Its potential in management of AD deserves further investigations.

From a different perspective, nerve growth factors have been found to increase cholinergic neurons in the nucleus basalis in animals, and may attenuate rate of degeneration of surviving cholinergic neurons in AD. Some of these neurotrophic agents also are entering phase 2 clinical trials.

Conclusion

Although we are still far from a cure, there are now moderately effective treatments that can improve the cognitive symptoms of AD, with the goal of maintaining the patient functionally independent as long as possible. This not only improves the quality of life of the patients, but that of the caregivers as well. Another important aspect of management of dementia patients is the control of behavioural and psychiatric symptoms of AD, but this is beyond the scope of the current review. Several promising new medications are now on the horizon, which will hopefully strengthen our armamentarium against the devastating effects of dementia. ◆

Dr. Hsiung has received travel fellowship from Pfizer Inc. Dr. Feldman has received research funding and consulting fees from Pfizer, GlaxoSmithKline, Boehringer Ingelheim, Janssen, Novartis and AstraZeneca.

References

1. CSHA. The incidence of dementia in Canada. The Canadian Study of Health and Aging Working Group. Neurology 2000;55:66-73.
2. Ostbye T, Crosse E. Net economic costs of dementia in Canada. CMAJ 1994;151:1457-64.
3. Iversen SD. The pharmacology of memory. C R Acad Sci III 1998;321:209-15.
4. Bartus RT, Dean RL 3rd, Beer B, et al. The cholinergic hypothesis of geriatric memory dysfunction. Science 1982;217:408-14.
5. Olin J, Schneider L. Galantamine for Alzheimer's disease (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.
6. Birks J, Grimley Evans J, Iakovidou V, et al. Rivastigmine for Alzheimer's disease (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.
7. Birks J, Melzer D, Beppu H. Donepezil for mild and moderate Alzheimer's disease (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.
8. Lanctot KL, Herrmann N, Yau KK, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. CMAJ 2003;169:557-64.
9. Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001;57:613-20.
10. Winblad B, Engedal K, Soininen H, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001;57:489-95.
11. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 1993;361:31-9.
12. Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333-41.
13. Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999;14:135-46.
14. Farlow M, Tariot PN, Grossberg GT, et al. Memantine/Donepezil dual therapy is superior to placebo/donepezil therapy for treatment of moderate to severe AD. Neurology 2003;60 (Suppl 1):A412.
15. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997;336:1216-22.
16. Moore AH, O'Banion MK. Neuroinflammation and anti-inflammatory therapy for Alzheimer's disease. Adv Drug Deliv Rev 2002;54:1627-56.
17. Aisen PS, Davis KL, Berg JD, et al. A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's Disease Cooperative Study. Neurology 2000;54:588-93.
18. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. Arch Intern Med 1996;156:2213-7.
19. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 1997;48:1517-21.
20. Asthana S, Baker LD, Craft S, et al. High-dose estradiol improves cognition for women with AD: results of a randomized study. Neurology 2001;57:605-12.
21. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's Disease Cooperative Study. JAMA 2000;283:1007-15.
22. Birks J, Grimley Evans J, van Dongen M. Ginkgo biloba for cognitive impairment and dementia. In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.
23. Wolozin B, Kellman W, Ruosseau P, et al. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol 2000;57:1439-43.
24. Jick H, Zornberg GL, Jick SS, et al. Statins and the risk of dementia. Lancet 2000;356:1627-31.
25. Phiel CJ, Wilson CA, Lee VM, et al. GSK-3alpha regulates production of Alzheimer's disease amyloid-beta peptides. Nature 2003;423:435-9.