abstract

Alzheimer's disease is the most common cause of dementia among older adults. After a century of research, there have been significant scientific advances in the understanding of this disorder. Over the past 15 years, treatment for Alzheimer's disease exists but it is symptomatic and its effects are modest at best. Currently, newer disease-modifying treatments are being investigated that have the potential of slowing the progression of the disease.

Key words: *Alzheimer's disease, disease-modifying agents, amyloid, tau, neuroprotection*

Emerging Drug Therapies in Alzheimer's Disease

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that is characterized clinically by the insidious onset and the slow progressive impairment of multiple cognitive domains, including memory, executive function, judgment, and visual perception. The signs and symptoms reflect dysfunction of specific brain regions and result from the presence of senile (amyloid) plaques and neurofibrillary tangles, the pathological hallmarks of AD (Figure 1).[1,2]

Alzheimer's disease is the most common cause of dementia among older adults and accounts for more than half of all cases. More than a quarter of a million older Canadians have dementia.[3] This number is estimated to rise to more than 750,000 by the year 2031.[3] Both the incidence and prevalence of AD increases with age and exponentially increases after the age of 65.[4] Alzheimer's disease is an important public health problem because of its physical and psychological cost to families caring for an individual with dementia, adding to the financial cost of $100 billion per year for direct patient care.[4] It is estimated that if interventions could delay onset of the disease by two years, after 50 years there would be almost two million fewer cases than projected; if onset could be delayed by one year, there would be nearly 800,000 fewer prevalent cases.[5] Consequently, any therapy in the treatment and/or prevention of AD will reduce the economic, medical, and social burdens.

The current approved therapies for AD are acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and an NMDA (N-methyl-D-aspartate)-receptor antagonist (memantine). Used for individuals in the mild to severe stages of AD, these medications are symptomatic in nature and have been shown to produce modest improvements in cognition, activities of daily living, and behaviour.[2] However, these medications do not stop disease progression. Research is ongoing in therapies that target the underlying pathogenic mechanisms and have the potential to modify the biology of the disease. The following is an overview of the future pharmacotherapy of AD.

Strategies for Future Treatment of Alzheimer's Disease

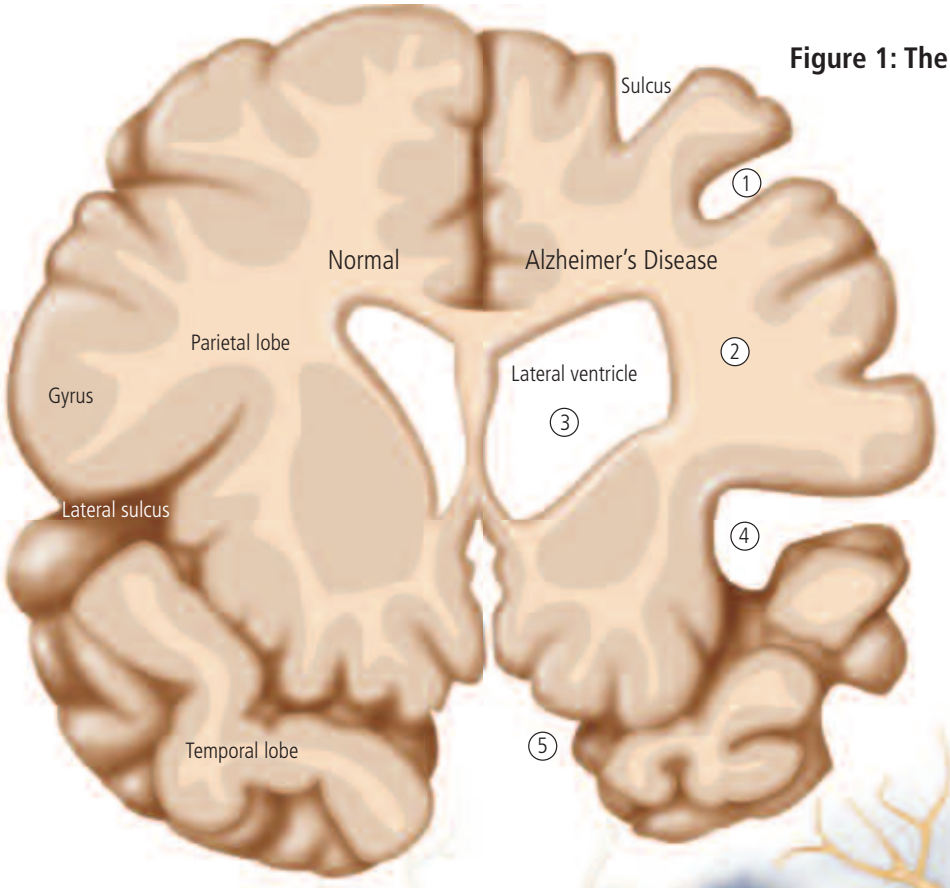
The steps involved in the pathophysiology of AD represent ideal targets for therapy (Table 1). Unlike the current symptomatic treatments, these future therapies, when available, will have disease-modifying properties and will have the potential to slow disease progression.[6–9] Many therapies may have more than one mechanism of action, thus broadening their therapeutic appeal.

Inhibiting the formation of the main pathological findings of AD, the senile plaque and the neurofibrillary tangle, is one strategy. The amyloid cascade hypothesis, the dominant theory in the pathogenesis of AD, states that the aggregation of β-amyloid (Aβ) fragments, produced from the proteolytic cleavage of the amyloid precursor protein by β- and γ-secretase enzymes, initiate a cascade of events resulting in inflammatory responses, neurofibrillary tangle formation, loss

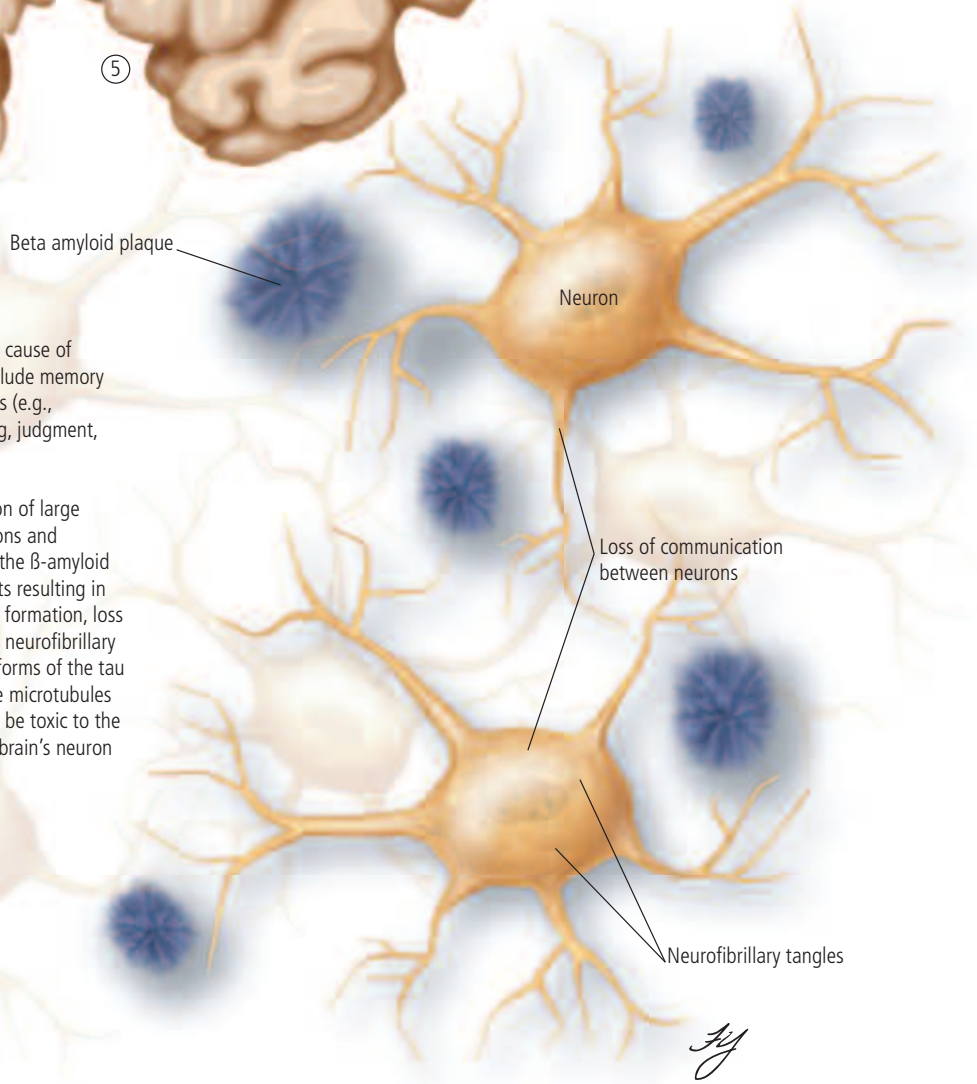
Table 1: Summary of Potential and Future Pharmacotherapies of Alzheimer's Disease

MECHANISM			Pathophysiology of Alzheimer's Disease						
	Genetics	Inflammation	Amyloid Plaque β-amyloid			Neurofibrillary Tangles Tau		Neuroprotection	Symptomatic
DEVELOPING MEDICATIONS (IN VITRO AND ANIMAL MODELS)	Gene therapy	Anti-inflammatory agents (e.g., NSAID such as ibuprofen, COX-2 inhibitors)	Disease production	Disease aggregation	Increase degradation	Regain the normal function of tau protein by reducing its hyper-phosphorylation	Decrease aggregation of tau	• Glutamate NMDA-receptor antagonists • Antioxidants • Promote nerve growth factors	Increase or enhance neuro-transmitters, mainly acetylcholine
	Genes encoding nerve growth factors		• α-secretase inhibitor (AF267B)[7,8] • β-secretase inhibitor[7,8] • Ibuprofen[19] • Statins[40]	• Cyclohexa-nehexol		• Lithium51 • Indolocarbazoles[7] • Valproic acid [47] • Memantine (?)	• Anthraquinones[52] • Cyanine dye (N744)[53]		
CLINICAL TRIALS	Genes encoding nerve growth factors		• γ-secretase inhibitor (LY450139)[11] • R-flurbipro-phen (Flurizan)[45,46] • Valproic acid[47] • Lithium[48] • Statins[40] • 8-OH-quinolone (PBT-2)	• 3-amino-1 propanesulfonic acid (tramiprosate, ALZHEMED)[12] • Clioquinol (PBT-1)50 • 8-OH-quinolone (PBT-2)	• AN-1792 (active immu-nization)[13,14] • AAB-001 (passive immunization)[15]			Glutamate NMDA-receptor antagonists • Neramexane[22] Antioxidants • Vitamins E, C • Alpha-lipoic acid • Coenzyme Q • TV3326 (Ladostigil)[54] • Rasagiline (Azilect)[54] • Xaliproden[23] • Raloxifene[55] • Huperzine A[56] • MK0952[57] • SR-57667 • Dimebon[58] • Valproic acid[47] • Rosiglitazone[43]	• Hyperzine A (Debio-9902 SR/Zt-1SR)[24,25] • Rivastigmine patch • Lecozotan SR (SRA-333)[27] • AC-3933

Figure 1: The Pathology of Alzheimer's Disease



1. Enlarged sulcus
2. Atrophy of brain tissue
3. Enlarged lateral ventricle
4. Atrophy of brain tissue resulting in damage to multiple cognitive areas
5. Atrophy of the inner temporal region affecting an individual's memory



Alzheimer's disease (AD) is the most common cause of dementia in older adults. Symptoms of AD include memory loss, impairment of multiple cognitive domains (e.g., language), compromised executive functioning, judgment, and visual perception.

The pathology of AD includes the accumulation of large amounts of ß-amyloid plaques between neurons and neurofibrillary tangles. It is hypothesized that the ß-amyloid plaques initiate a cascade of destructive events resulting in inflammatory responses, neurofibrillary tangle formation, loss of synapses, neuronal loss, and dementia. The neurofibrillary tangles are abnormally hyperphosphorylated forms of the tau protein that do not properly bind and stabilize microtubules in the neuron. Neurofibrillary tangles can also be toxic to the neuron and contribute to the decrease in the brain's neuron population.

Table 2: Possible Preventative Therapies in Alzheimer's Disease

Exercise	Dietary Changes	Medications
Physical exercise (e.g., aerobics)[28]	Increasing antioxidants	Antihypertensives[39]
Cognitive exercise[29]	• vitamins A, B complex, B_{12}, C, and E[20,30,31]	Cholesterol-lowering agents[40]
	• omega-3 fatty acids[31]	Insulin-sensitizing agents[41–43]
	• flavenoids[32]	Anti-inflammatory agents[17,44]
	• folate[33–34]	
	• curcumin[35]	
	• red wine[36]	
	• blueberries[37]	
	Mediterranean diet[38]	

of synapses, neuronal loss, and dementia.[10] Increasing evidence also suggests that the soluble forms of Aβ are toxic to neurons. Amyloid-modifying strategies include decreasing the production of Aβ, such as secretase inhibitors (e.g., LY45013911), interfering with the aggregation of Aβ into amyloid plaques (e.g., tramiprosate [Alzhemed™][12] or clioquinol),[49] and promoting Aβ-removal or degradation (e.g., active and passive Aβ-immunization).[13–15]

Neurofibrillary tangles are composed from the aggregation of the abnormal hyperphosphorylated forms of the tau protein, preventing its ability to bind and to stabilize microtubules in the neuron.[1,2] In addition, abnormal forms of tau are also toxic to the neuron. Although there are no human clinical trials yet, scientific research has discovered several promising compounds that act by either regulating the phosphorylation of tau through inhibition of tau kinases and/or activation of tau phosphatases, or inhibiting the aggregation of tau filaments.[7] Ideally, any medication that is shown to interfere with the abnormal function of tau will not only be able to treat AD, but also other neurodegenerative disorders associated with abnormal tau—the tauopathies such as frontotemporal dementia or progressive supranuclear palsy.

In addition to senile plaques and tangles, neuroinflammation is also present in AD.[16] Retrospective observational and prospective studies have indicated that NSAID exposure may be preventative in the development of AD.[17,18] Although some NSAIDs such as ibuprofen have also been shown to reduce the production of β-amyloid,[19] they do not slow the rate of cognitive decline.[18]

Neuroprotective strategies act by preserving the existing neurons. Mechanisms of neuroprotective agents include the use of antioxidants (e.g., vitamin E),[20] prevention of glutamate excitotoxicity (e.g., memantine or neramexane),[21,22] and by promotion of nerve growth factors (e.g., xaliproden).[23]

In AD, the degeneration of the cholinergic neurons in the basal forebrain results in decreased central cholinergic transmission and is one of the causes for the symptoms of cognitive loss.[1,2,7] This cholinergic hypothesis provides another rational target for therapy and any medication that increases acetylcholine is potentially beneficial. The current acetylcholinesterase inhibitors (AChEI), such as donepezil, act by inhibiting the enzyme acetylcholinesterase, leading to an increase in the synaptic concentration of acetylcholine. Currently, newer AChEIs such as huperzine A,[24–25] or improved methods of delivery such as the rivastigmine patch[26] or a rapidly dissolving donepezil tablet, are being investigated. Other medications act by stimulating release of acetylcholine, such as lecozotan.[27]

Preventative Therapies

The current strategy of AD treatment is aimed at those who have the disease. One other aspect is the investigation of any preventative measure. Both observational and experimental studies have suggested possible preventative strategies and appear to revolve around a healthier lifestyle and the use of certain medications (Table 2).

Conclusions

AD is the most common cause of dementia among older adults and its prevalence increases exponentially after the age of 65. It is an important public health issue as it is associated with high economic, medical, and social burdens. The current approved therapies of AD are symptomatic in nature, modest in effectiveness, and do not stop disease progression. The emerging therapies in AD are disease-modifying with the potential of slowing disease progression. Many of these therapies are currently being evaluated in clinical trials.

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Key Points

The current approved therapies for Alzheimer's disease produce modest symptom improvement, but do not stop disease progression.

Ideally, newer therapies will have more than one mechanism of action and disease-modifying effects.

New therapies may have amyloid-modifying strategies that could decrease the production of Aβ such as secretase inhibitors.

Other scientific research of promise may lead to development of medications that interfere with the abnormal function of tau or control neuroinflammation.

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