Advances in the pharmacotherapy of Alzheimer's disease

Review

Synthèse

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Case

Mrs. S is a 66-year-old woman who has been brought in by her husband because she got lost in a familiar camping ground and is now afraid to go out unaccompanied. There has been a progressive decline in her short-term memory for the past 2 years, and she has a family history of Alzheimer's disease (mother and one older sister). Her Mini Mental State Exam (MMSE) score is 23, and she cannot draw or set a clock at 11:10. After 2 months of treatment with a cholinesterase inhibitor her MMSE score increases to 25, and she is described as having more drive to do things in the house. After 6 months of treatment she is reading novels again and wants to participate in volunteer work; her MMSE score is still 25. After 13 months her MMSE score is 22; she is reading less but is still keen on completing her word puzzles.

Alzheimer's disease was first identified in 1907 by psychiatrist Alois Alzheimer. He described neurofibrillary tangles and plaque formation found on autopsy in the cerebral cortex of a 51-year-old woman with dementia. These tangles and plaques remain the pathognomonic signs of the disease to this day. Clinical diagnosis was relatively unimportant until the recent discovery of pharmacologic agents that appear to offer efficacious and safe treatment. Thus, to benefit patients, modern clinicians must be able to diagnose Alzheimer's disease in life. This is most often accomplished using a structured history obtained from the patient and the caregiver in order to identify the characteristic clinical features (Table 1). The current trend is toward early diagnosis, when symptoms are minimal and limited to memory complaints (mild cognitive impairment).

There are 3 stages of Alzheimer's disease — mild, moderate and severe — with cognitive and functional decline stretching over 5–8 years (Table 2). The initial, mild stage usually lasts 2–3 years, during which time patients show short-term memory impairment often accompanied by symptoms of anxiety and depression. During the moderate stage these symptoms appear to abate as neuropsychiatric manifestations such as visual hallucinations, false beliefs and reversal of sleep patterns emerge. The severe and final stage is characterized by motor signs such as motor rigidity and prominent cognitive decline. Cognitive and functional decline tend to be linear throughout the 3 stages of the disease, whereas caregiver burden peaks with the onset of neuropsychiatric symptoms and declines somewhat during the final stage, when the patient is more sedentary.

Objective measures of the dysfunction associated with Alzheimer's disease have been developed to help clinicians and to serve as yardsticks for clinical trials of therapy (Table 2). The Global Deterioration Scale consists of 7 stages based on a progressive need for assistance in daily life, such as travelling in unfamiliar areas, choosing clothes and dressing.[2] The scale ranges from 1–2 (normal) to 6–7 (severe dysfunction); for example, a patient with a score of 4–5 would be unable to travel alone and handle finances, and someone with a score of 6–7 would be unable to dress and bathe. The Mini Mental State Exam (MMSE) was developed to measure cognitive function.[3] This 22-item scale generates scores from 0 (severe dysfunction) to 30 (excellent cognitive function) and can easily be applied in clinical practice and as a research tool. Finally, global autonomy can be measured in 3 broad categories: fully independent living, need for some supervision and inability to live alone.

Cholinergic loss as a cause of neurologic and psychiatric impairment

In the late 1970s it was discovered that the brains of patients with Alzheimer's disease were deficient in acetylcholine,[4] one of the main neurotransmitters of the central nervous system that serves to increase attention and facilitate learning. This discovery led to the development of the cholinergic hypothesis, which states that cognitive, functional and behavioural dysfunction associated with Alzheimer's disease may be caused by an inability to transmit neurologic impulses across cholinergic synapses. Today, the symptomatic treatment of Alzheimer's disease is based on cholinergic pharmacologic enhancement, an approach supported by 3 distinct sets of facts:

- Brain biopsies and autopsy studies have clearly shown that patients with Alzheimer's disease have reduced activity of cortical choline acetyltransferase,[4] an enzyme that synthesizes acetylcholine from choline[5] (Fig. 1). Levels of choline acetyltransferase correlate with the number of neuritic plaques and with MMSE scores.[6] Additional postmortem studies have shown a pattern of cholinergic denervation with a reduction in presynaptic muscarinic type 1 and nicotinic receptors, with relative preservation of postsynaptic muscarinic type 2 receptors.[5]
- The loss of cholinergic neurons in the nucleus basalis of Maynert and other subcortical nuclei that are characterized by their diffuse cortical projections support this hypothesis (Fig. 2).[7] These large neurons are mainly responsible for the supply of acetylcholine to the cerebral cortex and play an important role in mediating attention and new learning. Neuropathologic studies have revealed the presence of neurofibrillary tangles in these neurons.[8] The selective vulnerability of these large cholinergic neurons may be explained in part by the loss of the calcium-binding protein calbindin-D28k with age, rendering the neurons more vulnerable to high intracellular levels of calcium.[9]
- Finally, extensive animal and human pharmacology studies have shown that cholinergic antagonists such as

Table 1: Diagnostic criteria for Alzheimer's disease*

- Multiple cognitive deficits manifested by memory impairment and one or more of aphasia, apraxia, agnosia or disturbance in executive functioning†
- Significant impairment in social or occupational functioning
- Gradual onset and continuing cognitive decline
- Symptoms not due to neurologic, systemic or substance-abuse conditions known to cause dementia

*Modified from DSM-IV criteria.[1]
†Executive functioning is the ability to initiate, plan and execute daily tasks.

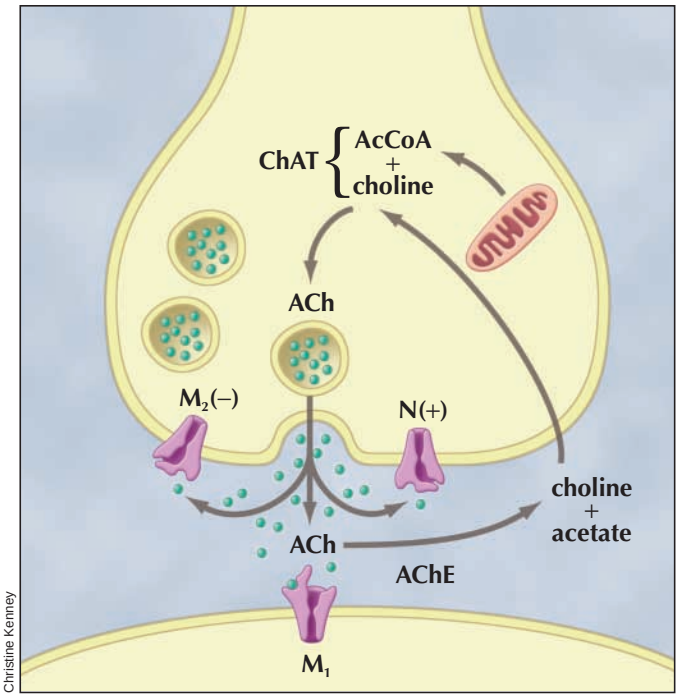

Fig. 1: Synthesis of the neurotransmitter acetylcholine (ACh) from acetyl coenzyme A (AcCoA) and choline through the action of the enzyme choline acetyltransferase (ChAT). Acetylcholine is released into the synaptic cleft and acts on multiple sites including presynaptic nicotinic (N) and muscarinic type 2 (M_2) receptors — exerting positive (+) and negative (–) action on further release of acetylcholine — and postsynaptic muscarinic type 1 (M_1) receptors. Acetylcholinesterase (AChE) breaks acetylcholine down into choline and acetate.

Table 2: Measures of global and cognitive dysfunction associated with the 3 stages of Alzheimer's disease

		Measure		
Stage	Duration, yr	Global Deterioration Scale,* score	Mini Mental State Exam,† score	Global autonomy
Mild	2–3	3–4	26–18	Independent living
Moderate	2	5	17–10	Supervision required
Severe	2–3	6–7	9–0	Total dependence

*Scale measures progressive need for assistance in daily activities (e.g., choosing clothes, dressing); scores range from 1–2 (normal) through 6–7 (severe dysfunction).[2]
†This 22-item scale measures cognitive function; scores range from 30 (excellent function) to 0 (severe dysfunction).[3]

scopolamine interfere with learning ability. In addition, cholinergic agonists have been found to facilitate learning,[10] which lends support to the important physiologic role of acetylcholine in attention and learning.

Management of Alzheimer's disease

Although the focus of this article is on the modern management of Alzheimer's disease with newer pharmacologic agents, it is crucial that physicians develop a global management strategy for their patients with Alzheimer's disease and their caregivers. Global management includes accurate diagnosis, education of the patient and caregiver, treatment of concomitant disorders such as depression and use of atypical neuroleptics when required.[11] Because comprehensive support and counselling programs have been shown to increase the length of time spouses or other caregivers are able to care for patients with Alzheimer's disease at home, a judicious combination of support programs from community and lay associations as well as pharmacotherapy with a cholinergic-enhancing drug is currently the best therapeutic approach for managing mild to moderate Alzheimer's disease. With this approach one can expect a stabilization of symptoms for a year or longer.[12]

Cholinesterase inhibitors

Among the different types of drugs that can modify cholinergic neurotransmission, the only class of drugs that have been effective so far for the symptomatic treatment of Alzheimer's disease are the cholinesterase inhibitors. These drugs act by slowing the biochemical breakdown of acetylcholine and thereby, at least theoretically, prolonging cholinergic neurotransmission. Of interest is that humans have 2 types of cholinesterase: acetyl and butyryl. The physiological role of butyrylcholinesterase is unknown, but levels of this enzyme have been shown to increase as Alzheimer's disease progresses, whereas levels of acetylcholinesterase decrease.[13] Both enzymes are found in neuritic plaques, and their inhibition with cholinesterase inhibitors may modify the deposition of beta-amyloid, a key component of the pathophysiology of Alzheimer's disease as we currently understand it. The clinical significance of this action, if any, in terms of slowing progression of the disease has yet to be established.

Among the different cholinesterase inhibitors, only donepezil, rivastigmine and galantamine have been shown to be efficacious and relatively safe. The randomized controlled trials supporting these claims have involved patients with mild to moderately severe Alzheimer's disease

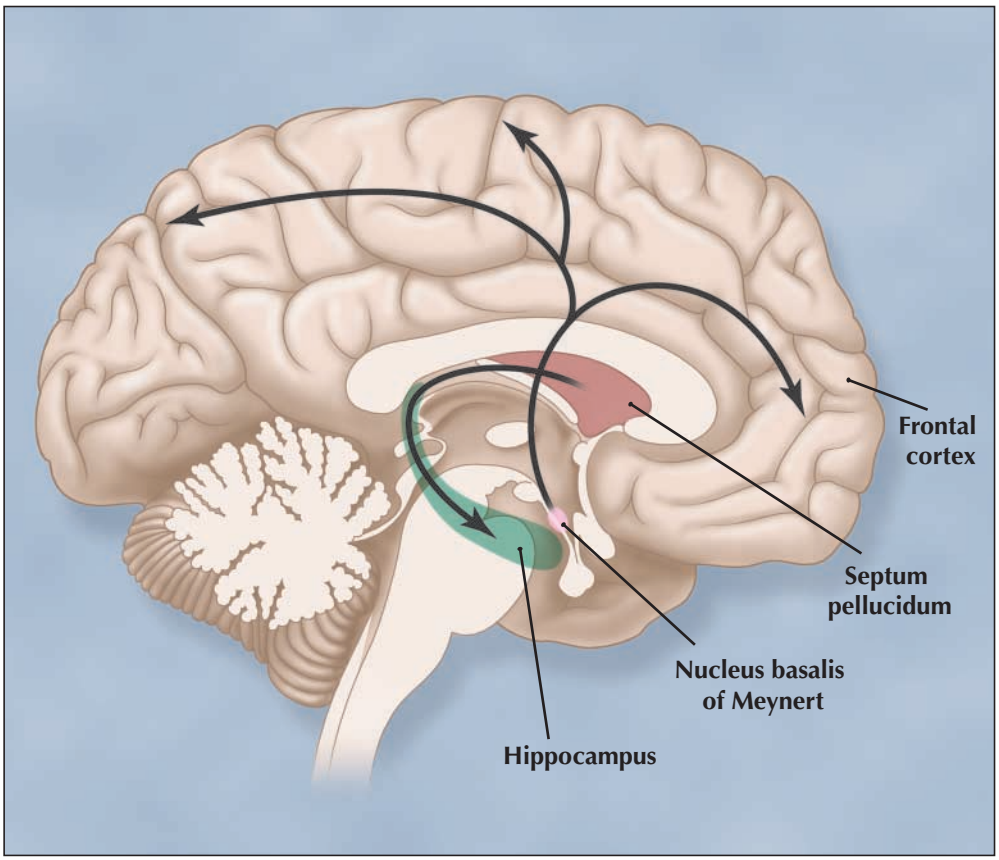

Fig. 2: Projections from the nucleus basalis of Meynert and other cholinergic cell groups in the septum pellucidum to the hippocampus and neocortex.

(MMSE scores of 5 to 26, or stages 3 to 6 on the Global Deterioration Scale). Characteristics of these agents appear in Tables 3 and 4.

Donepezil

Donepezil has been compared with placebo in 6 randomized controlled trials.[14–21] Both 5-mg and 10-mg doses of the drug were found to be effective in improving cognitive and global functioning after 6 months of treatment. When data were pooled across the studies, the higher dose appeared to be more effective.[22] One of the trials in which donepezil was given for 12 months showed sustained improvement in MMSE scores above baseline for 9 months, after which the scores declined steadily to below the starting point, parallel to the scores of patients given placebo.[19] In one trial, functional decline was shown to be slower in the group given 10 mg of donepezil than in the control group.[20] One study looked at the effects of treatment over 24 weeks in patients with moderate to severe Alzheimer's disease (MMSE scores of 5 to 17);[21] all outcomes improved, including the global impression of change ($p < 0.001$) (Fig. 3), behaviour (treatment difference between groups of 5.6 on the Neuropsychiatric Inventory, $p = 0.0083$) and activities of daily living (treatment difference between groups of 9.0 on the Disability Assessment for Dementia [Fig. 4], $p < 0.0001$, which is equivalent to what is lost over 18 months[23]). In randomized clinical trials in which the doses of donepezil were increased from 5 to 10 mg after 2 weeks, the proportion of patients with gastrointestinal side effects such as nausea ranged from 17% to 24%, and dropout rates related to adverse events such as autonomic side effects ranged from 8% to 18%.[15–17]

Rivastigmine

Rivastigmine has been evaluated in 2 randomized placebo-controlled trials.[24,25] In doses ranging from 3 to 6 mg twice daily, the drug had a statistically significant effect on cognitive function, global impression of change and activities of daily living. A dose-effect relation was also seen, with 3 mg twice daily being the minimally effective dose. At the higher doses, improvements in cognitive function, as measured with the cognitive subscale of the Alzheimer's Disease Assessment Scale, were as high as 4.9 ($p < 0.001$), in large part because of the cognitive decline observed in the placebo group. Four points on this scale are lost per 6 months in untreated patients. Gastrointestinal side effects were more frequent with rivastigmine than with donepezil, at least in the titration period.[26] In randomized clinical trials in which doses of rivastigmine were increased from 3 mg/d to 6, 9 and 12 mg/d every 2 weeks, the proportion of patients with gastrointestinal side effects ranged from 48% to 50%, and dropout rates related to adverse events ranged from 23% to 28%.[24,25] Thus, the use of rivastigmine requires good collaboration between patients, caregivers and clinicians to find the best tolerated and effective dose for each

Table 3: Pharmacokinetic characteristics of cholinesterase inhibitors available in Canada

Drug	Elimination half-life, h	Metabolized by cytochrome P450 enzymes	Protein binding, %	Oral bioavailability, %	Food interaction
Donepezil	70–80	Yes	96	100	No
Rivastigmine	0.6–2*	No	40	35	Yes
Galantamine	7–8	Yes	8	89	Yes

*Enzyme inhibition significantly outlasts elimination half-life.

Table 4: Frequency of side effects of cholinesterase inhibitors in studies using weekly titration

	Side effect; frequency (% drug / % placebo)*					
Drug	Nausea	Vomiting	Diarrhea	Dizziness	Insomnia	Muscle cramps
Donepezil[14–27]						
5 mg	1.2	1.0	2.3	1.4	1.7	3.3
10 mg	3.5	3.4	3.6	1.7	2.8	5.0
Rivastigmine[24,25]						
6–12 mg	4.7	7.4	1.5	2.4	NS	NS
Galantamine[27–29]						
16 mg	3.0	4.4	2.1	1.7	NS	NS
24 mg	3.2	5.0	1.1	2.1	NS	NS

Note: NS = not significant (less than 5% difference between treatment and placebo group).
*For example, patients given 5 mg of donepezil experienced nausea 1.2 times more often than those given placebo.

patient. Most neurologists recommend starting at a dose of 1.5 mg twice daily and then gradually increasing the dose every 4 weeks by 1.5 mg, to a maximum of 6 mg twice daily, if tolerated and if cognitive and global functioning continue to improve. The need for 2 daily doses of rivastigmine will usually require more supervision for patients living alone.

Galantamine

Three randomized controlled trials have compared galantamine with placebo.[27–29] The doses ranged from 4 to 16 mg twice daily. All studies showed improvements in global impression of change, cognitive function, activities of daily living and behaviour. For example, in a multinational study,[29] an analysis of observed cases showed a difference of 3.1 on the cognitive subscale of the Alzheimer's Disease Assessment Scale between the treatment group given 12 mg of galantamine twice daily and the placebo group and a difference of 4.1 between the group given 16 mg of the drug twice daily and the placebo group (Fig. 5). In the more rigorous intention-to-treat analysis, the difference in scores on the cognitive subscale was significant between the group given the maximal clinically recommended dose of 12 mg twice daily and the placebo group (2.9; $p < 0.001$), as was the difference in the global impression of change ($p < 0.05$). In another study galantamine was found to delay the emergence of neuropsychiatric symptoms in patients with mild to moderately severe Alzheimer's disease: after 5 months, patients in the treatment group had no new symptoms, whereas the symptoms of those in the placebo group worsened (the Neuropsychiatric Inventory score decreased by 2.0) ($p < 0.05$).[28] An open-label extension of this study showed that cognitive function and activities of daily living were preserved in patients treated for 12 months at a dose of 12 mg twice daily without interruption. As with the other 2 cholinesterase inhibitors, the main side effects of galantamine are gastrointestinal, particularly in the 2 days following each dose increase. In randomized clinical trials in which the dose of galantamine was increased from 8 to 24 mg/d every 2 weeks, the proportion of patients with gastrointestinal side effects ranged from 17% to 37%, and the dropout rates related to adverse events ranged from 10% to 23%.[27–29] Most neurologists prescribing galantamine start patients at a dose of 4 mg twice daily and increase the dose after 1 month to 8 mg twice daily. If there is a no clear benefit at that dose, it can be increased to 12 mg twice daily.

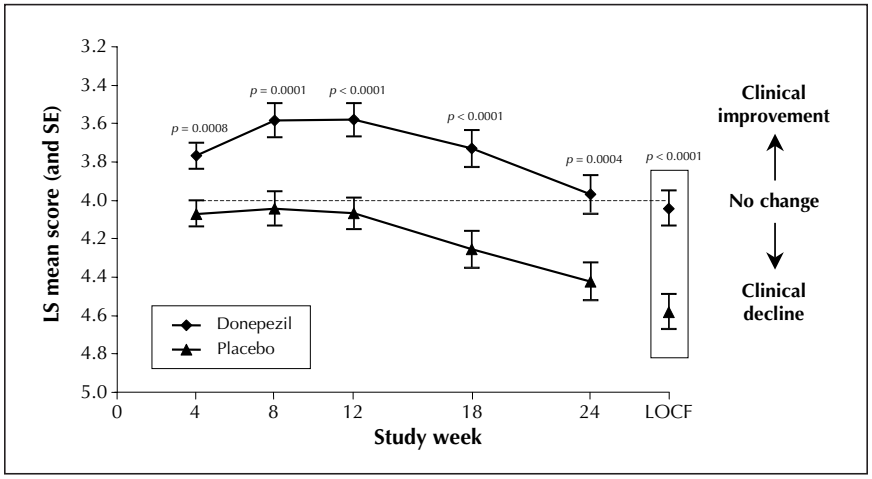

Fig. 3: Global impression of change. Clinician's interview-based impression, with caregiver input, of change in global function. Least squares (LS) mean change from baseline scores (and standard error [SE]) for donepezil- and placebo-treated patients through 24 weeks of treatment. LOCF = last observation carried forward. Reprinted, with permission, from Feldman et al.[21] Copyright © 2001 AAN Enterprises, Inc.

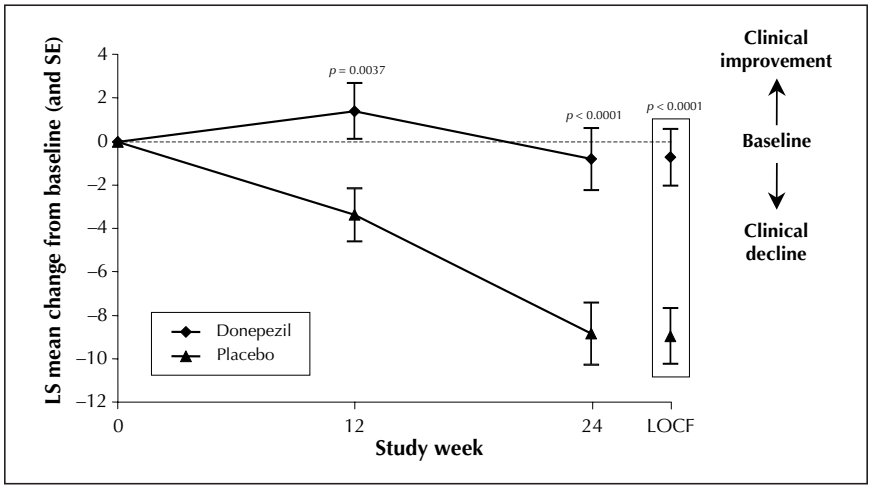

Fig. 4: Disability Assessment for Dementia. LS mean change from baseline scores (and SE) for donepezil- and placebo-treated patients through 24 weeks of treatment. Reprinted, with permission, from Feldman et al.[21] Copyright © 2001 AAN Enterprises, Inc.

Which cholinesterase inhibitor is best?

It is impossible to compare the efficacy of the 3 cholinesterase inhibitors because they have not been adequately studied in head-to-head trials. All 3 drugs appear to improve cognitive and global functioning, at least up to 6 months of therapy. The improvement in activities of daily living, shown for all 3 drugs, is best described as a slowing of

decline rather than an actual improvement in performing specific tasks. Improvements in neuropsychiatric symptoms, mainly a reversal of apathy and variable patterns of improvement in symptoms of anxiety, depression and hallucinations, were detectable, and the pattern of improvement appears to differ from that with atypical neuroleptics such as risperidone, olanzapine or quetiapine given to patients with Alzheimer's disease.[30] This pattern will require further characterization in placebo-controlled clinical trials.

It has been suggested that Alzheimer's disease progresses more rapidly in older patients with multiple comorbidity than in younger patients, in women than in men, and in patients possessing the apolipoprotein E genotype than in those without the genotype. Post-hoc analysis of data from several of the clinical drug trials showed that, after these factors were controlled for, the improvements seen with the cholinesterase inhibitors were not due to differences in the distribution of these factors in the treatment and placebo arms of the studies. Disease stage within the mild to moderate range also does not appear to be a factor. In other words, all patients with probable Alzheimer's disease in these earlier stages seem to have similar chances of improved functioning when given a cholinesterase inhibitor.

Side effects

The frequency of side effects may be another factor clinicians will use in selecting a cholinesterase inhibitor. Gastrointestinal side effects (nausea, vomiting, diarrhea and anorexia) are the most common. They are dose-related and generally transient. Their frequencies are summarized in Table 4.[26] Thin, small (weight below 45 kg) patients may be less able to tolerate these particular side effects. Cardiovascular side effects, mainly symptomatic bradycardia and syncope, are infrequent and appear to occur with all 3 drugs. Caution should be used if prescribing any of these cholinesterase inhibitors to patients with sick sinus syndrome or other supraventricular conduction defects. Syncope has occurred even in the absence of a prior history of cardiac disease and in the presence of normal electrocardiogram results. Muscle cramps can occur and result from cholinergic stimulation at the neuromuscular junction; they are dose-related and usually transient. Less common central side effects are insomnia (unique to donepezil when given at bed time) and worsening of depressive symptoms, which can be prevented by treating depression first with a selective serotonin reuptake inhibitor before initiating any cholinesterase therapy. Finally, it is important to remember that donepezil and galantamine are metabolized by P450 liver enzymes. Because this pathway is shared by other drugs, physicians should take the usual precautions when prescribing either of these 2 cholinesterase inhibitors.

Switching drugs

There is some preliminary evidence that, if a patient does not respond to one cholinesterase inhibitor, switching to another may be beneficial.[31] Switches can also be done to cope with side effects.[32] In general it is not difficult to switch from one drug to another among these 3 cholinesterase inhibitors. Recommendations for switching are shown in Table 5.[33]

Table 5: Recommendations for switching from one cholinesterase inhibitor to another

- No wash-out period is required before switching unless there are unresolved side effects from the first drug, in which case a wash-out period of 1 week or until symptoms resolve is recommended
- Standard dose escalation using monthly titration is recommended
- Efficacy and tolerability of the drug should be monitored on a monthly basis for the first 3 months
- Combination of cholinesterase inhibitors is not recommended

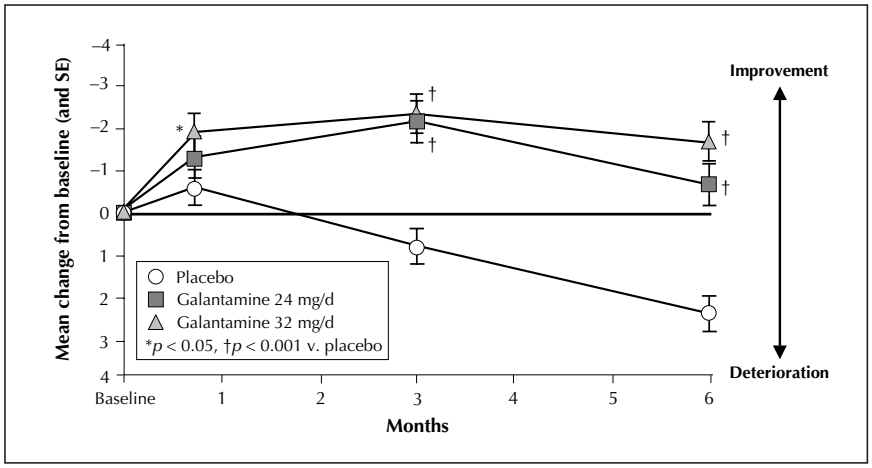

Fig. 5: Mean change from baseline scores (and SE) on cognitive subscale of Alzheimer's Disease Assessment Scale for galantamine- and placebo-treated patients over time. Reprinted, with permission, from Wilcock et al.[29] Copyright © 2000 BMJ Publishing Group.

Table 6: Testable hypotheses and potential therapies for delaying the progression of Alzheimer's disease

Hypothesis	Potential therapy	Mechanism of action
Excessive deposition of beta-amyloid fibrils	Gamma-secretase inhibitors	Increased amyloid metabolism by alpha-secretase and shift to nontoxic pathway
	Immunotherapy (amyloid "vaccine")	Breakdown of amyloid-containing plaques by antibodies to beta-amyloid
	Cholinesterase inhibitors	Inhibition of acetylcholinesterase and butyrylcholinesterase in neuritic plaques
	Alzhemed	Prevention of fibrillinogenesis and plaque formation
Excessive brain inflammation	NSAIDs	Suppression of microglial and complement activation
Insufficient brain plasticity due to mutation of apolipoprotein E	Statins	Induction of apolipoprotein E to compensate for lower cholesterol levels
	Neotrophin	Enhanced activity of nerve growth factor
Premature cell death	Vitamin E	Antioxidant protection
Systolic hypertension in middle age causing leukoaraiosis and stroke	Calcium-channel blockers	Control of blood pressure

The future of Alzheimer's disease therapy

Epidemiological and postmortem studies have established a number of testable hypotheses (Table 6).[34] The favourite study design currently is to give patients with mild cognitive impairment, known to carry a risk of conversion to Alzheimer's disease of 12% to 15% per year,[35] a cholinesterase inhibitor, vitamin E or a cyclooxygenase-2 inhibitor for 3 years. If these treatments delay the diagnosis of Alzheimer's disease, a great number of middle-aged and older people will be coming to our offices requesting assessment for their memory complaints and early therapy. Evidence-based guidelines will be needed for the diagnosis and treatment of mild cognitive impairment, as was done previously for mild to moderate Alzheimer's disease.[36] The Consortium of Canadian Centers for Clinical Cognitive Research (C5R) will be holding a consensus conference on mild cognitive impairment in 2003 to formulate guidelines.

Treatment for Mrs. S

Since there is loss of efficacy after 13 months of treatment with the first cholinesterase inhibitor, Mrs. S will likely prefer to switch to a second cholinesterase inhibitor. She is given the opportunity to join one of the disease stabilization studies using a combination design of stable-dose cholinesterase inhibitor for 3 or more months in addition to a disease-modifying agent or a placebo for 6–12 months. She joins a day program, and her spouse caregiver joins a support group of the Alzheimer Society of Canada. Their children express an interest in future preventive studies.

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