The term Mild Cognitive Impairment (MCI) brings to light the recent efforts of physicians to recognize the subtle classifications of normal and abnormal aging. While MCI clinical trials are currently underway, it will be years before their results are known. This article reviews the current status of symptomatic and preventive therapies available for managing MCI, and discusses their efficacy.

by Howard Chertkow, MD, FRCPC

Clinicians are becoming increasingly aware of the number of elderly individuals who fall into that borderzone between normality and dementia. While a number of terms have been applied to this group, by far the most common term used is Mild Cognitive Impairment (MCI). In 2003, an international working group agreed on general criteria for MCI: the subject was not judged to be normal or demented, the cognitive decline was reported by self and/or informant, there was impairment on objective cognitive tasks and there was evidence of decline over time on such tasks. In addition, there were preserved basic activities of daily living, or else minimal impairment only in complex instrumental functions.

While this article does not address the larger question of whether MCI is a clinical entity that deserves attention, (which has been addressed in a number of articles), it does address current therapies for individuals with MCI, and assess their efficacy.

Reasons to Treat MCI

The first question to ask is: why should we treat MCI? One answer is that the symptom of memory loss is upsetting to some patients. In other words, treatment may be symptomatic because of the individual’s concerns over memory loss in MCI. Notice that this level of concern varies from individual to individual. Many patients recruited into a recent MCI trial at our centre stated that they did not feel sick, were not bothered by their memory lapses, and did not require medication. A second reason to treat MCI is to prevent development of future dementia since MCI is a “high-risk” state for future dementia (see Figure 1). A third reason to treat MCI subjects is that in fact many of the individuals with MCI already have significant early Alzheimer’s disease (AD) pathology and with time the majority of members of any MCI cohort will progress to AD. In this sense we are not attempting treatment to prevent AD, so much as treating to modify and slow the disease at its earliest presentation.

While accepting the above, it must be emphasized that MCI is heterogeneous, and not all MCI individuals (at least in our experience and that of others) progress to AD. Therefore in some cases, one would be treating individuals to prevent progression, who would not in fact have progressed. Thus, the “risk:benefit” ratio for treating MCI differs from that of AD. The bar for acceptable medications must therefore be set higher. The question is not whether we should treat, but what should constitute current recommended therapy.

Cognitive Training and Stimulation

Let us first look at non-pharmacologic approaches. There are intriguing hints in the normal elderly that...
engagement in stimulating cognitive activities is associated with better memory and verbal abilities. Case control and longitudinal studies have shown that participation in intellectually stimulating and social activities in midlife was associated with reduced risk of developing AD. What about randomized controlled trials (RCTs) of cognitive stimulation? A number of studies have shown that memory training improved performance on targeted memory tasks and that the effect sizes for the training effects were in the moderate range and were sustained over a two-year follow-up. We do not know, however, if such interventions would in any way prevent or decrease dementia.

Several open and randomized controlled trials have been reported on the effect of cognitive training and intervention in MCI. These studies provide encouraging findings of benefit, but there are many questions remaining. The effort required to implement cognitive training on a large scale is not trivial, and before widespread recommendation of this therapy can occur, more replication studies are required with properly controlled RCT designs, larger sample sizes, and analyses that control for Type 1 error. Thus, the evidence at the present time is insufficient to conclude that organized cognitive intervention is beneficial in preventing progression in MCI or warrants prescription. On the other hand, given that there is little or no “down-side” to cognitive activity, it is reasonable for physicians and therapists to promote engagement in cognitive activity as part of an overall “healthy lifestyle” formulation for elderly individuals with and without memory loss.

**Physical Training**

The situation with physical training and exercise is quite similar. Several longitudinal cohort studies carried out in normal elderly individuals indicate that physical exercise is associated with reduced cognitive decline and reduced risk of dementia. However, there are also studies that failed to find a protective effect of physical exercise on cognitive decline and on incident dementia. Two recent meta-analyses have been published regarding the impact of physical exercise programs on the cognitive function of older adults. Both meta-analyses reported moderate effect sizes for the exercise training effect on global cognitive scores and executive control. There are important implications of such research in terms of potential public health measures to prevent dementia and cognitive decline. More studies are needed to assess the optimal exercise training modalities in older adults, particularly in terms of intensity and duration. No studies have been carried out specifically with MCI persons to assess the effect of physical training on their cognitive capacities and cognitive decline. Keeping this in mind, the Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia recommended that physicians and therapists may promote physical activity at an intensity level that is adapted to the persons’ overall physical capacities, as part of a “healthy lifestyle” for older individuals with and without memory loss.
Treatment of Exacerbating and Co-morbid Conditions

There are a series of other conditions that can exacerbate memory loss in MCI, or even produce MCI in an otherwise cognitively normal elderly individual. Attention to these factors is recommended, even in the absence of formal RCTs.

For instance, it is increasingly clear that stress, via cortisol levels, acts as a direct toxin on the hippocampus, capable of amplifying disease-related hippocampal dysfunction.28-30 Recent studies on emotional factors such as proneness to distress show this to be a significant risk factor for AD.31 Attempts to reduce stress levels in MCI seem a reasonable goal. Although there have not been direct clinical studies, untreated depression will exacerbate and amplify memory loss.35-39

An important study in the Kungsholmen district of Stockholm demonstrated that a poor or limited social network increased the risk of dementia by 60% and a significant gradient was found for increasing degrees of social connections. It appears that an extensive social network seems to protect against dementia.40 Clearly this requires a lifelong commitment to building social interactions, but this may be a modifiable risk, and social interaction can be encouraged in MCI individuals.

Also, patients with sleep disorders often present with memory loss, and this seems a reasonable factor to modify and control.32-34 Assessment and treatment of sleep apnea in MCI patients is recommended if there is a sleep complaint.

Symptomatic Therapy

There is no current treatment for MCI sufficiently substantiated to have obtained government approval from FDA or Canadian government regulators. This contrasts with the situation in Europe, where medications such as Ginkgo biloba and hydergine have been approved broadly for “memory impairment.” While some reviews have tended to be fairly positive about treatment effects,41 symptomatic therapy is generally found to be disappointing, although the occasional patient appears to have a significant improvement on each of the medications listed in Table 1.

Cholinesterase inhibitors. The three available cholinesterase inhibitors (CIs) in North America—donepezil, rivastigmine, and galantamine—are approved for treatment of mild to moderate AD, not MCI. These all produce modest improvement and stabilization in the majority of patients.42,43

Symptomatic treatment of the memory complaints in MCI with CIs is generally disappointing. Clinicians have anecdotally reported that certain MCI patients benefit from treatment with CIs in terms of memory and global function. Salloway et al studied 270 patients across 20 centres meeting criteria for amnestic MCI.45 Half were treated with donepezil 10 mg for six months and a series of cognitive and global tests were administered. Two thirds of the donepezil-treated cohort completed the study, and change in a paragraph recall test as well as the Clinical Global Impression of Change-MCI instrument were used as the primary outcome measures. Neither of these measures showed significant beneficial effects of therapy at the end of six months. However, a major secondary measure, the ADAS-Cog, did show a symptomatic benefit. Subjectively, patients treated with donepezil reported greater improvement in memory function than those given placebo. They reported feeling sharper mentally, more organized, and more confident of their memory. All of this suggests that at least some MCI individuals will have a significant clinical benefit from CIs, but overall the effects are mild. The recent
Canadian Consensus Conference on dementia therapy did not recommend CIs as therapy in MCI.27

**Ginkgo biloba.** At present, Ginkgo biloba is commonly prescribed in Europe for all memory-impaired patients, with the idea that it improves blood and oxygen flow to the brain and supports memory function, mental sharpness and circulation. There are few if any well-designed clinical trials that support this conclusion.46 There was one placebo-controlled study of Ginkgo biloba in AD, with a high dropout rate. This showed a significant symptomatic benefit in AD, albeit approximately a quarter of the efficacy of CIs.47 It is notable that in some countries such as Germany, Ginkgo biloba is routinely prescribed for AD because of its greater accessibility and lower cost to patients.

There is an ongoing long-term study testing the hypothesis that Ginkgo biloba, as an anti-oxidant, might prevent onset or slow progression of AD. Data are not yet available. The Canadian Consensus Conference concluded that there is currently fair evidence to recommend against the use of Ginkgo biloba therapy in MCI.

**Nootropics.** There are a number of over-the-counter “dietary supplements” which have been suggested to strengthen and protect neurons of the brain involved in memory, serving as “memory nutrients.” These “nootropics” have non-specific mechanisms of action, with putative effects on energy metabolism, cholinergic mechanisms, excitatory amino acid receptor-mediated functions, as well as hormonal mechanisms.49 In this class, one would list phosphatidyl-serine (PS), acetyl-l-carnitine and piracetam. These are available through health-food stores as diet supplements, not medications. Evidence of their efficacy is slim, but they have few if any side effects. Presumably, these nootropics would have symptomatic rather than preventive effects in MCI.

PS is obtained from cows and more recently a form derived from soy lecithin is being sold. A PS study from 1991 had subjects with mild memory loss, similar to MCI, taking PS 300 mg for three months. The subjects showed some modest improvement in their memory. The effects tended not to occur in everyone and there was no benefit in AD patients.50 There have been no serious studies of PS in the past ten years. Piracetam was tested in several studies in individuals who
may have had MCI. There was evidence of mild improvement in memory and attention.

Overall, despite lofty claims for dramatic effects of nootropics, (generally from those involved in marketing of these agents), the proven benefit of each of these agents is modest. One broad review stated in conclusion “All in all, we believe that the current data do not allow strong scientifically based recommendations for any of these memory nutrients (including PS and ginkgo). However, the data also do not allow us to conclude that these nutrients are ineffective in boosting memory.”

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Memory Stimulants and Future Smart Drugs

The media have been reporting the “imminent” arrival of medications that will impact the neurochemical processes of memory itself. Such medications have the potential to compensate for the neurochemical deterioration thought to be part of MCI and even AD, without changing or retarding the underlying pathological processes. The candidate drugs directed at improving memory fall into one of two categories: those that target the initial induction of long-term potentiation, and those that target the later stages of memory consolidation. Drug candidates include ampakines which are already beginning to enter Phase II clinical trials for MCI treatment. The efficacy and side-effect profiles of these cognitive enhancers are unknown. In the second category we find drugs aimed at increasing CREB (cyclic-AMP response element binding protein), the element-binding protein which in turn activates genes to produce proteins that strengthen the synapse in response to experience—the basis of long-term memory. A number of mechanisms are being explored that can impact on the CREB level. Human trials are still years away.

Prevention of AD by Intervention at the MCI Stage

The most critical interest from physicians, patients, and the pharmaceutical industry is in pharmacologic interventions that can be instituted at the MCI stage to prevent progression to dementia, specifically AD. Most readers will be aware that no such effective medication currently exists, has been substantiated by multiple or convincing randomized placebo-controlled clinical trials, or is available in pharmacies. There are nine kinds of potential prevention therapies that cannot currently be recommended (see Table 2). These each could theoretically delay or prevent progression to AD from the MCI state, but have failed to reach sufficient strength of evidence to be recommended. The theoretical arguments are based on understanding of AD pathophysiology or evidence from population studies. Studies testing most of these mechanisms are currently underway. It is important to point out, however, that retrospective observational studies are not the same as carefully controlled randomized intervention studies. This has been brought harshly to the forefront by the failure of a number of RCTs to confirm efficacy of interventions derived from epidemiologic studies. In these cases, either the population evidence was simply wrong, or the “critical period” for the pharmacologic intervention was missed, and MCI was simply too late a time to treat. We will mention only one of these, vitamin E, along with positive therapy recommendations for treating vascular risk factors, and perhaps suggesting dietary manipulations.

Should We Be Using Vitamin E and Anti-oxidants?

Vitamin E, an anti-oxidant, has had a roller-coaster profile as a medication to prevent dementia, and this highlights the challenges and difficulties
in deriving preventive therapies for a chronic disease like AD. The case for anti-oxidant therapy to prevent onset of AD (as well as other neurodegenerative diseases and aging in general) is relatively strong, and new evidence continues to accumulate, although none reach the level of recommendations for therapy. Oxidative damage can be found in a number of neurodegenerative conditions including AD. In a widely cited study of vitamin E in AD, patients taking high-dose vitamin E for up to 24 months reached the functional milestone of institutionalization more slowly than individuals on placebo. The treatment was regarded as safe; vitamin E was not associated with increased risk of death. Indeed, an identical number of subjects taking vitamin E died during the course of the trial compared to patients taking placebo. Based on this single study, and the theoretical benefits of anti-oxidants in preventing AD and cognitive decline as well as aging in general, a large number of AD and MCI subjects are currently prescribed vitamin E, or obtain it themselves from pharmacies.

The evidence for a benefit from vitamin E in preventing or delaying AD derives from a set of epidemiologic studies. In contrast to this is new evidence from the large “Memory Impairment Study,” in which individuals with MCI were recruited and randomized into a vitamin E therapy arm, a donepezil therapy arm, or a placebo arm. The crucial primary endpoint was the number of subjects classified as progressing to dementia at the end of three years. This study assessed the effects of five daily capsules of vitamin E (2000 IU) and

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Table 2
Non-recommended Therapies Aimed at Preventing Progression from MCI to AD

<table>
<thead>
<tr>
<th>Class</th>
<th>Name of medications</th>
<th>Mechanism of action</th>
<th>Evidence for use</th>
<th>Negative trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>Vitamin E</td>
<td>Reduces oxidative stress</td>
<td>Population studies [61-63], RCT [60] Meta-analyses [64,65]</td>
<td></td>
</tr>
<tr>
<td>Alternative anti-oxidants</td>
<td>Vitamins A, C, Gingko biloba</td>
<td>Reduce oxidative stress</td>
<td>As above, also [81] RCT [64]</td>
<td></td>
</tr>
<tr>
<td>Vitamins B complex</td>
<td>Vitamins B6, B12, folic acid</td>
<td>Reduce homocysteine levels</td>
<td>Framingham Study [77]</td>
<td>No RCTs as yet</td>
</tr>
<tr>
<td>Omega fatty acids</td>
<td>Docosahexaenoic acid (DHA)</td>
<td>Role in neuronal communication</td>
<td>Observational studies</td>
<td>No RCTs as yet</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>Donepezil, rivastigmine, galantamine</td>
<td>Increase synaptic acetylcholine availability</td>
<td>Memory Impairment Study [64] (for ApoE4 carriers)</td>
<td>RCTs [64],[66]</td>
</tr>
<tr>
<td>Anti-inflammatory agents</td>
<td>Ibuprofen, indomethacin, prednisone</td>
<td>Reduce inflammatory response</td>
<td>Observation study [82]</td>
<td>RCT [83]</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Estradiol, raloxifene</td>
<td>Multiple mechanisms of action</td>
<td>Observation studies [84,85], RCT [86] RCTs: WHIMS [87,88] Nurses Health Study [89]</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>Atorvastatin, five others</td>
<td>Block liver enzyme essential for cholesterol production</td>
<td>Observational studies [90, 91], RCT [92] No RCTs in MCI as yet</td>
<td></td>
</tr>
<tr>
<td>Anti-amyloid therapy</td>
<td>GAG-mimetics, immunotherapy</td>
<td>Prevents production (immunotherapy) or aggregation (GAG-mimetics) of A-beta amyloid fragments</td>
<td>Promising RCTs [93,94], but immunotherapy complications (encephalitis) No RCTs in MCI as yet</td>
<td></td>
</tr>
</tbody>
</table>
found no overall benefit in the vitamin E group in terms of prevention of progression to AD at the end of three years.64

Furthermore, a recent meta-analysis raised questions about the safety of vitamin E when given at such a high dose. Miller et al examined the number of deaths in 19 clinical trials of vitamin E, including a total of 136,000 subjects.65 None of the individual studies showed an increase in risk of death for subjects taking vitamin E alone. However, when the studies were arranged by dose of vitamin E (above or below the 400 IU/day median dose), it appeared that individuals taking low to moderate doses of vitamin E had a very slight protection against death while those taking high-dose vitamin E were at a very slightly higher risk of death. There are, however, numerous methodological weaknesses in this study.

Despite the meta-analysis, the risk of vitamin E also appears minimal. Might a single 400 IU vitamin E tablet be beneficially and safely prescribed for an MCI individual? They receive this in my own clinic, albeit with some hesitation. The recent Canadian Consensus Conference concluded that there is currently fair evidence to recommend against the use of vitamin E therapy in MCI.

**Can Cholinesterase Inhibitors Slow and Prevent AD?**

The “Memory Impairment Study” described earlier was an important three-year trial co-sponsored by the National Institute of Aging (NIA), the Alzheimer Disease Cooperative Study group (ADCS), and Pfizer. In this study, individuals with MCI were recruited and randomized into a vitamin E arm (2000 IU daily), a donepezil arm (10 mg daily), or a placebo arm. The crucial primary endpoint was the number of subjects classified as progressing to dementia at the end of three years. The result was negative—no significant differences between the three groups were found at three years.64 This disappointing result seems to put to rest the possibility of CIs as effective therapies to prevent AD, but there are sub-analyses that seem still to offer promise. For instance, it is clear that the group of individuals taking donepezil performed better than the others over the first 18 months, in terms of neuropsychological measures and global outcomes. It is also clear that the majority of individuals progressing to AD had an Apo-E4 allele, and if the analysis is restricted only to those individuals, there were indeed less “conversions to dementia” with donepezil at the end of three years. Currently, debate rages on whether this “negative study” might be reinterpreted as a positive result for a particular subgroup of patients. There are also the usual methodological concerns (heterogeneity of patients, weak outcome measure) that make it hard to achieve significant results even with large numbers of subjects.

The other main CIs are also being assessed for their potential to slow progression to AD. The galantamine trial was a two-year study focusing on amnestic MCI patients with memory below a cutoff on paragraph recall. There was no difference in the primary analysis of conversion from amnestic MCI to AD. There did appear to be a reduced rate of whole-brain atrophy in the patients treated with galantamine.66 However, therapy with this medication was associated with a small but statistically significant increased risk of dying. The sponsoring company discontinued the trial and has not recommended therapy for MCI with galantamine.67

The bottom line is that from the current evidence, if there is a benefit of CIs in slowing progression to AD, it appears to be transient as well as limited.68

There are nine kinds of potential prevention therapies that cannot currently be recommended. These each could theoretically delay or prevent progression to AD from the MCI state, but have failed to reach sufficient strength of evidence to be recommended.
Therapy for Vascular Risk Factors
It is clear that vascular damage impacts on the occurrence of AD and mixed dementia. Risks for vascular disease (diabetes, hypertension, smoking, obesity, hyperlipidemia) are being proven to be risk factors for the development of dementia. In the Rotterdam Study in the Netherlands, individuals with diabetes had nearly double the risk of dementia. Presumably, the microvascular damage from diabetes is the culprit, although it is possible that higher-than-normal levels of glucose in the blood might be toxic. The Framingham Heart Study demonstrated an impact of hypertension on cognition six years later. The Cardiovascular Health Study showed that cognitive decline occurred even without frank stroke in individuals with vascular risk factors.

These data give us additional approaches to therapy of MCI, namely aggressively treating vascular risk factors. Several randomized controlled studies of antihypertensives after stroke have shown a clear effect in reducing the subsequent incidence of dementia. One clinical trial evaluated the role of hypertension treatment in individuals with mild cognitive deficits broadly defined as a Mini-Mental Status Examination score between 20 and 28. Patients with the best response to treatment, in terms of reduction of their diastolic blood pressure, significantly improved on two cognitive tests. Note that this therapy is unproven in the sense that no one has yet mounted a long-term study proving that intervention at the MCI stage will be effective in reducing or preventing dementia or AD. However, treating these risks makes sense in its own right—a patient with uncontrolled hypertension should be treated anytime. Thus, in recommendations to family physicians, those working to prevent AD are now giving strong advice to “do what you already do”—namely, aggressively treat any risk factors for vascular disease, in a patient with MCI. The risk of dementia thus represents an additional reason to treat the patient.

The MCI Diet
Given the factors identified above, it is interesting to note that dietary interventions are possible in the treatment of MCI or prevention of dementia. A healthy diet helps prevent hypertension (via reduced saturated fats and sodium), prediabetes (reduce sweets and caloric intake and consume more fibre), and stroke (dietary change to reduce cholesterol). Obesity is to be avoided by dietary limitation and exercise. One study reported a higher risk of AD in seniors who ate more saturated and trans fat and less unsaturated fat, but another study did not find the same link.

Analysis of the Framingham study produced the somewhat surprising result that higher homocysteine levels were associated with increased risk of sporadic AD. It is known that increased serum homocysteine is associated with histopathologic evidence of vascular endothelial injury, vascular smooth muscle proliferation, and progressive arterial stenosis. The factors in homocysteine levels are well known—vitamin supplements (folate, B6, B12) lower the levels, while caffeine, smoking, and lack of exercise increase levels. Current management of elevated homocysteine has been to increase folate in the diet or treat with supplements when increased homocysteine was greater than 15 µmol/L. Simple treatment with folate (3 mg daily), B6 (25 mg daily), and B12 (250 to 500 µg daily) keeps the homocysteine level low. Homocysteine levels (high or even normal) can in theory be reduced by a good intake of folic acid, B6, and B12 found in green leafy vegetables. Several multi-vitamins a day will also supply these amounts.

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Omega fatty acids, particularly DHA (docosahexaenoic acid), can be obtained by eating cold-water fatty fish such as salmon, sardines, mackerel, and bluefish. There is evidence that individuals whose diets are high in omega-3 fatty acids, especially DHA, have a 50% reduction in their risk of developing dementia.\textsuperscript{79,80} Some doctors are now recommending that MCI patients eat such fish (or take two 200 mg DHA capsules) three times weekly.\textsuperscript{79,80} This therapy also did not receive recommendation from the Canadian Consensus Conference on dementia, however. About 180 mg of DHA daily intake is suggested and this amount can be achieved by eating the fish previously mentioned about three times per week. Thus, there is a theoretical basis for considerable dietary manipulation in MCI, none yet supported by RCTs.

**Thus, in recommendations to family physicians, those working to prevent AD are now giving strong advice to “do what you already do”—namely, aggressively treat any risk factors for vascular disease, in a patient with MCI.**

Given the lack of clear prognostic markers, heterogeneity in the natural history of MCI individuals, and lack of proven therapies to prevent decline, the management of MCI patients remains largely non-specific. The strongest evidence supports suggestions to “maintain a healthy lifestyle” with adequate exercise, avoidance of obesity, mental and physical stimulation, control of stress, treatment of medical illnesses and depression, and control of vascular risk factors such as diabetes, hypotension, and hypercholesterolemia.

Currently we lack proven pharmacologic approaches to prevent cognitive decline or progression from MCI to dementia. It makes good sense to aggressively treat vascular risk factors in MCI individuals using lifestyle interventions, diet and medications when necessary. Pharmacologic treatment of depression is also indicated. Drugs with known anticholinergic activity, as well as sleeping pills and sedatives, should be avoided.

Physicians should inform patients that there is no current specific treatment for MCI sufficiently substantiated to have obtained government approval. Treating MCI individuals (or the healthy elderly) in order to prevent subsequent AD using CIs, anti-inflammatory agents, estrogen, statins, various antioxidants or even vitamin E, represents prescription beyond proven therapies. It is advisable to refer the eager MCI patient to a research clinic where RCTs of these and other preventive medications are currently underway.

The Memory Impairment Study raises significant therapeutic issues. Since there was a delay in progression to AD in MCI individuals with a positive ApoE4 perhaps “a discussion of therapy” with donepezil is warranted. But what discussion? Should MCI patients be offered genetic testing with ApoE prior to a therapy decision? Should donepezil be offered with the hope that the symptomatic benefit will make up for our uncertainty regarding its long-term prevention role? Should its role in MCI (and the role of CIs in general) be downplayed as a major part of our therapeutic armamentarium, rather than using them up at the MCI stage?

In our own clinic, we have exploited the dietary possibilities noted above as a way to maximize the potential beneficial effects of anti-oxidants and omega fatty acids, and to control homocysteine levels. Our patients generally are encouraged to take one or two multivitamins daily, which deliver adequate doses of vitamin E (400 IU), along with B6 and folate supplementation. This is really all they are offered at the current time. The rest remains in the realm of current research and future possibilities.


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88. Wolozin B, Kellman W, Rousseau P, et al. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyl-


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