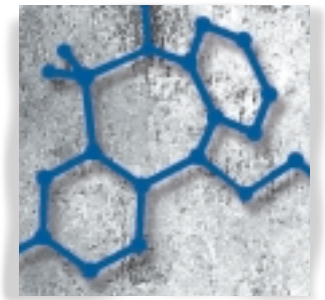
Pharmacotherapy of mild cognitive impairment

Serge Gauthier, MD, FRCPC



Amnestic mild cognitive impairment (MCI) can be considered as a state with a high risk of developing Alzheimer's disease within 5 years, or as a prodromal stage of this condition. Randomized clinical trials comparing the acetylcholinesterase inhibitor donepezil with placebo have shown some symptomatic benefit on (i) cognition in one short-term (6-month) study; and (ii) conversion to dementia in one long-term (3-year) study, but not for the full duration of the study, except in subjects with the apolipoprotein E4 (APOE-4) mutation, in whom the benefit was sustained throughout the 3 years. Results from studies on galantamine are still being analyzed; and a rivastigmine study will close in the fall of 2004. It is premature to recommend that acetylcholinesterase inhibitors be used systematically in amnestic MCI. However, important lessons have been learned from studies in this prodromal stage of AD, allowing the testing of hypotheses for disease modification.

Dialogues Clin Neurosci. 2004;6:391-395.

Keywords: *mild cognitive impairment; amnestic subtype; clinical trial; acetylcholinesterase inhibitor*

Author affiliations: Director, Alzheimer Disease Research Unit, McGill Centre for Studies in Aging, Montreal, Canada

Address for correspondence: McGill Centre for Studies in Aging, 6825 LaSalle Blvd, Verdun (Montreal), Quebec, Canada H4H 1R3
(e-mail: serge.gauthier@mcgill.ca)

There is great interest in mild cognitive impairment (MCI) as an intermediate state between normal aging and dementia. In its broadest sense, the term MCI encompasses a number of causes of cognitive decline, each with their own symptomatic treatment *(Table I)*. This list is not exhaustive, but includes the most common causes of consultation in memory clinics for cognitive decline over age 50: MCI of dysthymic, vascular, and amnestic etiologies.[1] This article will focus on the pharmacotherapy of the amnestic type of MCI because of the associated high risk of conversion to Alzheimer's disease (AD) and the availability of randomized clinical trials (RCTs) studying the safety and efficacy of a number of medications, over periods ranging from 6 months to 4 years.

What is amnestic MCI?

Amnestic MCI was defined by Petersen et al[2] in the context of a natural observation study, which demonstrated a rate of conversion to AD that was well above the incidence of age-matched populations. The original amnestic MCI criteria are as follows[2]:

- Memory complaint, preferably corroborated by an informant.
- Memory impairment relative to age- and education-matched normal subjects.
- Relatively normal general cognitive function.
- Largely intact activities of daily living (ADL).
- Not demented.

A more recent subclassification of MCI has been proposed by Petersen[3] on the basis of findings from cognitive testing in larger number of subjects:

- Amnestic or single-memory MCI.
- Multiple-domain MCI.
- Single non–memory-domain MCI.

The first two groups (single-memory MCI and multiple-domain [including memory] MCI) seem to share the

Selected abbreviations and acronyms

AChEI	*acetylcholinesterase inhibitor*
AD	*Alzheimer's disease*
ADAS-cog	*Alzheimer Disease Assessment Scale–Cognitive Component*
ADL	*activities of daily living*
CDR	*clinical dementia rating*
CGIC	*Clinical Global Impression of Change*
InDDEx	*Investigation in the Delay to Diagnosis of AD with Exelon (rivastigmine)*
MCI	*mild cognitive impairment*
MIS	*Memory Impairment Study*
PGA	*patient global assessment*
RCT	*randomized clinical trial*

same risk of conversion to AD, whereas the third group (single non–memory-domain MCI) may be a prodrome to the nonAD dementias.

For the purpose of RCTs, operational criteria with specific inclusion/exclusion criteria have been specified. The criteria for the study completed by the Alzheimer Disease Cooperative Study comparing donepezil with tocopherol and placebo[4] are listed in *Table II*; this study will be referred to in this monograph as the Memory Impairment Study (MIS). Although not fully analyzed and published, entry criteria for the twin studies (with and without magnetic resonance imaging [MRI]) comparing galantamine and placebo are available[5] and are summarized in *Table III*. The Investigation into the Delay to Diagnosis of AD with Exelon (rivastigmine) (InDDEx) study is not yet completed, but the entry criteria of this 4-year RCT comparing rivastigmine with placebo have been published.[6] These are listed in *Table IV* for purposes of comparison between the MIS, the galantamine studies, and the InDDEx study.

Etiology	Symptomatic treatment
Amnestic	Cholinesterase inhibitors? Cognitive training?
Cerebrovascular	Control of vascular risk factors
Dysthymic	Antidepressants; psychotherapy
Hypothyroidism	Thyroid supplementation
Substance abuse	Abstinence; psychotherapy

Table I. Causes of mild cognitive impairment.
Modified from reference 1: Gauthier S, Touchon J. Subclassification of mild cognitive impairment in research and in clinical practice. In: Gauthier S, Scheltens P, Cummings JL, eds. *Alzheimer's Disease and Related Disorders*. London, UK: Martin Dunitz; 2004:61-79. Copyright © 2004. Martin Dunitz.

Hypothesis leading to RCTs for amnestic MCI

The fact that most patients with amnestic MCI convert to AD led to the hypothesis that they were suffering from a reduction in cholinergic activity, which is the basis for the so-called "cholinergic hypothesis of AD," at least in terms of its mainline symptomatic therapy. On the other hand, observations made by DeKosky et al[7] of increased choline acetyltransferase activity in the superior frontal cortex and hippocampus of subjects with MCI compared with controls and with subjects with mild AD suggested that a cholinergic deficit in amnestic MCI may not be as prominent as was initially postulated. The safety and efficacy of the acetylcholinesterase inhibitors (AChEIs) donepezil, galantamine, and rivastigmine have been studied extensively versus placebo in amnestic MCI . To date, results are available from a short-term (6-month) symp-

- Memory complaint, corroborated by an informant
- Abnormal memory function, documented by delayed recall of one paragraph from the Logical Memory III subtest of the Wechsler Memory Scale–Revised, adjusted for age and education
- Normal general cognitive function as determined by a clinician's judgment based on the CDR and MMSE
- No or minimal impairment in ADL
- Not clinically demented
- Age 55 to 90 years
- In good general health with no significant cerebral vascular disease, with Hachinski Ischemic Score ≤4
- Not depressed, with a Hamilton Depression Rating Scale score ≤12
- CT or MRI without infection, infarction, or focal lesions
- CDR global score 0.5, with ≥0.5 in the memory domain

Table II. Entry criteria into the Alzheimer Disease Cooperative Study (here referred to as the Memory Impairment Study [MIS]). ADL, activities of daily living; CDR, Clinical Dementia Rating; MMSE, Mini-Mental-State Examination; CT, computed tomography; MRI, magnetic resonance imaging.
Modified from reference 4: Grundman M, Petersen RC, Ferris SH, et al. Mild cognitive impairment can be distinguished from Alzheimer's disease and normal aging for clinical trials. *Arch Neurol*. 2004;61:59-66. Copyright © 2004. American Medical Association.

tomatic study with donepezil and long-term studies with galantamine and donepezil.

Etiological approaches to AD include anti-inflammatory drugs and it was logical to test cyclooxygenase-2 (COX-2)–selective inhibitors, such as refecoxib. Unfortunately, there have only been negative results reported from such studies and so these agents will not be discussed further in this monograph. Non–transmitter-specific drugs, such as piracetam, have also been tested, with negative results and will not be discussed further.

Trial designs and outcomes to test symptomatic benefit in amnestic MCI

There has been much interest in the short-term benefit of drugs in amnestic MCI, with particular attention to cognitive outcomes. A 6-month study comparing donepezil with placebo was performed using parallel groups, with the Alzheimer's Disease Assessment Scale–Cognitive Component (ADAS-cog)[8] and a Clinical Global Impression of Change modified for MCI (CGIC-MCI) as primary outcomes; secondary outcomes included the New York University (NYU) Paragraph test, Digit Span Backwards test, Symbol Digit Modalities test, and a Patient Global Assessment (PGA).[9]

Trial design and outcomes to test delay in conversion from amnestic MCI to AD

The possibility of delaying conversion from amnestic MCI to AD has attracted a lot of interest since it offers good face validity. Designs have included parallel groups with conversion to AD as a primary end point. This conversion has been defined operationally in different ways, ranging from a clinical opinion to a change in the Clinical Dementia Rating (CDR) scale Global Score from 0.5 to 1. Conversion committees were asked to monitor conversions taking place in the different RCTs and to analyze the key factors leading to conversion. This information will be very useful to design future RCTs and also for practicing clinicians who want reassurance in the very early diagnosis of AD, when ADL changes are minimal. Secondary outcomes in these studies include a number of cognitive, ADL, and global outcomes.

Results of symptomatic studies

The 6-month donepezil RCT has shown a statistically significant but small improvement in ADAS-cog, driven by the ADAS-cog Immediate Word Recall test. In the fully evaluable population, scores on the NYU Paragraph Immediate and Delayed Recall tests as well as the Digit Span Backwards test were significantly better in the donepezil group.[9] The CGIC measured by the clinician failed to detect a difference, but the self-rated impression of change from the subjects (PGA) showed a highly statistically significant difference between donepezil and placebo. Side effects were predominantly gastrointestinal (diarrhea, nausea, and vomiting) and nocturnal (abnormal dreams) at a higher frequency than patients with AD at a similar dose of 10 mg at bedtime.[10]

Results of conversion studies

The 2-year galantamine studies showed no difference in the primary analysis of conversion from amnestic MCI to AD.[11] Analysis of secondary outcomes is under way, but it is apparent that a reduced rate of whole-brain atrophy has been found in patients treated with galantamine.[12]

- Cognitive decline of gradual onset and slow progression
- Abnormal memory function, documented by a Delayed Recall Score ≤10 on the NYU Paragraph Recall test
- Insufficient impairment on ADL to warrant a diagnosis of dementia
- Age 50 or older
- CDR global score 0.5, with ≥0.5 in the memory domain

Table III. Entry criteria in the galantamine studies. ADL, activities of daily living; CDR, Clinical Dementia Rating; NYU, New York University.
Modified from reference 5: Gold M, Wang D, Truyen L. Galantamine for the treatment of mild cognitive impairment: 2 double-blind, placebo-controlled studies. Paper presented at: 11th Congress of the International Psychogeriatric Association; August 17-22, 2003; Chicago, Ill.

- Memory complaints
- Abnormal memory function, documented by the NYU Delayed Paragraph Recall with a cutoff inclusion <9
- Not clinically demented
- Ages 55 to 85 years
- Not depressed, with a Hamilton Depression Rating Scale score <13, with Item 1 (depressed mood) score ≤1
- CDR global score 0.5

Table IV. Entry criteria in the Investigation in the Delay to Diagnosis of AD with Exelon (InDDEx) study. CDR, Clinical Dementia Rating; NYU, New York University.
Modified from reference 6: Feldman H, Scheltens P, Scarpini E, et al. Behavioral symptoms in mild cognitive impairment. *Neurology*. 2004;62: 1199-1201. Copyright © 2004. Lippincott, Williams and Wilkins.

Baseline demographics of the 3-year MIS have been reported[4] and are listed in *Table V*. An annual conversion rate of the order of 13% was reached with this amnestic MCI population, which most investigators would consider as prodromal AD.[13]

Results of the primary analysis of MIS have been presented at the 9th International Conference on Alzheimer's Disease and Related Disorders: there was no difference in the primary analysis of conversion from amnestic MCI to AD after 3 years.[14] Analysis of secondary outcomes is under way, and it is already apparent that there is a statistically significant delay of conversion between subjects treated with donepezil and placebo at 6, 12, and 18 months into the study, with the conversion curves overlapping at 24, 30, and 36 months. Patients carrying the apolipoprotein E4 (*APOE-4*) mutation were at a much higher risk of converting to AD and had a statistically significant protective effect from conversion on treatment with donepezil from month 6 until month 36.

The results of the 4-year rivastigmine study should be available early 2005.

Tolerability of AChEI in long-term amnestic MCI appears to be similar to patients with AD in terms of a predominance of gastrointestinal transient side effects. Their incidence and severity are slightly higher than in AD and lead to a higher rate of discontinuation, particularly in the first year of treatment.

Lessons so far

Although not all the data are in and not all subanalyses on the available data have been performed, it is apparent that the AChEI class does not delay the conversion from amnestic MCI to AD beyond 18 months. This suggests that the AChEIs have a symptomatic and potentially clinically significant effect, but one that is transient. This is congruent with the AD2000 study, which demonstrated a sustained benefit of donepezil on cognition using the Mini-Mental-State Examination (MMSE) and an ADL measure over 2 years.[15]

In terms of safety, the gastrointestinal side effects of AChEIs appear to be more prominent in MCI than in AD, and lower doses may be preferred in both RCTs and clinical practice.

Earlier diagnosis of AD has been facilitated by research on amnestic MCI. More patients presenting because of memory complaints will get a full assessment, seeking reversible causes, concomitant disorders, and risk factors, all of which are amenable to treatment. AChEIs will be one option for treatment, most likely at lower doses than are usual in AD. This option should not be recommended at this stage of our knowledge, but should not be denied for people who ask for it. It is premature to recommend that subjects with amnestic MCI be screened for *APOE-4* genotype and only those with the *APOE-4* mutation be treated, but genotyping must be done at entry into RCTs for MCI because of its strong effect on conversion rate; in other words, we must stratify for *APOE-4* alleles between treatment arms.

The future

It is still early days in the analysis of what has been achieved with AChEIs and noncholinergic drugs in amnestic MCI. Already, RCT protocols are being created for other classes of drugs with (i) potential cognitive effects demonstrable in short-term 6-month studies; and (ii) potential effects delaying conversion to AD over 3 years. Placebo-controlled studies are not an issue in amnestic MCI, in contrast to mild-to-moderate AD. The prodromal stage of AD may be the most promising stage to test the efficacy and safety of disease-modifying drugs, when the neurons are still salvageable. ❑

MMSE score	27.3±1.9
Immediate paragraph recall score	6.3±3.1
Delayed paragraph recall score	3.3±2.5
CDR global score	0.5±0
CDR sum of boxes	1.8±0.8
• Memory score	0.6±0.2
• Orientation score	0.3±0.3
• Judgment score	0.4±0.2
• Community affairs score	0.2±0.3
• Hobbies score	0.3±0.3
• Personal care score	0±0.1
Hamilton Depression Scale score	2.7±2.8
Hachinski score	0.5±0.7
Global Deterioration Scale	2.7±0.6
ADCS MCI-ADL score	45.9±5.1

Table V. Baseline characteristics of the Memory Impairment Study (MIS). Values are means±SD. CDR, Clinical Dementia Rating; MMSE, Mini-Mental-State Examination; ADCS, Alzheimer Disease Cooperative Study; MCI, mild cognitive impairment; ADL, activities of daily living. Reproduced from reference 4: Grundman M, Petersen RC, Ferris SH, et al. Mild cognitive impairment can be distinguished from Alzheimer's disease and normal aging for clinical trials. *Arch Neurol*. 2004;61:59-66.

Farmacoterapia del deterioro cognitivo leve

*El deterioro cognitivo leve con amnesia puede considerarse como un estado con un alto riesgo de desarrollar la enfermedad de Alzheimer dentro de cinco años, o como una etapa prodrómica de esta enfermedad. Ensayos clínicos aleatorios que comparan el donepezilo, inhibidor de la acetilcolinesterasa, con placebo han mostrado beneficios para algunos síntomas: (a) de tipo cognitivo en un estudio a corto plazo (6 meses) y (b) en la conversión a demencia en un estudio a largo plazo (3 años), pero no para la duración completa del estudio, excepto en sujetos con la mutación del gen de la apolipoproteína E4 (*APOE-4*), en quienes el beneficio se mantuvo a lo largo de los tres años. Aun se están analizando los resultados de estudios con galantamina y de uno con rivastigmina que terminará en el otoño de 2004. Es prematuro recomendar el empleo sistemático de inhibidores de la acetilcolinesterasa en el deterioro cognitivo leve con amnesia. Sin embargo, se han aprendido importantes lecciones de estos estudios en esta etapa prodrómica de la enfermedad de Alzheimer, las que han permitido el análisis de hipótesis para la modificación de la enfermedad.*

Pharmacothérapie du déficit cognitif léger (MCI)

*Le déficit cognitif léger (*Mild Cognitive Impairment, *MCI) avec amnésie peut être considéré comme un état à risque élevé de développement d'une maladie d'Alzheimer (MA) dans les 5 ans, ou comme une phase prodromique de cette pathologie. Des essais cliniques randomisés comparant le donépézil, inhibiteur de l'acétylcholinestérase, à un placebo ont montré un certain bénéfice symptomatique sur : (1) la cognition dans une étude à court terme (6 mois) ; et (2) la transformation en démence dans une étude à long terme (3 ans), mais pas pour toute la durée de l'étude, sauf pour les sujets présentant la mutation de l'apolipoprotéine E4 (*APOE-4*), chez lesquels le bénéfice était maintenu pendant les 3 ans. Des résultats d'études sur la galantamine sont en cours d'analyse, et une étude sur la rivastigmine s'achèvera en automne 2004. Il est prématuré de recommander l'utilisation systématique des inhibiteurs de l'acétylcholinestérase dans le MCI avec amnésie. Cependant, des leçons importantes ont été tirées des études sur ce stade prodromique de la MA, permettant d'évaluer des hypothèses pour modifier la maladie.*

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