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Dementia (E McDade, Section Editor)

Treatment of Mild Cognitive Impairment

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Opinion statement

It is increasingly evident that early identification of cognitive impairment in older adults presents opportunities for interventions that aim to mitigate the impact of cognitive symptoms on daily function and that attempt to delay (or ultimately prevent) progression from mild cognitive impairment (MCI) to dementia. To date, no intervention has proven protective in ultimately preventing conversion to dementia. However, several lifestyle, dietary, and pharmacologic interventions have suggested symptomatic benefit for those having MCI. A number of diet and lifestyle recommendations have been associated with decreased risk of dementia both in cognitively intact older adults and in those having mild cognitive impairment. Thus, these recommendations may be appropriate for both people presenting with subjective cognitive concerns and for those having objective evidence of memory problems. It remains less certain whether adopting these lifestyle habits in later life confers the benefits seen in epidemiological cohorts (where people have likely practiced them for many years). Discussion of starting on a cholinesterase inhibitor is appropriate for those having MCI, particularly those in whom the MCI is thought to have a vascular etiology or to represent the prodromal stage of a neurodegenerative disease. Recent meta-analyses exploring the use of cholinesterase inhibitors in patients having MCI have concluded that there is no evidence to support this practice. Although meta-analytic techniques seemingly strengthen the confidence in a recommendation via the incorporation of a large number of subjects analyzed, the technique is not capable of overcoming any inherent weaknesses of the individual studies included in the analysis. It is arguable whether studies in MCI may have employed endpoints poorly adapted to investigating effect of cholinesterase inhibitors. Most studies have used cognitive screening examinations, all of which stretch their detection ability to identify subjects with MCI, let alone discriminate subtle differences between them. Some have used conversion from MCI to dementia as an endpoint, which may not be the best measure for a symptomatic treatment. Further, once conversion to dementia has occurred, a cholinesterase inhibitor would be started in most (if not all) clinical settings, a reality not well reflected in most study designs. Additionally, several large studies have not permitted subject stratification by

APOE carrier status, another important defect in assessing outcome. In clinical practice, our center typically *does* recommend cholinesterase inhibitors for patients having MCI. Despite the modest effect size, many patients do wish to start on treatment. It appears that this is a generally accepted practice and experience, as most clinical trials for prodromal Alzheimer's disease specify that participants should be taking a cholinesterase inhibitor.

Introduction

Mild cognitive impairment (MCI) was defined as an "intermediate" state to describe individuals who are not cognitively "normal for age," but who would not meet a clinical diagnosis of dementia. Much of the differentiation between MCI and dementia centers around the severity of the cognitive deficits and their impact on daily activities. Several sets of criteria for MCI have been suggested, with the most widely adopted for clinical practice having been proposed by Petersen et al. [1•, 2]. MCI that primarily affects short-term memory is referred to as "amnestic MCI" and has a strong association with risk of progression of Alzheimer's disease [3, 4]. Outcomes of "non-amnestic MCI" are less well defined, and this is an area of ongoing research [5].

The clinical diagnosis of MCI permits clinicians and patients to have meaningful conversations surrounding memory complaints and what those symptoms may portend. The diagnostic classification also acknowledges the ability for patients and families to recognize early changes in the insidious progression from normal cognition to Alzheimer's disease, and encourages them to bring the noticed changes to medical attention. It is expected that this may also provide an opportunity to identify a suspected etiology for mild cognitive impairment and, when possible, formulate a management strategy to mitigate (or in some cases reverse) the cognitive changes.

Another aim for constructing a set of MCI diagnostic criteria is to identify people at elevated risk of developing Alzheimer's disease within the timespan of a typical interventional or observational clinical trial. In that regard, the definition of MCI has been very successful, creating a common language and degree of codification of diagnosis which has formed the basis of many clinical research trials and observational cohorts, including the Mayo Clinic Study of Aging [6]. Indeed, the success of this diagnostic construct has been further extended by incorporation of advanced biomarkers such as CSF, FDG-PET, or amyloid-PET for use in clinical research protocols [7••, 8••, 9]. Most interventional clinical trials targeting MCI (or even earlier "pre-MCI" or asymptomatic cerebral amyloid deposition [10]) now incorporate one or more of these biomarkers, with the aim to enroll people having prodromal Alzheimer's disease.

While the history of mild cognitive impairment is rooted in research aims, this diagnosis has moved into clinical practice, and we are daily faced with treatment decisions and questions from patients who meet these clinical diagnostic criteria. The purpose of this review is to explore what is known about treatment strategies or recommendations applicable to clinical practice.

Treatment

Diet and lifestyle

- Mediterranean-style diet: Numerous epidemiologic cohorts have reported that greater adherence to a Mediterranean-style diet is associated with decreased risk of cognitive decline and decreased rate of cognitive change among those already having cognitive impairment (or even dementia) [11••]. The Mediterranean-style diet is perhaps best considered a dietary pattern that describes a specific pattern of increased (or

decreased) consumption of specific foods. This would imply the consumption of a variety of micronutrients and macronutrients that are present in these foods. Many of these micronutrients have been separately proposed as potential protective factors against dementia and MCI. Studies of numerous micronutrients taken in isolation (including B vitamins [12], vitamin E [13], docosahexaenoic acid [14], and antioxidant supplements [15]) have not reliably demonstrated a protective effect against dementia, suggesting that the benefit seen in association with the Mediterranean-style diet may be related to taking these foods in the larger context of the dietary pattern.

- Cognitive stimulation: Many observational studies have associated greater cognitive stimulation with decreased risk of cognitive decline or older age at onset of dementia [16–18]. However, some cohorts have reported that higher educational attainment is associated with steeper decline once a person has been classified as having MCI or dementia [19, 20]. Older age at retirement has been associated with decreased risk of dementia [21]. Relatively few interventional studies have been conducted. A study investigating cognitive stimulation therapy on pre- and post-intervention performance on neuropsychological measures reported improvement on several measures, although this study lacked a control group, randomization, or assessment of durable effect of the intervention [22]. A Cochrane review of cognitive stimulation interventions found "consistent evidence from multiple trials that cognitive stimulation programs benefit cognition in people with mild to moderate dementia over and above any medication effects. However, the trials were of variable quality with small sample sizes and only limited details of the randomisation method were apparent in a number of the trials." [23]
- Exercise: Regular physical exercise has been associated with benefit in numerous health outcomes, including showing a reliably replicated reduction in risk of cognitive decline and dementia [24, 25•]. A Cochrane review found few studies that met its inclusion criteria; the minimal available evidence suggested possible benefit on activities of daily living [26]. One high-quality study investigated the impact of moderate-intensity walking versus low-intensity relaxation over 1 year and reported no benefit on a measure of memory or in quality of life [27]. Another reported that a 6-month exercise intervention improved cognitive performance and independence in daily activities in patients having AD [28].
- Social engagement: Greater social engagement was associated with decreased risk of progression of symptoms in a cohort of 816 community-dwelling older adults having MCI at enrollment [29]. In earlier work, a similar protective effect was observed in a community-based cohort of 1203 non-demented people in Sweden [30••, 31] A study of personal attitudes, which likely correlate with degree of social engagement and self-reports of satisfaction with social connectedness, found that late life cynical distrust was independently associated with an increased risk of dementia [32]. Social connectedness is also recognized

as an important quality-of-life indicator for people having MCI and dementia [33, 34]. It is also interesting to speculate that interventions using physical exercise or cognitive activity delivered in a group setting may have an unsuspected confounding benefit due to an increase in social engagement.

Pharmacologic treatment

- Cholinesterase inhibitors
- Memantine

Class of drugs (if applicable)

Cholinesterase inhibitors

The three commonly prescribed cholinesterase inhibitors in the USA are donepezil, rivastigmine, and galantamine. All three are approved for use in Alzheimer's disease, and clinical trial data have shown symptomatic benefit of a comparable magnitude for all three. Clinical trial evidence has also demonstrated a benefit for people having vascular cognitive impairment [35••], dementia associated with Parkinson's disease [36, 37], and Lewy body dementia [38]. Clinical trials of cholinesterase inhibitors in MCI have produced more variable results. A 2012 meta-analysis suggested that use of cholinesterase inhibitors did not prevent conversion from MCI to dementia [39]. However, a protective effect would not be expected based upon the mechanism of action for cholinesterase inhibitors. A 3-year study of donepezil in amnestic MCI reported a symptomatic benefit in the active treatment arm at 12 months, with no significant difference in conversion from MCI to AD at 3 years [13]. Thus, although the study was "negative" on its primary endpoint, there did seem to be some symptom amelioration conferred to the active treatment arm. There is good evidence of symptomatic benefit for all three cholinesterase inhibitors in mild dementia, and it seems likely that the ability to detect effect may be impacted by the instruments available to measure the effect. Further, once a patient has converted from MCI to dementia, starting on a cholinesterase inhibitor becomes standard of care. Therefore, it could be argued that the clinical trials in MCI likely report "negative" findings due to the definition of the study endpoint and that clinical distinction between "amnestic MCI suspected to represent prodromal AD" and "very early AD" is arbitrary. Our center typically does recommend cholinesterase inhibitors for patients having MCI. It appears that this is a generally accepted practice, as evidenced in a study of practices among neurologists [40] and "real world" practice decisions among providers in California Department of Public Health Alzheimer's Disease Research Centers of California [41]. Further, most clinical trials for prodromal Alzheimer's disease specify that participants should be taking a cholinesterase inhibitor.

Standard dosage Target dosage varies by the specific cholinesterase inhibitor.

	Donepezil: 5 mg daily for 4–6 weeks, then 10 mg daily. Rivastigmine patch: 4.6 mg/day for 4 weeks, then 9.5 mg/day Rivastigmine pill: 1.5 mg twice daily for 4 weeks, then 3 mg twice daily for 4 weeks, then 4.5 mg twice daily for 4 weeks, then 6 mg twice daily Galantamine : 4 mg twice daily for 4 weeks, then 8 mg twice daily for 4 weeks, then 12 mg twice daily Galantamine extended release: 8 mg once daily for 4 weeks, then 16 mg once daily for 4 weeks, then 24 mg once daily
Contraindications	Hypersensitivity to the drug or one of its components Monitor weight and toxicity in patients having low body weight Galantamine: Dose should be adjusted for impaired renal function Galantamine: Use with caution in severe hepatic impairment
Main side effects	Gastrointestinal side effects in up to 5–6 % of patients. Sleep disruption in up to 10 % of patients taking the medication before bedtime. Can slow cardiac conduction Transdermal rivastigmine can be associated with rash or skin irritation
Special points	Better tolerability when taken with meals In Alzheimer's disease, cholinesterase inhibitors may also improve neuropsychiatric symptoms of the disease.
Cost/cost-effectiveness	It is difficult to assess cost-effectiveness for interventions that may reduce or delay home-care costs and/or maintain independence in daily functions. Most prescription coverage plans provide coverage for one or more cholinesterase inhibitors.

Memantine

	Memantine is a NMDA-receptor antagonist that has demonstrated a benefit in moderate and severe Alzheimer's disease [42]. A study of memantine in mild Alzheimer's disease reported no benefit at this stage of the disease [43]. There is no evidence to support use of memantine in patients having MCI.
Standard dosage	Memantine is titrated in 5 mg increments weekly from an initial dose of 5 mg once daily to a target dose of 10 mg twice daily Memantine extended-release: titrated in 7 mg increments weekly from an initial dose of 7 mg once daily to a target dose of 28 mg once daily
Contraindications	Hypersensitivity to the drug or one of its components Dose should be adjusted for impaired renal function Use with caution in severe hepatic impairment
Main side effects	Headache, dizziness, constipation, confusion
Special points	In Alzheimer's disease, some evidence suggests a benefit in neuropsychiatric symptoms of the disease.
Cost/cost-effectiveness	There is no evidence to support use of memantine in patients having MCI. Thus, the cost-effectiveness of memantine would be regarded as "poor."

Interventional procedures

- Cerebrospinal fluid analysis
- Brain FDG-PET
- Amyloid-PET

Cerebrospinal fluid analysis

Standard procedure	Cerebrospinal fluid analysis of levels of amyloid, tau, and phosphorylated tau can be used to improve the accuracy of a clinical diagnosis of Alzheimer's disease [44–46]. Finding this profile in a patient having MCI may increase the likelihood that the patient's MCI represents prodromal AD and may predict an increased risk of progression from MCI to AD [46, 47•, 48].
Standard procedure	Cerebrospinal fluid is collected via lumbar puncture, which can be performed in an outpatient clinic using local anesthetic
Contraindications	Contraindication to lumbar puncture would include bleeding diathesis, current use of anticoagulant, contraindication to lumbar puncture
Complications	Headache, bleeding, infection
Special points	Insurance coverage for this analysis is uncertain, and the cost to the patient may be significant
Cost/cost-effectiveness	Not generally cost-effective, as the impact on clinical management is small

Brain FDG-PET

Standard procedure	Brain FDG-PET has demonstrated ability to distinguish between AD and other forms of dementia, including frontotemporal dementia [49–51]. Several studies have reported AD-like changes in people having milder degrees of cognitive impairment (such as MCI) [52, 53]. Some research provides evidence that FDG-PET can play a role in predicting short-term conversion from MCI to AD [54].
Standard procedure	Brain FDG-PET is typically collected at "resting state," during which the subject lays quietly in the scanner awake, but not engaged in a particular cognitive activity. The PET tracer is [F18] fluoro-deoxyglucose (FDG) and image acquisition is usually 30–40 min after injection of the tracer. Brain FDG-PET typically has an integrated CT scanner, for registration of the PET images to a structural image set and to permit volume-loss correction of the PET data.
Contraindications	Pregnancy is a contraindication to PET imaging.
Complications	Headache, injection site irritation
Special points	Insurance coverage for this analysis is uncertain, and the cost to the patient may be significant
Cost/cost-effectiveness	Not generally cost-effective, as the impact on clinical management is small

Amyloid-PET

Standard procedure	Brain amyloid-PET has demonstrated ability to distinguish between AD and control in several studies, including ones having pathological confirmation of the AD diagnosis [55, 56]. Analysis is generally reported as a "binary" read, with the scan being interpreted as "consistent with AD" or "not consistent with AD." Use of this imaging in asymptomatic individuals or those having mild cognitive impairment has not yet been adequately studied [57].
Standard procedure	Amyloid-PET is collected using a small molecule that binds to amyloid which is bound to a F18 molecule, which provides the positron-emission. In the USA, florbetapir [56, 58], flutemetamol [59], and florbetapen [60] have received FDA approval.

Contraindications	Pregnancy is a contraindication to PET imaging.
Complications	Headache, injection site irritation
Special points	Although approved by the FDA, insurance coverage for this clinical use of amyloid-PET is generally denied, with significant cost passed on to the patient.
Cost/cost-effectiveness	Not generally cost-effective, as the impact on clinical management is small or negligible

Assistive devices

- Memory Support System

Memory support system

Usage	The memory support system incorporates a calendar and organization system paired with a 6-week curriculum designed for individuals with progressive memory impairment. A clinical trial demonstrated adherence to the behavioral rehabilitation regimen of 95 % at completion of training and 89 % at the study endpoint 8 weeks later [61]. The authors reported a "medium effect size" for improvement of independence in daily activities including medication management, improved social activities, decreased anxiety, and improved mood. A follow-up study reported similar results extending out to 6 months follow-up and also reported a benefit in caregiver burden (compared with the non-intervention arm of the trial) [62].
Special points	This represents one of the few behavioral rehabilitations studies in patients having amnestic MCI or AD which assessed both the adherence to the regimen and the impact on retained daily activities.
Cost/cost-effectiveness	Inexpensive

Complementary and alternative medicine

- Ginkgo biloba
- Huperzine A
- Piracetam

Ginkgo biloba

Standard dosage	Ginkgo biloba extracts have been used in traditional medicine for thousands of years to treat a variety of ailments. The standard Ginkgo biloba extract EGb 761 has been well studied for use in cognitive impairment and dementia. A review of meta-analyses of studies using EGb 761 reported weak evidence that ginkgo biloba may be helpful for people having dementia and mild cognitive impairment [63]. However, specific studies in Alzheimer's disease [64] and a group of older adults who were cognitively intact or had MCI [65] both identified no protective effect from ginkgo biloba. A 5-year, placebo-controlled study of 2854 participants having memory complaints (though not necessarily meeting clinical criteria for a diagnosis of MCI) reported no reduction in risk of dementia.

Standard dosage	For age-related memory difficulties, the typically recommended doses range from 240 to 600 mg daily.
Contraindications	Allergy to the extract or any component of the supplement
Complications	Safety and tolerability are generally reported as "excellent" with no serious adverse events reported in the available clinical trials.
Special points	Studies in Alzheimer's disease [66] and MCI [67] both suggested benefit in neuropsychiatric symptoms.
Cost	Inexpensive

Huperzine A

Standard dosage	Huperzine A is a chemical derived from a Chinese club moss that has been used for a variety of medicinal purposes for centuries. Recent studies have characterized extraction techniques and have identified one site of activity as being inhibition of acetylcholinesterase [68, 69]. A dose of 200 μg twice daily showed no benefit in a phase II trial in mild-to-moderate Alzheimer's disease [70]. A systematic review and meta-analysis of Huperzine A for treatment of Alzheimer's disease found evidence of beneficial effects on improvement in cognitive function, daily living activity, and global clinical assessment of function with the caveat that the composite trials were of poor quality due to small sample size and poor study design [71].
Standard dosage	For age-related memory difficulties, the typically recommended dose is 200 μg twice daily, with doses ranging from 200 mg to 800 μg daily.
Contraindications	Hypersensitivity to the extract or any component of the supplement As the proposed mechanism of action is inhibition of acetylcholinesterase, currently taking a prescribed cholinesterase inhibitor should be considered a contraindication.
Complications	Safety and tolerability are generally reported as "good" with a side effect profile comparable to prescribed cholinesterase inhibitors.
Special points	Some authors suggest possible antioxidant or neuroprotective properties in addition to inhibition of acetylcholinesterase, although the physiologic or clinical significance of these reports is not known.
Cost	Inexpensive

Piracetam

Standard dosage	Piracetam, a derivative of GABA, was first marketed for the treatment of vertigo and events associated with aging in 1971. It was christened the first of a new class of pharmaceuticals, the "nootropics," in 1973 [72]. Its mechanism of action is uncertain, and it has not received approval for any indication by the US FDA, nor is it approved for sale as a supplement in the USA. It is available to be prescribed in other countries, including the UK. A phase II clinical trial of 8 g piracetam daily in AD reported no benefit [73]. A Cochrane review of piracetam for treatment of cognitive impairment reported no benefit in cognition, mood, or dependency [74].
Standard dosage	Use for cognitive impairment is typically considered "off-label." The general dosing recommendation is 1.6 to 9.6 g daily, although some studies have investigated doses up to 24 g daily.
Contraindications	Hypersensitivity to piracetam, Huntington's chorea, cerebral hemorrhage Dosage should be adjusted for patient having renal impairment.

Complications	Side effects are generally reported to be "few, mild, and transient." In a study of piracetam in patients having Alzheimer's disease, the compound was well tolerated.
Cost/cost-effectiveness	Although well-tolerated in clinical trials, no effect has been clearly demonstrated or suggested in studies of piracetam for cognitive impairment. Thus, the cost-effectiveness would be rated as "poor."

Compliance with Ethics Guidelines

Conflict of Interest
Brendan J. Kelley declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the author.

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