The Diagnosis and Management of Mild Cognitive Impairment
A Clinical Review

Kenneth M. Langa, MD, PhD; Deborah A. Levine, MD, MPH

The Patient’s Story

Mrs J, aged 81 years with hypertension and hyperlipidemia, requested a referral to a neurologist, stating: “I am forgetting things I just heard.”

Mrs J and her husband began noticing mild memory problems 1.5 years earlier and reported slow progression since. Her husband noticed changes in problem solving and time management. Mrs J was easily distracted and had difficulty remembering recent conversations. She misplaced objects and spent time looking for them; she read and wrote less than before. She repeatedly asked how to do things on her computer and cell phone. Her husband reported that she exhibited no initiative and that their home seemed more disorganized. She had difficulty planning dinner and her cooking was simpler. Both reported no changes in language or speech. She continued to drive locally without accidents but had difficulty remembering directions to familiar places. Mrs J had no hallucinations or delusions. She slept well, her mood was fine, and she exhibited no behavioral problems or personality changes.

Functionally, she remained independent in all activities of daily living (ADLs). She experienced urinary frequency and over the past couple of months has had a few incidents of urinary incontinence, especially when awakening from a nap. In instrumental activities of
daily living (IADLs), Mr J had recently assumed the responsibility of paying bills. Even with use of a compartmentalized pillbox, Mrs J occasionally forgot to take her medications (amlodipine, 5 mg daily; losartan, 50 mg twice daily; and ergocalciferol, 1000 units daily).

**Perspectives**

Mrs J (Asked when her memory first became a concern): Would you believe I’m about to say: I forget?...It’s just been gradual...I was asked to play my monthly bridge game...and I declined. I thought: I’ll never remember the cards.

Mild cognitive impairment (MCI) is a clinical stage on the continuum of cognitive decline where what is considered normal aging and dementia. MCI is characterized by impairment in cognition that is not severe enough to require help with ADLs and IADLs. Mrs J’s declining memory has clearly affected daily life in ways that both she and her husband have noticed, but she has remained generally independent and therefore has MCI.

**Methods**

We searched PubMed for English-language articles in peer-reviewed journals from inception through July 2014 using MeSH terms: mild cognitive impairment/diagnosis OR mild cognitive impairment/treatment OR mild cognitive impairment/therapy. We also searched the Cochrane Library database for mild cognitive impairment; we reviewed the updated 2011 National Institute on Aging—Alzheimer’s Association (NIA-AA) diagnostic guidelines for dementia, MCI, and preclinical Alzheimer disease. Additionally, we reviewed a recent analysis of diagnostic testing for Alzheimer disease from the Institute for Clinical and Economic Review, and a Centers for Medicare & Medicaid Services decision memo regarding β-amyloid (Aβ) positron emission tomography (PET) imaging for dementia. Our PubMed search yielded 4977 unique articles and our Cochrane Library search yielded 22 systematic reviews—the titles and abstracts of which were examined for relevance. For each of the relevant articles identified, we then screened the references and checked related citations in PubMed. Randomized double-blind placebo-controlled trials with results reported as intention-to-treat analyses were considered highest-quality data. Large prospective cohort studies, meta-analyses, and systematic literature reviews were also included as appropriate for supplementing the randomized-controlled trial results. Our results and discussion cite the articles that both authors found most relevant to the diagnosis and management of MCI. We developed recommendations using evidence from these sources, as well as our clinical experience.

**Definitions and Diagnostic Criteria**

In 2011, the NIA-AA convened workgroups to revise the 1984 diagnostic criteria for dementia, as well as dementia due to Alzheimer disease. Diagnostic criteria for MCI, the symptomatic predementia phase of the trajectory of cognitive decline, were subsequently established (Box 1). The key criteria that distinguish MCI from dementia are preservation of independence in functional abilities (ADLs and IADLs) and lack of significant impairment in social or occupational functioning. MCI subtypes are sometimes defined by presence or absence of memory difficulties (amnestic vs nonamnestic MCI) and the number of affected cognitive domains.

### Box 1. Diagnosis Criteria for Mild Cognitive Impairment (MCI) and MCI Due to Alzheimer Disease

**Criteria for Diagnosing MCI**
- Concern regarding a change in cognition from the patient, knowledgeable informant, or from a skilled clinician observing the patient
- Objective evidence of impairment (from cognitive testing) in 1 or more cognitive domains including memory, executive function, attention, language, or visuospatial skills
- Preservation of independence in functional abilities (although individuals may be less efficient and make more errors at performing activities of daily living and instrumental activities of daily living than in the past)
- No evidence of a significant impairment in social or occupational functioning (ie, not demented)

**Clinical Characteristics Suggestive That MCI Is Due to Alzheimer Disease**
- Memory impairment present
- Progressive decline in cognition over months to years (very rapid decline may suggest prion disease, neoplasm, or metabolic disorders)
- Lack of parkinsonism and visual hallucinations (suggestive of dementia with Lewy bodies)
- Lack of vascular risk factors and extensive cerebrovascular disease on brain imaging (suggestive of vascular cognitive impairment)
- Lack of prominent behavioral or language disorders (suggestive of frontotemporal lobar degeneration)

*Data are adapted from Albert et al.

The NIA-AA criteria define MCI due to Alzheimer’s disease as “those symptomatic but non-demented individuals whose primary underlying pathophysiology is AD [Alzheimer disease].” MCI due to Alzheimer disease is characterized by memory impairment, longitudinal decline in cognitive function, and lack of evidence for vascular, traumatic, or other medical causes of cognitive decline (Box 1). The NIA-AA guidelines also proposed research criteria for the use of biomarkers—measures of Aβ deposition and of neuronal injury—to further refine the likelihood that a patient’s MCI is due to Alzheimer disease, but these tests are not yet recommended for routine clinical use.

Two other recently developed clinical classification systems identify a symptomatic but non-demented stage of cognitive decline, but use different terminology than the NIA-AA criteria. The International Working Group criteria use the terms prodromal AD or predementia AD to refer to individuals with cognitive impairment that is not severe enough to significantly affect ADLs, while the new Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5) refers to this stage as mild neurocognitive disorder.

**Epidemiology and Risk Factors**

Recent clinical and population-based samples suggest an MCI prevalence of 10% to 20% for adults aged 65 years and older, although lack of standardized diagnostic criteria and differences in sample characteristics across studies have led to significant uncertainty around these estimates. The likelihood that MCI will progress to dementia depends on the specific diagnostic criteria used and...
Evaluation of the Patient With Suspected MCI

Dr F: Somebody who tells me that their memory has always been bad...[is] less worrying to me than a patient like [Mrs J] who told me that over the past 1.5 years there’s been a discrete and distinct decline in her ability to remember things. And, she had an informant...who agreed with that.

All patients with suspected MCI should undergo a comprehensive history and physical examination focusing on cognitive function, functional status, medications, neurological or psychiatric abnormalities, and laboratory testing. The main goals are to distinguish MCI from normal aging or dementia and to identify potentially reversible forms of MCI due to other conditions (eg, depression, medication effects, thyroid disease, and vitamin B₁₂/folate deficiency) (Figure).

Cognitive Function

A history of cognitive changes over time, verified by knowledgeable informants if available, is important for identifying the first diagnostic criterion—decline in cognitive function (Box 2). 14,15 Critical features that may elucidate a cause are onset, trajectory, time course, and nature of the cognitive symptoms. Very rapid cognitive decline (weeks to months) is not typical of MCI due to Alzheimer disease and should raise concerns for other causes such as neoplasm, metabolic disorders, or prior disease (Box 1). Patients and informants (such as family members) may report conflicting views regarding the presence and severity of cognitive symptoms, either from lack of insight or because cognitive decline can be emotionally charged and symptom reporting may be minimized to avoid difficult or disrespectful discussions. 14

Patients with suspected MCI should have cognitive function assessments at baseline and at follow-up visits. A recent US Preventive Services Task Force systematic review on screening for cognitive impairment in older adults examined a number of instruments for primary care settings. 16 The review concluded that brief cognitive assessments can successfully detect dementia in primary care, but the sensitivity of those instruments for detecting MCI is generally lower, and it is still unclear whether early diagnosis of cognitive impairment improves important patient or caregiver outcomes. 16 The Montreal Cognitive Assessment (MoCA) is a screening tool that was developed specifically for detection of MCI and takes approximately 10 minutes to administer. 17 Using a cut point of 25/26 (lower scores indicate worse cognitive function), the MoCA has a sensitivity of 80% to 100% and a specificity of 50% to 76% for detecting MCI. 16 The Mini-Mental State Examination (MMSE) has a sensitivity of 45% to 60% and a specificity of 65% to 90% for detecting MCI using cut points of 27 or 28 (lower scores indicate worse cognitive function). 16 A recent study directly comparing the MoCA and MMSE found the MoCA to be more sensitive for accurately differentiating individuals with MCI from those with normal cognition. 16 Clinicians may also consider the Mini-Cog test (which combines the Clock Drawing Test with a 3-word recall test) because it also has acceptable test performance characteristics and can be performed in 3 minutes or less. 16 Referral for formal neuropsychological testing may help diagnose MCI in patients with subtle cognitive decline. The eTable

Figure. Suggested Approach for Diagnosing and Managing Mild Cognitive Impairment

| Concern regarding a decline in cognition obtained from patient, informant, or clinician, or as the result of worsening performance on cognitive testing |
| Perform history focused on the following: Changes in cognitive function (onset, trajectory, examples) Changes in functional status (activities of daily living and instrumental activities of daily living, especially a change in ability to manage finances) Current prescription and over-the-counter medications Neurological symptoms (vision, hearing, speech, sleep-disordered breathing, gait, and numbness and tingling) Psychiatric symptoms (depression, anxiety, and behavioral or personality changes) |
| Perform physical and neurological examination |
| Perform laboratory testing including the following: Complete blood cell count, electrolytes, glucose, calcium, thyroid function, vitamin B₁₂, and folate |
| Perform cognitive testing including the Montreal Cognitive Assessment (MoCA) or the Mini-Cognitive Assessment Instrument (Mini-Cog) |
| No Evidence of mild cognitive impairment from evaluation? |
| Yes |
| Reassure patient and family Perform follow-up for reevaluation in approximately 6 months or with significant change in status |
| Optimize vascular risk factor control Treat depression if present Address polypharmacy; stop medications that negatively affect cognitive function Optimize vision, hearing, and sleep-disordered breathing Counsel patient and family on beneficial behaviors, safety, finances, long-term care, and prognosis (See Box 3) Perform follow-up for reevaluation in approximately 6 months or with significant change in status (See Box 3) |

Box 2. Descriptions of Cognitive Problems

Changes in memory (is the patient misplacing things more, using notes and reminders more, repeating questions, having trouble keeping track of dates and appointments?)

Changes in language (word-finding difficulties?)

Changes in visuospatial function (new driving difficulties, including being slow to identify roadway hazards, late to apply brakes, or difficulty staying in lane?)

Changes in attention/executive function (easily distracted, new difficulties preparing meals or using household appliances, new difficulty writing checks, new safety concerns from family members?)

*Data are adapted from McCarten 14 and Holsinger et al. 16

Copyright 2014 American Medical Association. All rights reserved.
in the Supplement contains more information on selected cognitive tests. Although Mrs J scored in the normal range on the MMSE (29 of 30 points), her formal neuropsychological testing showed objective deficits in memory function.

Clinicians can collect standardized information on cognitive function from informants using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), the Dementia Severity Rating Scale (DSRS), and the AD8. The NIA-AA criteria for MCI note that scores on cognitive tests for individuals with MCI are typically 1 to 1.5 standard deviations below age- and education-adjusted normative means. However, it is emphasized that these score ranges should be considered guidelines rather than firm cut-offs for making an MCI diagnosis.

**Functional Status**
Assessment of functional status determines whether a patient can function independently (MCI), or whether cognitive decline is severe enough to require consistent help with ADLs or IADLs (dementia). The Functional Activities Questionnaire is a brief standardized instrument for clinicians obtaining IADL information from an informant. When using the Functional Activities Questionnaire, patients with MCI have more IADLs that require assistance when compared with those who have normal cognition (mean number of deficits, 2.7 vs 0.1; \( P < .01 \)). and using a cut point of 6 points or greater on the Functional Activities Questionnaire was found to have an 85% accuracy rate for distinguishing patients with MCI from those with dementia. Mrs J was still generally independent, but had become slower and less efficient with customary activities (eg, cooking and driving); increasing difficulties with finances may be another sensitive indicator of early cognitive decline.

**Medication Review**
Certain classes and combinations of medications can contribute to cognitive impairment so all current prescription and over-the-counter medications should be reviewed. Drug classes most likely to contribute to cognitive impairment include anticholinergics, opiates, benzodiazepines and nonbenzodiazepine hypnotics (eg, zolpidem), digoxin, antihistamines, tricyclic antidepressants, skeletal muscle relaxants, and antiepileptics. Hormonal therapy (estrogen alone or estrogen plus progesterin) for menopause has been shown to increase risk for the combined end point of MCI or dementia. In addition, hypotension related to intensive treatment of hypertension and hypoglycemia related to intensive treatment of diabetes may also contribute to cognitive decline.

**Neurological and Psychiatric Evaluation**
Clinicians should perform a focused review of neuropsychologic and psychiatric symptoms, a complete neurological examination, and a depression assessment in patients with suspected MCI. Review of symptoms should probe vision and hearing problems, sleep-disordered breathing, behavioral or personality changes (which may suggest depression, thyroid disease, or frontotemporal dementia), visual hallucinations (dementia with Lewy bodies or depression with psychotic features), numbness or tingling in the extremities (neuropathy), dizziness upon standing (orthostatic hypotension), changes in speech (stroke or Parkinson disease), and changes in gait (stroke or normal-pressure hydrocephalus). A complete neurological examination, including orthostatic hypotension, extraocular movements, vision, hearing, speech, focal weakness, ability to stand from a chair, and gait is useful for identifying potential contributors to cognitive decline, including stroke, Parkinson disease, normal-pressure hydrocephalus, or neuropathy due to toxins or vitamin deficiency.

Depression is associated with cognitive impairment in older adults and the relationship is likely bidirectional. Depression can be screened in older adults using assessment tools such as the Geriatric Depression Scale, on which a score of 6 or greater is suggestive of depression. Clinicians can query the informant about the patient’s depressive and behavioral symptoms using the Neuropsychiatric Inventory.

**Diagnostic Testing**

**Neuroimaging**
Structural
The NIA-AA diagnostic guidelines do not recommend routine neuroimaging in the typical clinical assessment of MCI, but do propose research criteria in which neuroimaging may help in determining MCI etiology and prognosis. Some studies suggest that structural magnetic resonance imaging (MRI) may be useful for identifying MCI and those at greater risk for progression from MCI to dementia. However, lack of standardization and validation for these measures limits their usefulness in clinical practice, and they are not currently recommended for informing prognosis. Structural brain MRI may rule out other potential causes for cognitive decline, such as subdural hematoma, stroke, NPH, or tumor, so should be considered if the history, physical, or laboratory studies suggest one of these causes.

Functional and Amyloid Imaging
Fludeoxyglucose PET can detect regions of hypometabolism in the brain that may be characteristic of MCI due to Alzheimer disease, dementia caused by Alzheimer disease, or other causes for cognitive impairment. Most recently, PET imaging of the extent of A\( \beta \) plaques in the brain has become more feasible with the radiopharmaceutical tracer florbetapir, and has been studied for its utility in identifying individuals with, or at high risk for developing, Alzheimer disease. A recent Centers for Medicare & Medicaid Services review of PET amyloid imaging noted that this technology accurately identifies the presence of amyloid, but there is not yet sufficient evidence that the imaging results will affect medical decision making or improve health outcomes for older adults with suspected MCI or Alzheimer disease. Use of the technology is therefore currently only recommended and covered by Medicare when used in the context of a research study.

**Laboratory Testing**
Laboratory testing of complete blood count, electrolytes, glucose, calcium, thyroid function, vitamin B\( \text{_{12}} \), and folate is recommended to identify potentially reversible forms of MCI including infection, renal failure, hypomagnesemia or hypermagnesemia, hyperglycemia, hypocalcemia or hypercalcemia, hypothyroidism or hyperthyroidism, and vitamin B\( \text{_{12}} \), or folate deficiency. Laboratory testing for
Diagnosing and Managing Mild Cognitive Impairment

We summarize potential interventions for MCI from recent clinical trials (Table 1 and Table 2), systematic reviews, meta-analyses, and observational studies. Participants in MCI clinical trials have often had more education, healthier behaviors, and less comorbidity (including lower rates of smoking, hypertension, and heart disease) compared with age-

Table 1. Selected Randomized Controlled Trials of Pharmacologic Treatments and Behavioral Interventions for Mild Cognitive Impairment (MCI)

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients</th>
<th>Mean Age, y</th>
<th>Intervention</th>
<th>Trial Length</th>
<th>Primary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacologic Treatments</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salloway et al,&lt;sup&gt;44&lt;/sup&gt; 2004</td>
<td>270 Adults with MCI</td>
<td>72</td>
<td>Donepezil, 10 mg/d vs placebo</td>
<td>24 wk</td>
<td>No significant differences between treatment groups in the 2 primary outcomes: New York University Paragraph Delayed Recall test and the ADCS-CGIC-MCI.&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Petersen et al, 2005&lt;sup&gt;45&lt;/sup&gt;</td>
<td>769 Adults with amnestic MCI</td>
<td>73</td>
<td>Donepezil, 10 mg/d vs 2000 IU/d of vitamin E vs placebo</td>
<td>3 y</td>
<td>Compared with placebo, there were no significant differences in the probability of progression to Alzheimer disease in the vitamin E group (HR, 1.02; 95% CI, 0.74-1.41; P = .91) or the donepezil group (HR, 0.80; 95% CI, 0.57-1.13; P = .42).</td>
</tr>
<tr>
<td>Doody et al,&lt;sup&gt;46&lt;/sup&gt; 2009</td>
<td>821 Adults with amnestic MCI</td>
<td>70</td>
<td>Donepezil, 10 mg/d vs placebo</td>
<td>48 wk</td>
<td>The dual primary efficacy end point was not reached. At 48 weeks, there was a small, significant decrease in modified ADAS-cog&lt;sup&gt;b&lt;/sup&gt; (&gt;0.90 [SE, 0.37]) favoring donepezil (P = .01). Changes in CDR-SB scores&lt;sup&gt;6&lt;/sup&gt; were minimal and not significantly different between treatment groups.</td>
</tr>
<tr>
<td>Koontz and Basky,&lt;sup&gt;47&lt;/sup&gt; 2005</td>
<td>19 Men with MCI</td>
<td>71</td>
<td>Galantamine, 12 mg twice daily vs placebo</td>
<td>16 wk</td>
<td>The primary outcome was the CANTAB.&lt;sup&gt;b&lt;/sup&gt; At 16 weeks, only 1 of the 6 subtests of the CANTAB (stockings of Cambridge test)&lt;sup&gt;6&lt;/sup&gt; differed significantly between galantamine and placebo groups (mean [SD], 8.3 [1.9] vs 7.0 [1.4]; P = .02).</td>
</tr>
</tbody>
</table>

| **Cognitive Intervention**<sup>a</sup> | | | | | |
| Buschert et al,<sup>48</sup> 2011 | 39 Adults with MCI or mild Alzheimer disease | 73 | Group-based multicomponent cognitive intervention vs active control | 6 mo | There were significant improvements in the ADAS-cog<sup>b</sup> (P < .02) and nonsignificant improvements in the MMSE.<sup>b</sup> (P = .07), favoring the intervention MCI group. |
| Barnes et al,<sup>49</sup> 2009 | 37 Adults with MCI | 74 | Intensive, computer-based cognitive training vs passive computer activities | 6 wk | RBANS<sup>5</sup> total scores improved 0.36 SDs in the intervention group (P = .097) vs 0.03 SDs for controls (P = .88). Between-group difference was 0.33 SDs (P = .26). |
| Barnes et al,<sup>50</sup> 2013 | 126 Adults with memory concerns | 73 | A 2 × 2 factorial design with 4 groups: mental activity intervention (MA-I, intensive computer) to exercise intervention (EX-I, aerobic); MA-I to exercise control (EX-C, stretching and toning); mental activity control (MA-C, educational DVDs) to EX-1; and MA-C to EX-C | 12 wk | Global cognitive scores improved significantly over time (mean, 0.16 standard deviations; P < .001) but did not differ between groups in the comparison between the mental activity groups (P = .17), the exercise groups (P = .74), or across all 4 randomization groups (P = .26). |

| **Multidisciplinary Care**<sup>a</sup> | | | | | |
| Wolfs et al,<sup>51</sup> 2008 | 235 Adults with a suspected diagnosis of dementia or a cognitive disorder (>15% had MCI) | 78 | Integrated multidisciplinary diagnostic clinic vs usual care | 52 wk | At 12 mo, no significant difference between groups on change in mean score on EQ-5D VAS<sup>5</sup> (5.2 points; 95% CI, −0.58 to 10.94 points). |

Abbreviation: HR, hazard ratio.<sup>a</sup> All studies used cholinesterase inhibitors. <sup>b</sup> ADAS-cog (Alzheimer Disease Assessment Scale-Cognitive Subscale) scores range from 0 to 70 and modified ADAS-cog scores range from 0 to 89; for both higher scores indicate worse cognitive performance. ADCS-CGIC-MCI (Alzheimer Disease Cooperative Study Clinician’s Global Impression of Change for MCI) rates the clinician’s impression of change from baseline on a 7-point Likert-type scale from 1 indicating marked improvement to 4 indicating no change to 7 marked worsening. CANTAB (Cambridge Automated Neuropsychiatric Test Assessment Battery) stockings of Cambridge test scores represent the number of problems solved in the minimum number of possible moves. CDR-SB (Clinical Dementia Rating Sum of Boxes) scores range from 0 to 18 with higher scores indicating greater dementia severity. MMSE (Mini-Mental State Examination) scores range from 0 to 30, with higher scores indicating better cognitive performance. The EQ-5D VAS score (EuroQol five dimension visual analog scale) measures individuals’ ratings for health states and ranges from 0 (worst imaginable state) to 100 (best imaginable health state). The RBANS (Repeatable Battery for Assessment of Neuropsychological Status) is a brief neurocognitive battery measuring immediate and delayed memory, attention, language, and visuospatial skills with higher scores indicating better cognitive performance. Behavioral interventions were subcategorized as cognitive intervention, physical activity, multidisciplinary care, or psychotherapeutic intervention studies.

Medical Therapy

We summarize potential interventions for MCI from recent clinical trials (Table 1 and Table 2), systematic reviews, meta-analyses, and observational studies. Participants in MCI clinical trials have often had more education, healthier behaviors, and less comorbidity (including lower rates of smoking, hypertension, and heart disease) compared with age-

Liver function, syphilis, Lyme titers (Borrelia), and HIV may reveal rarer causes for cognitive impairment.<sup>34</sup> The proportion of dementia cases thought to be due to potentially reversible causes is about 5%.<sup>39</sup> While studies have suggested that levels of biomarkers in the cerebrospinal fluid (eg, Aβ42 and τ protein) may help identify patients with MCI who are more likely to progress to Alzheimer disease,<sup>40</sup> routine lumbar puncture is not generally recommended for clinical evaluation.<sup>41</sup>
matched general populations. More trials in MCI patients with less favorable demographic and health profiles are needed to increase generalizability, especially regarding prognosis.

### Pharmacologic Treatment of MCI

Currently, no drug has proven effective in treatment of MCI. Cholinesterase inhibitors have not been shown to decrease risk of progression from MCI to dementia at 1 and 3 years. In addition, cholinesterase inhibitors have limited or no significant effects on cognitive function over the short term (<12 months; Table 1) and may substantially increase adverse effects, based on a meta-analysis of 4 trials (1960 participants) and another meta-analysis of 9 trials (5149 participants). Consequently, cholinesterase inhibitors and memantine are not recommended for MCI treatment and there are currently no FDA-approved medications for MCI. Ginkgo biloba, a widely used herbal supplement to improve cognition and memory, has not been shown in randomized trials to prevent cognitive decline in those with MCI or normal cognition. Similarly, testosterone supplementation in older men showed no benefit for cognitive function in a randomized controlled trial.

### Vascular Risk Factor Control

Stroke prevention and vascular risk factor control may reduce risk of progression from MCI to dementia, regardless of radiographic evi-

---

### Table 2. Selected Randomized Controlled Trials of Behavioral Interventions for Mild Cognitive Impairment (MCI)

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients Characteristics</th>
<th>Mean Age, y</th>
<th>Intervention</th>
<th>Trial Length</th>
<th>Primary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joosten-Weyn et al, 2011</td>
<td>93 Adults with MCI</td>
<td>70</td>
<td>Group cognitive behavioral therapy (patients) vs a waiting list (controls)</td>
<td>10 wk</td>
<td>For patients, acceptance assessed using a subscale of the Illness Cognition Questionnaire increased more in the intervention group vs the waiting-list group (P = .03) with an estimated between-group difference of 3.49 (95% CI, -6.21 to -0.73; P = .01).</td>
</tr>
<tr>
<td>Banningh et al, 2013</td>
<td>88 Significant others of adults with MCI</td>
<td>69</td>
<td>Group cognitive behavioral therapy (significant others) vs a waiting list (controls)</td>
<td>10 wk</td>
<td>For significant others, sense of competence assessed with the Sense of Competence Questionnaire was not significantly different between the waiting list control group vs the intervention group (P = .39).</td>
</tr>
<tr>
<td>Lautenschlager et al, 2008</td>
<td>170 Adults with memory concerns, 60% of whom had MCI</td>
<td>69</td>
<td>Home-based physical activity program vs education and usual care</td>
<td>24 wk</td>
<td>At 18 mo, 0.73-point improvement on the ADAS-cog among patients in the intervention group vs a 0.04-point improvement for those receiving placebo (0.69-point treatment difference; P = .04); at 6 mo, 0.26-point improvement on the ADAS-cog among patients in the intervention group vs a 1.04-point decrease for those receiving placebo (1.3-point treatment difference, P &lt; .001). Results were similar in subgroup of patients with MCI. The intervention group also showed modest improvements in word list delayed recall (verbal memory) and CDR-SB (functional impairment due to cognition).</td>
</tr>
<tr>
<td>Baker et al, 2010</td>
<td>33 Adults with amnestic MCI</td>
<td>70</td>
<td>High-intensity aerobic exercise vs stretching (control group)</td>
<td>6 mo</td>
<td>Compared with stretching, high-intensity aerobic exercise significantly improved performance on tests of executive function with stronger effects among women than men.</td>
</tr>
<tr>
<td>Suzuki et al, 2012</td>
<td>50 Adults with amnestic MCI</td>
<td>75</td>
<td>Multicomponent exercise program vs education (controls)</td>
<td>12 mo</td>
<td>Patients in the exercise group showed superior improvements of cognitive function at treatment end for the MMSE (group-by-time interaction, P = .04), the logical memory subtest of the Wechsler Memory Scale-Revised (group-by-time interaction, P = .03), and the Letter Verbal Fluency Test (group-by-time interaction, P = .02).</td>
</tr>
<tr>
<td>Nagamatsu et al, 2012</td>
<td>86 Women with subjective memory concerns</td>
<td>75</td>
<td>Resistance training twice weekly, aerobic training twice weekly, or balance and tone training twice weekly (control group)</td>
<td>26 wk</td>
<td>Compared with the balance and tone training (control) group, the resistance training group significantly improved performance on the Stroop test (executive function) (mean change, 1.4 seconds vs 9.1 seconds; P = .04). Changes in Stroop performance scores did not differ significantly between the aerobic training vs the balance and tone training groups (mean change, 1.4 seconds vs 8.8 seconds; P value not given).</td>
</tr>
<tr>
<td>Barnes et al, 2013</td>
<td>126 Adults with memory concerns</td>
<td>73</td>
<td>A 2 x 2 factorial design with 4 groups: mental activity intervention (MA-I, intensive compute) vs exercise intervention (EX-I, aerobic); MA-I to exercise control (EX-C, stretching and toning); mental activity control (MA-C, educational DVDs) to EX-1; and MA-C to EX-C</td>
<td>12 wk</td>
<td>Global cognitive scores improved significantly over time (mean, 0.16 SD; P &lt; .001) but did not differ between groups in the comparison between the mental activity groups (P = .17), the exercise groups (P = .74), or across all 4 randomization groups (P = .26).</td>
</tr>
</tbody>
</table>

* ADAS-cog (Alzheimer Disease Assessment Scale-Cognitive Subscale) scores range from 0 to 70 with higher scores indicating worse cognitive performance. CDR-SB (Clinical Dementia Rating Sum of Boxes) scores range from 0 to 18 with higher scores indicating greater dementia severity. MMSE (Mini-Mental State Examination) scores range from 0 to 30 with higher scores indicating better cognitive performance. Behavioral interventions were subcategorized as cognitive intervention, physical activity, multidisciplinary care, or psychotherapeutic intervention studies.
idence of cerebrovascular injury. An acute stroke and subclinical infarcts can accelerate cognitive decline and precipitate dementia in patients with MCI. Vascular contributions to cognitive impairment are common, and many MCI patients have pathological evidence of neurodegenerative and cerebrovascular disease. Strategies for primary or secondary stroke prevention include blood pressure control, smoking cessation, statin therapy, antiplatelet therapy, and anticoagulation or antithrombotic therapy for atrial fibrillation. Independent of clinical stroke prevention, blood pressure control may reduce dementia risk. In the Systolic Hypertension in Europe (Syst-Eur) trial of 2418 adults (mean age 70 years), treatment of isolated systolic hypertension reduced incidence of dementia by 50% (3.8 vs 7.7 cases per 1000 patient-years; P = .05) over 2 years. A meta-analysis of 4 placebo-controlled trials (16 595 patients) also suggested that antihypertensive treatment may reduce incident dementia (HR, 0.87; 95% CI, 0.76–1.00; P = .045). The robustness of the evidence base for antihypertensive therapy to prevent cognitive decline, particularly in the oldest old, is debated because several randomized controlled trials (RCTs; including the HYVET-COG [Hypertension in the Very Elderly Trial cogni
tive function assessment]) and meta-analyses have shown negative results. Elevated or worsening systolic blood pressure and cigarette smoking each increase the risk of cerebral white matter lesion progression, which is associated with cognitive decline in the domains of information processing speed and executive function. Trials have not established that statins or intensive glycemic control reduce the risk for dementia independent of stroke prevention.

The Eighth Joint National Committee (JNC 8) recently recommended treating hypertensive adults aged 60 years and older to a blood pressure goal of less than 150/90 mm Hg. Given that higher variability in systolic blood pressure is associated with stroke, cerebral white matter lesion progression, lower hippocampal volume, and cognitive impairment, clinicians may consider medications that reduce blood pressure variability (calcium channel blockers or thia
dize diuretics) when selecting antihypertensive regimens, particularly in patients with marked variability in blood pressure, although this is unsettled. It is important to avoid overtreatment of hypertension and diabetes because hypotension and hypoglycemia may increase the risk of cognitive decline and other patient harms.

Treatmen

t of the Patient

Although there are no drugs proven or approved to treat MCI, optimizing patients’ general medical and functional status, and providing counseling regarding issues such as driving and home safety can maximize patient and caregiver well-being, and reduce risk of negative outcomes (Box 3). Individuals with MCI are at increased risk for gait dysfunction, mobility decline, and falls. Gait assessment, while performing an attention-demanding task (dual-task testing), may identify motor control and performance problems that could benefit from tailored interventions. Optimizing visual and auditory acuity may enhance functioning because untreated vision and hearing problems are associated with cognitive decline. Use of a CPAP (continuous positive airway pressure machine) for patients with sleep-disordered breathing may also reduce risk of progression of cognitive decline, although definitive clinical trials are still necessary.

Counseling on Behaviors

Dr F: Sometimes a physical therapy referral to facilitate aerobic exercise is useful. I also suggested that she stay mentally engaged...being out of the house and...around other people is a very important way of stimulating the brain...and helps preserve brain function.
There is modest evidence from RCTs and clinical studies that various behavioral interventions, particularly aerobic exercise and mental activity, may have small but beneficial effects on cognitive function in older adults with MCI (Tables 1 and 2).16 Several RCTs of community-dwelling adults with or at risk for MCI have shown that home-based or professionally-supervised programs of aerobic exercise or resistance training modestly improve cognition, particularly executive function, over 18-month follow-up (Table 2). The combination of aerobic exercise and mental activity may benefit patients with MCI. The Mental Activity and eXercise (MAX) RCT of 126 inactive older adults with memory concerns demonstrated that a 12-week program of combined physical and mental activity was associated with small significant improvements in global cognitive function, regardless of the types of physical activity (aerobic vs stretching and toning) and mental activity (intensive vs educational videos).48 Observational studies suggest that the Mediterranean diet also may reduce the risk of converting from MCI to dementia.77

Other observational studies suggest that social engagement may reduce the risk of cognitive decline and preserve memory, particularly in adults with less than 12 years of education or those with vascular disease.78 Little is known about the effectiveness of multidisciplinary care programs or supportive care interventions (eg, counseling, education, support groups) for patients with MCI or their families because well-designed RCTs are lacking49 and one RCT that included many patients with dementia showed negative results (Table 1).49 A few, small RCTs found that psychotherapy may modestly increase patients’ acceptance of an MCI diagnosis and also provide knowledge, insight, acceptance, and coping skills for significant others (Table 2),50,51 but larger RCTs are needed.

Small RCTs46-48 and clinical studies suggest that cognitive interventions may improve cognitive function moderately over 6 to 12 months for persons with MCI or mild dementia; however, improvements are often specific to targeted cognitive domains, may not be greater than active controls, and may not improve daily functioning (Table 1).16,79 Moreover, it is difficult to recommend specific components of cognitive interventions because of heterogeneity across studies.

An issue that often arises in patients with MCI is driving safety.80 Although there is general consensus among medical and transportation societies that those with moderate to severe dementia should not drive due to significantly increased risk of crashes, evidence of driving impairment for patients with MCI is less clear.80,81 The clinician should probe the patient and family for indicators of driving impairment, including recent motor vehicle accidents or near misses, changes in the patient’s driving behaviors (eg, speed, ability to stay in lane, road sign comprehension), or episodes of getting lost in familiar areas.80 Testing for deficits in visuospatial and executive function (Clock Drawing Test and Trail-making tests), cognitive domains thought to be important for driving safety, or formal driving evaluation may provide useful information.81 Patients are often reluctant to stop driving even on recommendations by their physician, family, or both, so early and repeated discussions suggesting that driving cessation may be necessary and referral to public transportation or other options may be useful in early counseling sessions. There is no legal requirement for physicians to report a patient with MCI to a local department of motor vehicles, but some states have mandatory reporting for patients with diagnosed dementia (see eBox in the Supplement).80

Follow-up

Serial assessments of cognition are recommended because “progressive cognitive decline provides additional evidence that the individual has MCI due to AD.”2 Longitudinal follow-up and serial cognitive assessments are also useful since they allow a clearer assessment of a patient’s true baseline and trajectory of cognitive function over time, and decrease the risk that poor performance on a single assessment due to anxiety, fatigue, or acute illness leads to a false positive diagnosis of MCI. However, the optimal timing, choice, and cost effectiveness of longitudinal cognitive assessments are unclear. Tests of episodic memory identify MCI patients with high likelihood of progressing to Alzheimer disease within a few years.2 General cognitive screening instruments (eg, MoCA) are recommended for detecting dementia in individuals with suspected MCI.82 Serial assessments of daily functioning may identify MCI patients who are more likely to develop dementia,83 may indicate incident dementia, and may identify need for additional resources.

No neuroimaging or laboratory test is currently recommended for predicting MCI progression to dementia in clinical practice.2 Although specific brain imaging findings (eg, Aβ deposition, medial temporal lobe atrophy, hippocampal atrophy, or hypoperfusion or hypometabolism in the temporoparietal cortex) are associated with an increased risk of progression, these findings currently lack specificity. Cerebrospinal fluid tests showing low levels of Aβ42, elevated levels of τ, or a low Aβ42 to τ ratio confer an increased likelihood of progressing to dementia; however, results may be ambiguous or contradictory for a given patient, may vary across sites, and diagnostic accuracy and positive predictive value are suboptimal.40,84 It is not recommended to perform routine genetic testing for mutations in amyloid precursor protein, presenilin 1, or presenilin 2 in adults with cognitive changes presenting before age 65 years, or the APOE e4 allele in older adults.

A common question is whether patients with suspected MCI require specialist consultations. Given the current limited evidence for effective MCI treatments, consultation would serve primarily to confirm the diagnosis and help identify reversible causes.

Prognosis

Mr J: You’re worried…[whether] this thing is going to get worse, which it probably will, but at what rate? … It’s uncertainty of the future regarding all of these things, whether it’s safety or whether it’s decision making. …. And doctors don’t seem to know either. It’s very frustrating.

Prognosis is uncertain for patients with MCI and, as articulated by Mr J, uncertainty about the future is a major source of worry. Although patients with MCI have a greater risk of developing dementia compared with the general population, studies report substantial variability. Reported annual rates of MCI conversion to dementia span from less than 5%85 to 12% to 20%,9
Diagnosing and Managing Mild Cognitive Impairment

Competing risks are another important consideration—although patients with MCI have an increased risk of dementia, they also have greater mortality. Risk-prediction models should estimate the likelihood that MCI patients will develop dementia prior to dying from competing causes, especially cardiovascular disease and cancer. Unfortunately, clinicians currently have insufficient information regarding Mrs J’s absolute risk of developing dementia compared with her risks of dying from a nondementia cause or experiencing stable or improved cognition in the next few years.

Future Directions

Older adults fear cognitive decline and most patients prefer testing that would indicate future Alzheimer disease risk. These factors, combined with changes in diagnostic technologies for risk stratification, portend that guidelines for the diagnosis and management of MCI will likely be in flux and debated over the next decade.

The limited efficacy of currently available interventions to prevent or delay progression of MCI to dementia increases the importance of clinicians discussing the balance of benefits and risks of interventions, as well as patients’ goals and preferences regarding medical interventions in later life. Given that there can be significant financial costs associated with diagnostic testing for MCI, as well as emotional distress and social stigma, some patients and families may prefer to forego the diagnostic evaluation. Clinical decision-making regarding when and how to diagnose and treat MCI (and preclinical Alzheimer disease) will likely change significantly if and when a safe and effective disease-modifying agent for preclinical Alzheimer disease and dementia is identified. In the meantime, primary care clinicians can support patients like Mrs J in practicing healthy lifestyle behaviors, minimizing risks from polypharmacy and comorbidities, and counseling patients and families about how best to plan for the future.

ARTICLE INFORMATION

Funding/Support: Dr Langa reports receipt of support, in part, by National Institutes of Health (NIH) grant U01 AG009740. Dr Levine reports receipt of support from NIH grant K23 AG040278. The Care of the Aging Patient series is made possible by funding from The SCAN Foundation.

Care of the Aging Patient Series: Authors interested in contributing Care of the Aging Patient articles may contact the section editor Dr Livingston at edward.livingston@jamanetwork.org.

Care of the Aging Patient: From Evidence to Action is produced and edited at the University of California, San Francisco, by Kenneth Covinsky, MD, Louise Walter, MD, Louise Aronson, MD, MFA, and Anna Chang, MD; Amy J. Markowitz, JD, is managing editor.

REFERENCES


62. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable...


