

# A 60-Year-Old Woman With Mild Memory Impairment

## Review of Mild Cognitive Impairment

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**DR LIBMAN:** Ms E, a 60-year-old divorced woman living independently in active semiretirement, described her cognitive health as good until the summer of 2005. At that time, she and her children noticed her difficulty recalling where she placed objects, her forgetfulness about recent conversations, and her growing reliance on written reminders. As part of an evaluation by her primary care physician, a magnetic resonance image (MRI) was obtained and revealed bilateral subcortical and periventricular discrete and confluent T2-enhancing white matter lesions with no significant cortical atrophy (FIGURE and interactive eFigure, available at <http://www.jama.com>). She was treated with paroxetine, 30 mg/d, to address concurrent symptoms of depression and anxiety, and she was referred for further neurocognitive assessment. Her only other medication was low-dose aspirin. She had no prior history of hypertension, diabetes mellitus, head trauma, or psychiatric illnesses. A history of tick bites was elicited, and she had been smoking 1 pack of cigarettes per day for 30 years. She denied abuse of alcohol, illicit drugs, or prescription medications. Her family history was negative for dementia. Physical examination showed a blood pressure of 118/70 mm Hg and a regular pulse of 60/min, and was noteworthy only for brisk symmetric reflexes and a right-sided upgoing great toe. Her mental status examination showed a depressed and anxious mood. Attention and naming were intact. On a brief test of memory, she recalled only 1 of 4 words after a delay but recognized the other 3. She had some difficulty drawing a clock correctly. Her complete blood cell count, erythrocyte sedimentation rate, glucose, electrolytes, thyrotropin, and vitamin B<sub>12</sub> levels were normal, and her Lyme disease and syphilis serologic studies were nonreactive. Her serum cholesterol was mildly increased at 207 mg/dL (5.36 mmol/L) with a low-

density lipoprotein component of 120 mg/dL (3.11 mmol/L). Lumbar puncture showed no abnormalities. Antinuclear antibody was present at 1:40 dilution with a speckled pattern. Apolipoprotein E (ApoE) genotype revealed the presence of a heterozygous state, *e3/e4*.

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See also Patient Page.



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dition to forgetfulness, she newly reported increased difficulty balancing her checkbook. She described emotional distress despite continuation of paroxetine. Her delayed recall appeared more impaired, with spontaneous recall of 0 of 4 words after a brief delay, recognition of only 2, and generation of 2 false positives. A formal test of memory, the California Verbal Learning Test, showed impaired learning of new words, impaired delayed recall, and a number of false positives among the words she recognized. Her clock drawing appeared more impaired, and she showed executive function deficits in her Trails B performance. Verbal fluency was below expectation, with phonemic dysfunction greater than semantic dysfunction. A single-photon emission computed tomographic scan showed no focal or regional cortical perfusion abnormalities. On the 30-item Geriatric Depression Scale she scored 12 points, which is consistent with mild depression. She was given a diagnosis of early Alzheimer disease (AD). She continued paroxetine, 30 mg/d, and began taking donepezil, which was titrated up to 10 mg/d.

### MS E: HER VIEW

I have always been in good health, and I've prided myself with my health. I walk 3 to 5 miles a day, and I've done so for years. It was in 2005 that I first noticed I was forgetful. I remember thinking, "This is not right."

There were things that I couldn't remember, and then I would panic because that's not like me. I began to take notes as to what I did for the day and started keeping a journal, which helped. But I was at the time in some sort of denial. I had had a viral infection, and I thought it might be the aftereffect of that.

I had sold real estate, and then I decided to just chill a little bit and work in a garden center. I have loved it. Last summer, a couple times I would forget where I left my garden gloves or my scissors, or some plants, within the nursery. But that was my "little secret." I never told anyone, and I eventually found them.

I think it's gotten worse. But I think what I struggle with mostly is self-doubt now, because I know I have this condition. I don't have the confidence within me that I used to have in terms of taking my pills. So I check them off and I make sure, and then I question whether I took them.

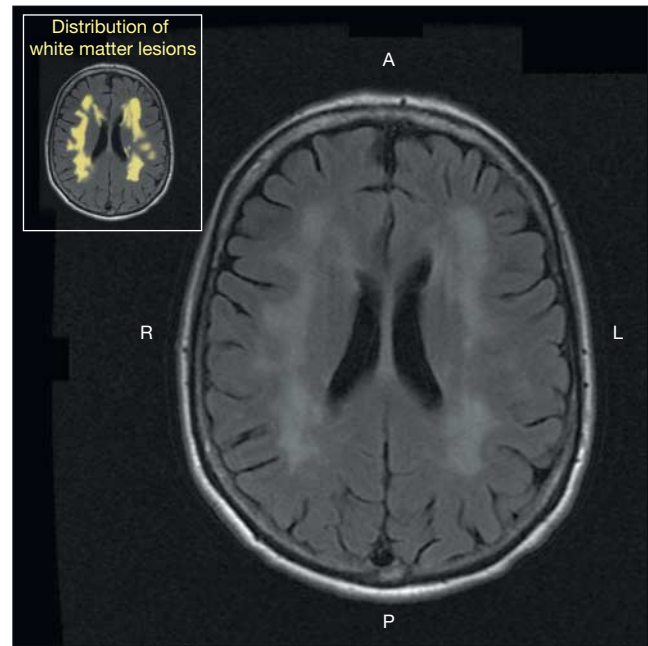
Just since my recent visit with my doctor, I've been very concerned and upset about myself. He gave me a time frame, and I refused to hear it.

My family has been very supportive. I've sort of played it down, and I guess with this most recent diagnosis, I'm going to have to make some decisions as to what I'm going to do. I just keep hoping for a cure for this disease. I think my days are numbered. I can't imagine what will come; it's frightening for me.

### AT THE CROSSROADS: QUESTIONS FOR DR ELLISON

How can mild cognitive impairment be distinguished from normal cognitive aging? Should case-finding of sympto-

**Figure.** T2-Weighted Fluid-Attenuated Inversion Recovery Magnetic Resonance Image of Ms E's Brain



matic but undiagnosed elders be encouraged and if so, how should case-finding be accomplished? When mild cognitive impairment is suspected, what diagnostic assessment should be performed? Which conditions should be considered in the differential diagnosis of cognitive decline in older adults? How do lifestyle, nutrition, and psychosocial or pharmacologic interventions affect cognition in aging? How should concerns about driving, employment, financial issues, and residential arrangements be addressed? What would you recommend for Ms E?

**DR ELLISON:** The clinical significance of cognitive changes associated with aging or disease has attracted increasing attention in recent years. Baby boomers nearing retirement share with neuroscientists and clinicians a desire to understand typical patterns of age-associated cognitive changes and to improve techniques for earlier detection of pathological signs. Aging adults are encouraged by the media to do crossword puzzles, to use software programs that claim to offer beneficial cognitive stimulation, to attend groups that teach memory skills, and to consult the many self-help books containing tips about physical and mental exercise, diet, and use of food supplements purported to enhance brain functioning and mitigate adverse consequences of aging. Many vigorous older adults approach these activities with enthusiasm, even in the absence of strong evidence that these interventions effectively prevent or delay cognitive decline. Within the medical system, memory diagnostic clinics that provide comprehensive evaluations have become increasingly available.

### Normal Cognitive Aging, Mild Cognitive Impairment, and Dementia

Cognition, like other bodily functions, shows typical age-associated decrements. The *Diagnostic and Statistical Manual of Mental Disorders*, for example, defines *age-related cognitive decline* (ARCD) as impairment of cognitive functioning that is “within normal limits given the person’s age.”<sup>1</sup> Episodic memory (recall of experiences and events) begins to decline as early as the 20s,<sup>2</sup> and spontaneous recall (of names, for example), working memory, processing speed, selective attention, and ability to multitask are among the faculties that decline during the usual course of aging. Semantic memory (factual and conceptual knowledge), procedural memory, and language abilities can be preserved until late in life.<sup>3</sup>

Among older adults, memory complaints are reported by as many as 56%.<sup>4</sup> Even complaints without objectively demonstrable memory impairment may predict a mildly increased risk for later dementia.<sup>5</sup> This *subjective memory impairment* (SMI)<sup>6</sup> may also reflect the presence of depression,<sup>7</sup> neuroticism,<sup>8</sup> anxiety, fatigue, stress, chronic pain,<sup>9</sup> disordered sleep, substance abuse, untoward effects of prescription medications, and/or other medical conditions.

Cognitive functioning abnormal for age and education without meeting criteria for dementia, as seen in Ms E, should not be attributed to normal aging. A syndrome of cognitive impairment–no dementia (CIND) was estimated in one large cross-sectional population study to affect 16.8% of an elderly population.<sup>10</sup> A more restrictively defined syndrome with lower expected prevalence, mild cognitive impair-

ment (MCI), has been defined to include a cognitive complaint, objectively impaired neuropsychological test performance, and essentially intact activities of daily living.<sup>11</sup> Depending on whether a single or multiple areas of cognitive impairment can be demonstrated, and on whether memory is or is not significantly impaired, MCI patients are divided into 4 subgroups: amnesic single domain, amnesic multiple domain, nonamnesic single domain, and nonamnesic multiple domain.<sup>11</sup> The characteristics of normal cognitive aging (ARCD), subjective memory impairment, mild cognitive impairment, and dementia are contrasted in the TABLE.

By *Diagnostic and Statistical Manual of Mental Disorders* criteria,<sup>1</sup> the diagnosis of dementia requires that an acquired impairment of memory and an additional domain of cognitive impairment (either aphasia, apraxia, agnosia, or executive dysfunction) be demonstrated. These decrements must not be explained by delirium or other medical or psychiatric disorders. In addition, memory and the other abnormal cognitive function must each be associated with significant social and/or occupational impairment.<sup>1</sup> The clinician’s judgment about the degree of functional incapacitation of a patient, based in part on the reports of family members or others, will in many cases determine whether a diagnosis of amnesic multiple-domain MCI or early dementia is made.

### Detection and Assessment of MCI

A diagnosis of dementia sets in motion profound life changes that affect self-esteem, autonomy, interpersonal relation-

**Table.** Clinical Features of Age-Related Cognitive Decline, Subjective Memory Impairment, Mild Cognitive Impairment (MCI), and Dementia

	Age-Related Cognitive Decline <sup>1</sup>	Subjective Memory Impairment <sup>6</sup>	Mild Cognitive Impairment <sup>11</sup>	Dementia <sup>1</sup>
Subjective concern	Often present	Present	May be absent	May be absent
Observer concern	Typically not present	Typically not present	Typically present	Present
Memory impairment	Present: mild (episodic memory, spontaneous recall, working memory) Preserved procedural and semantic memory	Subjectively present, not demonstrated on testing	Present in amnesic MCI (episodic memory)	Present sufficiently to impair social and/or occupational functioning
Nonmemory cognitive dysfunction	Present: mild (processing speed, selective attention)  Preserved attention span and language	Complaints on individual tasks of daily living	Present in amnesic multiple domain and in nonamnesic MCI (executive dysfunction, aphasia, apraxia, agnosia, and/or impaired visuospatial function) Essentially intact basic activities of daily living	Present sufficiently to impair social and/or occupational functioning
Functional impairment	Not present	Not present	Mild if present (may have increased difficulty performing more complex instrumental activities of daily living)	Present
Behavioral abnormalities	Not typically present	May be present (depression or anxiety)	Often present (depression, anxiety, apathy)	Often present (depression, anxiety, apathy, agitation)
Neuroimaging abnormalities	May be present (mild age-related atrophy and/or white matter disease)		Often present (mild to moderate atrophy and/or white matter disease)	Often present (atrophy and/or white matter disease)

ships, employment, income, medical care, residential decisions, and plans for the future. Dementia, therefore, should be diagnosed with considerable caution and on the basis of appropriate evidence. Ms E, with relatively unimpaired function despite her subjective distress and objective neuropsychological findings, was prematurely given the diagnosis of early AD. A diagnosis of amnesic multiple-domain MCI would more accurately reflect her level of functioning at the time of examination, which was below expectation for normal aging but not so impaired as to warrant a diagnosis of dementia. Even the designation of MCI, however, is often a distressing one.

Evidence suggests that amnesic MCI is often an intermediate-stage neurocognitive disorder between normal cognitive aging and AD. The brain of a patient with amnesic MCI shows neuropathological changes<sup>12</sup> and hippocampal atrophy.<sup>13</sup> Furthermore, the diagnosis of MCI is associated with an increased lifetime risk for dementia,<sup>14</sup> although many patients with MCI do not progress to dementia over as long as a decade of follow-up.<sup>15</sup>

Given the prognostic significance of MCI, the feasibility of identifying symptomatic individuals (“case finding”) has been explored.<sup>16</sup> The familiar Mini-Mental State Examination (MMSE)<sup>17</sup> and Clock Drawing Test<sup>18</sup> are often used in primary care settings, although their sensitivities (75% and 51%, respectively) and specificities (36% and 39%) are modest.<sup>19</sup> Detecting asymptomatic and mildly symptomatic individuals is most justified when the detection process is unlikely to cause harm and early recognition is likely to result in improved quality of life.<sup>20</sup> Although more than half of older adults have memory complaints,<sup>4</sup> objective cognitive impairment is found in a smaller number and MCI is by definition a syndrome of minimal functional impairment. Therefore, the modest clinical value of identifying individuals with MCI using tests of limited sensitivity and specificity<sup>21</sup> must be weighed against the possible harm associated with the assignment of a diagnostic label that might result in emotional stress or costly life consequences such as a decrease in insurability.<sup>22</sup> Furthermore, current suggestions for lifestyle modifications overlap substantially with recommendations already made for healthier aging.<sup>23,24</sup> Because of these considerations, the clinical value of large-scale case-finding for MCI remains controversial.<sup>25-27</sup>

In contrast, even mild dementia is appropriate for case-finding. Unrecognized dementia is associated with such complications as an increased risk for motor vehicle crashes, delirium, and hip fracture.<sup>28,29</sup> Dementia is often undiagnosed by primary care physicians,<sup>30</sup> perhaps related to patient denial, resistance to cognitive assessment, or the burden of other tasks that must be completed during a medical encounter. Increased recognition of dementia through proactive case-finding is justified by its frequency and severity in older adults, the availability of brief cognitive assessment instru-

ments with reasonable sensitivity and specificity,<sup>31</sup> modestly but significantly effective interventions,<sup>32</sup> and the potential for improving quality of life and safety. A review of dementia screening tests validated in primary care and community samples reported sensitivities and specificities of commonly used tests as follows: MMSE (69% and 89%), General Practitioner Assessment of Cognition (85% and 86%), Mini-COG (76% and 89%), and Memory Impairment Screen (80% and 96%). Each would be suitable for use as an initial screen for dementia case-finding in a primary care setting.<sup>33</sup>

Detection of MCI requires more sensitive brief instruments than detection of dementia. Failure to recall all 3 words on the MMSE despite the total score being in the normal range can suggest amnesic MCI.<sup>34</sup> The Montreal Cognitive Assessment, a brief instrument, has been shown more sensitive in detecting MCI than the MMSE (90% vs 18%), although less specific (87% vs 100%).<sup>35</sup> More extensive neuropsychological tests, when available, can add more precise characterization of cognitive deficits and establish a reference baseline.<sup>21</sup>

Although some individuals with MCI are improved at follow-up, approximately 12% of patients with MCI in some studies have progressed annually to dementia, compared with 1% to 2% of an elderly community population.<sup>11</sup> Despite the absence of a consensus-based standardized disease management protocol, identification of individuals with MCI can provide an opportunity to identify and address with them potentially remediable medical and lifestyle factors as well as other concerns they may have. For Ms E, diagnostic questions are raised by her white matter disease and upgoing toe, smoking and hypercholesterolemia represent modifiable risk factors, and her concerns and depressive symptoms suggest the value of focused counseling in addition to her antidepressant treatment.

Laboratory tests and neuroimaging studies will not diagnose MCI but can help identify treatable causes, since cognitive impairment has a range of potential etiologies, including many treatable conditions such as depression, delirium, nutritional deficiencies, sleep disorders, metabolic and endocrine disorders, autoimmune diseases, infections, neoplasms, adverse medication effects, misuse of alcohol or drugs, and cardiopulmonary disorders (most are addressed in<sup>32</sup>). Tests such as antinuclear antibody and single-photon emission computed tomography, administered early in the assessment of Ms E, are not a routine part of the initial evaluation of MCI unless clinical history or physical findings are atypical or suggest that these tests may contribute to establishing the diagnosis. In patients whose cognitive impairment is accompanied by symptoms suggesting seizures, infection, or delirium, an electroencephalogram and lumbar puncture may add diagnostic clarity. Structural neuroimaging with computed tomography or MRI is recommended in the assessment of individuals with dementia<sup>36</sup> and may have value in the assessment of MCI.<sup>37</sup> In

Ms E's case, the MRI-determined pattern of white matter disease suggests small-vessel disease. The concurrent finding of a positive Babinski sign, which is frequently found in conjunction with small-vessel disease in patients with vascular dementia,<sup>38</sup> is consistent with that suggestion. The history of tick bites, white matter disease, and changes in mood and cognition made it important to consider Lyme disease.

### Associated Lifestyle and Medical Factors

Lifestyle, genetic, metabolic, and disease factors affect the risk of dementia and probably the risk for the conversion of MCI to dementia. One community sample showed an odds ratio of 3.4 (95% confidence interval, 1.4-8.0) for the development of AD among current smokers, while former smokers' risk of AD did not differ from that of nonsmokers.<sup>39</sup> ApoE genotype is not routinely tested or recommended as a clinical assessment at present, although patients with amnesic MCI and ApoE *e4* genotype such as Ms E have been found to have greater memory and functional impairment and hippocampal atrophy.<sup>40</sup> Dyslipidemic states have been linked with dementia risk in some, but not all, studies,<sup>41</sup> and mild hypercholesterolemia has been associated with increased Alzheimer amyloid pathology at autopsy.<sup>42</sup> Few studies have evaluated the effects of reducing hyperlipidemia with statins and their findings are mixed.<sup>43</sup> One randomized trial of atorvastatin (80 mg/d) in patients who, like Ms E, had relatively mildly increased cholesterol levels, a mild degree of cognitive impairment, and an ApoE *e4* allele showed modest but significant cognitive benefits.<sup>44</sup>

At least as important as treating Ms E's hypercholesterolemia is smoking cessation, both to reduce her risk of progressive cognitive impairment and for stroke prevention.<sup>45</sup> Other common modifiable risk factors, though not directly relevant to Ms E's care, include diabetes mellitus<sup>46</sup> and hypertension.<sup>47</sup> Treatment of type 2 diabetes has been linked with amelioration of cognitive decline,<sup>48</sup> and some but not all studies find a reduced risk for developing dementia with antihypertensive treatment.<sup>47</sup>

Ms E's tick bite history and MRI findings of white matter disease prompted evaluations for autoimmune and infectious disorders, but the white matter disease is not inconsistent with MCI. Milder white matter hyperintensities than hers are found in many cognitively normal older individuals and white matter lesions are highly prevalent in individuals with vascular dementia or AD.<sup>49</sup> Changes in the white matter are associated with altered permeability of the blood-brain barrier, ischemic damage, or demyelination. Confluent white matter intensities are associated with microvascular changes at autopsy.<sup>50</sup> The constellation of findings that include Ms E's white matter disease, cigarette smoking, hypercholesterolemia, executive dysfunction, visuospatial difficulties, depressive symptoms, and relative lack of hippocampal atrophy on MRI all can be understood in the context of an MCI syndrome reflecting vascular or mixed etiology.

Depressive symptoms in individuals with MCI are frequent<sup>51</sup> and are thought to represent neuropathological change as well as a psychological reaction to impaired functioning. A history of depression was associated with greater risk for dementia in a meta-analysis<sup>52</sup> and a diagnosis of major depressive disorder in individuals with amnesic MCI was associated with a relative risk of 2.6 for developing AD in a prospective cohort study with a mean follow-up of 3 years.<sup>53</sup>

Special considerations are relevant to the use of an antidepressant in a patient with cognitive impairment. Anticholinergic medications such as paroxetine, the antidepressant Ms E takes, can adversely affect cognitive functioning.<sup>54</sup> In one study, healthy nondepressed volunteers aged 30 to 50 years treated with paroxetine (20 to 40 mg/d), in contrast to those treated with sertraline (50 to 100 mg/d) or placebo, showed impaired delayed recall.<sup>55</sup> For patients with MCI, a selective serotonin reuptake inhibitor (SSRI) antidepressant such as citalopram or sertraline can provide a nonanticholinergic, generically available treatment option with once-daily dosing, minimal pharmacokinetic interactions with other medications, and significant evidence of safety and efficacy in late-life depression.<sup>56</sup> Interestingly, a small randomized trial in which fluoxetine was given to nondepressed patients with MCI showed a statistical trend toward improvement in MMSE total score ( $P = .052$ , preintervention vs postintervention; MMSE changes for placebo and fluoxetine, respectively, were 0.6 vs 2.8 points). The investigators attributed this to the promotion of hippocampal neurogenesis.<sup>57</sup> Depressed, cognitively impaired patients who experience SSRI adverse effects, such as fatigue, weight gain, or sexual dysfunction, may find bupropion an acceptable alternative drug.<sup>56</sup> The safety and efficacy of nonserotonergic antidepressants in late-life depression are comparable with that of serotonergic antidepressants overall, but early experience with bupropion prompted warning of an increased seizure risk in patients with a history of a convulsive or eating disorder. In patients with no eating disorder and no prior risk factors for seizure, the seizure risk associated with sustained-release bupropion appears acceptably close to that of other antidepressants.<sup>58</sup>

### Nutritional and Pharmacologic Interventions

The Mediterranean diet—high in vegetables, legumes, fruits, nuts, cereals, fish, and olive oil and low in saturated fats—has been linked with a lower risk for AD.<sup>59</sup> Daily administration of the omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid (0.6 g) for 6 months was associated with a significant decrease ( $P = .02$ ) in expected decline of MMSE scores in a subgroup of individuals with very mild AD (baseline MMSE  $>27$ ); their scores declined only 0.5 points during that interval as compared with a 2.6-point decline for placebo-treated individuals.<sup>60</sup> Folate supplementation for 3 years conferred benefits in memory, processing speed, and sensorimotor speed in a Netherlands commu-

nity cohort,<sup>61</sup> but similar benefits were not found with a folate-B<sub>12</sub>-B<sub>6</sub> supplement administered for 2 years to a cohort studied in the United States, where folate fortification of flour is mandated.<sup>62</sup> Use of antioxidants or anti-inflammatory drugs, such as ginkgo biloba extract,<sup>63</sup> vitamin E,<sup>64</sup> aspirin,<sup>65</sup> or rofecoxib,<sup>66</sup> is not consistently supported by evidence, and a possible risk of cognitive impairment was associated with use of estrogen/progestin hormone treatment in the Women's Health Initiative's cognitive study.<sup>67</sup> Consistent physical exercise has been advocated for dementia risk reduction<sup>68</sup> and shown to improve cognitive function in older adults with subjective memory impairment or MCI,<sup>69</sup> and it merits further investigation in MCI cohorts.

No medication has been approved by the US Food and Drug Administration (FDA) for the treatment of MCI, and pharmacotherapy recommendations are based on limited evidence. Individuals with amnesic MCI who took donepezil, but not those in comparison groups treated with placebo or vitamin E, showed a relative risk reduction for conversion to AD of 58% at 12 months and 36% at 24 months but no risk reduction for conversion at 36 months.<sup>64</sup> A possible 3-year benefit of unclear significance was noted for carriers of 1 or more ApoE *e4* alleles. Adverse effects led to discontinuation of donepezil in 36% of participants compared with 25% of those receiving placebo.<sup>63</sup> The time-limited improvement and significant incidence of adverse effects in this study suggest donepezil to be a poorly supported pharmacotherapy for MCI in general, though specific patients might be appropriate for treatment. Rivastigmine for MCI was not better than placebo in decreasing progression to dementia.<sup>70</sup> Galantamine was associated with greater improvement on a secondary measure of cognition in each of 2 controlled MCI treatment trials, without significant differences noted on the cognitive items of the Alzheimer Disease Assessment Scale (ADAS-cog) or in the rate of conversion to dementia measured after 24 months of treatment.<sup>71</sup> Increased mortality of unclear significance was observed with galantamine.<sup>72</sup>

Memantine, a glutamatergic cognitive enhancer indicated by the FDA for treatment of moderate to severe AD, was tested on a small group of patients with age-associated memory impairment, a condition that, like MCI, lies between normal cognitive aging and dementia but differs in that cognitive impairment is defined based on younger adult normative values. Compared with placebo, memantine produced a statistically nonsignificant trend toward improvement on a computerized battery of tests of attention and information processing speed. However, no significant change was observed on measures of memory performance.<sup>73</sup>

As the population ages, more treatments for MCI will be developed. Pharmaceuticals currently being investigated for this diagnosis include a selective metabotropic glutamate receptor antagonist, a novel L-type calcium channel blocker, a phosphodiesterase inhibitor, a  $\gamma$ -aminobutyric acid receptor antagonist, and a serotonin 5HT<sub>6</sub> antagonist, among oth-

ers.<sup>74</sup> Furthermore, it is possible that one or more of the anti-amyloid therapies currently under investigation for the treatment of AD<sup>75</sup> may prove efficacious when administered for MCI or the earliest recognizable stage of dementia.

### Psychosocial Interventions

Psychosocial interventions play a prominent role in the management of cognitive impairment. For Ms E, individual counseling and cognitive training might alleviate distress associated with self-esteem and lifestyle changes while offering strategies for memory optimization. Problem-solving therapy, which can improve generation of alternatives and decision-making skills, reduced disability and diminished depressive symptoms (75% remission with problem-solving therapy vs 22% remission with supportive therapy) in a group of elderly adults with major depression and significant executive dysfunction.<sup>76</sup> Cognitive training interventions have been explored both in adults with normal cognition and in those with dementia, and to a lesser degree in individuals with MCI. A recent review distinguished between the goals of cognitive training (teaching strategies and skills to optimize cognitive functioning) and those of cognitive rehabilitation (which focuses on specific activities of daily living) or cognitive stimulation (involvement in activities designed to increase cognitive and social functioning in a nonspecific manner).<sup>77</sup> Current data are limited but suggest that a combination of these approaches may be useful in at least some MCI patients, for example, creating an appropriate environment for learning or for activities that require concentration, learning to organize information more efficiently by categorizing, combining, or using mnemonics, and adopting memory aids such as a memory notebook to organize reminders and other notes in a single location.<sup>78</sup> Printed or computerized exercises for attention and memory may be combined with advice regarding diet, exercise, and stress reduction. One recent small study evaluated the effects of a 4-week structured group cognitive rehabilitation program with components such as these in 18 individuals with MCI, comparing them with the outcomes of 10 individuals with MCI on a waitlist. Among those receiving the intervention, performance on activities of daily living improved, depression score on the Beck Depression Inventory decreased by 50%, and verbal memory as measured by the California Verbal Learning Test increased by a mean of 2.8 points ( $P < .001$ ) while these measures showed no significant change among controls.<sup>78</sup>

### Lifestyle Modifications

Over time, an individual with MCI will need to address issues of driving, employment, finances, long-term residential planning, and decision-making autonomy. Discussion of driving becomes important at an early stage because impaired visual perception and executive function are strongly associated with an increased risk for at-fault involvement in a motor vehicle collision.<sup>79</sup> Although the optimal time

for intervention and the ideal interval for driver reassessment remain unclear,<sup>80</sup> active monitoring and intervention by family or caregivers is often appropriate because the majority of cognitively impaired elders may otherwise continue driving until a collision occurs.<sup>81</sup> It is common for patients and families to resist a suggestion to cease driving, a limitation that may greatly interfere with independence and autonomy, and physicians are not mandated reporters of impaired drivers in most states.<sup>82</sup> Options that are available to a concerned clinician include a frank discussion of risks and, in the United States, a recommendation to seek retesting through the Registry of Motor Vehicles or from a Driver Rehabilitation Specialist, or a letter to the Registry of Motor Vehicles requesting that the patient's license be suspended pending mandatory testing.<sup>82</sup>

For patients with MCI who continue to work or perform other duties that require intact executive function and memory, additional supports or role modifications should be considered. If the diagnosis of MCI results in a change in employment status, however, the effects on both self-esteem and income can be distressing to the patient.

Because of attentional and executive function impairment, MCI is associated with an increased error rate in financial transactions and an overall decrease in capacity to understand and manage monetary affairs.<sup>83</sup> Denial, desire to protect a loved one's self-esteem, and practical considerations may postpone family action in this area. Failure to address financial capacity in a cognitively impaired individual can have costly consequences. When necessary and with appropriate safeguards, family members eventually may need to obtain power of attorney or guardianship in order to assume control of an incapacitated person's financial decisions and transactions.

Patients and families may require assistance in decisions regarding medical care and residential plans. A health care proxy should be identified and advance directives prepared while an individual is still competent. For residential planning, discussions should be individualized. Some families and patients prefer to preserve a current living arrangement for as long as possible by addressing safety issues, simplifying the demands associated with maintenance activities, addressing transportation needs, and assisting with shopping and other activities outside the home. Other families feel that moving patients to an assisted living facility at an earlier stage facilitates an easier transition to a new environment. Referral to appropriate professionals such as elder law attorneys or geriatric care managers may aid families during a stressful and confusing transition.

Adjustment to the cognitive decline of a loved one who may previously have been a highly responsible and competent member of a family is disruptive at best and can be devastating. Both the patient and his/her support system will often require a considerable amount of psychoeducational and emotional assistance while they adjust to the implications of a diagnosis of cognitive impairment at risk for pro-

gression. Aside from emergencies, however, a competent patient's agreement should be obtained before discussing diagnostic, prognostic, and treatment issues with others. The patient may prefer to limit the discussion to specific areas and/or participants. Topics of importance for a family discussion include clarification of roles, advice on dealing with a person's repetitive questioning or irritability, ways to communicate more effectively, understanding prognostic issues, accessing resources, addressing safety issues, and confronting denial regarding the patient's level of ability and appropriate degree of autonomy. If dementia develops and a patient's ability to make safe and appropriate decisions is in doubt, discussion of guardianship may become appropriate. When an integrated care team is available, the family may find the team's collaborative treatment and advice increasingly useful over time.

### Recommendations for Ms E

Ms E appears to have amnesic MCI of the multiple domain type with a probable vascular or mixed etiology and she may be at increased risk for future progression to dementia. However, she should be reassured that her current limitations are mild and conversion may be delayed or may not occur. Serial visits and periodic neuropsychological reassessment should be performed to monitor her cognitive status and functional autonomy. For further diagnostic assessment, it is reasonable to check her vitamin B<sub>12</sub> and folate levels and to obtain carotid ultrasound studies to determine whether blood flow is compromised to the point of requiring intervention for stroke prevention. Continuation of donepezil treatment at this stage is discretionary and this option can be discussed with Ms E, taking into account a recent report of cognitive deterioration following cholinesterase inhibitor discontinuation in individuals with MCI.<sup>84</sup> Adopting a Mediterranean diet and taking an appropriate omega-3 fatty acid dietary supplement could be considered as possibly helpful interventions that are unlikely to harm. Ms E's mild depressive syndrome, in the context of her stressful circumstances, should benefit from psychotherapeutic treatment. If her evolving symptoms suggest that she should continue to receive antidepressant treatment, paroxetine likely should be replaced by a less anticholinergic agent.

Ms E should assess her lifestyle to make sure that her current living arrangements and activities are appropriate. She should quit smoking through a smoking cessation program as soon as possible, modify her diet as needed, and participate in a regular physical exercise program. If her mild hypercholesterolemia does not improve with these interventions, treatment with a statin should be considered. A cognitive training program may be beneficial now or in the future to improve her mnemonic and organizational strategies. She may wish to consult an elder-law attorney and/or a geriatric care manager to begin to address planning for the future including financial planning, power of attorney, health care proxy, driving, and residential supports. Ms E's life has

clearly been made more complicated by her cognitive difficulties, but these interventions may help her continue functioning optimally and maximize her level of autonomy and quality of life for a significant number of years.

## QUESTIONS AND DISCUSSION

**QUESTION:** I'm wondering about the psychosocial piece of this. For example, if her marriage had not broken up and she was with somebody, could there have been a delay in some of the symptoms?

**DR ELLISON:** That's an important question but as yet there is no definitive answer with respect to patients with MCI. One study found that marriage decreased the risk of developing AD,<sup>85</sup> while others have reported no benefit<sup>86</sup> or even a trend toward increased risk.<sup>87</sup> Whether or not the patient is benefited, however, it's clear that a demented person's caregiving spouse experiences very significant stress. Mittleman and colleagues<sup>88</sup> have shown the efficacy of psychoeducation in reducing caregiver stress and delaying nursing home placement.

**QUESTION:** Could you say something about the specific guidelines for when you would consider a PET (positron emission tomography) scan in comparison to MRI data that you have on hand in this case?

**DR ELLISON:** The PET scan is an expensive test and should not be used clinically unless the results will contribute meaningfully to a patient's treatment planning. In research settings, abnormal PET findings are significantly linked with conversion to dementia,<sup>89</sup> but the clinical role of PET in the management of MCI and dementia is limited at present. As more effective early stage interventions are identified or developed, the use of PET may become more clinically relevant. The PET scan, incidentally, is covered by Medicare when considered medically necessary, which is currently defined as when it is used to aid in the differential diagnosis between AD and frontotemporal dementia. Experimental PET ligands hold promise for improving the early identification of AD.

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