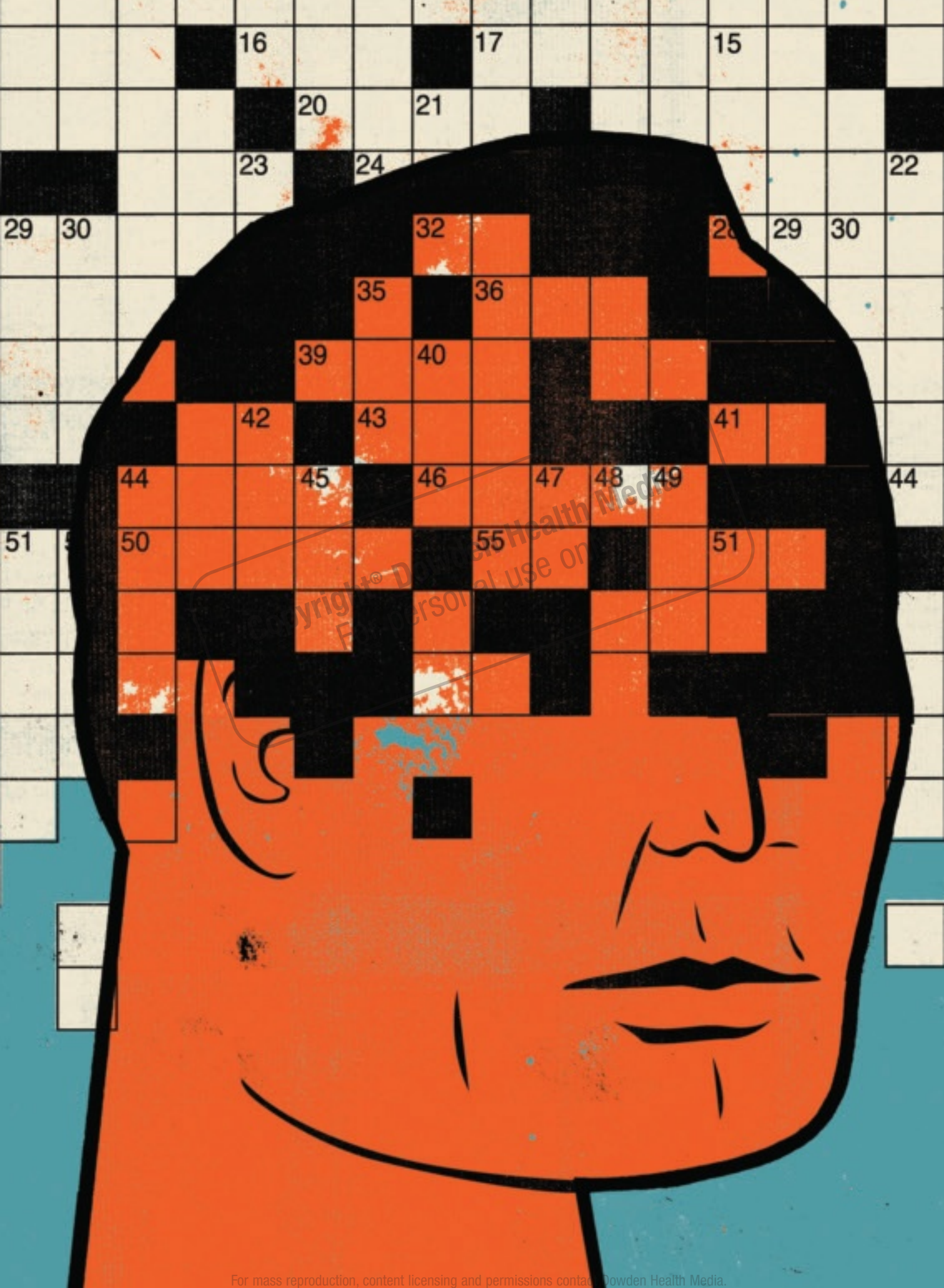

Current PSYCHIATRY

MILD COGNITIVE IMPAIRMENT
HOW CAN YOU BE SURE?

USE EVIDENCE-BASED COGNITIVE AND FUNCTIONAL TESTS TO DIFFERENTIATE MCI FROM DEMENTIA AND NORMAL HEALTHY AGING

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Mr. R, age 67, presents with what he describes as uncharacteristic "memory loss" that is affecting his ability to run his accounting business. He and his wife relate that he was doing well until approximately 9 months ago, when he started showing difficulties remembering clients' names and addresses.

His wife became extremely concerned when he made serious accounting errors in a 1-month period that resulted in the loss of a longtime customer. Mr. R has become easily distracted and absentminded as well, and his wife reports he is misplacing things around the house.

Screening for mild cognitive impairment (MCI) is not recommended for asymptomatic, cognitively healthy older persons, but memory complaints in individuals age >50—especially when corroborated by a reliable informant—warrant further assessment. Your challenge is to determine whether subtle cognitive changes in patients such as Mr. R are part of normal aging, caused by medical or mental illnesses, or a harbinger of Alzheimer's disease (AD) or another dementia.

continued

Mild cognitive impairment

Clinical Point

Amnestic MCI substantially increases the risk of Alzheimer's disease, compared with patients having normal cognition

Table 1

Amnestic MCI: Proposed diagnostic criteria

Subjective memory impairment, preferably corroborated by a reliable informant
Reduced performance on objective memory tests, compared with persons of similar age and educational background
Typical general cognitive function
Intact basic activities of daily living and intact or minimally impaired instrumental activities of daily living
Absence of dementia

MCI: mild cognitive impairment
Source: Reference 8

Although no treatments can yet prevent dementia, substantial new research is defining the MCI diagnosis for clinicians. This article describes:

- the evolving understanding of MCI and its subtypes
- risk factors for converting from MCI to AD
- an evidence-based work-up (including functional, cognitive, and neuropsychological testing)
- neuroprotective strategies for patients with an MCI diagnosis, including evidence on cholinesterase inhibitors, vitamin E, and anti-inflammatory agents.

MCI's evolving definition

MCI is characterized by subjective and objective cognitive decline greater than expected for an individual's age and education but less than the functional deficit required for a dementia diagnosis. MCI is proposed to identify persons with early but pathologic cognitive impairment that has a high risk to progress to AD and possibly other dementias.

MCI is thought to be a transitional state between normal aging and dementia.[1] Its estimated prevalence in the general population is 19% among individuals age <75 and 29% in those age >85.[2]

MCI subtypes. Some experts view MCI as a single entity, whereas others suggest amnestic (aMCI) and nonamnestic (nMCI) subtypes.[1,3] Each subtype is further divided into single and multiple cognitive domains. So, for example, the diagnosis would be:

- ***aMCI-single cognitive domain*** for memory impairment only
- ***aMCI-multiple cognitive domains*** for memory impairment plus nonmemory deficits, such as in language, executive function, or visuospatial function
- ***nMCI-single or multiple cognitive domains*** for nonmemory deficits without memory impairment.

MCI subtypes may have different outcomes for progression to dementia, and all progressive dementias may have their own predementia states.[4] Vascular MCI, for instance, is thought to result from cerebrovascular disease and is proposed to describe a prodrome of vascular dementia.[5]

Determining a patient's MCI subtype is still a research activity and calls for comprehensive neuropsychological testing. MCI patients perform at least 1.5 standard deviations below the average for age- and education-matched healthy individuals on objective measures of memory.[1]

Conversion to dementia

In longitudinal population studies patients with MCI have shown an 11% to 33% risk of developing dementia within 2 years, whereas 44% reverted to normal 1 year later. Reasons for reversibility may include variable definitions of MCI among the longitudinal studies and the possibility that patients who recovered or improved may have had reversible causes of dementia.[1]

When patients with MCI are followed over time, they progress not only to AD but also to non-AD dementias. For example, patients with Parkinson's disease (PD) and MCI may be at higher risk of progressing to dementia than cognitively intact PD patients.[6] MCI patients with the e4 allele of the apolipoprotein E gene (ApoE e4) are at increased risk to convert from MCI to AD.[7]

Individuals with aMCI (***Table 1***)[8] progress to AD at a rate of 10% to 15% per year, compared with 1% to 2% per year

Table 2

Factors shown to predict conversion from MCI to dementia

Category	Predictors of conversion
Clinical	**Cognitive:** Amnestic MCI **Neuropsychiatric:** Depression, apathy, and possibly nighttime behaviors and anxiety
Neuropsychological tests	Clock-drawing test, Trail-Making Test B, Symbol Digit Modalities Test, Delayed 10-Word List Recall, New York University Paragraph Recall Test (Delayed), ADAS-Cog total score
Neuroimaging	**MRI:** Entorhinal cortex and hippocampal atrophy **PET:** Medial temporal region, parietotemporal association cortex, and posterior cingulate hypometabolism **fMRI:** Abnormal hippocampal, posterior cingulate, and medial temporal region activation on memory tasks
CSF markers	**Increase:** t-tau, p-tau **Decrease:** Aß 42
Genetic markers	ApoE e4 carriers

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; ApoE e4: apolipoprotein E gene, e4 allele; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; fMRI: functional MRI; PET: positron-emission tomography
Source: References 7,9-15

in normal elderly persons. The Mayo AD research center studies reported a conversion rate of up to 80% from aMCI to AD within 6 years.[9]

Research focuses on identifying preclinical AD states and potential targets for intervention using disease-modifying therapies. Some experts consider MCI to be the earliest clinical manifestation of AD, at least in a subgroup of patients.

Identifying markers to predict which patients are likely to convert from MCI to dementia also is a major research objective. In addition to ApoE status (***Table 2***),[7,9-15] predictors of conversion may include:

- hippocampal atrophy[13]
- reduced metabolism in the temporoparietal cortex and posterior cingulum[14]
- elevated CSF tau and the 42 amino acid form of ß-amyloid (Aß 42).[15]

Research techniques such as structural neuroimaging, positron-emission tomography, functional magnetic resonance imaging (fMRI), and cerebrospinal fluid biomarkers have not been defined for clinical use, however.

Neuropsychiatric symptoms. Individuals with MCI and neuropsychiatric symptoms may be at particular risk for progressing to dementia. Agitation or depression are more prevalent in persons with MCI than in normal elderly but less prevalent than in those with dementia (***Table 3, page 40***).[10,16]

The cross-sectional, community-based Cardiovascular Health Study showed one or more neuropsychiatric symptom in:

- 16% of normal healthy elderly
- 43% of MCI patients
- 75% of dementia patients.[16]

Depression (20%), apathy (15%), and irritability (15%) were the neuropsychiatric symptoms reported most frequently in MCI patients, compared with apathy (36%), depression (32%), and agitation/aggression (30%) in dementia patients.

Sleep disturbances and anxiety in persons with MCI may predict progression to AD.[10] A baseline high frequency of apathy in aMCI patients has been associated with progression to AD within 1 year.[11]

Depression and MCI

Depression and cognitive complaints overlap considerably in older adults. Depressed patients without dementia show persistent cognitive deficits even after depression remits. In some patients, new-onset geriatric

Clinical Point

Apathy, depression, and possibly anxiety in patients with MCI have been associated with rapid progression to AD

Mild cognitive impairment

Clinical Point

In the differential diagnosis of MCI, significant functional impairment points toward dementia

Table 3

Neuropsychiatric symptoms: Rising prevalence mirrors cognitive deterioration in elderly patients*

Neuropsychiatric symptoms	Normal elderly	MCI	Mild AD
Depressed mood/dysphoria	+	++	+++
Nighttime behaviors/sleep	+	++	+++
Irritability	+	++	+++
Anxiety	+/-	++	+++
Apathy/indifference	+/-	++	+++
Agitation/aggression	+/-	+/++	+++
Eating/appetite disturbance	+/-	+	++
Disinhibition	+/-	+/-	++
Aberrant motor behavior	0	+	++
Delusions	0	+/-	++
Euphoria	0	+/-	+/-
Hallucinations	0	0	+

* 0 = 0%; +/- = 1% to 5%; + = 6% to 10%; ++ = 11% to 20%; +++ = 21% to 40%
MCI: mild cognitive impairment; AD: Alzheimer's disease
Source: References 10,16

depression is considered a prodrome of MCI and AD. Given that AD neuropathologic changes precede clinical symptoms by many years, depression and AD have been proposed as different clinical manifestations of AD pathology.[17]

Among patients with MCI, 20% meet criteria for major depression and 26% for minor depression. Symptoms often include sadness, poor concentration, inner tension, pessimistic thoughts, lassitude, and insomnia.[18]

Depressed MCI patients are at higher risk of developing dementia than those without depression, especially if cognitive measures do not improve after depression is treated.[12] Similarly, cognitively intact older persons who develop depression are at increased risk for MCI, particularly if they carry the ApoE e4 genotype.[19]

In the only study in which MCI patients' neuropsychiatric symptoms have been treated, 39 elderly patients with depression and MCI received open-label sertraline, ≤200 mg/d, for 12 weeks. Among the 26 patients who completed the trial, 17 showed moderate improvement in depressive symptoms, attention, and executive function, and 9 showed no response.[20]

Recommendation. In clinical practice, antidepressant treatment—usually a selective serotonin reuptake inhibitor (SSRI), with or without psychotherapy—is recommended for the MCI patient with comorbid major depression.

CASE CONTINUED

No signs of depression

Mr. R's medical, neurologic, and substance use history is unremarkable. Family history includes AD in a paternal aunt diagnosed at age 82. Mr. R reports no history of mood, sleep, or appetite changes and no psychotic symptoms. He shows no deficits in activities of daily living (ADL), although his wife recently took over paying household bills after he forgot to make a payment.

Evidence-based workup

Functional assessment. In the differential diagnosis of MCI, give special attention

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trials: ***Body as a Whole***—asthenia, back pain, accidental injury, chest pain; ***Cardiovascular***—hypertension; **Digestive**—dry mouth, increased appetite, thirst, constipation, increased salivation; ***Metabolic and Nutritional***—weight gain, peripheral edema, edema; ***Nervous System***—somnolence, tremor, depression, dizziness, speech disorder, amnesia, paresthesia, apathy, confusion, euphoria, incoordination; ***Respiratory***—pharyngitis, dyspnea; ***Skin and Appendages***—sweating, acne, dry skin; ***Special Senses***—amblyopia, abnormal vision; ***Urogenital***—dysmenorrhea, vaginitis.

Adverse Events with an Incidence ≥1% in Intramuscular Trials—The following treatment-emergent adverse events were reported at an incidence of ≥1% with intramuscular olanzapine for injection (2.5-10 mg/injection) and at incidence greater than placebo in short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania: ***Body as a Whole***—asthenia; ***Cardiovascular***—hypotension, postural hypotension; ***Nervous System***—somnolence, dizziness, tremor.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms—In an acute-phase controlled clinical trial in schizophrenia, there was no significant difference in ratings scales incidence between any dose of oral olanzapine (5±2.5, 10±2.5, or 15±2.5 mg/d) and placebo for parkinsonism (Simpson-Angus Scale total score >3) or akathisia (Barnes Akathisia global score ≥2). In the same trial, only akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significantly greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence of patients reporting any extrapyramidal event was significantly greater than placebo only with the highest dose of oral olanzapine (15±2.5 mg/d). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

Other Adverse Events—Dose-relatedness of adverse events was assessed using data from this same clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations >24.2 ng/mL (female) or >18.77 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and dizziness, 20 vs 40 mg/d.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661 patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. ***Body as a Whole***—*Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* chills and fever, hangover effect, sudden death. ***Cardiovascular***—*Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare:* arteritis, heart failure, pulmonary embolus. ***Digestive***—*Frequent:* flatulence, increased salivation, thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. ***Endocrine***—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. ***Hemic and Lymphatic***—*Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. ***Metabolic and Nutritional***—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. ***Musculoskeletal***—*Frequent:* joint stiffness, twitching; *Infrequent:* arthritis, arthrosis, leg cramps, myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. ***Nervous System***—*Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. ***Respiratory***—*Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, stridor. ***Skin and Appendages***—*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; *Rare:* hirsutism, pustular rash. ***Special Senses***—*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. ***Urogenital***—*Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation*, amenorrhea*, breast pain, cystitis, decreased menstruation*, dysuria, female lactation*, glycosuria, gynecomastia, hematuria, impotence*, increased menstruation*, menorrhagia*, metrorrhagia*, polyuria, premenstrual syndrome*, pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged*, vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, oliguria. (*Adjusted for gender.)

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. ***Body as a Whole***—*Frequent:* injection site pain; *Infrequent:* abdominal pain, fever. ***Cardiovascular***—*Infrequent:* AV block, heart block, syncope. ***Digestive***—*Infrequent:* diarrhea, nausea. ***Hemic and Lymphatic***—*Infrequent:* anemia. ***Metabolic and Nutritional***—*Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. ***Musculoskeletal***—*Infrequent:* twitching. ***Nervous System***—*Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. ***Skin and Appendages***—*Infrequent:* sweating.

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

DRUG ABUSE AND DEPENDENCE: Olanzapine is not a controlled substance.

Literature revised October 1, 2007

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to functional impairment, which points toward dementia. ADL generally are preserved in MCI, and minimal deterioration is seen in instrumental activities of daily living (IADL). A relatively easy way to assess function is to use the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS), which is based on 16 ADL and IADL items (***Table 4***).[21]

A substantial functional decline precludes an MCI diagnosis, although the degree of functional decline can be difficult to assess in older adults with physical limitations caused by medical comorbidities.

Cognitive assessment. Because most individuals with MCI score in the normal range on the Folstein Mini-Mental State Examination (MMSE), the modified MMSE (3MS)[22] may be more sensitive for detecting MCI. The 3MS retains the MMSE's brevity (≤10 minutes to administer) but incorporates 4 additional items, has more graded scoring responses, and broadens the score range to 0 to 100. The clock-drawing test also is sensitive for MCI, especially in detecting early visuoconstructional dysfunction.

The Montreal Cognitive Assessment (MoCA) is a 10-minute, 30-point scale designed to help clinicians detect MCI (see *Related Resources, page 49*). The MoCA usually is given with the modified MMSE for a comprehensive cognitive assessment.

Nasreddine et al[23] administered the MoCA and MMSE to 94 patients who met clinical criteria for MCI, 93 patients with mild AD, and 90 healthy cognitively normal elderly persons, using a cutoff score of 26. MoCA showed:

- 90% sensitivity for detecting MCI (compared with 18% for the MMSE)
- 87% specificity to exclude normal elderly persons.

The average MoCA score in patients with AD was much lower than in individuals with MCI, but score ranges of these 2 groups overlapped. Therefore, a score <26 could indicate either MCI or AD, and the distinction depends on assessing the patient for functional impairment.

Neuropsychological testing can be more sensitive than office-based screening tools in defining MCI subtypes. In the Alzheimer's Disease Cooperative Study (ADCS), the neuropsychological measures that most accurately predicted progression of patients with aMCI to AD within 36 months were the:

- Symbol Digit Modalities Test

- New York University Paragraph Recall Test (Delayed)
- Delayed 10-Word List Recall
- Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) total score.[24]

Laboratory tests, imaging. Use laboratory studies (***Table 5, page 48***) to rule out reversible causes of MCI symptoms.[8] Reserve CSF studies for suspected CNS infection (such as meningitis, human immunodeficiency virus, or neurosyphilis) and brain imaging for suspected cerebral pathology (such as infarct, subdural hematoma, normal pressure hydrocephalus, or tumor).

CASE CONTINUED

Subtle cognitive deficits

Mr. R scores 27/30 on the MMSE (losing 3 points on recall) and 25/30 on the MoCA (losing points on visuospatial/executive function, fluency, and delayed recall). Thyroid stimulating hormone, vitamin B12, folate, and rapid plasma reagin tests are unremarkable; brain MRI shows no significant abnormalities.

You refer Mr. R for neuropsychological testing, and most cognitive domains are normal. Exceptions include moderate impairment in immediate and delayed verbal and visual memory and mild executive dysfunction.

Based on your clinical evaluation and neuropsychological testing, you diagnose amnestic MCI. Mr. R shows abnormalities in memory and executive functioning without significant decline in basic and instrumental ADLs, is not taking medications, and has no other medical or psychiatric condition that could explain his cognitive deficits.

You discuss the diagnosis with him and his wife, including evidence on his risk for progression to dementia, neuroprotective strategies, and medications.

After an MCI diagnosis

Neuroprotection. Eliminate medications with anticholinergic effects, including:

- tricyclic antidepressants
- conventional antipsychotics
- antihistamines
- drugs used to treat urinary incontinence, such as oxybutynin
- muscle relaxants, such as cyclobenzaprine
- certain antiparkinsonian drugs, such as benztropine.

Encourage patients to avoid alcohol and sedatives. Collaborate with primary care providers to control cerebrovascular risk factors such as hyperlipidemia, diabetes mellitus, hypertension, and obesity. Treat depression, which may be a risk factor for developing dementia.

Monitoring. The American Academy of Neurology recommends monitoring patients diagnosed with MCI every 6 to 12 months for cognitive and functional decline.

continued

Table 4

Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)

Basic ADL	Instrumental ADL (IADL)
Toileting	Use of telephone
Feeding	Household tasks
Dressing	Using household appliances
Personal hygiene and grooming	Managing money
Bathing	Shopping
Walking	Food preparation
	Ability to get around inside and outside home
	Hobbies and leisure activities
	Handling personal mail
	Grasp of situations and explanations

The 16-item ADFACS total score ranges from 0 to 54 (best to worst):

- Rate basic ADLs from 0 (no impairment) to 4 (very severe impairment), for a total score range of 0 to 24.
- Rate IADLs from 0 (no impairment) to 3 (severe impairment), for a total score range of 0 to 30.

Use total scores to assess for functional decline from baseline. A decline from 0 to 1 on individual ADL and IADL items is not considered clinically significant.

ADL: activities of daily living

Source: Reprinted with permission from reference 21

Clinical Point

Give the 10-minute Montreal Cognitive Assessment (MoCA) with the modified MMSE for a comprehensive cognitive assessment

Mild cognitive impairment

Clinical Point

To protect the brain, work with the MCI patient's physician to stop anticholinergics and control diabetes, blood pressure, and hyperlipidemia

Table 5

Lab studies to rule out reversible causes of MCI

Complete blood count with differential
Basic metabolic panel
Liver function tests
Serum calcium
Serum vitamin B12 and folate
Thyroid function tests
Rapid plasma reagin
HIV in high-risk individuals
CSF studies if CNS infection is suspected

CSF: cerebrospinal fluid; HIV: human immunodeficiency virus; MCI: mild cognitive impairment
Source: Reference 8

In these visits, include:

- repeat office-based cognitive assessment, especially the modified MMSE, clock-drawing test, and MoCA
- careful history-taking from the patient and reliable informant
- repeat neuropsychological testing annually or when dementia is suspected
- assessment of the caregiver for distress.

Compensating for memory loss. Many individuals with MCI have insight into their cognitive deficits and are interested in making lifestyle changes. Experts recommend:

- moderate exercise (at least 30 minutes per session, 3 times a week)
- cognitively stimulating activities that involve language and psychomotor coordination, such as dancing, crossword puzzles, and volunteer work.

Potentially helpful tools include calendars, reminder notes, electronic cuing devices, pill boxes, and "speed-dial" telephones. Encourage patients to participate in local senior organizations and to use community resources.[1]

Medications—yes or no? Cholinesterase inhibitors, rofecoxib, and vitamin E have not been shown to prevent MCI from progressing to AD. Thus, insufficient evidence

exists to recommend medications for patients with MCI.

Donepezil has shown possible short-term benefits, however, and patients may choose to try this medication. Some find comfort in seeking this "extra time" to make decisions about advanced directives, attend to estate and will issues, and optimize relationships while they have only mild cognitive deficits and possess decision-making capacity.

Donepezil. The Alzheimer's Disease Cooperative Study—supported by the National Institute on Aging—was designed to determine whether daily doses of donepezil or vitamin E can delay or prevent progression of aMCI to AD.[25] In the double-blind, placebo-controlled, parallel group study, 769 patients with aMCI were randomly assigned to receive donepezil, 10 mg/d; vitamin E, 1,000 IU bid; or placebo for 3 years.

Overall progression to AD was 16% per year, and the 3-year risk of progression was the same in all 3 groups. Donepezil therapy was associated with a reduced rate of progression to AD compared with placebo during the first year of treatment. Donepezil's benefit was evident among ApoE e4 carriers at 2-year follow-up, but none of the 3 groups showed statistically significant differences after 3 years. Vitamin E showed no effect on AD progression throughout the study.

Rivastigmine. A randomized, placebo-controlled trial in which 1,018 MCI patients received rivastigmine or placebo for 4 years found no statistically significant benefit of rivastigmine on AD progression.[26]

Galantamine. Two international randomized, double-blind, placebo-controlled trials failed to show a statistically significant benefit of galantamine in slowing progression from aMCI to AD. MRI data from one of these studies suggested that galantamine may have reduced the rate of brain atrophy over a 2-year period.[27]

Rofecoxib. Epidemiologic studies indicate that anti-inflammatory drugs may reduce the risk of developing AD, but the COX-2 inhibitor rofecoxib did not delay progression to AD among aMCI patients in a large, placebo-controlled trial.[28]

Related Resources

- Rosenberg PB, Johnston D, Lyketsos CG. A clinical approach to mild cognitive impairment. *Am J Psychiatry* 2006;163:1884-90.
- Montreal Cognitive Assessment (MoCA). 10-minute screening test designed to help clinicians detect mild cognitive impairment. www.mocatest.org.
- Alzheimer's Association. www.alz.org.
- National Institute on Aging. www.nia.nih.gov.

Drug Brand Names

Benztropine • Cogentin
Cyclobenzaprine • Flexeril
Donepezil • Aricept
Galantamine • Razadyne
Oxybutynin • Ditropan
Rivastigmine • Exelon
Rofecoxib • Vioxx
Sertraline • Zoloft

Disclosures

Dr. Goveas and Dr. Dixon-Holbrook report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Kerwin is a consultant to Pfizer and a speaker for Pfizer and Novartis.

Dr. Antuono receives research support from Eisai, Pfizer, and Elan and is a speaker for Pfizer and Forest Pharmaceuticals.

Educate patients and family members about supportive nonpharmacologic treatments and cholinesterase inhibitors. The Alzheimer's Association, National Institute on Aging, and local department of aging agencies offer useful resources (see *Related Resources*).

CASE CONTINUED

Dealing with uncertainty

Mr. R and his wife are unsettled by his MCI diagnosis. They prefer to take a "wait and watch" approach, decline initiation of a cholinesterase inhibitor, and agree to adhere to nonpharmacologic interventions you discussed. You schedule a follow-up visit in 6 months and encourage them to call you with questions.

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continued

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Clinical Point

After an MCI diagnosis, monitor the patient and repeat the MoCA and modified MMSE every 6 to 12 months

Mild cognitive impairment

Clinical Point

Cholinesterase inhibitors, rofecoxib, and vitamin E have not been shown to prevent MCI from progressing to Alzheimer's

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Bottom Line

Consider mild cognitive impairment (MCI) when patients age >50 present with memory loss. Assess cognition with the MoCA and modified MMSE; noticeable activities of daily living decline points toward dementia. Neuropsychological tests predict risk of MCI progressing to dementia. Treat comorbid depression, and discuss neuroprotective treatments with patient and family. Repeat test battery every 6 to 12 months. Research focuses on identifying preclinical AD states and potential targets for disease-modifying therapies.