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Cognitive Impairment Evaluation and Management



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KEYWORDS

- Dementia • Mild cognitive impairment • Mental status examination
- Alzheimer's disease • Neuropsychiatric symptoms

KEY POINTS

- The goal of the diagnostic evaluation for cognitive impairment is to determine both the severity of impairment and the likely cause or causes.
- A knowledgeable informant is crucial for a reliable evaluation and, depending on the cause, patient care.
- The mental status examination should incorporate one or more validated instruments to assess cognition.
- An assessment of functional status informs both the diagnostic work-up and patient care.
- Environmental, psychological, and behavioral interventions are first line for neuropsychiatric symptoms and can be beneficial for cognition and function in cognitively impaired patients.

INTRODUCTION

Cognitive impairment is highly prevalent in the elderly and increases with advancing age.^{1–3} Worldwide, dementia is estimated to affect 1.8% of people in their 60s, 5.1% of people in their 70s, 15.1% of people in their 80s, and 35.7% of people in their 90s.³ A study from the Centers for Disease Control and Prevention using the 2011 Behavioral Risk Factor Surveillance survey found that 12.7% of respondents aged 60 years and older self-reported memory loss and confusion that had worsened in the preceding year.⁴ Clinicians providing primary care to the elderly are often tasked with evaluating and managing cognitive concerns in their patient population.

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APPROACH

To diagnose and treat a patient presenting with a cognitive complaint, the clinician uses a systematic approach that identifies the presence and severity of the impairment, the cognitive domains involved, the likely underlying causes, and the most appropriate interventions. Although some aspects of the work-up are completed for all patients (eg, selected laboratory tests and imaging), the decision to pursue a more detailed work-up is influenced by the goals of the evaluation. A brief discussion with the patient and family about the goal of the visit provides the necessary information to customize the approach.

The decision to refer a patient to a specialist can be considered at the close of the initial assessment. Cases of early-onset, rapidly progressive, or otherwise atypical cognitive impairment (eg, prominent language or social-behavioral symptoms with little or no memory loss) should be referred to a specialist.⁵⁻⁷ Other factors that might influence a decision to refer include provider experience, clinic resources, patient preference, and availability of specialty centers.² One particularly compelling reason to refer to an academic center is interest in participation in clinical research.²

EVALUATION

History of Present Illness

A concern for cognitive change (commonly called a chief complaint of memory loss) triggers a work-up for cognitive impairment. This concern can be voiced by the patient or a knowledgeable informant. In general, a knowledgeable informant provides the most helpful historical information. The interview with the informant is best done privately, although this is not always practical or possible. Privacy allows the informant to feel comfortable describing the full extent of the problem. However, there is no need to hide this conversation from the patient. In our experience, patients are agreeable to allowing the informant to speak privately with the clinician if they are told that this is a routine part of the cognitive evaluation and they will have private time as well with the clinician.

The informant interview should begin with an assessment of how long the informant has known the patient and how frequently interaction with the patient occurs. An open-ended question about the reason for concern often provides a great deal of information. Next, it is helpful to take a step back and learn about the patient's cognitive achievements and background, including education, occupation, and living situation. The history covers all cognitive domains, including memory, attention, language, visuospatial processing, executive function, and social comportment, and addresses aspects of timing and tempo. Domains that are not covered when the informant answers an open-ended question can be addressed with a few key targeted questions (**Box 1**).

It is helpful to ask for examples that illustrate the patient's symptoms. These contextual details aid the physician in assessing the severity of the problem.

After establishing the pattern of cognitive impairment, the clinician should assess the functional impact of the symptoms. The activities of daily living are the instrumental activities of daily living (IADL), such as handling finances, cooking, managing medications, and using transportation, and the basic activities of daily living (BADL), which include bathing, dressing, grooming, feeding, and toileting.⁸ An ecologically valid and holistic way to assess function is to begin by asking what a typical day is like or what the patient does to stay busy. The clinician should then ask questions to determine whether the patient's day-to-day activities represent a change from the baseline and, if so, are the result of cognitive problems. Questions should probe whether the

Box 1**Targeted questions to address cognitive domains**

- Memory
 - Does the patient forget appointments or have difficulty keeping track of the day or time?
 - Does the patient repeat questions or comments?
 - Does the patient forget recent events or conversations?
- Attention
 - Does the patient have periods of decreased alertness?
 - Is the patient easily distracted?
- Language
 - Does the patient have word-finding difficulties? Struggle to find common words?
 - Does the patient have trouble communicating thoughts or understanding what is being said to them?
- Visuospatial processing
 - Does the patient tend to get lost or turned around?
 - Does the patient ever fail to see something that is right in front of them?
- Executive function
 - Can the patient successfully complete tasks that require multiple steps; for example, planning a trip or throwing a dinner party?
 - Can the patient use appliances and devices as well as they used to?
- Social comportment
 - Does the patient behave appropriately in social situations?
 - Has the patient become impulsive, careless, or unguarded?

Note: these questions refer to “the patient,” but a more personal term, such as “your wife” or “your father,” is used in practice.

patient is less efficient at performing tasks (ie, takes them longer) or makes errors and needs help.

Neuropsychiatric symptoms should be discussed, both because mood disorders, especially depression, can be a primary (and treatable) cause of cognitive change and because neurodegenerative diseases can cause various neuropsychiatric symptoms. For example, dementia with Lewy bodies (DLB) often results in anxiety, systematized delusions, and formed visual hallucinations.⁹

Sleep should be discussed, both because untreated sleep disorders (eg, obstructive sleep apnea [OSA]) may affect cognitive function in some older adults¹⁰ and because neurodegenerative conditions are associated with sleep disturbance.^{11,12} The possibility of rapid eye movement sleep behavior disorder (RBD), which is commonly seen in DLB, can be assessed for by asking whether the patient’s arms and legs move during sleep, as if acting out dreams.¹³

A focused review of systems should inquire about gait dysfunction, falls, tremor, incontinence, and dysphagia. The past medical history should elucidate vascular risk factors and general medical, psychiatric, or neurologic diseases that could affect cognition. The social history assesses for illicit drug use, problematic alcohol use, and social stressors. The family history identifies genetic risk factors. In addition, the medication reconciliation should flag drugs that contribute to cognitive decline, particularly anticholinergic drugs.

The interview with the patient should include questions about cognitive symptoms and a typical day. This history from the patient is a part of the cognitive examination because it provides information about the patient’s insight. Patients should be asked directly about their mood and hallucinations, because informants do not always know

this very subjective information. Validated instruments for assessment of cognitive symptoms, functional decline, and neuropsychiatric features can augment the history of present illness and provide quantitative values that are helpful for both baseline and longitudinal assessments (**Table 1**).

Examination

The mental status examination should include both a “bedside” examination and the use of one or more validated instruments to assess cognition and, if applicable, mood (**Table 1**). There are some scenarios in which the results of formal cognitive tests must be interpreted with caution. For example, the psychometric test performance of persons with limited education, particularly less than high school, and for whom English is a second language may underestimate their cognitive abilities. In addition, certain cognitive deficits, such as marked impairments in language or attention, can cause performance on tests that is markedly poorer than expected.

The bedside mental status examination touches on the various cognitive domains. From the start of the encounter with the patient, the clinician makes observations regarding the patient’s cognition and behavior. While taking the history, the clinician is also taking note of the patient’s affect, social comportment, speech, facial expressions, and insight. The versions of the bedside mental status examination are limitless, and clinicians often tailor the examination based on preference, patient factors, and the evolving differential diagnosis. The various bedside tests available are best organized according to the cognitive domains they test (**Box 2**).

Next, the clinician should perform a focused neurologic examination designed to detect findings that the chief complaint and history suggest might be present (**Box 3**).

A brief general medical examination with attention to the cardiac and pulmonary systems assesses for signs of a non-neurologic problems that could affect cognition.

Referral for a formal neuropsychological evaluation should be considered when there is significant psychiatric comorbidity or when there is a mismatch between the history and the cognitive test results—for example, a patient whose cognitive test performance is normal but in whom a decline from baseline is still suspected. More in-depth testing may reveal deficits too subtle to show up on simpler office-based tests. Neuropsychologists can also assist in refining the differential diagnosis by identifying patterns of cognitive dysfunction.

Determining Level of Impairment

The history and examination provide clinicians with the data needed to characterize the level of impairment:

- *Subjective cognitive decline (SCD)* describes patients who have expressed concern for cognitive change but perform normally on cognitive testing.¹⁴
- *Mild cognitive impairment (MCI)* describes patients with concern for cognitive change, voiced by the patient or the informant; objective evidence of impaired cognition in one or more cognitive domains; and relative preservation of independent function, such that the patient does not meet criteria for dementia. Typically, a person with MCI is less efficient in performing IADLs.¹⁵ MCI can be staged as early or late, depending on the severity of symptoms.
- *Dementia* describes a patient with concern for cognitive decline, objective cognitive impairment, and disability. Dementia is distinguished from MCI in that the cognitive symptoms of dementia are severe enough to interfere with performance of day-to-day activities.¹⁶ Dementia can be further characterized as mild, moderate, or severe, based on functional status. In mild-stage dementia,

Table 1
Selected validated instruments for assessment of cognition, functional status, and neuropsychiatric symptoms

Instrument	Description	How It Is Administered	Scoring	Considerations
Functional Activities Questionnaire	Informant questionnaire about patient's performance of day-to-day tasks	Examiner administers to informant	Score range: 0–30; lower scores c/w less impairment; ≥ 9 , impaired function and possible cognitive impairment	<ul style="list-style-type: none"> • Takes 5 min • Must have reliable informant • May help identify safety concerns and areas of need
General Practitioner Assessment of Cognition	Psychometric test of memory, language, executive function, and structured informant interview	Examiner administers psychometric test to patient and interviews informant	Patient examination (out of 9): 0–4, cognitive impairment; 5–8, need more information (interview informant); 9, normal. Informant interview (out of 6): 0–3, cognitive impairment	<ul style="list-style-type: none"> • Takes 4–5 min • >80% sensitivity and specificity
GDS	30 yes/no questions about depressive symptoms; 15-item version also available (GDS-15)	Examiner administers to patient, or patient self-administers	Score range (full version): 0–30; ≥ 14 , increased depressive symptoms; 11–13, borderline	<ul style="list-style-type: none"> • May be less reliable for more impaired patients
IQCODE	26-item informant questionnaire with 5-point Likert scale; shorter 16-item version (Short IQCODE) also available	Informant self-administers	Score range 1–5 (mean Likert score); higher scores c/w more impairment	<ul style="list-style-type: none"> • 75%–87.6% sensitive and 65%–91% specific for dementia • 71.1%–82.6% sensitive and 69.0%–83.0% specific for MCI • Unknown optimal cut points
Memory Impairment Screen	Brief psychometric delayed and cued recall test	Examiner administers to patient	Score range: 0–8; ≤ 4 , possible cognitive impairment	<ul style="list-style-type: none"> • Takes 4 min • 43%–86% sensitive and 93%–97% specific for dementia • Works for visually impaired (no writing or drawing component)

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Table 1
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Instrument	Description	How It Is Administered	Scoring	Considerations
Mini-Cog	Psychometric test of memory, executive function, language, and praxis using clock draw and 3-word recall test	Examiner administers to patient	Score range 0–5; higher score c/w less cognitive impairment	<ul style="list-style-type: none"> • Takes 3–4 min • 76%–100% sensitive and 54%–85.2% specific for dementia • Low sensitivity for MCI • May perform better in low-education populations
Mini Mental State Examination	Psychometric test of memory, attention, orientation, language, and praxis	Examiner administers to patient	Score range: 0–30; 21–24, mild dementia; 13–20, moderate dementia; 3-point change considered clinically significant	<ul style="list-style-type: none"> • Takes 7–10 min • 88.3% sensitive and 86.2% specific for dementia with a cut point of 23/24 or 24/25 • Limited sensitivity and specificity for MCI • Has copyright restrictions
Montreal Cognitive Assessment	Psychometric test of memory, executive function, language, and praxis; designed to detect MCI	Examiner administers to patient	Score range 0–30; higher score c/w less cognitive impairment	<ul style="list-style-type: none"> • Takes 10 min • 80%–100% sensitive and 50%–76% specific for MCI using cut point of 25/26
NPI-Q	Informant questionnaire on 12 behavioral symptoms (items are yes/no; yes answers get 1–3 severity rating) and caregiver distress (1–5)	Informant self-administers	NPI-Q severity score range: 0–36. NPI-Q distress score: 0–60; higher scores c/w more severe behavioral symptoms and caregiver distress	<ul style="list-style-type: none"> • Takes 5 min • Must have reliable informant • Assesses for behavioral symptoms associated with multiple dementia syndromes

See the text for definitions of MCI and dementia.

Abbreviations: c/w, consistent with; GDS, Geriatric Depression Scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MCI, mild cognitive impairment; NPI-Q, Neuropsychiatric Inventory Questionnaire.

Data from Lin, J. S., et al. Screening for cognitive impairment in older adults: A systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013 159(9): 601-612.

Box 2**Selected components of a bedside mental status examination grouped by cognitive domain**

- Orientation
 - State name, month, date, year, day of the week, season, and current location
- Attention
 - Spell “world” forward and backward
 - State months of the year in reverse order
 - Count backward from 100 by 7s
- Memory
 - Repeat 3 words and remember them for 5 minutes
 - Describe what has been going on in the news lately
- Language
 - Name 3 common items (eg, thumb, knuckles, collar, pointed to by the examiner)
 - Repeat a phrase (eg, “Traffic conditions are expected to be heavy today.”)
 - Provide a speech sample (eg, by describing a picture or current event)
- Visuospatial processing
 - Draw a clock (also tests executive function)
 - Bisect a line
- Executive function
 - Name as many words that begin with the letter F as you can think of in 1 minute
 - State the letters of the alphabet, alternating with sequential numbers (ie, “A1B2” and so on)

Box 3**Focused neurologic examination for a patient with a cognitive complaint**

- Cranial nerves:
 - Assess for masked facies or reduced eye blink rate
 - Listen for dysarthria
 - Look for facial asymmetry, including flattening of the nasolabial fold
 - Determine whether eye movements and visual fields are full
- Motor, sensory, and reflexes
 - Test briefly, assessing for focal weakness, fasciculations, or hyperreflexia concerning for amyotrophic lateral sclerosis, which is sometimes comorbid with frontotemporal dementia, or other asymmetry suggestive of a focal lesion (eg, stroke, tumor)
- Tone
 - Assess for cogwheel rigidity at the elbows, wrists, and neck by asking the patients to relax and allow you to move their bodies for them
- Coordination and extrapyramidal function
 - Evaluate rapid alternating movements (eg, by having the patients alternate striking their thighs with a closed fist and open palm)
 - Evaluate for emergence of a rest tremor by having the patients rest their hands in their laps and count backward from 20 to zero with eyes closed
- Gait and postural stability
 - Have patients stand without the use of their hands
 - Observe gait (noting arm swing, posture, stride length, and turn)
 - Assess tandem gait
 - Use pull test to assess for postural instability

the patient is independent in BADL and requires some assistance with IADL. In the moderate stage, the patient requires some assistance with BADL and requires assistance with or is dependent in IADL. In the severe stage, the patient requires assistance with or is dependent in BADL and is dependent in IADL.

The labels MCI and dementia both denote a concern that a disease, most likely a brain disease, is causing the cognitive problems, and so should not be applied if the deficits are explained by delirium or some other cause that is not a brain disease, such as decompensated congestive heart failure.

Work-up

Patients with cognitive impairment should be screened for hypothyroidism and vitamin B₁₂ deficiency, because these entities can cause cognitive decline that may improve with treatment.^{17–19} It is reasonable to obtain a complete blood count with differential and comprehensive metabolic panel to screen for other general medical problems (eg, anemia, kidney or liver failure, electrolyte derangements) that could affect cognition.^{17,20} Depending on clinical context, clinicians may consider ordering other laboratory tests, such as folate, vitamin D, heavy metal screen, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, Lyme serologies, human immunodeficiency virus-1/2 immunoassay, and rapid plasma reagin.^{16,20,21} Patients in whom OSA is suspected should undergo a sleep study or be referred to a sleep specialist.

All patients with cognitive impairment should undergo structural brain imaging. Brain imaging is not indicated in patients with SCD because normal age-related changes can overlap with the early atrophic changes seen in neurodegenerative disease.²² Thus, structural brain imaging, in the absence of objective cognitive impairment, is often clinically uninterpretable, because mild atrophy could be age related, and a normal result does not rule out the small possibility of occult disorder.

Although both computed tomography (CT) and magnetic resonance imaging (MRI) are acceptable, the preferred brain imaging modality for cognitive impairment is MRI without contrast, which has greater diagnostic yield and avoids ionizing radiation. CT without contrast, which is generally less costly, is a suitable alternative when MRI is contraindicated or otherwise unable to be obtained.¹⁶ Imaging enables the clinician both to assess for unexpected structural findings that could be affecting cognition (eg, a tumor, silent stroke, or subdural hematoma) and to identify features suggestive of specific underlying neurologic diagnoses.²³ Several of the diseases that cause dementia have characteristic imaging findings (eg, hippocampal and posterior parietal atrophy in Alzheimer disease [AD]) (**Table 2**).²⁴ However, these findings can be subtle, and the relationship between imaging findings and underlying disorder is best thought of as probabilistic, with the most compelling cases being those in which the clinical symptoms and the imaging findings align.

MRI is also helpful for identifying cerebrovascular disease, because many types of vascular brain injuries have identifiable imaging correlates. White matter hyperintensities, which are suggestive of chronic small vessel ischemic disease, are commonly related to typical cardiovascular risk factors (eg, hypertension, smoking),^{25,26} but are also commonly seen in AD.^{27,28} Similarly, cerebral microbleeds (CMBs) are commonly seen in both vascular cognitive impairment and AD. Deep subcortical CMBs are usually hypertensive in origin, whereas lobar CMBs are more often associated with cerebral amyloid, and thus are suggestive of AD.²⁹

Normal-pressure hydrocephalus (NPH) can be suggested, but not definitively diagnosed, by characteristic imaging findings, including ventriculomegaly and disproportionately enlarged subarachnoid space.³⁰ There has been growing recognition that

Neurologic Disease	Common MRI Findings
AD	Atrophy affecting the hippocampi, MTLs, and posterior parietal lobes ^a
DLB	Normal MRI or mild, nonspecific atrophy with relative sparing of MTLs ^b
Frontotemporal dementia	Atrophy of frontal and temporal lobes ^c
Vascular cognitive impairment	Multiple bilateral chronic lacunar strokes; white matter hyperintensities ^c
Normal-pressure hydrocephalus	Ventriculomegaly; disproportionately enlarged subarachnoid space ^d

Abbreviation: MTLs, medial temporal lobes.

^a Data from Whitwell, J. L. Progression of atrophy in Alzheimer disease and related disorders. *Neurotox Res.* 2010 **18**(3-4): 339-346.

^b Data from Yousef, T., et al. Neuroimaging in Lewy body dementia. *J Neurol.* 2019 **266**(1): 1-26.

^c Data from Masdeu, J. C. Neuroimaging of Diseases Causing Dementia. *Neural Clin.* 2020 **38**(1): 65-94.

^d Data from Graff-Radford, N. R. and D. T. Jones. Normal Pressure Hydrocephalus. *Continuum (Minneapolis)*. 2019 **25**(1): 165-186.

mixed dementia (ie, multiple disorders together causing the impairment) is common, particularly in the elderly.^{31,32}

If the diagnosis is still unclear, additional studies or a referral to a cognitive specialist may be needed. A fluorodeoxyglucose-PET scan of the brain can distinguish between frontotemporal dementia (FTD) and AD. Amyloid PET scans are approved for the detection of amyloid by the Food and Drug Administration (FDA) in the United States, but, as of this writing, are not covered by any insurance plans. Cerebral spinal fluid from a lumbar puncture (LP) can be tested for biomarkers of specific diseases, including AD (with amyloid-beta-42 and phosphorylated tau),³³ sporadic Creutzfeldt-Jakob disease (with real-time quaking-induced conversion),^{34,35} autoimmune and paraneoplastic encephalitides (with respective panels),³⁶ and other inflammatory entities (with protein and white blood cell counts).³⁷ A high-volume LP, preceded and followed by cognitive and timed walking tests, can evaluate for NPH, in the appropriate context of the clinical triad (gait disturbance, urinary incontinence, and dementia) and suggestive neuroimaging.³⁰

Providing a Diagnosis

Discussions about the diagnosis should include information about the level of impairment (MCI or dementia) and the causes. If the patient has SCD, the clinician should explain that cognitive testing was normal and provide prognostic information. Individuals with SCD are at a modestly increased risk of progression to MCI and dementia over subsequent years, compared with the general population.³⁸⁻⁴⁰ It is reasonable to follow the patient over time with repeated cognitive assessments to assess for onset of objective cognitive decline. Education about cognitive aging is warranted as well.

Clinicians giving a diagnosis of MCI discuss with patients and their families the meaning of the diagnosis and its prognosis.² People with MCI can progress to dementia, remain in an MCI state, or revert to normal cognition, and studies have shown that all 3 outcomes are common.² Each year, 5% to 20% of patients with MCI progress to dementia.²⁰

A diagnosis of dementia merits disclosure of the disease that is causing it, or, if that cause is uncertain, an offer for referral to a specialist. **Table 3** lists abbreviated diagnostic criteria of selected commonly diagnosed neurodegenerative diseases that cause dementia. Some common dementia syndromes, such as NPH and vascular dementia, do not have a single set of widely agreed-on diagnostic criteria.

If the patient has a neurodegenerative disease, it is important to stage the disease. Diagnostic disclosure should explain that these conditions are gradually progressive, and the goal of any intervention is to slow down or stabilize the functional decline and other symptoms. Family members in particular need to understand this so they can

Table 3 Abbreviated diagnostic criteria for commonly diagnosed neurodegenerative dementias	
Diagnosis	Abbreviated Diagnostic Criteria
AD dementia ^a	<ul style="list-style-type: none"> • Progressive, insidious decline with dementia-level impairment • Amnesic or nonamnesic presentation <ul style="list-style-type: none"> ◦ Amnesic (most common): impairment in learning and episodic memory ◦ Nonamnesic: language (particularly word finding), visuospatial, or executive function • Not better explained by another entity • Can increase certainty with imaging or CSF biomarkers
Behavioral variant frontotemporal dementia ^b	<ul style="list-style-type: none"> • Progressive cognitive and/or behavioral decline • Need 3 of the following: <ul style="list-style-type: none"> ◦ Behavioral disinhibition ◦ Apathy or inertia ◦ Compulsive, ritualistic, or perseverative behavior ◦ Hyperorality ◦ Dysexecutive presentation with relative sparing of memory and visuospatial function • Can increase certainty with imaging biomarkers
DLB ^c	<ul style="list-style-type: none"> • Progressive cognitive decline with dementia-level impairment • Core clinical features: <ul style="list-style-type: none"> ◦ Fluctuating cognition ◦ Well-formed visual hallucinations ◦ RBD ◦ Parkinsonism • Supportive features: sensitivity to antipsychotics, postural instability, falls, dysautonomia, delusions, anxiety, apathy, depression • Probable DLB: 2 core features or 1 core feature plus 1 indicative biomarker • Possible DLB: 1 core feature or 1 indicative biomarker

Abbreviation: CSF, cerebrospinal fluid.

^a Data from McKhann, G. M., Knopman D.S., Chertkow H., et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011 7(3): 263-269.

^b Data from Rascovsky K., Hodges J.R., Knopman D., et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain.* 2011 134(Pt 9): 2456-2477.

^c Data from McKeith I. G., Boeve B.F., Dickson D.W., et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology.* 2017 89(1): 88-100.

help the patient live well with the disease and prepare for the future. Each cause of dementia has its own prognosis, but clinicians should emphasize that there is variability in rates of progression.

TREATMENT OF COGNITIVE IMPAIRMENT

If the work-up uncovers an alternative cause of cognitive impairment (eg, hypothyroidism, OSA), it should be treated. Vascular contributors to cognitive decline, such as hypertension, diabetes, and smoking, should be addressed. Medications that contribute to cognitive impairment, particularly anticholinergic medications, should be tapered or stopped, if possible.² NPH is treated with ventriculoperitoneal shunting.

Pharmacotherapy

As of 2020, there are no approved therapies shown to modify neurodegenerative disorders, although many are being studied in clinical trials. The available medications are symptomatic treatments.

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors, including donepezil, galantamine, and rivastigmine, are labeled for use in AD dementia and may also be effective for vascular dementia and DLB.⁴¹ Acetylcholinesterase inhibitors can worsen behaviors in FTD,⁴² and there is insufficient evidence of efficacy in MCI.² The goal of treatment with acetylcholinesterase inhibitors is to improve or stabilize memory and attention by inhibiting the breakdown of acetylcholine, a neurotransmitter released by cholinergic neurons in the basal forebrain, an area known to be affected by AD.⁴³ Common side effects include diarrhea, nausea, leg cramps, abnormal dreams, and bradycardia. Patients with a history of bradycardia or conduction abnormalities should not be prescribed acetylcholinesterase inhibitors. Some patients who cannot tolerate oral donepezil because of gastrointestinal side effects are able to tolerate the rivastigmine patch.⁴¹ If the side effects persist and are bothersome, the clinician should consider discontinuing the medication because any mild symptomatic benefit is likely to be overshadowed by side effects. Patients and families should be advised that, because the benefits of acetylcholinesterase inhibitors tend to be subtle, it is often not obvious that the medication is helping, even in patients who are doing a little better than they otherwise would be.

Memantine

Memantine, an *N*-methyl-*D*-aspartate (NMDA) receptor antagonist, is thought to work by blocking the effects of excess glutamate and by upregulating NMDA receptor expression.⁴⁴ Memantine is indicated for use in moderate to severe AD,⁴⁵ and there is also evidence to support off-label use in mild to moderate vascular dementia.⁴⁶ Memantine has been shown to confer modest improvements in thinking, everyday functioning, behavior and mood.⁴⁷ Although memantine is generally well tolerated, the most common side effect is dizziness.⁴⁷ As is the case with acetylcholinesterase inhibitors, patients and families should be counseled that the benefits of memantine tend to be subtle.

A common practice for patients with AD, vascular dementia, or mixed dementia is to start an acetylcholinesterase inhibitor at the mild dementia stage and to add memantine to the drug regimen when the patient progresses to a moderate stage of dementia.

Environmental, Psychological, and Behavioral Interventions

Various lifestyle interventions, which can both improve quality of life and slow functional decline, are paramount in the management of cognitive impairment. When

giving a dementia diagnosis, clinicians should counsel patients and families to work to create a safe, structured, social, and engaged day. All patients with SCD, MCI, and dementia should be active physically, mentally, and socially. Activities that combine physical, mental, and social activity in some way are especially valuable; for example, joining a book club (which is mentally and socially stimulating) or taking a dance class (which is stimulating in all 3 regards). Unfortunately, the Covid-19 pandemic has rendered many common lifestyle measures unsafe for elderly individuals because of infection risk in group settings. Caregivers should endeavor to facilitate stimulating experiences that are also safe; for example, home exercise programs and video conference–based social experiences.

Exercise

In people with dementia, exercise programs have been shown to improve or stabilize functional status⁴⁸ and cognition.⁴⁹ The type and amount of exercise with the best evidence basis in people with MCI or AD is 3 or 4 ~45-minute moderate-intensity aerobic exercise workouts per week.⁴⁹ Mind-body exercises (eg, yoga, tai chi) have also been shown to improve cognition in MCI.⁵⁰

Cognitive stimulation

Studies have shown some benefit to cognitively stimulating activities, including computer activities, video games, and virtual reality programs for MCI⁵¹ and dementia.^{52,53} It is reasonable to refer patients to cognitive fitness/rehabilitation programs to the extent that they are available and affordable. Clinicians should also encourage pursuit of cognitively stimulating activities in day-to-day life. The choice of activity depends on the abilities and interests of the patient. Mindfulness meditation may help patients with MCI build cognitive reserve, become more socially engaged, and feel better about their diagnoses.⁵⁴ Speech therapy can be helpful for people with prominent language disturbance.

Social engagement

Poor social engagement (ie, loneliness) is associated with an increased risk of dementia,^{55,56} and community cultural engagement (eg, visiting museums, going to the theater) may be a protective factor for dementia risk.⁵⁷ Social engagement is most stimulating when it involves people outside the patient's innermost circle. Some caregivers try to provide round-the-clock care and companionship, but it is in the best interest of both patients and caregivers to intersperse interactions with other people, which can take the form of visiting aides, an adult day program, or having an old friend take the patient out for lunch once a week.

Nutrition

The Mediterranean diet has been associated with a lower risk of conversion from MCI to dementia.^{58,59} Patients with dementia are at increased risk of malnutrition, and nutritional status may have some bearing on functional status.⁶⁰ For patients at risk for malnutrition, caregivers should provide routine meals and snacks. (Often, even if they say they are not hungry, they will eat once a meal is served to them.) Nutrition supplements, such as shakes, can provide additional nutrition.⁶¹ Patients should avoid moderate or heavy alcohol use.

Sleep

Behavioral interventions for sleep disturbance include counseling about sleep hygiene, light therapy, and referral for cognitive behavioral therapy for insomnia.^{62,63} Sleep disturbance can be exacerbated by excessive napping and insufficient daytime

activity. Crafting a more active day that involves leaving the house during daylight hours can result in improved sleep.

MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS

Neuropsychiatric symptoms are common in people with cognitive impairment. Depression can itself cause cognitive impairment (pseudodementia), which can improve with appropriate treatment.⁶⁴ Depressive symptoms are also a common neuropsychiatric manifestation of dementing disorders, as are anxiety, irritability, agitation, apathy, hallucinations, and delusions. Although it is common for patients to require pharmacologic interventions, nonpharmacologic strategies (ie, behavioral interventions, environmental modifications, and lifestyle changes) are first line for management of dementia-related neuropsychiatric symptoms.

Nonpharmacologic Management of Neuropsychiatric Symptoms

Nonpharmacologic strategies for management of neuropsychiatric symptoms should always be considered first line instead of pharmacologic treatments, especially antipsychotic medications. Assessment for underlying causes of neuropsychiatric symptoms should be the first step. Issues such as pain, fatigue, or problems with the environment (eg, temperature, lighting) should be addressed. Environmental adaptations can range from raising the shades during the day; to building a soothing multi-sensory environment with music, art, plants, and aromatherapy⁶⁵; to relocating the patient to a memory care facility. Interventions designed to equip family caregivers with strategies to manage neuropsychiatric symptoms have the best evidence basis.⁶⁶ Caregivers should be encouraged to seek out caregiving workshops, support groups, and other resources. Caregiver training can teach cognitive reframing, stress reduction techniques, and other skills for addressing neuropsychiatric symptoms in ways that are personalized to the needs of individual patients.

Pharmacologic Treatment of Neuropsychiatric Symptoms

Selective serotonin reuptake inhibitors (SSRIs) are often used for treatment of depression and anxiety in dementia, despite a weak evidence basis for this practice.^{67,68} Nevertheless, because SSRIs are first line for late-life depression,⁶⁹ it is reasonable to treat dementia-related depression and anxiety with SSRIs.⁴¹ The SSRIs most commonly used in this population are sertraline, citalopram, and escitalopram.⁶⁹ SSRIs are also used to treat dementia-related agitation and psychosis, often in an effort to avoid the notable side effects of antipsychotics. The SSRI with the most solid evidence basis for this practice is citalopram.^{67,70} Our practice is to start with sertraline, because it is associated with a lower risk of QT prolongation than citalopram or escitalopram.⁷¹

Antidepressants with other mechanisms of action (eg, duloxetine, bupropion, mirtazapine, trazodone) are also sometimes used to target dementia-related mood symptoms in tandem with some other symptom (eg, targeting neuropathic pain and depression with duloxetine, or low appetite and anxiety with mirtazapine). Tricyclic antidepressants are often avoided because of their anticholinergic side effects.⁴¹ Buspirone, which is labeled to treat generalized anxiety disorder, can be used to manage anxiety in this population, and there is weak evidence to suggest that it could be helpful in managing dementia-related agitation.^{72,73} Benzodiazepines should be avoided. They increase the risk of falls, worsen cognition, and soon lead to dependence.

Atypical antipsychotic drugs, such as quetiapine, olanzapine, risperidone, and pimavanserin, are often used to treat dementia-related agitation and psychosis,

despite an FDA warning of increased mortality.⁷⁴ Because of the risks, it is imperative that nonpharmacologic interventions be tried before initiating treatment with antipsychotics.⁷⁵ Hallucinations and delusions should only be treated pharmacologically to the extent that they are distressing to the patient or disruptive for care or safety. Clinicians should advise patients and their families about the risks and plan to withdraw the drug if there is no response in 4 weeks and, if there is a response, to attempt to wean the drug within 4 months.⁷⁵ Pimavanserin is labeled for treatment of Parkinson disease psychosis, and there is evidence to support its use in dementia-related psychosis.⁷⁶

Sleep disturbances are common in cognitive disorders.⁷⁷ If nonpharmacologic strategies fail, there are several medication options. Despite studies indicating a lack of efficacy, melatonin is commonly used for insomnia in people with dementia because of its good safety profile.⁷⁸ Trazodone may be an effective and reasonably safe treatment of dementia-related sleep disturbance.⁷⁸

CONSIDERATIONS

Safety is a major issue for patients with cognitive impairment. Clinicians should be prepared to discuss driving with patients and families. Some patients with MCI and mild dementia can drive safely, whereas others cannot. People with moderate or severe dementia should not drive. Some states mandate that clinicians formally report unsafe drivers. When in doubt, a driver evaluation, performed at a rehabilitation center by an occupational therapist, can clarify whether the patient is safe behind the wheel.

Varying levels of supervision are needed for patients with cognitive disorders. Many patients with MCI or mild dementia need little supervision except in error-prone domains, particularly managing finances and medications. Patients with moderate to severe dementia should have near-constant supervision. Potential hazards for cognitively impaired patients should be addressed proactively; for example, removing guns from the home and turning off the gas to the stove. Gait instability during the examination or report of falls warrants referral to physical therapy to aid in fall prevention. Patients with dysphagia should see a speech pathologist.

Patients with cognitive impairment should be advised, together with their families, to plan for the future, which could include discussions about advance directives, powers of attorney, finances, and living arrangements.²

CLINICS CARE POINTS

- A knowledgeable informant is a crucial source of important historical information.
- Ensure cognitive impairment is objectively present before ordering a work-up. Structural neuroimaging is not indicated in patients with subjective decline only.
- The standard of care for MCI is lifestyle interventions. If prescribing a medication for MCI (eg, donepezil), patients must be counseled that the treatment is off label.
- Behavioral interventions are first line for neuropsychiatric symptoms of dementia. Interventions designed to educate and support caregivers are particularly effective.

SUMMARY

In conclusion, clinicians should take a systematic approach to evaluating and managing patients with cognitive impairment. A careful history, with input from a knowledgeable informant, often provides the most salient information. The patient's cognitive testing, examination, imaging, and laboratory results help complete the picture. The

diagnosis consists of 2 parts: a level of impairment (eg, MCI or dementia) and probable cause (eg, AD, DLB, vascular dementia). Patients with unusual presentations or who are interested in research should be referred to an academic memory or cognitive center. Regardless of the underlying disorder, treatment is symptomatic, and nonpharmacologic interventions are preferred to pharmacologic ones for neuropsychiatric symptoms. Safety is a “moving target” in patients with cognitive impairment and should be a focus for clinicians.

DISCLOSURE

The authors have nothing to disclose.

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