

in the clinic
Dementia

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Dementia is defined as a decline in cognitive function from baseline. It is a syndrome caused by a variety of disorders, the most common of which are Alzheimer disease, vascular dementia, Lewy body dementia, and frontotemporal dementia. The incidence and prevalence of dementia increase with age. It is estimated that by the year 2047, more than 9 million Americans will have some form of it (1). Institutionalization is ultimately required for many patients with dementia, and 67% die in nursing homes (2). Although there is currently no cure for most forms of dementia, research findings and accumulated clinical experience support a set of practices that serve to maximize the function and overall well-being of patients with dementia and their caregivers.

Prevention

What medical interventions or health behaviors can help patients prevent dementia?

Although there are several risk factors for different types of dementia, data supporting the effectiveness of specific preventive measures are limited.

Hypertension

Untreated hypertension in mid-life and later is a proven risk factor for both Alzheimer disease and vascular dementia (3). A number of randomized, controlled trials (RCTs) have shown that treating hypertension reduces the risk for dementia.

A large, placebo-controlled RCT with 2418 participants demonstrated that treating systolic hypertension in patients over the age of 60 years reduced the incidence of dementia by 50%, from 7.7 cases to 3.8 cases per 1000 patient-years (4).

Another placebo-controlled RCT with 6106 participants showed that treating hypertension with the angiotensin-converting enzyme inhibitor perindopril with or without the thiazide diuretic indapamide reduced the incidence of recurrent stroke with dementia by 34% and of recurrent stroke with any cognitive decline by 45% in patients with past stroke or transient ischemic attack (5).

Hypercholesterolemia and Diabetes Mellitus

Hypercholesterolemia, particularly in mid-life, is associated with an increased incidence of both Alzheimer disease and vascular

dementia (6), and case-control studies have shown an association between use of cholesterol-lowering medications and reduced incidence of dementia (7). Diabetes has been shown in both longitudinal cohort and case-control studies to be an independent risk factor for vascular dementia (8, 9). However, as with hypercholesterolemia, there are no trials that demonstrate that treating diabetes prevents dementia.

Lifestyle Modifications

Cigarette smoking is associated with an increased risk for stroke, although the evidence for an association with Alzheimer disease is mixed (10). Head injury earlier in life has been shown in a number of epidemiologic studies to be associated with dementia later in life (11). Finally, physical inactivity, both in mid-life and later, has been associated with an increased risk for dementia in both retrospective and prospective studies (12, 13). Thus, counseling patients to quit smoking; engage in behaviors to reduce the risk for head injury, such as wearing seat belts and bike helmets; and be physically active may reduce the risk for dementia.

Medications

Clinicians should regularly review the medication regimens of elderly patients and minimize use of

1. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health.* 1998;88:1337-42. [PMID: 9736873]
2. Mitchell SL, Teno JM, Miller SC, et al. A national study of the location of death for older persons with dementia. *J Am Geriatr Soc.* 2005;53:299-305. [PMID: 15673356]
3. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging.* 2000;21:49-55. [PMID: 10794848]
4. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet.* 1998;352:1347-51. [PMID: 9802273]
5. PROGRESS Collaborative Group. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med.* 2003;163:1069-75. [PMID: 12742805]
6. Notkola IL, Sulkava R, Pekkanen J, et al. Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. *Neuroepidemiology.* 1998;17:14-20. [PMID: 9549720]
7. Jick H, Zornberg GL, Jick SS, et al. Statins and the risk of dementia. *Lancet.* 2000;356:1627-31. [PMID: 11089820]
8. Curb JD, Rodriguez BL, Abbott RD, et al. Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. *Neurology.* 1999; 52:971-5. [PMID: 10102414]
9. Meyer JS, McClintic KL, Rogers RL, et al. Aetiological considerations and risk factors for multi-infarct dementia. *J Neurol Neurosurg Psychiatry.* 1988;51:1489-97. [PMID: 3221215]

medications that can cause cognitive impairment, such as benzodiazepines, anticholinergics, barbiturates, and other sedative-hypnotics. A number of studies have shown that elderly patients taking benzodiazepines or other sedative-hypnotics perform more poorly on cognitive tests than those not taking these medications (14).

Because inflammation is present in the brains of patients with Alzheimer disease and epidemiologic evidence links use of non-steroidal anti-inflammatory drugs (NSAIDs) earlier in life to a lower risk for Alzheimer disease (15), some have questioned whether

NSAIDs might prevent dementia. However, prospective studies to date have not shown a protective effect of NSAIDs, and they are not recommended for prevention of dementia (16).

Significant epidemiologic evidence links mid-life estrogen use to a lower incidence of dementia later in life (17). However, in prospective prevention trials, including the large Women's Health Initiative Memory Study, use of estrogen plus progesterin for prevention of dementia was associated with an increased incidence of dementia, as well as other medical complications (18).

Prevention... Although there are few data to support specific measures to prevent dementia, clinicians should treat cardiovascular risk factors, such as hypertension, hypercholesterolemia, and diabetes, and encourage smoking cessation and regular exercise. They should also counsel patients about avoiding head injury and avoid prescribing medications that can alter cognitive function. Neither NSAIDs nor estrogen should be recommended for prevention of dementia.

CLINICAL BOTTOM LINE

Screening

Should clinicians screen for dementia?

The U.S. Preventive Services Task Force concluded that there is insufficient evidence to recommend for or against widespread screening for dementia in elderly patients (19). However, many patients with dementia in the primary care setting, even those in more advanced stages of the disease, remain undiagnosed despite having routine general medical care (20).

Moreover, patients referred to dementia specialists after "screening" have been diagnosed at an earlier stage of illness than those referred from physicians or families (21). Therefore, given the high prevalence of dementia and its associated morbidity, the clinician should consider secondary case-finding

measures for dementia in elderly patients with unexplained functional decline, deterioration in hygiene, questionable adherence to medication regimens, or new-onset psychiatric symptoms.

What methods should clinicians use when looking for dementia?

When looking for dementia in elderly patients, clinicians should use a standardized screening instrument together with a brief history from the patient and a knowledgeable informant. The screening instrument should be easy to use, demonstrate high sensitivity, be widely available, and be supported by normative population data relevant to the patient. Two examples of such instruments are the Mini-Mental Status Examination (22) and the Mini-Cog (23).

10. Lee PN. Smoking and Alzheimer's disease: a review of the epidemiological evidence. *Neuroepidemiology*. 1994;13:131-44. [PMID: 8090255]
11. Mortimer JA, van Duijn CM, Chandra V, et al. Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int J Epidemiol*. 1991;20 Suppl 2:S28-35. [PMID: 1833351]
12. Broe GA, Henderson AS, Creasey H, et al. A case-control study of Alzheimer's disease in Australia. *Neurology*. 1990;40:1698-707. [PMID: 2146525]
13. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology*. 1995;45:1161-8. [PMID: 7783883]
14. Larson EB, Kukull WA, Buchner D, et al. Adverse drug reactions associated with global cognitive impairment in elderly persons. *Ann Intern Med*. 1987;107:169-73. [PMID: 2886086]
15. Etminan M, Gill S, Samii A. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. *BMJ*. 2003;327:128. [PMID: 12869452]
16. ADAPT Research Group. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). *PLoS Clin Trials*. 2006;1: e33. [PMID: 17111043]
17. Cache County Memory Study Investigators. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. *JAMA*. 2002;288:2123-9. [PMID: 12413371]

Screening... There is insufficient evidence to recommend for or against screening asymptomatic people for dementia. However, clinicians should be alert for unexplained functional decline, deterioration in hygiene, questionable adherence to medication regimens, or new-onset psychiatric symptoms in elderly patients and use standardized instruments, such as the Mini-Mental Status Examination or the Mini-Cog, to look for cognitive dysfunction in such patients.

CLINICAL BOTTOM LINE

Diagnosis

Clinical Diagnosis of Alzheimer Disease (AD)

Definite AD:

- Clinical criteria for probable AD plus histopathology confirmation

Probable AD:

- Dementia by clinical examination and standardized instrument (e.g., Mini-Mental State Examination)
- Deficits in >2 areas of cognition
- Progressive cognitive decline
- Normal levels of consciousness
- Onset between age 40 and 90 years
- No other cause
- Supportive factors, including positive family history, cerebral atrophy on neuroimaging, normal electroencephalogram and lumbar puncture

What elements of the history are most important in evaluating patients with suspected dementia?

Clinicians should use the patient's history to characterize the cognitive deficits, generate a differential diagnosis, and attempt to determine the cause of the dementia. This is best accomplished by identifying medical, neurologic, and psychiatric symptoms that may be clues to the cause of the cognitive problems and detailing their order of appearance, severity, and associated features. In the case of cognitive difficulties, it is mandatory to try to obtain collateral information from a knowledgeable informant, because cognitive dysfunction can impair the patient's ability to serve as an accurate reporter. It is often easier to collect this information, as well as information about psychiatric symptoms, without the patient present.

In taking the history, it is critical for clinicians to be knowledgeable about the differential diagnosis and natural history of the most common types of dementia (Table 1). For example, in classic Alzheimer disease, early symptoms are dominated by difficulties with short-term memory, subtle language and visuospatial perception difficulties, and changes in executive function with significant reductions in efficiency and organizational abilities of which the patient may or may not be aware. Symptoms begin insidiously and are slowly progressive. Overall level of alertness remains unimpaired. Patients or

families may not label these difficulties as memory problems per se but may instead report multiple repetitions of questions or conversations with no recollection of previous discussions, increased forgetfulness manifested by losing objects or becoming confused while shopping, or simply overall increased disorganization and decreased efficiency. Symptoms are often first noticed or reported at the time of a life change, such as the death of a spouse or a move into a new residence. See the Box for clinical diagnostic criteria for definite and probable Alzheimer disease (24).

Many elderly patients report minor cognitive problems, such as mild forgetfulness, difficulty remembering names, and mildly reduced concentration. In patients without dementia, these symptoms are typically sporadic, do not worsen significantly over time, are easily compensated for, and do not affect function. In contrast, in early dementia, the symptoms insidiously become established as a pattern, worsen over time, are difficult to compensate for, and eventually affect speech fluency and hamper the performance of routine activities, such as meal preparation, bill paying, and financial planning. Patients with memory problems should be screened for dementia as described previously, but a complete dementia evaluation should be reserved for those with the clinical syndrome of dementia.

18. WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003;289:2651-62. [PMID: 12771112]

19. U.S. Preventive Services Task Force. Screening for dementia and other diseases. Guide to clinical preventive services. 2nd ed. Baltimore: Williams & Wilkins; 1996: 531-40. Accessed at www.guideline.gov/summary/summary.aspx?doc_id=3690 on 7 February 2008.

20. Valcour VG, Masaki KH, Curb JD, et al. The detection of dementia in the primary care setting. *Arch Intern Med*. 2000;160:2964-8. [PMID: 11041904]

Table 1. Differential Diagnosis of Cognitive Difficulties*

Disease	Characteristics	Notes
Alzheimer disease	Early symptoms include gradual memory loss, preserved level of consciousness, impaired IADL performance, subtle language errors, and worsened visual-spatial perception. Middle-stage symptoms include apraxia, disorientation, and impaired judgment. As the illness progresses, aphasia, apraxia, agnosia, inattention, and left-right confusion develop. In the final stages patients are dependent for IADL care, and lose the ability to ambulate and even swallow	The presenting problem to the physician may not relate to cognition. Earliest presenting symptoms may be paranoid delusions or depression, which are only later appreciated as part of a dementia. Dementia may initially become manifest with a major life change. Neurologic signs, such as falls, tremor, weakness, or reflex abnormalities, are not typical early in the disease. Seizures occur frequently in advanced disease; their presence earlier suggests a diagnosis other than Alzheimer disease.
Vascular dementia	Ideally, loss of function should be correlated temporally with cerebrovascular events. "Stepwise" deterioration may be seen. Level of consciousness should be normal. May be present in patients with "silent" strokes, multiple small strokes, or severe diffuse cerebrovascular disease.	Should be suspected in any patient with cerebrovascular risk factors, even if a neurologic examination does not suggest a stroke.
Lewy body dementia	Mild parkinsonism; unexplained falls; hallucinations and delusions early in the illness; extreme sensitivity to extrapyramidal side effects of antipsychotic medications; gait difficulties and falls; and fluctuating cognition.	May account for up to 20% of total dementia cases. Should be suspected in patients with nonvascular dementia but abnormal neurologic examination.
Frontotemporal dementia	Onset often before age 60 years. Language difficulties are common. Memory often preserved early on. Prominent personality changes, often with behavioral disturbances, such as hyperphagia, worsened impulsivity or aggression, or prominent apathy.	Includes such disorders as progressive supranuclear palsy, primary progressive aphasia, semantic dementia, amyotrophic lateral sclerosis with dementia, and corticobasal degeneration. Functional neuroimaging often demonstrates diminished function in frontal or temporal lobes.
Delirium	Altered and fluctuating level of alertness and attention, often with globally impaired cognition. May have abrupt onset. Patients may have psychomotor retardation and mental status abnormalities of depressed or elevated mood, hallucinations, delusions, and agitated behavior.	Must be excluded in order to diagnose dementia. Diagnosis is critical because delirium may reflect serious systemic disturbance, such as metabolic abnormalities, medication effects, or infection.
Major depression	Low mood; anhedonia; diminished sense of self-worth; hopelessness; altered appetite, libido, and sleep; increased somatic complaints; irritability; and wishes for death.	Cognitive impairment may result solely from major depression. Major depression may also be the initial presentation of dementia.
Medications	Common offenders include benzodiazepines, barbiturates, anticholinergics, and other sedative-hypnotics.	Cognitive impairment of patients with dementia may be exacerbated by medications.
Mild cognitive impairment	Evidence of memory impairment in the absence of other cognitive deficits or functional decline.	Many progress to dementia at a rate of about 12%–15% per year.
Subdural hematoma	May or may not occur in setting of falls or head injury. Nonspecific headache. Level of consciousness may wax and wane.	Classic presentation is the exception rather than the rule. Neurologic deficits may be minor.
Traumatic brain injury	Clinical features may vary according to site of injury. Personality and mood changes are common.	The postconcussion syndrome may include inattention.
Normal-pressure hydrocephalus	Dementia, gait abnormality (slow, broad-based, impaired turning), and urinary incontinence. Dementia is often associated with psychomotor slowing and apathy.	If suspicion is high, lumbar puncture with pre- and post-tap gait monitoring is performed. Ventriculoperitoneal shunting can be curative in some patients.
Brain tumor (primary or metastatic)	Frontal or corpus callosum tumors result in memory impairment with global intellectual decline. Parietal lobe tumors may produce apraxia, aphasia, agnosia, agraphesthesia, astereognosia, and neglect.	Neuroimaging rules the diagnosis in or out.
Vitamin B ₁₂ deficiency	Insidious onset. May be associated with depression. Neurologic examination may reveal diminished proprioception and vibratory sense, ataxia, and positive Babinski sign.	If serum B ₁₂ is in the low-normal range, elevated serum methylmalonic acid and homocysteine levels indicate low intracellular vitamin B ₁₂ . Anemia may be absent.
Thyroid disease	Both hypo- and hyperthyroidism can lead to cognitive difficulties.	Thyroid-stimulating hormone should be checked at the beginning of the dementia work-up.
Chronic alcohol use	Chronic alcohol use appears to lead to a mild-to-moderate dementia, which may reverse after a period of abstinence.	This is distinct from the Korsakoff syndrome, an isolated loss of short-term memory without global dementia.
Toxins	Aromatic hydrocarbons, solvents, heavy metals, marijuana, opiates, and sedative-hypnotics.	Urine or serum toxicology and heavy metal screens are useful.
Parkinson disease	Features of subcortical dementia, cortical dementia, or both. Free recall may be impaired with preservation of recognition memory. May have impaired visual-spatial function.	In contrast to Lewy body dementia, patients with Parkinson disease and dementia typically have motor symptoms of Parkinson disease long before dementia, and do not have prominent psychotic symptoms or fluctuating consciousness.
Other causes	Multiple sclerosis, CNS vasculitis, neurosarcoidosis, systemic lupus erythematosus, advanced liver or renal disease, Wilson disease, chronic CNS infection, electrolyte abnormalities, neurosyphilis, HIV-associated dementia, Huntington disease, and Creutzfeldt-Jacob disease.	

*CNS = central nervous system; IADL = instrumental activities of daily living.

Elements of the Cognitive Examination

- Standardized instrument (e.g., Mini-Mental State Examination)
- Object naming
- Task demonstration
- Word recall
- Proverb or situation interpretation
- Clock drawing or figure copying

How can clinicians distinguish dementia from delirium?

Clinicians evaluating a patient with a change in cognition or overall function must consider delirium.

Delirium is global impairment of cognition with characteristic worsening of alertness and attention. Onset may be abrupt or gradual, often with notable fluctuations in the level of impairment.

Although some patients may be agitated and manifest psychotic symptoms, others are slowed, drowsy, and appear mildly depressed or withdrawn. Prompt diagnosis of delirium is critical, because it usually reflects an underlying systemic condition, such as infection, metabolic derangement, medication effect, or malignancy.

How should clinicians evaluate patients with suspected dementia?

Clinicians should use the general physical examination to look for signs of conditions that can cause or worsen cognitive decline (Table 1). A complete mental status examination begins with an evaluation of alertness, general appearance, and cooperation. Speech should be evaluated both for its content (grammatical or semantic errors) and form (rate, fluency, volume). The patient's mood and affect should be assessed for evidence of depression, anxiety or mania, and suicidality, and thought content and perception are examined for the presence of delusions or hallucinations, as well as obsessions or compulsions.

The cognitive examination should include a standard instrument, such as the MMSE, which can be performed in about 5 minutes and provides an overview of orientation, immediate recall, concentration, naming, language function, praxis, and visual-spatial perception. The MMSE should be augmented by testing delayed recall by asking the patient to repeat 3 words from the MMSE 20 to 30 minutes after their initial presentation. Naming

and praxis can be further tested by asking the patient to name a series of common and uncommon objects and by asking them to demonstrate tasks, such as brushing hair or teeth or slicing bread. Abstract reasoning and judgment should be tested by asking for solutions to real-life problems, such as what to do if one smells smoke in the house, or for interpretation of proverbs or similes. Drawing a clock (spontaneously, or copying from an already drawn figure in the event of difficulty) is a quick test of visual-spatial perception, praxis, and planning ability. Corticostriatal deficits, such as neglect or left-right confusion, can be quickly tested for as well.

What laboratory tests are helpful in the evaluation of patients with cognitive dysfunction?

According to guidelines from the American Psychiatric Association and American Academy of Neurology, patients who are being evaluated for cognitive problems should have a laboratory evaluation for common medical disorders, with selected additional studies depending on the specific clinical situation (see Box on opposite page).

In general, patients with cognitive difficulties less than 3 years in duration should undergo a neuroimaging study (computed tomography [CT] or magnetic resonance imaging [MRI] scanning of the head) to exclude cerebrovascular disease, hemorrhage, tumor, or hydrocephalus as the cause of the cognitive dysfunction. Studies show that, in patients with cognitive problems, neuroimaging detects significant cerebrovascular disease even in patients in whom it was not suspected clinically (25). The yield is higher in patients with early age of onset, rapid progression, focal neurologic deficits, cerebrovascular disease risk factors, recent falls, central nervous system (CNS) infection, unexplained fluctuating level of consciousness, or symptoms atypical of Alzheimer disease. The

21. Barker WW, Luis C, Harwood D, et al. The effect of a memory screening program on the early diagnosis of Alzheimer disease. *Alzheimer Dis Assoc Disord.* 2005;19:1-7. [PMID: 15764864]
22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-98. [PMID: 1202204]
23. Borson S, Scanlan J, Brush M, et al. The mini-cog: a cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry.* 2000;15:1021-7. [PMID: 11113982]
24. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-44. [PMID: 6610841]

routine use of single-photon emission CT (SPECT) or positron emission tomography (PET) scanning is not recommended, although these tests may be useful in specific instances, such as in differentiating Alzheimer disease from frontotemporal dementia (26).

Genetic studies are not routinely indicated in the evaluation of dementia unless there is a specific concern about Huntington disease. There is evidence that testing for the *ApoE4* allele does not add substantially to the diagnosis (27). Testing for 1 of the 3 autosomal dominant gene mutations found in patients with familial Alzheimer disease is occasionally pursued when multiple family members are affected.

Other tests should be reserved for specific situations. Electroencephalography may be useful when there is a question of delirium, seizures, or encephalitis. Lumbar puncture may be indicated in patients under age 55 years and in those with rapidly progressive dementia, a positive rapid plasma reagin, suspicion of acute or chronic CNS infection or malignancy, or immunosuppression. Neuropsychological testing provides the most comprehensive assessment of cognitive function and is particularly useful when the diagnosis of dementia is unclear or it is necessary to precisely characterize the patient's cognitive impairment.

Laboratory Studies for Patients Being Evaluated for Cognitive Problems

- Comprehensive metabolic profile
- Complete blood count
- Thyroid-stimulating hormone level
- Vitamin B₁₂ level
- Rapid plasma reagin or fluorescent treponemal antibody

Selected patients may need to undergo additional tests, including:

- HIV
- Toxicology screen
- Erythrocyte sedimentation rate
- Heavy metal screen
- Folate
- Chest X-ray
- Urinalysis

Diagnosis... Clinicians should evaluate patients who present with cognitive and functional decline with a detailed history of medical, neurologic, and psychiatric symptoms from the patient and a knowledgeable informant and with a thorough physical, mental status, and cognitive examination. Basic laboratory studies include a comprehensive metabolic panel, complete blood count, thyroid-stimulating hormone level, and vitamin B₁₂ level. Selected patients may require additional laboratory tests. Clinicians should consider CT or MRI scanning of the head in patients with cognitive difficulties with a duration less than 3 years and in those with early age of onset, rapid progression, focal neurologic deficits, cerebrovascular disease risk factors, or atypical symptoms.

CLINICAL BOTTOM LINE

What should clinicians advise patients (and their caregivers) about their general health and hygiene?

Even in the early stages of dementia, patients may have difficulty comprehending the details of their medical care requirements; organizing their care; and keeping track of appointments, medications, or other recommendations. The clinician should be alert to these limitations and help prepare a care plan that compensates for them. Later in the illness, patients may be unable to identify physical signals, such as constipation, dysuria, tooth pain, or

diminished visual or auditory acuity, and the clinician should proactively look for these problems.

It is important to attend to general medical and preventive care as conscientiously as in patients without dementia. A major stroke or heart attack due to uncontrolled hypertension is likely to impair a patient's function and quality of life as much as the dementia itself, at least in the early and middle stages of the disease. For patients with more advanced dementia, ongoing attention to nutritional needs, skin care (particularly perineal), toileting

Treatment

25. Massoud F, Devi G, Moroney JT, et al. The role of routine laboratory studies and neuroimaging in the diagnosis of dementia: a clinicopathological study. *J Am Geriatr Soc.* 2000;48:1204-10. [PMID: 11037005]
26. Foster NL, Heidebrink JL, Clark CM, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain.* 2007;130:2616-35. [PMID: 17704526]
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schedules, and dental and denture care become more important.

What should clinicians advise about safety issues and other activities that may require supervision?

All patients with progressive dementia ultimately lose the ability to drive, but predicting when it is unsafe for an individual patient to continue to drive is difficult. Nonetheless, it is imperative to address the issue, as numerous studies have demonstrated that driving ability becomes impaired in early stages of the disease.

In a prospective, case-control study using the Washington University Road Test (with off-road and on-road components), 19% of patients with very mild Alzheimer disease failed the test, 41% with mild Alzheimer disease failed, and only 3% of controls failed (P < 0.001). Driving experience did not protect against this deterioration (28).

The clinician should inquire about recent motor vehicle accidents, near misses, or changes in the patient's driving ability. These inquiries should be made in a setting that facilitates an open exchange of information and may necessitate meeting with an informant without the patient present. Patients with early dementia who have deteriorating driving skills should be instructed to stop driving immediately. Patients with early dementia without any history of driving problems should undergo a driving evaluation through the local Motor Vehicle Administration (MVA) or an occupational therapy program at a local hospital. These evaluations should be repeated every 6 months to promptly detect deterioration.

State laws differ in regard to reporting patients with a diagnosis of dementia to local MVAs, and the clinician should be familiar with the applicable regulations. The overall approach to assessment of driving in patients with dementia is

outlined in detail in the American Academy of Neurology Evidence-Based Practice Parameter (29).

Clinicians should assess other safety issues with the patient and family on an ongoing basis. Medication administration, cooking, use of power tools and lawnmowers, and handling of firearms eventually become unsafe for all patients to perform independently. Occupational therapy home-safety assessments can be useful in determining which activities can be performed safely and which need to be limited or supervised. An activity can often be modified to allow ongoing participation in a safe fashion, such as cooking or gardening together with a family member or friend. Wandering away from home, a fairly common occurrence, presents significant safety concerns and must be addressed regularly.

What should clinicians advise about nonpharmacologic approaches to sleep problems, behavioral problems, and psychiatric manifestations of dementia?

Psychiatric symptoms, such as depression, anxiety, sleep problems, agitation, hallucinations, and delusions are common in patients with dementia and often require intervention (30). When symptoms are mild or do not pose immediate danger, nonpharmacologic management may be sufficient. Such approaches emphasize that many emotional and behavioral disturbances can be "decoded" or understood in terms of internal or environmental triggers. Clinicians and caregivers should consider the time of day, location, antecedent factors, people present or absent, proximity to eating or other activities, and the consequences of the behavior. If patterns are noted, targeted interventions can be developed, implemented, and refined. Approaching behavioral disturbances this way can often forestall the use of

28. Hunt LA, Murphy CF, Carr D, et al. Reliability of the Washington University Road Test. A performance-based assessment for drivers with dementia of the Alzheimer type. *Arch Neurol.* 1997;54:707-12. [PMID: 9193205]
29. Dubinsky RM, Stein AC, Lyons K. Practice parameter: risk of driving and Alzheimer's disease (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. *Neurology.* 2000;54:2205-11. [PMID: 10881240]
30. Lyketsos CG, Steinberg M, Tschanz JT, et al. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry.* 2000;157:708-14. [PMID: 10784462]
31. Qaseem A, Snow V, Cross JT Jr, et al. Current Pharmacologic Treatment of Dementia: A Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med.* 2008;148:370-8.
32. Raina P, Santaguida P, Ismail A, et al. Effectiveness of Cholinesterase Inhibitors and Memantine for Treating Dementia: Evidence Review for a Clinical Practice Guideline. *Ann Intern Med.* 2008;148:379-97.

psychotropic medications or physical restraints.

When should clinicians prescribe acetylcholinesterase inhibitors and memantine to slow cognitive decline?

Clinicians should consider prescribing acetylcholinesterase inhibitors, such as donepezil, galantamine, or rivastigmine, to delay cognitive decline in patients with mild, moderate, or advanced Alzheimer disease. These drugs are better tolerated if they are slowly titrated to reach the target dose. The appropriate duration of treatment has not been defined. Although there are no placebo-controlled trials beyond 2 years, and most trials only last 6 months, clinicians often continue these medications for much longer when they feel the patient is benefiting from them. When the benefit is unclear, clinicians can consider stopping the drug and resuming it

if an acute cognitive deterioration occurs. The neuropeptide-modifying agent memantine is approved for use in moderate-to-advanced Alzheimer disease and can be used in conjunction with acetylcholinesterase inhibitors. Table 2 lists specific recommendations for their use. Tacrine has more side effects and is no longer recommended.

Patients and families should be educated about realistic expectations from these agents. All of them have shown statistically significant improvement in scores on standardized tests in patients with dementia in clinical trials as well as improvement on global assessment, but the benefits have been modest and difficult to extrapolate to the clinical practice setting. Side effects of anticholinesterase inhibitors include dizziness, nausea, vomiting, and diarrhea and anorexia.

Table 2. Pharmacologic Therapy for Dementia*

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Donepezil	Acetylcholinesterase inhibition	Begin 5 mg/d. If tolerated, increase to target dose of 10 mg/day after 1 month.	Delayed symptom progression in mild, moderate, and advanced Alzheimer disease	Nausea, vomiting, diarrhea, anorexia	Routine liver function testing is unnecessary. The higher end of the dosing range may be harder for patients to tolerate.
Galantamine	Acetylcholinesterase inhibition	Start 4 mg twice daily. Target dose 24 mg total per day. Increase by 4 mg twice daily every 1 month until in target range. Begin extended-release (once daily) galantamine at 8 mg/d. Increase by 8 mg/d every 1 month to the target dose of 24 mg/d.	Delayed symptom progression in mild, moderate, and advanced Alzheimer disease Improvement in caregiver-rated quality of life was observed.	Nausea, vomiting, diarrhea, anorexia	Routine liver function testing is unnecessary. The higher end of the dosing range may be harder for patients to tolerate.
Rivastigmine	Acetylcholinesterase inhibition	Start 1.5 mg twice daily. Target range is 6 to 12 mg/d. Increase by 1.5 mg twice daily every 1 month until in target range.	Delayed symptom progression in mild, moderate, and advanced Alzheimer disease	Nausea, vomiting, diarrhea, anorexia	Routine liver function testing is unnecessary. The higher end of the dosing range may be harder for patients to tolerate. Also available in a transdermal patch.
Memantine	NMDA-receptor antagonism	Begin 5 mg/d. Increase by 5 mg/d every 1 month until reaching target of 10 mg twice daily.	Less functional decline, improved cognition, and reduced demands on caregivers in moderate-to-advanced Alzheimer disease	Dizziness, confusion, headache, constipation	Available in tablets or solution. Avoid concomitant use with amantadine.

* NMDA = N-methyl-D-aspartic acid.

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40. Olin JT, Schneider LS, Katz IR, et al. Provisional diagnostic criteria for depression of Alzheimer disease. *Am J Geriatr Psychiatry*. 2002; 10:125-8. [PMID: 11925273]

Memantine can cause dizziness, confusion, headache, and constipation. Neither class of agent should be used in patients with uncontrolled asthma, closed-angle glaucoma, the sick sinus syndrome, or left bundle-branch block. The American College of Physicians has issued new guidelines on pharmacologic treatment of dementia, recommending that clinicians base the decision to initiate therapy with these agents on individualized assessment and choose among them on the basis of tolerability, side effect profile, ease of use, and cost (31).

A systematic review of 59 studies of cholinesterase inhibitors and memantine found that all agents had consistent but modest effects on cognition and global assessment. Behavior and quality of life were assessed less frequently and showed less-consistent effects. The duration of most studies averaged only 6 months, and there were only 3 head-to-head comparative trials (32).

Which other pharmacologic agents may be helpful in treating less-common types of dementia?

The acetylcholinesterase inhibitor rivastigmine has been shown to be effective in improving cognitive performance in patients with mild-to-moderate Parkinson disease in doses similar to those used in Alzheimer disease, and it is believed that this benefit will be seen with the other acetylcholinesterase inhibitors (33). A number of trials have also demonstrated the benefits of acetylcholinesterase inhibitor treatment for cognition in dementia with Lewy bodies (34, 35).

Which pharmacologic agents are ineffective in treating dementia and should be avoided?

Vitamin E is no longer recommended for routine use in Alzheimer disease, because its use is associated with a possible increase in mortality and because of a lack of adequate evidence of

efficacy (36, 37). The effectiveness of the herbal supplement *Ginkgo biloba* is not supported by sufficient data to recommend its general use in patients with dementia (38). Similarly, NSAIDs, estrogen, and ergoid mesylates should not be prescribed for the treatment of cognitive decline.

When should clinicians prescribe antidepressants in patients with dementia?

Clinicians should consider prescribing antidepressants in patients with dementia who have coexisting depression. Major depression is highly prevalent among patients with dementia, with nearly one third of patients developing an episode of major depression following the onset of dementia (39). Certain symptoms of major depression may overlap with those of dementia, such as weight loss and disturbed sleep, and this sometimes complicates the diagnosis (40).

A number of RCTs have established the efficacy of antidepressant medications in the treatment of major depression in patients with dementia (41–43), although there have been a number of negative clinical trials as well. In general, the selective serotonin reuptake inhibitors are better tolerated than tricyclic agents, but tricyclic agents may be used in select patients. These agents may cause mild gastrointestinal upset at the start of treatment or when doses are changed and increase risk for falls, agitation, delirium, or parkinsonism. Tricyclic agents can also cause orthostatic hypotension, dry mouth, sedation, urinary retention, and constipation and can worsen narrow-angle glaucoma. Medications with greater anticholinergic properties, such as amitriptyline, should generally be avoided.

When should clinicians consider prescribing antipsychotic agents to treat behavioral disturbances or psychotic symptoms?

Psychotic symptoms, such as hallucinations, delusions, and agitated behavior, that are mild or infrequent can often be managed with supportive care. However, when symptoms cause significant distress or danger to the patient or others, pharmacotherapy is indicated. Second-generation antipsychotic agents are usually recommended because of a lower risk for tardive dyskinesia than first-generation agents, such as haloperidol, but first-generation agents may be used as well in certain patients. Overall, the efficacy of these agents is modest. Although the efficacy of risperidone and olanzapine is best supported in the literature, quetiapine and aripiprazole are often used. They should be prescribed at the lowest possible dose and for the shortest possible time once prescribed; use should be regularly monitored. They should not be used routinely as sleep agents alone, because of side effects, which include sedation, orthostatic hypotension, delirium, ataxia, dry mouth, urinary retention, constipation, and stroke. First-generation agents are more likely to cause tardive dyskinesia and neuroleptic malignant syndrome.

In a meta-analysis of all RCTs of second-generation antipsychotics for behavioral disturbance in patients with dementia, there was a relative risk of 1.54 (95% CI, 1.06 to 2.23) for mortality compared with placebo-treated patients (45).

In reports released by the manufacturers, rates of cerebrovascular events were 4% for risperidone-treated patients (compared with 2% for placebo-treated), 1.3% for olanzapine (0.4% for placebo), and 1.3% for aripiprazole (0.6% for placebo). There was no evidence of increased risk for stroke with quetiapine use (44).

Evidence of increased mortality and cardiovascular events in patients

treated with second-generation antipsychotics prompted the U.S. Food and Drug Administration to place a black-box warning on the label of these agents (44–47). Treatment with antipsychotic medications is also associated with the metabolic syndrome, as well as weight gain, hyperlipidemia, and diabetes mellitus. Clinicians must weigh the risks and benefits of these agents when prescribing them.

Which drugs should clinicians use to treat sleep problems in patients with dementia?

Clinicians should try nonpharmacologic methods to treat sleep problems before using medications in patients with insomnia because of the potential risks associated with sedative-hypnotic use in this population. Careful attention should be paid to sleep environment, caffeine consumption, daytime sleeping, afternoon and evening medications, and other elements of basic sleep hygiene. If necessary, trazodone 25 to 50 mg, zolpidem 5 to 10 mg, or a similar agent can be used cautiously (48).

What other steps should clinicians take to maximize quality of life in patients with dementia?

Clinicians should proactively address issues that have the potential to significantly affect quality of life. Examples include attending to the working order of sensory aides, such as glasses and hearing aides, to ensure proper function; dental care; levels of noise, lighting, and temperature; presence of sufficient social and cognitive stimuli; cleanliness; pain levels; and constipation.

When should clinicians consult a neurologist or psychiatrist and other professionals in patients with dementia?

Clinicians should consider consulting a geriatric psychiatrist, neurologist, geriatrician, or dementia specialist regarding the diagnosis of dementia in patients

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52. Teri L, Logsdon RG, Uomoto J, et al. Behavioral treatment of depression in dementia patients: a controlled clinical trial. *J Gerontol B Psychol Sci Soc Sci*. 1997;52:P159-66. [PMID: 9224439]
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55. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56:1143-53. [PMID: 11342678]

with atypical features, such as early onset, presence of early neurologic symptoms, rapid progression, early personality changes, or unusual symptom patterns.

Consultation with a geriatric psychiatrist or dementia specialist should also be considered for the evaluation or management of difficult-to-treat psychiatric symptoms, such as depression, psychosis, or behavioral disturbances, because these symptoms cause significant suffering, can sometimes create dangerous situations for the patient and others, and reduce quality of life.

Treatment of dementia ideally incorporates elements of many treatment modalities, including preventive medicine, psychoeducation, behavioral therapy, and pharmacotherapy. For optimum care, it is often necessary to interface with a broad range of professionals, including occupational therapists, social workers, physical therapists, and speech and language pathologists.

When should clinicians recommend hospitalization for patients with dementia?

During the assessment of cognitive impairment, hospitalization should be considered for patients who cannot be evaluated safely or comprehensively as an outpatient because of dangerous behavior, unsafe living conditions, compromised nutrition, neglected medical conditions, or inability to cooperate.

Psychiatric hospitalization is sometimes required because of the severity of psychiatric symptoms. For example, hospitalization should be seriously considered for depressed patients who exhibit suicidality, significantly decreased food and fluid intake, delusional depression, immobility, inability to attend to other medical conditions, and a need for electroconvulsive therapy.

Patients with behavioral disturbances who are dangerous to themselves or others, or who cannot be treated safely or successfully as an outpatient, may need hospitalization. Examples of such disturbances include wandering, violence, calling out, hyperphagia, and severely disordered sleep-wake cycle. Patients with hallucinations and delusions may also require hospitalization if the symptoms do not respond to outpatient treatment, require the addition of multiple medications, cause patient distress and behavioral disturbances, or present a danger to others. Involuntary commitment may be required.

How can clinicians help families make decisions about long-term care?

Generally, a move into an assisted-living facility or nursing home is prompted by physical limitations that cannot be managed at home, such as the need for full assistance with transferring, ambulation, toileting, or feeding. Other patients have to move because of unmanageable psychiatric symptoms or caregivers' inability to provide necessary care at home (49).

Families with ample financial resources may be able to provide many services at home that usually are provided in a facility. Periods of respite care may help families delay placement. Families should be supported and guided through the difficult and painful decision-making process. Clinicians should encourage families to investigate facilities in their region early in the course of dementia to avoid hurried decision-making should placement in a long-term care facility become necessary.

What specific caregiver needs should be addressed by the clinician?

Caregiving for a patient with dementia is physically and

emotionally taxing, and inquiring about caregiver wellbeing is a critical component of longitudinal dementia care. Common caregiver symptoms include guilt, anger, grief, fatigue, loneliness, demoralization, and depression. Untreated caregiver burden can also worsen the patient's emotional well-being and lead to nursing home placement earlier than may otherwise be necessary (50). Patient's symptoms and the consequent demands on the caregiver change over time, and therefore monitoring of caregiver well-being must be conducted at every visit. Caregivers should be informed about local respite

programs, and long-term planning should be supported.

Caregivers should also receive information about local educational programs and support groups. A number of large, well-conducted trials have shown that psychoeducational and support groups with a focus on problem-solving, communication, management of behavioral disturbances, and emotional support are effective in delaying nursing home placement for up to 1 year, and in diminishing caregiver and patient depression and patient agitation and anxiety (51–53).

Treatment... Clinicians should adopt a broad treatment approach that incorporates attention to quality of life, cognitive enhancement, management of behavioral and psychiatric symptoms, and caregiver well-being. In considering pharmacologic therapy for dementia, clinicians should base the decision to initiate an anticholinesterase inhibitor or memantine on individual assessment, taking into account tolerability, ease of use, and side-effect profile. It is important to identify and treat psychiatric symptoms, such as depression, psychosis, anxiety, and behavioral disturbances, with both behavioral and pharmacologic treatment to maximize treatment of cerebrovascular disease risk factors, and to treat any general medical conditions that could be negatively affecting cognition. Clinicians should attend to safety issues on an ongoing basis. It is important to attend to caregiver burden and consider referral to support groups and other psychoeducational activities.

CLINICAL BOTTOM LINE

What do professional organizations recommend with regard to screening, diagnosis, and treatment of dementia?

Guidelines from professional organizations include those from the American Psychiatric Association, published in their second edition in 2007 (54), the American Academy of Neurology, published in 2001 (55), and the U.S. Preventive Services Task Force, published in 2003 (19). The U.S. Preventive

Services Task Force document states that there is insufficient evidence to recommend general population screening for cognitive impairment. The American Academy of Neurology guideline covers detection, diagnosis, and management of dementia, and the American Psychiatric Association guideline also provides comprehensive recommendations on overall care. The American College of Physicians has just issued new guidelines on

Practice Improvement

56. Assessing Care of Vulnerable Elders (ACOVE). ACOVE Quality Indicator Library. Accessed at www.acove.com/QI/Acove.hta on 12 February 2008.

the treatment of dementia (31) based on the results of a systematic review (32). This guideline and review emphasize the modest effect of current drug therapy for dementia and the importance of individual patient assessment.

What measures do stakeholders use to evaluate the quality of care for patients with dementia?

The Center for Medicare & Medicaid Services has issued specifications for measures for its 2008 Physicians Quality Reporting Initiative. Despite lack of evidence for screening asymptomatic patients for dementia, one of these measures relates to dementia and evaluates the percentage of patients age 65 years or older who have documentation of screening for cognitive impairment using a standardized tool. Another measure relates to advance care planning. The Assessing Care of Vulnerable Elders (ACOVE) quality-of-care measurement program includes specific quality measures on dementia (56).

What is the role of patient education in optimizing care of patients with dementia?

In speaking with patients about their memory problems and the necessity to make lifestyle changes, clinicians should consult with caregivers about appropriate disclosure of the diagnosis and presentation of information. It is important to determine what the patient already knows about their condition and what else he or she wants to know. Clinicians should address safety concerns directly with patients and caregivers and eventually approach long-term issues, such as management of finances, medical decision-making, and possible placement, when appropriate.

It is essential to attend to the needs of the caregiver and to educate them about the course of dementia and the challenges they face. Referral to psychoeducational programs may be helpful in managing caregiver grief, anger, guilt, demoralization, and fatigue. Local respite programs should also be considered.

in the clinic Tool Kit

Dementia

PIER Modules

pier.acponline.org/physicians/diseases/d224/d224.html

pier.acponline.org/physicians/screening/S375/S375.html

Access PIER modules on dementia and screening for dementia

Patient Information Page

www.annals.org/intbeclinic

Download copies of the Patient Information sheet that appears on the following page for duplication and distribution to your patients

Washington University: Alzheimer Diseases Research Center

www.biostat.wustl.edu/adrc

Global clinical dementia rating

ACOVE Quality Indicator Library

www.acove.com/QI/Acove.hta

Evidence-based quality indicators to improve health care in older adults

American Academy of Neurology

www.aan.com/professionals/practice/pdfs/dementia_guideline.pdf

Detection, diagnosis, and management of dementia

in the clinic

WHAT YOU SHOULD KNOW ABOUT DEMENTIA

In the Clinic
Annals of Internal Medicine

People with dementia get forgetful and can later have problems doing everyday things, such as eating and getting dressed.

Medicines may help some people with dementia think better and keep from getting worse for a while.

Keeping active with family and friends also helps people with dementia

There is no cure for dementia. It usually gets worse over time.

When this happens, it is important to plan for the future.

Caring for People with Dementia

- Learn what to expect from the patient you help care for and find out what help he or she needs.
- Keep the patient busy with family and friends and ask about day programs that keep him or her active.
- Ask the doctor if and when medicines may help and which medicines may make things worse.
- Call the doctor if there are big changes in how the person is acting or thinking and have a plan for emergencies.
- Try to keep the patient from falling, getting lost, or getting hurt.
- Get a safe-return bracelet in case the patient gets lost. You can get one from the Alzheimer Association Safe Return Program at P.O. Box 9307, St. Louis, MO 63117-0307; 888-572-8566
- Be sure to take care of yourself by asking for help with caretaking; going to joint support groups; making time for yourself; staying healthy; and talking to your doctor if you feel very tired, sad, stressed, guilty, or burned out.
- Make a plan in case you can no longer care for the person at home.

Web Sites with Good Information about Dementia

Alzheimer Association

www.alz.org/alzheimers_disease_what_is_alzheimers.asp

ACP Foundation HealthTips

foundation.acponline.org/files/ht/dem_en.pdf

Family Caregiver Alliance

www.caregiver.org/caregiver/jsp/content_node.jsp?nodeid=569

National Institute on Aging

www.niapublications.org/agepages/forgetfulness.asp

1. A 72-year-old woman is brought to the office by her son for evaluation of gradually progressive forgetfulness over the past 18 months. On a recent week-long visit, she could not learn the name of the hosts' dog. She frequently re-reads the daily paper, and tends to ask the same questions repeatedly. She has no significant medical history and no abnormalities of gait, posture, coordination, speech, or dexterity. Personality is preserved. On examination, vital signs are normal, as is attention. Her score on Mini-Mental State Examination is 23/30, and she recalls 0/3 words after brief distraction. She has difficulty copying a geometric figure. Neurologic examination is otherwise normal.

Which of the following is the most likely diagnosis?

- A. Alzheimer dementia
- B. Frontotemporal dementia
- C. Dementia with Lewy bodies
- D. Vascular dementia
- E. Dementia secondary to vitamin B₁₂ deficiency

2. A 70-year-old woman is evaluated for an episode of abrupt cognitive decline that began 2 weeks ago when she was suddenly unable to read the newspaper during breakfast. She could not find the bathroom in her own home but could carry on a conversation and recognize family members. Her condition has since improved. She has a history of hypertension and coronary artery disease, and has been forgetful over the past few years. On examination, vital signs and general physical examination are normal. Her score on Mini-Mental State Examination is 22/30. She is not oriented to time or place. Neurologic examination is normal except for a left Babinski sign. Computed tomographic scan of the head shows bilateral periventricular white matter hypodensity. After 3 months, she is oriented to place and has improved daily function, a score on Mini-Mental State Examination of 24/30, and a normal neurologic examination, except for the Babinski sign.

Which of the following tests would be most useful for the diagnosis of this patient's cognitive impairment?

- A. Analysis of cerebrospinal fluid for 14-3-3 antigen
- B. Electroencephalography
- C. Repeat brain imaging
- D. Analysis of blood for presenilin 1 mutation

3. A 70-year-old man is evaluated in the emergency department for 2 episodes of bradycardia and is found to have second-degree atrioventricular block. The patient has Alzheimer dementia, type 2 diabetes mellitus, hypertension, and coronary artery disease. His medications are donepezil (dosage recently increased from 5 to 10 mg at bedtime); memantine, 10 mg twice daily (also recently started); vitamin E, 1000 IU twice daily; trazodone, 50 mg twice daily for agitation; glyburide; hydrochlorothiazide; pravastatin; and aspirin.

Which of the patient's medications is likely to explain these episodes?

- A. Donepezil
- B. Glyburide
- C. Vitamin E
- D. Trazodone

4. A 78-year-old woman is evaluated for progressive impairments of memory and other aspects of intellect, which have developed insidiously over 3 years. The patient's score on Mini-Mental State Examination is 22/30, and she recalls 0/3 words after a 3-minute delay. There are no other significant findings on physical examination.

Which of the following is most likely to improve this patient's symptoms?

- A. Vitamin E
- B. *Ginkgo biloba*
- C. Central cholinesterase inhibitor
- D. Memantine
- E. Estrogen

5. An 82-year-old woman with Alzheimer disease presents with her family for evaluation of worsening mental status. She has been taking galantamine for 3 years. Initially after treatment, her memory and attentiveness improved slightly, but she later declined and she cannot now manage her financial affairs and sometimes fails to recognize long-time acquaintances. Her score on the Mini-Mental

State Examination has fallen from 22/30 to 14/30. There are no other significant findings on physical examination.

Which of the following medications should be added to her treatment regimen?

- A. Vitamin E
- B. *Ginkgo biloba*
- C. Risperidone
- D. Memantine
- E. Estrogen

6. A 78-year-old man is brought to the office by his family for evaluation of confusion and memory problems, which have been worsening over the past 6 weeks. Initially, his symptoms were evident mainly in the morning, but they now seem to occur throughout the day. He wanders from the house and sometimes does not recognize his wife. He has visual hallucinations, and, while sitting in the kitchen, believes that he is on a bus. His medical history includes type 2 diabetes mellitus with painful peripheral neuropathy, coronary artery disease, depression, and congestive heart failure. Medications include glyburide, nortriptyline, digoxin, lorazepam, metoprolol, lisinopril, aspirin, and pravastatin. His daughter does not know how long he has been taking these medications. There is no family history of neurologic disease.

On examination, the patient has asterix and findings consistent with peripheral neuropathy. He is mildly lethargic and inattentive, and not oriented to time or place. His score on the Mini-Mental State Examination is 13/30, and he recalls 2/3 words after a delay. Electrolyte levels, oxygen saturation, liver and renal function, and computed tomographic scan of the head without contrast are normal.

Which of the following conditions is most likely the cause of the patient's cognitive impairment?

- A. Alzheimer disease
- B. Dementia with Lewy bodies
- C. Depression
- D. Cerebrovascular disease
- E. Toxic encephalopathy

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.