Is it Alzheimer’s?
How to pare down the possibilities

A clinical guide to rule out other dementing diseases and rare reversible causes

Accurate and early diagnosis of Alzheimer’s disease (AD) is evolving, and—although not yet definitive—is no longer one of exclusion. With a careful in-office work-up and routine assessment tools, you can accurately identify >90% of patients with late-onset AD.1

AD is by far the most common cause of dementia in older patients. To help you make the diagnosis, this state-of-the-art article discusses:

• AD’s clinical presentation and course
• the role of neuropsychological tests for assessing cognitive and functional status
• neuropsychiatric and medical findings that differentiate AD from other dementia causes
• indications for structural neuroimaging with CT or MRI.

Presentation and course

Variability. AD’s gradual onset and progression are characterized by prominent memory loss, anomia, constructional apraxia, anosognosia, and personality changes with affect deregulation, behavioral disturbance, and distorted perception.1 Amnesia—particularly deficits in anterograde episodic memory—is the most common presentation, but the disease course is heterogeneous and may be affected by:

• patient age at onset
• illness severity at diagnosis
• comorbid medical and neuropsychiatric illnesses
• premorbid cerebral reserves (amount of brain

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### Box 1

**Biomarkers show promise to improve AD diagnosis**

Researchers are investigating surrogates for detecting Alzheimer’s disease (AD) and monitoring disease progression.\(^5\)

**Serum and CSF markers.** AD is viewed as a series of sequential events, beginning with beta-amyloid (β-amyloid) accumulation and progressing through a pathophysiological cascade to cell death, transmitter deficit, and dementia. A unique biomarker may be associated with each event, either in the primary disease process of β-amyloid production and accumulation or intermediate processes such as tau hyperphosphorylation, oxidation, and inflammation.\(^6\)

These biochemical markers are found more consistently in cerebrospinal fluid (CSF) than peripherally. Lower CSF β-amyloid (especially β-amyloid 42) and higher CSF tau and tau-phosphorylated (p-tau) have been found in AD patients compared with normal and disease controls.\(^7\) Some overlap exists, however, among AD and other dementias. Other possible serum, CSF, and urine markers include isoprostanes, sulfatides, oxyterol, homocysteine, apolipoprotein E, alpha 1-antichymotrypsin, 3-nitrotyrosine, and more.\(^8\)

No biomarkers are available or recommended for clinical use at this time.

**Neuroimaging.** Amyloid imaging tracers may increase the capacity of single photon emission computed tomography (SPECT) and positron emission tomography (PET) to detect AD pathology. These tracers have high binding affinity for amyloid and may enable PET/SPECT to detect amyloid deposits in vivo.

Amyloid radioligands are being developed and tested as potential clinical diagnostic tools and surrogate biomarkers of anti-amyloid therapies. A radioligand that targets amyloid and neurofibrillary tangles in AD has been developed recently for use as a research tool.

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**Clinical Point**

Clinical assessment has low specificity in advanced stages, where all dementia subtypes are similar and comorbidities confuse the picture.

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damage a person can sustain before reaching a threshold for the clinical expression of dementia.\(^1,5\)

**Staging illness severity.** AD has 3 clinical stages of cognitive dysfunction:

- **Mild AD.** An individual or close companion may notice increased forgetfulness and word-finding difficulties, a tendency to lose or misplace things, repeated questioning, and some disorientation. Motor skills are intact.

- **Moderate AD.** Cognitive decline continues, memory deteriorates, and self-care ability is markedly impaired. The individual may undergo personality changes, confuse time and place, have trouble communicating and recognizing family members or friends, develop agitation, begin to wander, and experience delusions and hallucinations.

- **Severe AD.** An individual with late-stage disease has severe impairment and can be bedridden, incontinent, and unable to understand or speak. Full-time care is required.

**Staging informs treatment.** In clinical trials, patients with mild-to-moderate AD consistently show small improvements in cognitive and global function when treated with acetylcholinesterase inhibitors (AChEIs) such as donepezil, rivastigmine, and galantamine.\(^4\) Donepezil also is approved for use in severe AD.

Memantine is indicated for symptomatic treatment of moderate-to-severe AD. It differs in mechanism of action from the AChEIs and is thought to inhibit cytotoxic overstimulation of glutamatergic neurons.\(^5\)

For moderately advanced AD, memantine appears to be beneficial alone or in combination with AChEIs.

**Dementia assessment**

Clinical assessment has low sensitivity for early-phase AD and compromised specificity in advanced stages, where all dementia subtypes are similar and comorbidities may confuse the picture. Promising surrogate biomarkers and other diagnostic tools are being developed (Box 1),\(^5,6\) but definitive AD diagnosis still requires post-mortem histopathologic examination of the cerebral cortex.
Neuropsychological tests disclose a degree of intellectual impairment that correlates with functional impairment and may be particularly useful for assessing:

- mild cognitive impairment when diagnosis is doubtful
- cases where major lifestyle changes may be required, such as driving cessation or assisted-living placement.

These tests can examine performance across different domains of cognitive function, including orientation, memory, attention, naming, comprehension, and praxis.

Limitations. Neuropsychological tests have limitations, including cost and administration.

Source: References 13,14

History and physical exam. Depending on the AD stage at presentation, patients might not be a reliable source of information. For a realistic and unbiased history and evaluation, assess the patient separately and obtain collateral information from reliable informants.

In typical cases, the history guides the physical/neurologic examination. Advancing age and family history are confirmed risk factors for AD; others may include:

- female gender (after age 80)
- cardiovascular disease (such as cerebral infarcts, hypertension, elevated cholesterol/homocysteine, smoking, and diabetes mellitus)
- history of head trauma, especially with loss of consciousness.

Assess premorbid functioning and existing medical conditions. Apraxia, aphasia, and cortical visual impairment may reflect focal signs of atypical AD; consider other neurologic signs in the context of clinical data.

Early and accurate diagnosis of AD is challenging in patients with mixed dementia, comorbid neurologic diseases, or atypical features. Patients with these presentations may require referral to an expert clinician, extensive workup, or longitudinal follow-up before the diagnosis becomes clear.

Neuropsychological testing. Most mental status tests examine orientation, attention/concentration, learning, memory, language, and constructional praxis. The Folstein Mini-Mental State Examination (MMSE) is the most widely used and well-validated mental status test. A score of 10 to 20 on the MMSE is generally considered as moderate AD, and <10 is staged as severe AD. Other mental status testing options include:

- Blessed Information-Memory-Concentration (BIMC)
- Blessed Orientation-Memory-Concentration (BOMC)
- Short Test of Mental Status (STMS)
- Saint Louis University Mental Status (SLUMS).

Neuropsychological tests have limitations, but they can supplement clinical cognitive assessment by detecting milder cases and may help answer questions about a patient’s ability to drive or live alone (Box 2).

Reversible causes. If the patient is generally healthy, a core of laboratory tests is recommended in the diagnostic workup (Table 1, page 56). Other options include:

- CSF examination for atypical presentations, such as unusually rapid symptom
Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Anemia and signs of infection</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Related to reversible dementia, anemia</td>
</tr>
<tr>
<td>Folate</td>
<td>Related to reversible dementia, anemia</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>More accurate than individual B12/folate tests</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Ongoing inflammatory reaction</td>
</tr>
<tr>
<td>Thyroid function</td>
<td>Hypothyroidism (reversible dementia)</td>
</tr>
<tr>
<td>Liver function</td>
<td>Metabolic causes of cognitive impairment</td>
</tr>
<tr>
<td>Renal function</td>
<td>Uremia, metabolic causes of cognitive impairment</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Hypo/hypernatremia as a cognitive impairment cause</td>
</tr>
<tr>
<td>Glucose</td>
<td>Recurrent hypoglycemia, diabetes mellitus</td>
</tr>
<tr>
<td>Lipid panel</td>
<td>Vascular dementia risk factor</td>
</tr>
<tr>
<td>Baseline ECG</td>
<td>Cardiac abnormalities as vascular risk factors</td>
</tr>
<tr>
<td>STS (optional)</td>
<td>Neurosyphilis</td>
</tr>
</tbody>
</table>

**Neuroimaging.** Structural neuroimaging with a noncontrast CT or MRI is appropriate in the initial evaluation of patients with dementia. More routinely, it is used to exclude rare but potentially correctable dementia causes, such as space-occupying lesions. Hippocampal and entorhinal volume are measured most often in discriminating AD from non-demented aging and other dementias.

Positron emission tomography (PET) using fluorine-18-labeled deoxyglucose (FDG) may help differentiate characteristic patterns of cerebral hypometabolism in the temporoparietal lobes in AD from frontotemporal dementia (FTD) and other less common dementias, particularly during the earliest stages of the disease. Medicare reimbursement for brain PET is limited to differentiating FTD from AD.

**Diagnostic criteria**

**NINCDS-ADRDA.** Neuropsychological AD assessment criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) classify AD as probable, possible, or definite.

**Possible AD** is considered when a patient has an atypical onset, presentation, or course and other secondary illnesses capable of producing dementia are not believed to be the cause.

**Probable AD** is diagnosed when dementia is established by clinical exam and confirmed with cognitive testing, where ≥2 cognitive domains are progressively affected; includes gradual memory loss not caused by another systemic or brain disease, with age of onset between 40 and 90 years.

**Definite AD** requires histopathologic evidence of AD in addition to fulfilling criteria for probable AD.

**DSM-IV-TR.** Similar but broader DSM-IV-TR criteria describe an insidious progressive cognitive decline that affects recent memory and ≥1 other cognitive domain (apraxia, aphasia, agnosia, or executive functioning). This cognitive decline impairs social and occupational function, represents a change in cognitive function, and is not a result of another medical condition.

Progression, altered consciousness, or other neurologic manifestations

- EEG to differentiate delirium, seizure disorders, encephalopathies, or a rapidly progressing dementia such as Creutzfeldt-Jakob disease.

Only 1% of dementia causes are considered reversible, but keep them in mind in the AD differential diagnosis (Table 2, page 61). Depression, vitamin B12 deficiency, medication side effects, and hypothyroidism are common comorbidities in elderly patients, particularly in those with suspected dementia. Correcting these problems might or might not reverse the dementia.

Because delirium may be the initial presentation of AD or reversible causes, re-evaluate patients for dementia after delirium clears.
from a higher level, and is not due to other causes such as delirium.21

NINCDS-ADRDA and DSM-IV-TR criteria have comparable sensitivity and specificity for clinical AD diagnosis. Neither requires neuropathologic or genetic assessment (Box 3, page 62).15,17,22-24 Neuroimaging and other tests may be required to rule out other brain diseases that may cause dementia.

Other causes of dementia

**Mild cognitive impairment (MCI)** may represent a prodromal state for the earliest clinical manifestations of dementia. Symptoms include memory complaints but generally preserved activities of daily living.

Originally introduced to define a progressive, single-symptom amnestic syndrome, MCI has evolved into a classification of amnestic and non-amnestic MCI with single or multiple domains.25 Amnestic MCI is the most specifically correlated with AD.26 Neuropsychologic similarities between amnestic MCI and clinically diagnosed AD include:

- neuropsychiatric symptoms, such as apathy, mood disturbance, irritability and anxiety
- over-representation of the APOE ε4 allele
- volumetric loss in the entorhinal cortex and hippocampus as measured by MRI
- Glucose hypometabolism in AD-typical regions as measured by FDG-PET
- neuronal loss in vulnerable brain regions.26

Most patients with MCI go on to meet AD criteria within 5 to 10 years, and approximately 80% of those originally diagnosed with MCI prove to have AD at post-mortem histopathologic examination.26,27

**Dementia with Lewy bodies (DLB)** is the second most common dementing disorder

Table 2

<table>
<thead>
<tr>
<th>Cause</th>
<th>Examples</th>
<th>Suggested tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space-occupying lesions</td>
<td>Subdural hematoma, benign tumors, hydrocephalus</td>
<td>CT/MRI without contrast</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>AIDS dementia complex, syphilis, Lyme disease</td>
<td>Serologic tests</td>
</tr>
<tr>
<td>Endocrinopathies/metabolic/autoimmune disorders</td>
<td>Hypothyroidism, Cushing’s disease, uremia, hepatic encephalopathy, Wilson’s disease, recurrent hypoglycemia, chronic hypocalcemia, multiple sclerosis, disseminated SLE, sarcoidosis</td>
<td>Thyroid panel, renal and liver function tests, electrolytes, slit lamp test, serum ceruloplasmin</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Depression, alcohol dependence</td>
<td>Geriatric Depression Scale, assess vitamin deficiency states</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td>Vitamin B12, thiamine (Wernicke-Korsakoff syndrome), pyridoxine, niacin (pellagra)</td>
<td>Vitamin B12, homocysteine</td>
</tr>
<tr>
<td>Medication effects</td>
<td>Benzodiazepines, barbiturates, anticholinergics, opioid analgesics, antihypertensives, antiarrhythmics, antidepressants, anticonvulsants, cardiac drugs such as digitals and derivatives (among others)</td>
<td>Review patients’ medications for drugs that can cause cognitive changes</td>
</tr>
<tr>
<td>Others</td>
<td>Autoimmune diseases, heavy metals, illicit drugs, obstructive sleep apnea</td>
<td>Drug screens and specific tests</td>
</tr>
</tbody>
</table>

Clinical Point

Only 1% of dementia causes are considered reversible, but keep them in mind in the Alzheimer’s differential diagnosis.
in late life—after Alzheimer’s dementia—and two-thirds of DLB cases overlap with AD. Core DLB clinical features include early recurrent visual hallucinations, fluctuating cognition, spontaneous parkinsonism, and sensitivity to conventional antipsychotics.15,28

Parkinson’s disease (PD) and DLB may represent a clinicopathologic continuum, and substantial overlap exists among AD, DLB, and PD in underlying disease process and clinical presentation.15,29 Hallucinations, depression, delusions, and delusional misidentification are seen more often in patients with DLB than AD.15

Vascular dementia (VaD) was once thought to account for 15% to 20% of dementing illnesses, but discrete VaD is now viewed as much less common. Whatever the underlying vasculopathy, vascular lesions often coexist with other causes of dementia—usually AD (in 77% of presumed VaD cases).30

Compared with AD, patients with VaD have a more subcortical dementia with difficulty retrieving words, organizing and solving complex problems, “absent-mindedness,” and psychomotor slowing with relatively preserved language skills. VaD is thought to have a more abrupt onset than AD and “stepladder” deterioration.

Frontotemporal dementia (FTD)—such as Pick’s disease—is associated with focal atrophy of the frontal and/or temporal lobes. Mean onset is age 52 to 56, and FTD is less common than AD, VaD, or DLB.

FTD often presents with gradual personality changes (with inappropriate responses or activities) or language changes (with severe naming difficulty and problems with word meaning).31 Features that may help differentiate FTD from AD include:

- disinhibition/apathy with personality change
- affect disregulation
- behavioral disturbance (frontal type) and expressive/receptive language changes (semantic or primary progressive aphasia) with relatively mild memory loss.32,33

Unlike AD, memory usually is unaffected in early FTD, with problems largely secondary to poor concentration and relating to difficulties with working (immediate) memory.

Other neurodegenerative diseases that might present with dementia include PD, Huntington’s disease, progressive supranuclear palsy, corticobasal degeneration, and Creutzfeldt-Jakob disease.34

References

continued on page 66
ADVERSE REACTIONS: Associated with Discontinuation of Treatment: In the 12-week, placebo-controlled trial in elderly patients with dementia-related psychosis, 8% of patients treated with RISPERIDON® CX (11%, 23/220) patients than with placebo (13%, 18/138 patients). Incidence in Central and Peripheral Nervous System Disorders: Frequent: hypotension, dizziness, orthostatic hypotension. In the 12-week, placebo-controlled trial, orthostatic hypotension was observed in 2% of patients treated with 25 mg or 50 mg RISPERIDON® (see PRECAUTIONS). Weight Changes: In the 12-week, placebo-controlled trial, 9% of patients treated with RISPERIDON® CX compared with 8% of patients treated with placebo, experienced a weight gain of 7% or body weight at entry. Laboratory Test Changes: In the 12-week, placebo-controlled trial the following laboratory test changes were: WBC and platelet counts were increased, eosinophils were increased, triglycerides were decreased, total cholesterol was increased, alkaline phosphatase, blood urea nitrogen, glucose, uric acid, cholesterol, triglycerides and total cholesterol were decreased. The mean changes observed were not clinically significant. The incidence of all adverse reactions occurring at ≥ 1/1000 patients is presented in the section “Adverse Reactions.” The mean changes observed were not clinically significant. The incidence of all adverse reactions occurring at ≥ 1/1000 patients is presented in the section “Adverse Reactions.”

**Disclosures**

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Dr. Selkoe reports no financial relationships with industry.

Dr. Schon reports no financial relationships with industry.

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Dr. Stern reports no financial relationships with industry.

Dr. Tomlinson reports no financial relationships with industry.
Bottom Line

To make a clinical diagnosis of Alzheimer’s disease, start by eliciting a detailed history from the patient and seeking collateral information from reliable informants. Assess premorbid functioning, existing medical conditions, and neurologic signs. Order routine laboratory tests and neuroimaging to identify non-Alzheimer brain disorders. For early symptoms, consider neuropsychological testing to quantify the patient’s intellectual and functional impairment.