CASES THAT TEST YOUR SKILLS

Ms. A, age 83, is increasingly confused and agitated. She attacks caregivers and distrusts her friends at church. The challenge: diagnose her dementia, quell her aggressive behavior, and slow her cognitive decline.

After 62 years, her husband is a ‘stranger’

PRESENTING SYMPTOMS

Ms. A, age 83, has been experiencing increasing confusion, agitation, and memory loss across 4 to 5 years. Family members say her memory loss has become prominent within the last year. She can no longer cook, manage her finances, shop, or perform other basic activities. At times she does not recognize her husband of 62 years and needs help with bathing and grooming.

Ms. A’s Folstein Mini-Mental State Examination (MMSE) score is 18, indicating moderate dementia. She exhibits disorientation, diminished short-term memory, impaired attention including apraxia, and executive dysfunction. Her Geriatric Depression Scale (15-item short form) score indicates normal mood.

A neurologic exam reveals mild parkinsonism, including mild bilateral upper-extremity cogwheel-type rigidity and questionable frontal release signs including a possible mild bilateral grasp reflex. No snout reflex was seen.

This presentation suggests Ms. A has:
- Alzheimer’s disease
- Lewy body dementia
- or vascular dementia

The authors’ observations:

Differentiating among Alzheimer’s, Lewy body, and vascular dementias is important (Table 1, page 91), as their treatments and clinical courses differ.

The initial workup’s goal is to diagnose a reversible medical condition that may be hastening cognitive decline. Brain imaging (CT or MRI) can uncover cerebrovascular disease, subdural hematomas, normal-pressure hydrocephalus,
tumors, or other cerebral diseases. Laboratory tests can reveal systemic conditions such as hypothyroidism, vitamin B₁₂ deficiency, hypercalcemia, neurosyphilis, or HIV infection.

With a thorough history and laboratory testing, a diagnosis of “probable” AD can be as much as 85% accurate. Probable AD is characterized by progressive gradual decline of cognitive functions affecting memory and at least one other domain including executive dysfunction, apraxia, aphasia, and/or agnosia. These deficits must cause significant functional impairment.

Neurologic test results may support AD diagnosis after ruling out reversible causes of dementia. Neuropsychological testing can provide valuable early information when subtle findings cannot be ascertained on clinical screening. (For a listing of neuropsychological tests, see this article at currentpsychiatry.com.)

**Table 1**

<table>
<thead>
<tr>
<th>Differences in Alzheimer’s, Lewy body, and vascular dementias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alzheimer’s dementia</strong></td>
</tr>
<tr>
<td>Gradual onset and chronic cognitive decline</td>
</tr>
<tr>
<td>Memory difficulty combined with apraxia, aphasia, agnosia, or executive dysfunction</td>
</tr>
<tr>
<td>Psychosis common in middle to late stages</td>
</tr>
<tr>
<td>Day-to-day cognitive performance stable</td>
</tr>
<tr>
<td>Parkinsonism not apparent in early stages, may present in middle to late stages</td>
</tr>
<tr>
<td>Neurologic signs present in late stages</td>
</tr>
<tr>
<td>Cannot be explained as vascular or mixed-type dementia</td>
</tr>
<tr>
<td><strong>Lewy body dementia</strong></td>
</tr>
<tr>
<td>Cognitive, memory changes with one or more of the following:</td>
</tr>
<tr>
<td>• visual hallucinations</td>
</tr>
<tr>
<td>• fluctuating consciousness (“sundowning”)</td>
</tr>
<tr>
<td>• parkinsonian features</td>
</tr>
<tr>
<td>Visual hallucinations, other psychoses in early stages</td>
</tr>
<tr>
<td>Periods of marked delirium, “sundowning”</td>
</tr>
<tr>
<td>Cognitive performance fluctuates during early stages.</td>
</tr>
<tr>
<td>Parkinsonism in early stages</td>
</tr>
<tr>
<td>Tremor not common</td>
</tr>
<tr>
<td>Exquisite sensitivity to neuroleptic therapy</td>
</tr>
<tr>
<td>Cannot be explained as vascular or mixed-type dementia</td>
</tr>
<tr>
<td><strong>Vascular dementia</strong></td>
</tr>
<tr>
<td>Early findings often include depression or personality changes, plus incontinence and gait disorder</td>
</tr>
<tr>
<td>Temporal relationship between stroke and dementia onset, but variability in course</td>
</tr>
<tr>
<td>Day-to-day cognitive performance stable</td>
</tr>
<tr>
<td>Gait disorder and parkinsonism common, especially with basal ganglia infarcts</td>
</tr>
<tr>
<td>Increased sensitivity to neuroleptics</td>
</tr>
<tr>
<td>Imaging necessary to document cerebrovascular disease</td>
</tr>
</tbody>
</table>

Ms. A was diagnosed as having probable Alzheimer’s-type dementia based on the test results and the fact that her cognition was steadily declining. Other explanatory mechanisms were continued.
absent. She did not exhibit hallucinatory psychosis or fluctuating consciousness, which would signal Lewy body dementia.

The psychiatrist started galantamine, 4 mg bid, and vitamin E, 400 IU bid, to maximize her cognition and attempt to slow her functional decline. Ms. A, who was in an assisted living facility when we evaluated her, was transferred to the facility’s nursing section shortly afterward.

At follow-up 3 weeks later, Ms. A’s behavior improved moderately, but she remained unpredictable and intermittently agitated. Staff reported that she was physically assaulting caregivers two to three times weekly.
Which medication(s) would you use to control Ms. A’s agitation and paranoia?
- an SSRI
- a mood stabilizer
- an atypical antipsychotic
- a combination or two or more of these drug classes

The authors’ observations
Aside from controlling agitation, medication treatment in AD should slow cognitive decline, improve behavior, help the patient perform daily activities, and delay nursing home placement.
- Watch for drug-drug interactions. Many patients with AD also are taking medications for hypertension, hypercholesterolemia, diabetes, arthritis, and other medical comorbidities.
- Start low and go slow.

Older patients generally do not tolerate rapid dosing adjustments as well as younger patients (Table 2).

SSRIS. Selective serotonin reuptake inhibitors increase serotonin at the synaptic terminal. Serotonin has long been associated with impulsivity and aggression, and decreased 5-hydroxyindole acetic acid, a metabolite of serotonin, has been found in violent criminals and in psychiatric patients who have demonstrated inward or outward aggression.11

SSRIs generally are tolerable, safe, effective, and have little cholinergic blockade. Citalopram and sertraline minimally inhibit the cytochrome P-450 2D6 isoenzyme and have lower protein-binding affinities than fluoxetine or paroxetine. Thus, citalopram and sertraline are less likely to alter therapeutic levels of highly bound medications through displacement of either drug’s protein-bound portion.10

Anticonvulsants with mood-stabilizing effects are another option. Reasonably strong data support use of divalproex for managing agitation in AD, either as a first-line agent or as an adjunct after failed SSRI therapy. Unlike other anticonvulsants, divalproex also may be neuroprotective.3

Divalproex, however, is associated with white blood cell suppression, significant liver toxicity, and pancreatitis, although these effects are rare.13 Monitor white blood cell counts and liver enzymes early in treatment, even if divalproex blood levels below the standard reference range produce a response.14

Though not studied specifically for treating agitation in AD, carbamazepine has demonstrated significant short-term efficacy in treating dementia-related agitation and aggression.2 Scant data support use of gabapentin or lamotrigine in Alzheimer’s dementia, but these agents are often used to manage agitation in other disorders.

If psychosis occurs in early stage Alzheimer’s disease, rule out Lewy body dementia

Atypical antipsychotics. Psychosis usually occurs in middle-to-late-stage AD but can occur at any point. If psychosis occurs early, rule out Lewy body dementia.15

Choose an atypical antipsychotic that exhibits rapid dopamine receptor dissociation constants to reduce the risk of extrapyramidal symptoms, tardive dyskinesia, and cognitive decline with prolonged use. Quetiapine has shown efficacy for treating behavioral problems in Alzheimer’s and Lewy body dementia,7 and its sedating effects may help regulate sleep-wake cycles.
After 62 years, her husband is a ‘stranger’

Data support use of olanzapine for agitation in AD, but watch for anticholinergic effects including worsening of cognition. Fast-dissolving olanzapine and risperidone oral wafers may help circumvent dosing difficulties in patients who cannot swallow—or will not take—their medication. Intramuscular olanzapine and ziprasidone have shown efficacy in treating acute agitation, but no systematic studies have examined their use in agitation secondary to dementia.

Recent data suggest a modestly increased risk of cerebrovascular accidents in AD patients taking atypicals compared with placebo, but the absolute rate of such events remains low.

What treatment options are available at this point?

The authors’ observations

Treating agitation and delaying nursing home placement for patients with AD is challenging. When faced with inadequate or no response, consider less-conventional alternatives.

Vitamin E and selegiline were found separately to postpone functional decline in ambulatory patients with moderately severe AD, but the agents given together were less effective than either agent alone.16

Use of methylphenidate,17 buspirone,18 clonazepam,19 zolpidem,20 and—most recently—memantine21 for AD-related agitation also has been described.

CONTINUED TREATMENT

Memantine was added to address Ms. A’s agitation and preserve function. The agent was started at 5 mg/d and titrated across 4 weeks to 10 mg bid.

On clinical exam, Ms. A was more calm and directable and required less intervention. Her paranoia also decreased, allowing improved interaction with family, caregivers, and others. Ms. A remains stable on memantine, 10 mg bid; galantamine, 8 mg; quetiapine, 350 mg nightly; and vitamin E, 400 IU bid. Her cognitive ability has gradually declined over the past 18 months, as evidenced by her most recent MMSE score of 16/30.
Agitation in Alzheimer’s disease poses a clinical challenge. Successive single- or multiple-medication trials often are necessary to find a regimen that reduces agitation and slows cognitive decline. Consider tolerability, drug-drug interactions, and minimizing polypharmacy when planning treatment.

**References**


**Related resources**


**Drug brand names**

- buspirone • BuSpar
depakote, depakote er • Depakote, Depakote ER
- clonazepam • Klonopin
gabapentin • Neurontin
- fluoxetine • Prozac
- memantine
- methylphenidate • Concerta, Ritalin
- oxcarbazepine • Trileptal
- paroxetine • Paxil
- quetiapine • Seroquel
- risperidone wafers • Risperdal M-Tabs
- rivastigmine • Exelon
- seligiline • Eldepryl
- sertraline • Zoloft
- zolpidem • Ambien

**Disclosure**

Dr. Godoth is a speaker for Pfizer Inc., Forest Pharmaceuticals, and Bristol-Myers Squibb Co., and has received grant support from Pfizer Inc. He has also received support from the Bristol-Myers Squibb Fellowship in Geriatric Psychiatry through the American Association of Geriatric Psychiatry.

Dr. Rao is a speaker for Pfizer Inc.

Drs. Raval and Ruth report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.


