Current PSYCHIATRY

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'

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PRESENTING SYMPTOMS Marital memories

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,

continued on page 91

Table 1

Differences in Alzheimer's, Lewy body, and vascular dementias

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

tumors, or other cerebral diseases. Laboratory tests can reveal systemic conditions such as hypothyroidism, vitamin B_{12} deficiency, hypercalcemia, neurosyphilis, or HIV infection.[1]

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.)*

DIAGNOSIS An unpredictable patient

Ms. A received a CBC; comprehensive metabolic panel; urinalysis; screens for rapid plasma reagin, B_{12}, folate, and homocysteine levels; and a brain MRI. Hemoglobin and serum albumin were mildly depressed, reflecting early malnutrition. MRI showed generalized cerebral atrophy. Significant vascular disease was not identified.

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

Table 2

Medications for treating agitation in Alzheimer's dementia

Drug	Supporting evidence	Recommended dosage (mg/d)*	Rationale	Drawbacks
Anticonvulsants				
Carbamazepine	Tariot et al[2]	200 to 1,200 mg/d in divided doses	Commonly used for impulse control disorders	Agranulocytosis, hyponatremia, liver toxicity (all rare)
Divalproex	Loy and Tariot[3]	250 to 2,000 mg/d	Increasing evidence points to neuroprotective qualities	Possible white blood cell suppression, liver toxicity, pancreatitis (all rare)
Gabapentin	Roane et al[4]	100 to 1,200 mg/d	Safe in patients with hepatic dysfunction	Scant data on use in Alzheimer's disease
Lamotrigine	Tekin et al[5]	Start at 25 mg/d; titrate slowly to 50 to 200 mg/d	Possibly neuroprotective via N-methyl-D-aspartate mechanism	Rapid titration may cause Stevens-Johnson syndrome
Atypical antipsychotics				
Olanzapine	Street et al[6]	2.5 to 10 mg/d	Sedating effects may aid sleep	Anticholinergic effects may increase confusion, compound cognitive deficit
Quetiapine	Tariot et al[7]	25 to 300 mg/d	Tolerable Sedating effects may aid sleep	Watch for orthostasis, especially at higher dosages
Risperidone	DeVane et al[8]	0.25 to 3 mg/d	Strong data support use	High orthostatic potential, possible extrapyramidal symptoms with higher dosages
Ziprasidone	None	Oral: 20 to 80 mg bid IM: 10 to 20 mg, maximum 40 mg over 24 hours	Effective in managing agitation	No controlled trials, case reports in AD-associated agitation
SSRIs				
Citalopram	Pollock et al[9]	10 to 40 mg/d	Minimal CYP-2D6 inhibition	Effect may take 2 to 4 weeks
Sertraline	Lyketsos et al[10]	25 to 200 mg/d	Minimal CYP-2D6 inhibition	Effect may take 2 to 4 weeks

* No specific, widely accepted dosing guidelines exist for patients age > 65, but this group often does not tolerate higher dosages.
SSRI: Selective serotonin reuptake inhibitor
IM: Intramuscular

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.

Data support use of olanzapine for agitation in AD,[6] 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.

TREATMENT 3 months of stability

Ms. A's galantamine dosage was increased to 8 mg bid and sertraline—25 mg/d for 7 days, then 50 mg/d—was added in an effort to better control her agitation, but the behavior continued unabated for 2 weeks. Divalproex, 125 mg bid titrated over 4 weeks to 750 mg/d, was added. Still, her agitation persisted.

Over the next 4 to 6 weeks, Ms. A showed signs of psychosis, often talking to herself and occasionally reporting "people attacking me." She became paranoid toward members of her church, who she said were "trying to hurt" her. The paranoia intensified her agitation and disrupted her sleep. Physical examination was unremarkable, as were chest X-ray and urinalysis.

Sertraline and divalproex were gradually discontinued. Quetiapine—25 mg nightly, titrated across 2 weeks to 150 mg nightly—was started. Ms. A's agitation and psychosis decreased with quetiapine titration, and her sleep improved. Her paranoid delusions remained but no longer impeded functioning or prompted a violent reaction.

Then after remaining stable for about 3 months, Ms. A's paranoid delusions worsened and her agitation increased.

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—memantine[21] for AD-related agitation also has been described.

CONTINUED TREATMENT Medication changes

Quetiapine was increased to 350 mg nightly across 4 weeks, resulting in mild to moderate improvement. The higher dosage did not significantly worsen rigidity or motor function, and Ms. A tolerated the increased dosage without clinical orthostasis.

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.

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Bottom Line

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.

Related resources

- Cummings JL. Use of cholinesterase inhibitors in clinical practice: evidence-based recommendations. *Am J Geriatr Psychiatry* 2003; 11:131-45.
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DRUG BRAND NAMES

Buspirone • BuSpar
Carbamazepine • Tegretol
Citalopram • Celexa
Clonazepam • Klonopin
Clozapine • Clozaril
Divalproex • Depakote, Depakote ER
Fluoxetine • Prozac
Gabapentin • Neurontin
Galantamine • Reminyl
Lamotrigine • Lamictal
Memantine • Namenda
Methylphenidate • Concerta, Ritalin
Olanzapine • Zyprexa
Oxcarbazepine • Trileptal
Paroxetine • Paxil
Quetiapine • Seroquel
Risperidone wafers • Risperdal M-Tabs
Rivastigmine • Exelon
Selegiline • Eldepryl
Sertraline • Zoloft
Ziprasidone • Geodon
Zolpidem • Ambien

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