

Will CATIE-AD change dementia treatment?

Newer antipsychotics ‘not for long-term use’

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New findings questioning the value of second-generation antipsychotics (SGAs) for treating acute behaviors in patients with Alzheimer’s disease have raised more questions on when and how to use these agents in the elderly.

The National Institute of Mental Health-sponsored Clinical Antipsychotic Trial of Intervention Effectiveness-Alzheimer’s disease (CATIE-AD) concluded that SGAs offer no overall advantage over placebo. Although SGAs helped some trial patients, the medications were discontinued for approximately 8 in 10 patients because of intolerable side effects or ineffectiveness.

CATIE-AD’s principal investigator says the findings—published in the October 12 *New England Journal of Medicine*¹—will guide clinicians in adjusting SGA dosages and durations for older patients with dementia.

But other psychiatrists argue that the study—led by prominent researchers and published in a prestigious medical journal—will deter clinicians from trying SGAs for older patients with dementia-related psychosis, aggression, or agitation.

PARTICIPATING IN THIS DISCUSSION

Barbara Kamholz, MD

Clinical associate professor, department of psychiatry, University of Michigan Medical School; staff psychiatrist, VA Medical Center, Ann Arbor

Lon Schneider, MD

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Sumer Verma, MD

Director, geriatric psychiatry education program, McLean Hospital, Belmont, MA

“These drugs are not FDA-approved for dementia. They may cause diabetes. They cause weight gain. They carry boxed warnings that they could increase risk of stroke and—in patients over age 85—can increase risk of dying,” says Sumer Verma, MD, director of the geriatric psychiatry education program at McLean

Box

CATIE-AD study: Clinical highlights

Participants

421 outpatients with psychosis, agitation, or aggression, or who met DSM-IV-TR criteria for Alzheimer's-type dementia or probable Alzheimer's disease based on history, physical examination, structural brain imaging results, and Mini-Mental State Examination scores between 5 and 26, indicating some degree of cognitive deficit.

These patients:

- were ambulatory
- lived at home or in an assisted-living facility
- had delusions, hallucinations, aggression,

or agitation that developed after dementia onset, disrupted functioning, and justified treatment with an antipsychotic

- showed signs and symptoms of psychosis, aggression, or agitation almost daily during the previous week or intermittently for 4 weeks.

Trial duration

Up to 36 weeks

Study drugs/mean dosages at endpoint

- olanzapine (5.5 mg/d)
- quetiapine (56.5 mg/d)
- risperidone (1 mg/d)

Physicians could increase dosages

or prescribe a benzodiazepine or haloperidol if problem behaviors emerged.

Key findings

- **Time to discontinuing treatment** for any reason did not differ significantly among the treatment and placebo groups.

Source: Reference 1

- **Median time** to discontinuation because of lack of efficacy was significantly longer with olanzapine (22.1 weeks) or risperidone (26.7 weeks) than with quetiapine (9.1 weeks) or placebo (9.0 weeks).

- **Rates of discontinuation** because of intolerance, adverse effects, or death were 24% with olanzapine, 16% with quetiapine, 18% with risperidone, and 5% with placebo.

- **Overall rates of discontinuation** for any reason were 63% after 12 weeks and 82% after 36 weeks.

- **Parkinsonism** or extrapyramidal symptoms were more prevalent among the olanzapine and risperidone groups (12% in each) than among the quetiapine and placebo groups (2% and 1%, respectively).

- **Sedation** was more common with the three SGAs (15% to 24% of patients) than with placebo (5%).

- **Confusion** or mental status changes were more common with olanzapine (18%) and risperidone (11%) than with placebo (5%). Cognitive disturbances and psychotic symptoms were more common with olanzapine (5% and 7%, respectively) than with the other SGAs or placebo (0 to 2%).

- **Body weight** increased 0.4 to 1 lb/month among the SGA groups and decreased 0.9 lb/month in the placebo group.

- **Rates of improvement**—as measured with the Clinical Global Impression of Change scale—did not differ significantly among the treatment and placebo groups.

Hospital (Belmont, MA). “Doctors already were reluctant to use SGAs, and now these researchers publish this study in one of the country’s most respected journals and make an unqualified statement to the effect that [SGAs] are no better than placebo. How many clinicians will be comfortable prescribing them?”

‘DISCOURAGING’ DISCONTINUATION

CATIE-AD—a double-blind, multicenter, randomized trial (*Box*)—followed 421 ambulatory outpatients with Alzheimer’s disease and psychosis, aggression, or agitation. Patients received the SGAs olanzapine (mean dosage, 5.5 mg/d), quetiapine (mean 56.5 mg/d), risperidone (mean

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1 mg/d), or placebo. Dosages were adjusted as needed.

After 36 weeks, times to discontinuation because of lack of efficacy were longest for olanzapine and risperidone, but these drugs also had the highest rates of discontinuation because of intolerability (24% and 18%, respectively). Quetiapine's rate of discontinuation because of intolerability was 16%.

SGAs were stopped because of lack of efficacy or intolerable side effects—such as parkinsonism, extrapyramidal symptoms, sedation, or weight gain—in:

- 63% of treatment and placebo group patients within 12 weeks
- 82% of all patients within 36 weeks.

Lon Schneider, MD, principal investigator for CATIE-AD, acknowledged that the findings could discourage psychiatrists from prescribing SGAs for acute dementia-related behaviors, specifically in patients with Alzheimer's disease.

But although discontinuation because of intolerability was most prevalent among patients taking risperidone or olanzapine, both SGAs were more effective than placebo for treating problem behaviors in some participants, Dr. Schneider notes. He adds that the patient population and most SGA dosages in CATIE-AD reflected typical geriatric psychiatric practice in the community.

An editorial in the October 12 *New England Journal of Medicine*² praised CATIE-AD for allowing physicians to titrate and stop SGA regimens as needed while maintaining the double-blind design. Results of fixed-dose trials with pre-specified time points are more difficult to apply to clinical practice because the course of Alzheimer's disease and patients' ability to tolerate specific drugs change over time.²

"This study can inform clinicians that they

should not be prescribing medication and then not following up or maintaining it indefinitely," says Dr. Schneider, who is professor of psychiatry, neurology and gerontology, University of Southern California, Los Angeles.

'BLACK BOX' FEARS?

Dr. Verma, however, reports that many clinicians have been hesitant to prescribe SGAs to older patients since last year—when the FDA ordered that SGAs carry "black box" warnings of a possible increased mortality risk in that population.

"CATIE-AD will intensify clinicians' fears of litigation by implying that the risks of using SGAs outweigh their benefits, especially when SGAs are reported to be no better than placebo," Dr. Verma predicts.

"A lawyer could say to a clinician, 'You used an SGA on Mr. Smith despite the risks, and he developed XYZ complication?' Try to work yourself out of that one.

"A paper like this will be snapped up by pharmacy and therapeutics committees around the country, as well as Medicare, Medicaid, and other insurers,"

Dr. Verma adds. "They'll say, 'These expensive drugs are no better than

placebo. Why bother covering them?'"

Echoing Dr. Verma's fears, the American Association for Geriatric Psychiatry (AAGP) responded to CATIE-AD by urging regulatory agencies not to overreact to the findings or "prevent physicians from exercising clinical judgment."³ AAGP also is calling for more research "based on clinical and evidence-based protocols designed to help physicians know when and how to start, continue, and discontinue psychotropics" for older patients.³

Another problem with generalizing the CATIE-AD findings, Dr. Verma says, is that many Alzheimer's patients are more severely impaired than those who participated in CATIE-AD.

Dr. Schneider: 'Don't prescribe SGAs without following up. Also, don't maintain them indefinitely.'

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“These are people who cannot be managed,” adds Barbara Kamholz, MD, clinical associate professor, University of Michigan, and staff psychiatrist, VA Medical Center, Ann Arbor. “They can’t get through the day. They can’t eat or use the bathroom properly. You can’t treat their medical problems if you can’t manage grossly abusive or violent behaviors.”

Dr. Schneider, however, notes that the outpatients in CATIE-AD were nearly as symptomatic as patients in nursing homes—as suggested by CATIE-AD patients’ mean Brief Psychiatric Rating Scale and Neuropsychiatric Inventory scores (28 and 37, respectively).

Also, Dr. Schneider says, most trials of SGAs conducted among nursing home patients have not yielded statistically significant results.⁴

‘INFORMING’ PRACTICE

Dr. Schneider warns against drastic interpretation of CATIE-AD, saying the trial should guide clinical practice, not radically alter it. He says he will keep prescribing SGAs for short-term acute treatment of older patients whose behavioral problems do not respond to psychosocial interventions, distraction, redirection, environmental manipulation, or other treatments.

Dr. Verma: ‘SGAs are not perfect drugs, but they’re the best we’ve got and better than what we had.’

“I’m not sure this study has changed my use of [SGAs],” Dr. Schneider says. “What it has done is better inform my considerations in prescribing. But I use [SGAs] in patients with significant behavioral problems—and especially with delusions, paranoia and aggression—who can’t be otherwise treated.”

Studies show that despite their risks, SGAs:

- are associated with one-tenth the risk of tardive dyskinesia compared with first-generation antipsychotics (FGAs) such as haloperidol⁵
- are less likely to cause extrapyramidal symptoms than FGAs.⁶

Dr. Verma notes that the cardiac, cerebrovascular, and cardiopulmonary side effects described in the “black box” warnings on SGAs are prevalent conditions in the elderly, independent of medication.

“Despite the side effects, 20% to 30% of patients [in CATIE-AD] continued to take [SGAs] for the entire study,”

Dr. Verma adds. “[SGAs] are not perfect drugs, but they’re the best we’ve got right now and better than what we had.”

Dr. Schneider acknowledges that no evidence supports use of other drug classes to treat problem behaviors in the elderly. “Antidepressants have their own adverse effects, and you wouldn’t expect them to work for delusions or aggression. And benzodiazepines are strongly associated with falling and oversedation.”

Dr. Kamholz fears that some psychiatrists might eschew SGAs in older patients and prescribe another type of medication that carries a greater side-effect risk.

“If they’re not using [SGAs], they might be using something more dangerous,” Dr. Kamholz says. “For example, haloperidol is an old standby, but very few studies address its global effects. So we’re groping around in the dark. I’ve also seen some bad deliriums caused by benzodiazepines.”

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Managing dementia:
Risks of using vs. not using
atypical antipsychotics

► AUGUST 2005



Table

Recommended second-generation antipsychotic dosing for older patients

Drug	Starting dosage	Titration	Most-common side effects
Olanzapine	2.5 to 5 mg/d, depending on the patient's body mass and frailty	2.5 mg every 2 to 3 days to 15 to 20 mg/d or therapeutic effect	Weight gain, orthostasis, sedation
Quetiapine*	25 mg/d	25 mg every 2 to 3 days to 350 mg/d or therapeutic effect	Sedation, weight gain
Risperidone	0.25 mg bid	0.25 mg every 2 to 3 days to 2 to 3 mg bid or therapeutic effect	Extrapyramidal symptoms, orthostasis

* Recommended for patients with Lewy body dementia or parkinsonian movement problems.
Source: Sumer Verma, MD

WHEN TO PRESCRIBE SGAs

At what point does the need to manage psychosis, aggression, or agitation in Alzheimer's disease outweigh SGAs' risks?

"Frankly, I'd rather not use medications unless I have to—and then only enough to preserve function while treating the behavioral disturbance," Dr. Verma says. "I don't want to anesthetize these patients. I just want to maintain their function, dignity, and quality of life."

Seeking other causes of acute behaviors is essential before prescribing an SGA, Drs. Verma and Schneider say. Psychotic disorientation, for example, can occur with underlying psychiatric problems (such as delirium), hearing and sight deficits, disrupted schedules, poor sleep and appetite, incontinence, pain, unrelated medical complications, or environmental stressors.

For many older patients with problem behaviors, SGAs are worth the risk after other interventions have failed, Dr. Kamholz says. Weighing behavioral against pharmacologic risks is key, Dr. Schneider adds.

"What are the consequences of the behavior

or paranoid ideation?" Dr. Schneider asks. "What about when the patient is refusing food? Or when caregivers cannot approach the patient, or the behavior creates a rift between family members so that the patient's basic needs cannot be met? If psychosocial and environmental interventions haven't worked, [SGAs] are worth a try."

Because acute behavior hastens caregiver burnout—a major cause of nursing home admission⁶—appropriate SGA use also can help older patients remain at home, Drs. Schneider, Kamholz, and Verma say.

PRACTICAL APPLICATIONS

Drs. Schneider, Verma, and Kamholz agree that SGAs are a short-term intervention for problem behaviors in dementia. Because Alzheimer's symptoms wax and wane as the disease progresses, patients need to be monitored continually, and medication regimens should be modified as needed and discontinued if possible.

Dr. Verma advises starting risperidone, olanzapine, or quetiapine at low dosages, titrating slowly, and monitoring the patient carefully (*Table*).

continued

Dr. Schneider suggests discontinuing the SGA after 12 to 20 weeks in patients who have responded. If behavior worsens after an SGA is discontinued, restart the medication, he says.

“If patients have adverse events with SGAs, do not try to tough it out,” Dr. Schneider adds. “Either adjust medications to eliminate adverse events or change the medication. If patients have been tolerating the medication for, say, 12 weeks, that doesn’t mean adverse reactions cannot develop later, so be ready to make adjustments.”

To guard against medicolegal risk when prescribing SGAs to older patients, Dr. Verma suggests that you clearly document:

- the reason you are prescribing the SGA
- your understanding of the risk/benefit ratio in using SGAs and that, in your clinical judgment, using an SGA in this patient is warranted because the benefits outweigh the risks
- that you considered other medications and the reasons those medications are inappropriate (for example, “I opted against a benzodiazepine

Second-generation antipsychotics (SGAs) can help manage agitation, aggression, and psychosis in some patients with Alzheimer’s disease. The CATIE-AD findings remind clinicians that SGAs are a short-term treatment for older patients. Modify regimens as needed and discontinue if possible.

BottomLine

 **Related resources**

- ▶ American Association for Geriatric Psychiatry. AAGP position statement: Principles of care for patients with dementia resulting from Alzheimer disease. www.aagponline.org/prof/position_caredmnlz.asp.

DRUG BRAND NAMES

Haloperidol • Haldol
Olanzapine • Zyprexa

Quetiapine • Seroquel
Risperidone • Risperdal

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because it could be too sedating and could increase the risk of falls and consequent injury”).

Also, get updates from the patient’s primary care physician on the patient’s cardiopulmonary and cerebrovascular health. Finally, provide extensive information about SGAs’ risks to family members, and keep signed documentation that you provided these warnings.

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