

Commentary

■ Antipsychotics in the elderly: Reducing risks of stroke and death

To minimize cardiovascular dangers,
think twice about the evidence

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In early-stage Alzheimer's disease, Mrs. P enters a nursing home because her daughter, who usually takes care of her, is hospitalized for cancer chemotherapy. Mrs. P promptly develops paranoid delusions and refuses her medications for high blood pressure and high cholesterol. What are the treatment options? Is any one antipsychotic safer than another?

Writing an antipsychotic prescription for patients such as Mrs. P is no longer a quick scribble. First we learned that atypicals may alter glucose and lipid metabolism in clinically troublesome ways.^{1,2} Then we learned that antipsychotics can triple the risk for sudden death in older patients with dementia. (See *FDA advisory, Related resources, page 77.*)

How great are the risks, who is at risk, and how strong

is the evidence for these new risks? The debate is not yet settled, but the boundaries of good practice for antipsychotic use in older patients are being redrawn. This is particularly true for those with dementia, in whom antipsychotics' risk/benefit ratio is higher than for older patients with schizophrenia or bipolar disorder.

UNPROVEN EFFECTIVENESS

Antipsychotics are not FDA-approved for treating dementia-related psychosis. Though antipsychotics are commonly used off-label to treat behavioral disturbances in the elderly with dementia, no standard of care exists for managing these symptoms with drugs. So far, the evidence for antipsychotics' effectiveness for dementia's behavioral and psychological symptoms is spotty at best.

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continued

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Table 1

Timeline: Evidence on risks, efficacy of atypical antipsychotics

Year	Summary of study findings, FDA warnings
2002	Higher incidence of stroke seen with risperidone than with placebo in two of four clinical trials (Wooltorton ⁷) Health Canada and Janssen-Ortho warn Canadian physicians of possible link between risperidone and stroke
2003	FDA warns of increased risk of stroke with risperidone
2004	Threefold increased risk of sudden cardiac death associated with antipsychotic use in patients age >65, most without dementia (Straus et al ¹¹)
2005	Stroke risk reported no greater in older patients who took atypicals than in those who took typical antipsychotics (Gill et al ¹⁰) Analysis of 14 controlled trials finds “no clear evidence” that typical antipsychotics are effective in dementia; atypicals' effects seen as “modest” (Sink et al ³) FDA issues warning after finding 60% increase in risk of sudden death in review of 17 trials in older patients receiving atypical antipsychotics for dementia Efficacy of conventional and atypical antipsychotics found similar in patients with chronic schizophrenia (Lieberman et al ⁶)

Sink et al (*Table 1*)³ systematically reviewed 14 randomized, controlled trials and concluded “there is no clear evidence that typical antipsychotics are useful for treating neuropsychiatric symptoms [of dementia].” They concluded from 6 studies of atypicals that only olanzapine and risperidone had shown efficacy, but the effects were “modest and further complicated by risk of stroke.” When the benefits are modest, the risks are more difficult to justify.

When medication is necessary, on the other hand, the Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients reported in 2004 that “for agitated dementia with delusions, the experts’ first-line recommendation is an antipsychotic drug alone.... Risperidone (0.5 to 2.0 mg/day) was first line, followed by quetiapine (50 to 150 mg/day) and olanzapine (5.0 to 7.5 mg/day) as high second-line options.”⁴

CATIE studies. The definitive prospective study of antipsychotics’ effectiveness in dementia has not been completed. The National Institute of Mental

Health is sponsoring CATIE—Clinical Antipsychotic Trials of Intervention Effectiveness—a multi-site research program comparing the effectiveness and outcomes of antipsychotics in treating schizophrenia and Alzheimer’s disease. Results of the Alzheimer disease arm⁵ are expected next year.

The schizophrenia arm comparing four atypical antipsychotics (quetiapine, risperidone, ziprasidone, and olanzapine) and one typical antipsychotic (perphenazine) found:

- Typical and atypical antipsychotics were similarly effective in 1,493 patients with chronic schizophrenia
- 74% of patients discontinued assigned medications before 18 months for lack of efficacy, intolerable side effects, or other reasons.⁶

STROKE RISK

How strong is the evidence for stroke risk among older patients who take antipsychotics? Wooltorton⁷ first raised concern about increased

risk of stroke with risperidone in 2002 in a summary of four clinical trials. Though none was designed to examine stroke risk as the primary outcome, two showed significantly higher incidence of cerebrovascular events with risperidone than with placebo. The stroke rate with risperidone was double that with placebo (4% vs 2%) across the total 1,200 subjects in the four studies.

This preliminary report led to an FDA advisory but surprisingly no definitive studies or systematic reviews. No epidemiologic studies have examined stroke rates in those who take antipsychotics compared with those who don't, while controlling for common stroke predictors. So we have a warning based on post hoc analyses in two positive and two negative studies, but no sound estimate of how much antipsychotic use in general adds to the risk of stroke.

Atypicals vs. typicals. Are atypicals worse than typicals in their effect on stroke risk?

Herrmann et al^{8,9} reviewed a health care database of 11,400 older persons and found no statistically significant increase in stroke rate with risperidone or olanzapine compared with typical antipsychotics. This study did not assess whether patients had dementia or primary psychotic disorders.

In a larger retrospective study of 32,710 older persons with dementia, Herrmann's group¹⁰ found no greater stroke risk in those who took atypicals than in those who took typical antipsychotics.

So the evidence for the risk of stroke in older patients who take antipsychotics is based on a few reports and no definitive studies.

RISK OF EARLY DEATH

What about the risk of early death? After reviewing 17 clinical trials of atypical antipsychotics in older patients with dementia, the FDA issued its warning in April 2005 about increased mortality risk (see *Related resources*). Fifteen of the trials showed an increased mortality risk, resulting in

Related resources

- ▶ Food and Drug Administration. Advisory on increased risk of mortality with use of atypical antipsychotics to treat behavioral disturbances in older patients with dementia. www.fda.gov/cder/drug/advisory/antipsychotics.htm.

DRUG BRAND NAMES

Olanzapine • Zyprexa	Risperidone • Risperdal
Perphenazine • Trilafon	Ziprasidone • Geodon
Quetiapine • Seroquel	

DISCLOSURES

The author reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

an estimated 1.6- to 1.7-fold increase in risk of death, mostly by cardiac or infectious causes.

A year earlier, Straus et al¹¹ reported on risk of sudden cardiac death with antipsychotic use in a population-based, case-control study in the Netherlands. In this longitudinal, observational database of 250,000 patients, 75% were age >65 and <1% had dementia. Current use of antipsychotics was associated with a threefold increase in risk of sudden cardiac death (554 cases), after other predictors of sudden death were factored in. This risk increased with higher antipsychotic dosages and was similarly elevated for patients with and without schizophrenia-related disorders.

MECHANISMS UNKNOWN

By what mechanisms could antipsychotics precipitate stroke, sudden cardiac death, or pneu-

Restrict antipsychotic use in older patients to those with primary psychotic disorders or complex and dangerous behaviors that do not respond to nondrug treatments. Monitor cardiovascular risk, and document discussions of risks and benefits with the patient and family.

BottomLine

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Table 2

Strategies to minimize antipsychotic risk in patients age 65 and older

Review and document risk factors for cardiovascular disease—including stroke—with physical examination, laboratory tests (lipid profile, fasting glucose), and ECG in consultation with a primary care physician or specialist

Try nonpharmacologic approaches first whenever possible to manage behavioral disturbances in patients with dementia; document results before trying an antipsychotic

Review antipsychotics' risks and benefits with patient and family

Use low dosages and increase gradually, as sudden death risk is dose-related

Monitor antipsychotic effectiveness, and discontinue trials of questionable benefit

Monitor cardiovascular symptoms, heart rate, blood pressure and body mass index of patients with cardiovascular risk

Avoid using sedating antipsychotics for insomnia in patients without psychiatric disorders

monia? A clear biological mechanism has not been proposed, much less proven. The risks seen in clinical trials—usually lasting 12 weeks or less—suggest an acute effect rather than the more-gradual consequences of weight gain, altered lipid metabolism, or diabetes.

Speculations range widely. Possibilities awaiting study include postural hypotension, altered platelet aggregation, increased venous thromboembolism, peripheral vasodilation leading to cardiovascular collapse, acute dystonia, acute cardiomyopathy, arrhythmias related to QT prolongation, and other forms of cardiac toxicity.^{10,11}

REMAINING QUESTIONS

The few studies plus two FDA advisories force clinicians to make complex treatment decisions on insufficient evidence. Here's what we don't know:

- The magnitude of stroke or sudden death risk in older patients who take antipsychotics for any diagnosis. (All studies have limitations, and public health policy should not rely on one or two studies, no matter how good they may be.)

- Who is at higher or lower risk with antipsychotic use—men vs women? blacks vs whites? etc.

- Biological mechanisms of an association between antipsychotics and risks of stroke and premature death.

STRATEGIES FOR REDUCING RISK

We can minimize patients' clinical risk and our legal risk only by using the limited evidence, expert consensus, and sound clinical judgment. Suggested strategies are listed in *Table 2*.

References

1. Zimmermann U, Kraus T, Himmerich H, et al. Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. *J Psychiatr Res* 2003;37(3):193-220.
2. Ryan MC, Thakore JH. Physical consequences of schizophrenia and its treatment: the metabolic syndrome. *Life Sci* 2002;71(3):239-57.
3. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA* 2005;293(5):596-608.
4. Alexopoulos GS, Streim J, Carpenter D, Docherty JP. Using antipsychotic agents in older patients. *J Clin Psychiatry* 2004;65(suppl 2):5-99.
5. Schneider LS, Ismail MS, Dagerman K, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer's disease trial. *Schizophr Bull* 2003;29(1):57-72.
6. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209-23.
7. Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. *CMAJ* 2002;167(11):1269-1270.
8. Herrmann N, Mamdani M, Lanctot KL. Atypical antipsychotics and risk of cerebrovascular accidents. *Am J Psychiatry* 2004;161(6):1113-1115.
9. Herrmann N, Lanctot KL. Do atypical antipsychotics cause stroke? *CNS Drugs* 2005;19(2):91-103.
10. Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ* 2005;330(7489):445.
11. Straus SM, Bleumink GS, Dieleman JP, et al. Antipsychotics and the risk of sudden cardiac death. *Arch Intern Med* 2004;164(12):1293-7.