

# Review: Atypical antipsychotic drugs increase risk for death in dementia

Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294:1934-43.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆ Hospitalists ★★★★★☆ Geriatrics ★★★★★☆ Neurology ★★★★★☆

## QUESTION

In older patients with dementia, do atypical antipsychotic drugs (APDs) increase risk for death compared with placebo?

## METHODS

**Data sources:** MEDLINE (1966 to April 2005) and Cochrane Controlled Trials Register (Issue 1, 2005), conference abstracts and proceedings (from 1999), and pharmaceutical companies.

**Study selection and assessment:** Published and unpublished randomized, double-blind, placebo-controlled trials (RCTs) that evaluated mortality in older patients with dementia.

**Outcomes:** Death during the study period or within 30 days of discontinuing treatment.

## MAIN RESULTS

15 RCTs with 16 comparisons ( $n = 5110$ , mean age 81 y, 70% women) met the selection criteria. 9 RCTs were unpublished. 87% of patients had Alzheimer disease. Patients were nursing home residents in 11 RCTs and

outpatients in 4 RCTs. Median duration of treatment was 10 weeks (range 6 to 26 wk). The drugs studied included aripiprazole (3 RCTs), olanzapine (5 RCTs), risperidone (5 RCTs), and quetiapine (3 RCTs). About one third of patients in both intervention and placebo groups dropped out before completion. Analysis was by intention-to-treat. Atypical APDs led to higher mortality rates than did placebo; results were similar when analysis was done on a per-patient basis or extrapolated to per person-year (Table). Treatment effect was similar regardless of spe-

cific drug, cognitive function level, type of dementia, or setting.

## CONCLUSION

In older patients with dementia, atypical antipsychotic drugs increase risk for death more than placebo.

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*For correspondence:* Dr. L.S. Schneider, University of Southern California, Los Angeles, CA, USA. E-mail [lschmeid@usc.edu](mailto:lschmeid@usc.edu). ■

### Atypical antipsychotic drugs (APDs) vs placebo for dementia at 10 to 30 weeks\*

Outcomes	Number of comparisons (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
		APD	Placebo		
Death per patient	16 (5110)	3.5%	2.3%	52% (5.9 to 117)	85 (38 to 751)
Death per person-y	16 (874)	22%	13%	65% (19 to 129)	12 (6 to 40)

\*Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article using a fixed-effects model for death per patient and a random-effects model for death per person-year.

## COMMENTARY

Schneider and colleagues substantiate an April 2005 advisory from the U.S. Food and Drug Administration about increased mortality in older patients with dementia given atypical APDs (1). According to the review by Schneider and colleagues, atypical APDs will cause 1 death for every 85 patients treated, or 1 excess death for every 12 patient-years of treatment.

The risks associated with such conventional APDs as haloperidol and the phenothiazines are even greater. In an observational study, conventional APDs were associated with a 1.37 relative risk (RR) for death in older persons during the first 6 months of use and a 1.56 RR during the first 40 days, compared with atypical APDs (2).

These studies do not justify avoidance of APDs in patients with dementia, but underscore the need to carefully assess and document the risk-benefit ratio for each patient, which includes ruling out such reversible contributors as delirium and factoring in caregiver well-being. Delusions, hallucinations, and agitation or aggression affect 18%, 11%, and 30%, respectively, of persons with dementia (3). In about half of these individuals, the behaviors are considered highly disturbing to their caregivers. These psychiatric symptoms commonly increase over time, correlate with caregiver burden (4), and represent the most appropriate

indication for APD use in dementia. Clinical management should emphasize behavioral alternatives to medication, use of the lowest effective dose, and periodic tapering to determine the need for continued use.

*Calvin Hirsch, MD  
University of California, Davis  
Sacramento, California, USA*

## References

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