

## Does Antipsychotic Use Increase Risk of Death Among the Elderly?

Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005;353:2335–41.

### Study Overview

**Objective.** To determine whether the use of conventional antipsychotic medications is associated with higher risk of death compared with atypical antipsychotics among the elderly.

**Design.** Retrospective cohort study.

**Setting and participants.** 22,890 elderly patients (aged  $\geq 65$  years) in Pennsylvania who initiated therapy with a conventional or atypical antipsychotic medication between 1994 and 2003 were studied.

**Main outcome measures.** All-cause mortality at 180 days was the primary outcome. Secondary outcomes included death at less than 40 days, at 40 to 79 days, and at 80 to 179 days.

**Main results.** Use of conventional antipsychotic medications was associated with high rates of mortality as compared with use of atypical antipsychotic medications at 180 days (relative risk, 1.37 [95% confidence interval, 1.27–1.49]) as well as at other intervals studied. Much of the difference in the death rates was present in the first 30 days after medications were initiated. When alternative analytic techniques were used (eg, instrumental variable analysis), conventional antipsychotic medications were still associated with higher mortality rates.

**Conclusion.** Elderly patients treated with conventional antipsychotics seem to have higher rates of death compared with those who receive atypical antipsychotic medications. Further studies are needed to more convincingly demonstrate whether this association is true.

### Commentary

As the population ages, there is a growing need to find ways to treat psychosis or delirium in the setting of dementia. Antipsychotic medications are often used in these clinical contexts, even though they are not formally approved for such uses. While conventional antipsychotics have been the mainstay of delirium and psychosis management in the elderly, the new “atypical” agents have become increasingly favorable.

Recently, several studies found that atypical antipsychotics were associated with higher rates of mortality than placebo [1,2], but how they compared with conventional agents is largely unknown. Many physicians, concerned that atypical agents may increase the risk of death among the elderly, have switched to conventional agents. This study by Wang and colleagues is among the first to carefully examine differences in mortality rates between these 2 types of agents.

The investigators found that mortality was high for conventional antipsychotic medications in every prespecified time period. The differences were substantial (20%–50% higher risk of death, depending on the time period examined) and were statistically significant, even after adjusting for observed baseline differences between both groups. Because this was not a randomized trial and because patients who received conventional antipsychotics seemed sicker at baseline than those who received atypical antipsychotics, unmeasured clinical factors associated with the treatment (conventional versus atypical) and with outcomes may be an issue. This is the most important limitation of any observational study, and the authors tried to address this issue in 2 ways: by using propensity scores and an “instrumental variable.” Propensity scores are used to make 2 groups more comparable by trying to predict why a patient ends up in 1 group or another and factoring this prediction into the multivariable models. This complicated approach has many advantages in trying to account for observed differences between the 2 groups but ultimately cannot address the issue of unmeasured confounders.

Using an instrumental variable may be more useful in an observational study. An instrumental variable is a variable

(continued on page 15)

“Outcomes Research in Review” is edited by Stephen D. Persell, MD, MPH, Department of Medicine, Northwestern University, Chicago, IL; Harvey J. Murff, MD, MPH, and Christianne L. Roumie, MD, MPH, Division of General Internal Medicine, Vanderbilt University Medical Center, Nashville, TN; David R. Spiegel, MD, Sarah Cannon Research Institute, Nashville, TN; Ashish K. Jha, MD, MPH, Division of General Medicine, Brigham and Women’s Hospital, Boston, MA; and Mark S. Hornig, MD, VA Greater Los Angeles Healthcare System, Los Angeles, CA.

(continued from page 8)

that is clearly associated with the predictor (whether a patient received a conventional versus atypical antipsychotic) but not with the outcome (ie, mortality). Wang et al used a physician's general predilection for 1 type of antipsychotic versus another. Although this may seem to be an appealing instrumental variable, there is a potential problem: physicians who are younger or more up-to-date with trends in medical care are more likely to use antipsychotics and thus may better manage dementia in elderly patients and have better outcomes. Although instrumental variables can be useful, in this case they might have identified patients whose physicians were potentially better, and this might have confounded the analysis.

### Applications for Clinical Practice

While many clinicians have shied away from using atypical

antipsychotics, this study offers strong (although not convincing) evidence that conventional antipsychotics are even more dangerous. A randomized controlled trial of atypical antipsychotics versus conventional antipsychotics is needed to confirm these results. Until then, it is wise to limit the use of antipsychotics in general, and if they must be used, atypical antipsychotics are likely to be safer.

—Review by Ashish K. Jha, MD, MPH

### References

1. U.S. Food and Drug Administration. FDA public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. Available at [www.fda.gov/cder/drug/advisory/antipsychotics.htm](http://www.fda.gov/cder/drug/advisory/antipsychotics.htm). Accessed 3 Nov 2005.
2. Kuehn EM. FDA warns antipsychotic drugs may be risky for elderly. *JAMA* 2005;293:2462.

Copyright 2006 by Turner White Communications Inc., Wayne, PA. All rights reserved.