

# Conventional antipsychotic drugs increased risk for death more than did atypical antipsychotic drugs in elderly patients

Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ*. 2007;176:627-32.

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

## QUESTION

In elderly patients, is the use of conventional or atypical antipsychotic drugs (APDs) associated with increased risk for death?

## METHODS

**Design:** Cohort study.

**Setting:** British Columbia, Canada.

**Patients:** 37 241 patients  $\geq 65$  y of age who filled new (index) prescriptions of oral conventional ( $n = 12\ 882$ , mean age 80 y, 60% women) or atypical ( $n = 24\ 359$ , mean age 80 y, 65% women) APDs, used  $\geq 1$  medical service, and filled  $\geq 1$  prescription in the two 6-month intervals before the index date. Exclusion criteria were cancer and use of APDs in the year before the index date. The atypical APDs evaluated were risperidone, quetiapine, olanzapine, and clozapine; conventional APDs were loxapine, haloperidol, chlorpromazine, trifluoperazine, thioridazine, pimozide, promazine, perphenazine, fluphenazine, mesoridazine, and thiothixene.

**Risk factors:** Use of APDs, dose or duration of drug, dementia status, and residence in a nursing home. Results were adjusted for year, age, sex, race, diabetes, coronary or cardiovascular diseases, HIV, cancer, dementia, psychotic or psychiatric disorders, psychiatric or anticholinergic drug use, number of medications, hospitalization, and residence in a nursing home.

**Outcomes:** All-cause mortality within 180 days after the start of APD therapy.

## MAIN RESULTS

Multivariate analysis showed that within the first 180 days of APD therapy, the conventional group had more deaths than did the atypical group (14% vs 9.6%; Table). Higher doses of conventional APDs and APD therapy in the first 40 days were associated with the greatest increases in risk for death (Table). Regardless of dementia status or residence in a nursing home, the conventional group had more deaths than did the atypical group (Table).

### Risk factors for all-cause mortality within 180 days after the start of conventional vs atypical antipsychotic drug (APD) therapy in elderly patients\*

Risk factors	Adjusted hazard ratio† (95% CI)
Any conventional APD	1.32 (1.23 to 1.42)
High-dose conventional APD	1.67 (1.50 to 1.86)
Low-dose conventional APD	1.23 (1.14 to 1.33)
< 40 d after start of APD therapy	1.60 (1.42 to 1.80)
40 to 79 d after start of APD therapy	1.31 (1.14 to 1.51)
80 to 180 d after start of APD therapy	1.18 (1.06 to 1.31)
Dementia	1.26 (1.01 to 1.56)
No dementia	1.30 (1.21 to 1.40)
In a nursing home	1.25 (1.12 to 1.40)
Not in a nursing home	1.35 (1.23 to 1.49)

\*CI defined in Glossary.

†Adjusted for year, age, sex, race, diabetes, coronary or cardiovascular diseases, HIV, cancer, dementia, psychotic or psychiatric disorders, psychiatric or anticholinergic drug use, number of medications, hospitalization, and residence in nursing home.

## CONCLUSION

Use of conventional antipsychotic drugs increased risk for death more than did use of atypical antipsychotic drugs in elderly patients.

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## COMMENTARY

Safety concerns regarding APDs have been long-standing, but warnings from drug regulatory bodies have heightened attention on atypical APDs. In a meta-analysis by Schneider and colleagues (1), higher risk for death was associated with use of atypical APDs compared with placebo (odds ratio [OR] 1.54, 95% CI 1.06 to 2.23). Conventional APDs are also associated with increased risk. Pooled data from 2 studies showed a nonsignificant relative risk (RR) increase for death in patients taking haloperidol compared with placebo (1).

In the study by Schneeweiss and colleagues, conventional APDs were associated with a 32% increased risk for death compared with atypical APDs, consistent with results from a similar study of Medicaid beneficiaries (RR 1.37, CI 1.27 to 1.49) (3). The finding is further supported by a positive dose-response relationship, although it is difficult to determine the actual dose of APD used by patients from administrative data.

Critics of observational studies often cite the inability of statistical methods to control for confounding factors. Channeling bias is particularly difficult to overcome; if physicians selectively prescribed conventional APDs to patients who were more likely to die, an observed increased risk for mortality may not be attributable to drug exposure. Schneeweiss and colleagues used several analyses to control for con-

foundings factors. Examination of individual drugs showed highest risk for death associated with haloperidol compared with risperidone (OR 2.14, CI 1.86 to 2.45). This is higher than the placebo-controlled point estimate for haloperidol from the meta-analysis by Schneider and colleagues (1) but falls within the reported CI. The higher rate may indicate some channeling bias.

Since randomized evaluation of death associated with conventional APDs is unlikely to be forthcoming, observational data can assist in clinical decision making. Given the serious nature of adverse outcomes, the burden of evidence should be to prove superior safety rather than criticize evidence showing equivalence in toxicity. If APDs are required, the side effect profile and pharmacologic properties of each drug should be considered in the context of the individual patient. Given the balance of evidence, conventional APDs should be considered to have at least the same, if not higher, risk for death as atypical APDs.

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## References

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