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Original Investigation

# Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia

Number Needed to Harm

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## Abstract

**Importance** Antipsychotic medications are associated with increased mortality in older adults with dementia, yet clinical guidelines do not indicate how to balance harm or ascertain alternatives to care.

**Objective** To determine the absolute mortality risk associated with dose and number needed to harm (NNH) by number of patients who experienced mortality for antipsychotic, other psychotropic, and nonpsychotropic medications and antipsychotic use in patients with dementia relative to either no treatment or antidepressant treatment.

**Design, Setting, and Participants** A retrospective case control study was conducted in the Veterans Health Administration (VHA) nationwide. Veterans with dementia who were prescribed medications for 180 days were drawn from a cohort with a diagnosis of dementia. Post enrollment were evaluated for death.

**Exposures** A new prescription for antipsychotics (haloperidol, olanzapine, quetiapine, and risperidone), citalopram and sertraline, or a nonpsychotropic medication.

**Main Outcomes and Measures** Absolute change in mortality risk and NNH over 180 days of follow-up in matched cohorts of patients who received a new prescription for antipsychotics vs no treatment and antipsychotics vs citalopram and sertraline. Mortality risk was estimated using Kaplan-Meier survival analysis. Secondary comparisons were by dementia subtype (Lewy body dementia, vascular dementia, Alzheimer dementia, dementia NOS), by dose, and by dementia severity, presence of delirium, and other psychiatric and behavioral disorders. Secondary analyses compared dose-adjusted absolute mortality risk and NNH for all nonpsychotic, psychotropic, and nonpsychotropic.

**Results** Among 1 000 matched pairs, antipsychotic medication initiation increasing hospital bed-days at increased mortality risk (0.48% [95% CI, 0.25-0.70; P, <.001] vs 0.18% [95% CI, 0.07-0.29; P, .001]; 95% difference [95% CI, 0.29-0.12]; P, <.001) with an NNH of 27 (95% CI, 18-45); olanzapine, 0.0% (95% CI, 0.0-0.4; P, .0); citalopram, 0.0% (95% CI, 0.0-0.4; P, .0); quetiapine, 0.0% (95% CI, 0.0-0.4; P, .0); risperidone, 0.0% (95% CI, 0.0-0.4; P, .0); sertraline, 0.0% (95% CI, 0.0-0.4; P, .0); and haloperidol, 0.0% (95% CI, 0.0-0.4; P, .0). Mortality risk was highest for haloperidol (vs 0.2% [95% CI, 0.0% 0.5%; P, .07]) and lowest for citalopram (vs 0.2% [95% CI, 0.0% 0.5%; P, .07]) and sertraline (vs 0.2% [95% CI, 0.0% 0.5%; P, .07]). Mortality risk was highest for vascular dementia (0.7% [95% CI, 0.2-1.2; P, .01]) and lowest for Alzheimer dementia, unspecified dementia, and other psychotropic medications. Haloperidol showed a dose-response increase in mortality risk, with 0.5% greater mortality (95% CI, 0.2-0.8; P, .001) for 1 to 2 mg/d and 1.0% greater mortality (95% CI, 0.4-1.6; P, .001) for 3 to 5 mg/d. Among patients with delirium, dose adjusted mortality risk was increased with haloperidol (1.7%, 95% CI, 0.8%, 2.7%; P, <.001) and olanzapine (1.0%, 95% CI, 0.0%, 2.0%; P, .05).

**Conclusions and Relevance** The absolute difference in mortality in elderly patients with dementia may be higher than previously reported and increases with dose.

## Introduction

Individual clinical trials and meta-analyses have reported increased mortality risk from some antipsychotic agents (eg, use phasing for the treatment of psychosis in patients with dementia).[1] and that these increased mortality risks may extend after a medication is discontinued.[2] Potential harms antecipated with use of these medications in patients with dementia include cerebrovascular events,[3] pneumonia,[4] and hip fracture.[5] Although the US Food and Drug Administration issued a black box warning for antipsychotics,[6] these pharmacoepidemiologic studies, which have been criticized for confounding,[7] demonstrated an increased risk of cerebrovascular adverse events for which the US Food and Drug Administration issued a black box warning.[8] Although the US Food and Drug Administration issued a black box warning for antipsychotics, clinical guidelines do not indicate how to balance harm or ascertain alternatives to care. Although increased mortality risk, in April 2005, the FDA[9] issued a black box warning that the use of atypical antipsychotics in patients with dementia increased risk of death. Although the US Food and Drug Administration issued a black box warning for atypical antipsychotics,[10] these determinations that the general population experiences even higher mortality risk than the elderly population with dementia.[11] Although the FDA[12] issued black box warnings in 2008 for antidepressants, the US Food and Drug Administration did not issue a black box warning for antidepressants in patients with dementia because of insufficient clinical evidence.[13]

Using a large cohort registry of Veterans Affairs (VA) patients with dementia, Kales et al[14] published the first nationwide study of the association between the use of antipsychotics and mortality in patients with dementia. Kales et al[14] cited clinical trials, cohort studies, and case-control studies that demonstrated a "dose-response" association between antipsychotic use and mortality in patients with dementia. Although Kales et al[14] reported a dose-response association between antipsychotic use and mortality, the "dose-response" association could be explained by confounding.[15] Although Kales et al[14] reported a "dose-response"

22. Kales HC, Kamholz BA, Visnic SG, Blow FC. Recorded delirium in a national sample of elderly inpatients: potential implications for recognition. *J Geriatr Psychiatry Neurol*. 2003;16(1):32-38.
PubMed | Google Scholar | Crossref

23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
PubMed | Google Scholar | Crossref

24. Olfson M, Blanco C, Liu SM, Wang S, Correll CU. National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Arch Gen Psychiatry*. 2012;69(12):1247-1256.
Article | PubMed | Google Scholar | Crossref

25. Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho B-C. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. *Biol Psychiatry*. 2010;67(3):255-262.
PubMed | Google Scholar | Crossref

26. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med*. 1991;10(4):585-598.
PubMed | Google Scholar | Crossref

27. Maglione M, Maher AR, Hu J, et al. *Off-Label Use of Atypical Antipsychotics: An Update*. Rockville, MD: Agency for Healthcare Research & Quality; 2011.

28. Okura T, Plassman BL, Steffens DC, Llewellyn DJ, Potter GG, Langa KM. Neuropsychiatric symptoms and the risk of institutionalization and death: the aging, demographics, and memory study. *J Am Geriatr Soc*. 2011;59(3):473-481.
PubMed | Google Scholar | Crossref

29. Lopez OL, Becker JT, Chang Y-F, et al. The long-term effects of conventional and atypical antipsychotics in patients with probable Alzheimer's disease. *Am J Psychiatry*. 2013;170(9):1051-1058.
PubMed | Google Scholar | Crossref

30. Tun S-M, Murman DL, Long HL, Colenda CC, von Eye A. Predictive validity of neuropsychiatric subgroups on nursing home placement and survival in patients with Alzheimer disease. *Am J Geriatr Psychiatry*. 2007;15(4):314-327.
PubMed | Google Scholar | Crossref

31. Rabins PV, Lyketsos CG. Antipsychotic drugs in dementia: what should be made of the risks? *JAMA*. 2005;294(15):1963-1965.
Article | PubMed | Google Scholar | Crossref

32. Treloar A, Crugel M, Prasanna A, et al. Ethical dilemmas: should antipsychotics ever be prescribed for people with dementia? *Br J Psychiatry*. 2010;197(2):88-90.
PubMed | Google Scholar | Crossref


## Comment

4 Comments for this article

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April 1, 2015

### Population clinical characteristics are critical.

**Scott Mendelson** | VA

It is stated by the authors that \"it is conceivable that a portion of the increased mortality risk seen in medication users relative to nonusers or among the medication users could be related to the symptom or behavior that prompted the prescription.\" In my mind this is not a trivial concern, but a confound that completely voids the significance of the data. To draw the conclusion that antipsychotics, valproate and antidepressants are themselves increasing mortality, then the authors needed to have more clearly determined that the non-users with whom they are comparing drug-treated groups are of the same population as ...

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April 14, 2015

### Many Questions Remain Related to Antipsychotics and Dementia

**Virginia Dato MD MPH** | Department of Biomedical Informatics, University of Pittsburgh, School of Medicine

I read the article "Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia: Number Needed to Harm" [1] having reviewed literature in response to a black box warning for an antipsychotic prescribed for a beloved family member.This publication provides important data on over 45,000 individuals with dementia who were placed on anti-psychotics. Unfortunately, the types of dementia are not differentiated and no information is available on symptoms, quality of life or non-palliative treatments. A number needed to harm (with harm defined as death) of 50 would not be acceptable for treatment ...

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### Response to Dr Dato

**Donovan Maust, Lon Schneider, Helen Kales** | University of Michigan, University of Southern California

We agree with Dr. Dato that there is no "one size fits all solution" for either pharmacological or non-pharmacological treatment. We agree as well that antipsychotics should not be taken away as a treatment option. Their use, however, should be targeted and in conjunction with an understanding of risk and benefit (see Kales et al. [1]). The number needed to treat (NNT) is important to consider and, as we note in the paper, 5 to 14 patients need to be treated in order for one to show benefit [2], The benefits, however, are modest at best (i.e., one or ...

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April 27, 2015

### Response to Dr Mendelson

**Donovan Maust, Lon Schneider, Helen Kales** | University of Michigan, University of Southern California

Dr. Mendelson raises an important point about the comparability of our patient groups that we addressed through a variety of methods. First, we matched pairs on specific criteria and excluded from analysis any medication users for whom we could not find a match. Second, our mortality models included a range of patient-level clinical information (>30 variables listed in Tables 2 and 3) to account for the potential influence of these characteristics on mortality. Perhaps what Dr. Mendelson is suggesting, however, is that we do not have information about the burden of neuropsychiatric symptoms in the patient population—in this ...

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