



# Antipsychotic medication use in treatment of dementia: Is it associated with an increased risk of mortality?



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## Background

- At any time, approximately 80% of patients with dementia residing in long term care settings exhibit neuropsychiatric symptoms<sup>1</sup>
- Although first line treatment for these symptoms is non-pharmacological (psychosocial intervention), medications are often utilized instead, with an estimated prevalence of use of antipsychotics of 25-40% for long term care residents with dementia<sup>1</sup>
- Some typical antipsychotics and atypical antipsychotics have been shown to provide benefits in treating certain neuropsychiatric symptoms; however, those benefits may be outweighed by the risk of adverse events, including death<sup>1</sup>
- The safety of these medications is under careful consideration, and, although there has been a recent decline in use, antipsychotics continue to be used frequently in treating dementia<sup>1</sup>

## Question

- Is the use of antipsychotic medications safe in patients with dementia?

**P = Patients with dementia**  
**I = Antipsychotic pharmacological therapy**  
**C= Non-pharmacological or other pharmacological therapy**  
**O = Risk of mortality**

## Methods

- A literature search using PubMed was performed limited to papers that were freely available and published in English
- Searched terms included: antipsychotics, dementia, and mortality
- Articles selected were assessed for strengths, limitations, and ethical concerns based on the CHS 708-Epidemiology 2 worksheets provided, and the level of evidence was determined

## Results

STUDY DESIGN	SUMMARY	KEY FINDINGS
Kales, H., Kim, H., Zivin, K., Valenstein, M., Seyfried, L., Chiang, C., . . . Blow, F. (2012). Risk of Mortality Among Individual Antipsychotics in Patients With Dementia. <i>The American Journal of Psychiatry</i> . Retrieved April 22, 2015.		
Retrospective cohort Level of evidence: 4	This was a retrospective cohort study for patients ≥65 years old with dementia, beginning outpatient treatment with an antipsychotic (risperidone, olanzapine, quetiapine, and haloperidol) or valproic acid and its derivatives (as a non-antipsychotic comparison). The total sample included 33,604 patients. Individual drug groups were compared for 180-day mortality rates.	<b>Consistent across analyses was the finding that haloperidol had the highest mortality risk and quetiapine the lowest.</b> Valproic acid and its derivatives generally had mortality risks higher than quetiapine and similar to risperidone. Across all medications other than haloperidol, mortality risk was found to be on average 1.5 times higher in the first 120 days than for the subsequent period; for haloperidol, risk was highest in the first 30 days and then significantly and sharply decreased.
Liperoti, R., Onder, G., Landi, F., Lapane, K., Mor, V., Bernabei, R., & Gambassi, G. (2009). All-Cause Mortality Associated With Atypical And Conventional Antipsychotics Among Nursing Home Residents With Dementia. <i>The Journal of Clinical Psychiatry</i> , 70(10), 1340-1347.		
Retrospective cohort Level of evidence: 4	This was a retrospective cohort study to compare the risk of death associated with atypical and conventional antipsychotics in a large population of nursing home residents with dementia. The study identified new users of ATYPICAL ANTIPSYCHOTICS (n=6,524) and CONVENTIONAL ANTIPSYCHOTICS (n=1,581) living in 1,581 Medicare or Medicaid certified nursing homes in the US from 1998-2000. The outcome measure was all-cause mortality which was determined during 6 months of follow up.	<b>The rate of death was increased for users of conventional antipsychotics (HR, 1.26; 95% CI, 1.13-1.42).</b> Relative to risperidone (atypical antipsychotic) there was a higher rate of death for: Haloperidol (HR, 1.31; 95% CI, 1.13-1.53), Phenothiazines (HR, 1.17; 95% CI, 1.00-1.38), Other conventional medications (HR, 1.32; 95% CI, 0.99-1.80). No atypical antipsychotic was associated with a differential risk relative to risperidone.
Murray-Thomas, T., Jones, M., Patel, D., Brunner, E., Shatpathy, C., Motsko, S., & Staa, T. (2013). Risk of Mortality (Including Sudden Cardiac Death) and Major Cardiovascular Events in Atypical and Typical Antipsychotic Users: A Study with the General Practice Research Database. <i>Cardiovascular Psychiatry and Neurology</i> , 1-15.		
Retrospective cohort Level of evidence: 4	This was a retrospective cohort study using the UK General Practice Research Database. The primary objective was to assess the potential risk of cardiac mortality including sudden cardiac death in the antipsychotic exposed population. The secondary objective was to assess the risk of all-cause mortality (excluding suicide) and of major cardiac events (including AMI, CHD, and life-threatening ventricular arrhythmias in the antipsychotic exposed population. Attempts were made to adjust for additional known risk factors for sudden cardiac death not previously assessed in other studies, smoking status, body mass index, and alcohol status, and to address issues with the definition of sudden cardiac death. 183,392 antipsychotic users (115,491 typical and 67,901 atypical), 544,726 general population controls, and 193,920 psychiatric nonusers were identified.	<b>Atypical antipsychotics had lower adjusted relative ratios in various outcomes compared to typical antipsychotics:</b> All-cause mortality - 0.83 (95% CI: 0.80-0.85), Cardiac mortality - 0.89 (95% CI: 0.82-0.97), SCD secondary definition - 0.76 (95% CI: 0.55-1.04).
Schneider, L. (2005). Risk Of Death With Atypical Antipsychotic Drug Treatment For Dementia: Meta-analysis Of Randomized Placebo-Controlled Trials. <i>JAMA: The Journal of the American Medical Association</i> , 1934-1943. Retrieved April 21, 2015.		
Meta-analysis Level of evidence: 1	The goal of this study was to assess the evidence for increased mortality from atypical antipsychotic drug treatment for people with dementia. 3,353 (total 5,110) patients from 15 trials of aripiprazole, olanzapine, quetiapine, or risperidone. Trials included were parallel group, double-blinded, placebo-controlled with random assignment to an orally administered antipsychotic or placebo; patients had Alzheimer disease, vascular dementia, mixed dementia, or a primary dementia; and numbers of patients randomized, dropouts, and deaths were obtainable.	<b>Atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo.</b> This risk should be considered within the context of medical need for the drugs, efficacy evidence, medical comorbidity, and the efficacy and safety of alternatives. Individual patient analyses modeling survival and causes of death are needed.
Simoni-Wastila, L., Ryder, P., Qian, J., Zuckerman, I., Shaffer, T., & Zhao, L. (2009). Association of Antipsychotic Use With Hospital Events and Mortality Among Medicare Beneficiaries Residing in Long-Term Care Facilities. <i>American Journal of Geriatric Psychiatry</i> , 417-427. Retrieved April 22, 2015.		
Retrospective cohort Level of evidence: 4	Simoni-Wastila et. al chose to look at the use of antipsychotics in long term care use in hospital settings in the face of rising evidence that antipsychotic use raises mortality in the non-hospital settings. They looked at 2,363 Medicare beneficiaries receiving antipsychotics between 1999 and 2002, checking for both mortality and "hospital events." They controlled for sociodemographic, economic, and clinical differences and noted as well whether typical or atypical antipsychotics were used.	<b>No positive association between antipsychotic use and mortality, typical or atypical.</b> This was despite finding that AP use increased from 26.4% to 35.9% and atypical use specifically from 13.9% to 31.6% in the four years.

## Summary

- There is conflicting evidence regarding risk of mortality and antipsychotic use
- Meta-analysis shows atypical drugs may be associated with an increased risk for death compared with placebo in dementia patients
- Risk of mortality is lower with atypical compared to typical antipsychotics
- Haloperidol appears to be associated with the greatest increase in mortality risk
- The use of conventional agents is not advised for treating behavioral and psychological symptoms of dementia

## Recommendations

- Since there is potential for increased risk of mortality and other adverse events with the use of antipsychotics, non-pharmacological interventions should be considered first when available and proven effective
- When the use of psychotropic medications is necessary, atypical agents should be used rather than typical antipsychotics
- Relative risk of death may be lower in patients who discontinue antipsychotic therapy, so antipsychotic use should be limited to ≤ 3 mo<sup>2</sup>

## Additional References

1. Seitz, D., Gill, S., Herrmann, N., Brisbin, S., Rapoport, M., Rines, J., . . . Conn, D. (2013). Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: A systematic review. *INTERNATIONAL PSYCHOGERIATRICS*, 25(2), 185-203.
2. Yi-Ju, P., Wu, C., Gau, S., Chan, H., & Banerjee, S. (2013). Antipsychotic Discontinuation in Patients with Dementia: A Systematic Review and Meta-Analysis of Published Randomized Controlled Studies. *Dementia and Geriatric Cognitive Disorders*, 37, 125-140.

## Acknowledgements

We would like to thank Mary Shultz for her assistance in conducting a thorough literature search, and we would especially like to thank Dr. Julie Smith-Gagen for providing the guidance and tools to assess the literature appropriately and concisely report our findings.