Published in final edited form as:
Am J Psychiatry. 2012 January ; 169(1): 71–79. doi:10.1176/appi.ajp.2011.11030347.

Risk of Mortality Among Individual Antipsychotics in Patients with Dementia

Helen C. Kales, MD[1,2], **Hyungjin Myra Kim, ScD**[1,3], **Kara Zivin, PhD**[1,2], **Marcia Valenstein, MD, MS**[1,2], **Lisa S. Seyfried, MD, MS**[2], **Claire Chiang, PhD**[1,2], **Francesca Cunningham, PharmD**[4], **Lon S. Schneider, MD, MS**[5], and **Frederic C. Blow, PhD**[1,2]

[1]Department of Veterans Affairs, Ann Arbor Center of Excellence (COE), Serious Mental Illness Treatment, Research, and Evaluation Center (SMITREC), Ann Arbor, Michigan

[2]Department of Psychiatry, University of Michigan, Ann Arbor, Michigan

[3]Center for Statistical Consultation and Research, University of Michigan, Ann Arbor, Michigan

[4]VA Center for Medication Safety, Patient Safety Center of Inquiry, and Pharmacoepidemiologic/ Outcomes Research, Hines IL

[5]University of Southern California Keck School of Medicine

Abstract

Objective—The use of antipsychotics to treat the behavioral symptoms of dementia is associated with increased mortality. However, there remains limited information regarding individual agents' risks.

Method—This was a retrospective cohort study using national data from the US Department of Veterans Affairs (fiscal years 1999–2008) 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. Potential confounding was addressed using multivariate models and propensity adjustments.

Results—In covariate-adjusted intent to treat analyses, haloperidol users had the highest mortality rates (relative risk 1.54, 95% confidence interval 1.38–1.73) followed by risperidone (reference), olanzapine (RR 0.99, 95% CI 0.89–1.10), valproic acid and its derivatives (RR 0.91, 95% CI 0.78–1.06) and quetiapine (RR 0.73, 95% CI 0.67–0.80). Propensity-stratified and propensity-weighted models as well as analyses controlling for site of care and medication dosage showed similar patterns. Haloperidol risk was highest in the first 30 days and then significantly and sharply decreased. Among the other agents, mortality risk differences were most significant in the first 120 days and declined in the subsequent 60 days during 180-day follow-up.

Corresponding Author: Helen C. Kales MD, Department of Psychiatry, University of Michigan, 4250 Plymouth Road, Box 5765, Ann Arbor MI, 48109. kales@umich.edu.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

Conclusions—There may be differences in mortality risks among individual antipsychotic agents. Further, the use of valproic acid and its derivatives as alternative agents to address the neuropsychiatric symptoms of dementia may carry associated risks as well.

INTRODUCTION

The US Food and Drug Administration (FDA) has not approved any medication for treating the neuropsychiatric symptoms of dementia. However, atypical antipsychotics are commonly used off-label for treatment [1]. In April 2005, the FDA warned that use of atypical antipsychotics for behavioral disturbances in patients with dementia was associated with increased mortality. Subsequently, research reports confirmed the mortality risks associated with both conventional and atypical antipsychotics in dementia patients [2–5]. An FDA warning for conventional antipsychotics followed in June 2008 [6].

Information is limited about mortality with individual antipsychotic agents in patients with dementia. An earlier study [7] found no significant mortality differences between olanzapine and risperidone. However, the number of deaths during this trial was small with wide confidence intervals. In a meta- analysis [2], no increased risk of death was found with any individual atypical antipsychotic; however, there may have been inadequate power to detect significant differences after controlling for confounding variables between trials. A study [8] comparing the most frequently prescribed antipsychotic drugs in Canada found increased 180-day mortality ratios for haloperidol and loxapine, but no difference for olanzapine compared to risperidone. The most recent study, using case-control methodology, found that patients with dementia taking haloperidol, olanzapine, and risperidone, but not quetiapine, had short-term increases in mortality [9] as compared to patients with dementia not taking these agents.

Large-scale comparisons of mortality with individual antipsychotic agents controlling for important confounders are currently lacking. Using multivariate and propensity-scoring methods, this study examined mortality risks in outpatients with dementia in the 6 months following a new antipsychotic start of the individual agents most commonly used for US Department of Veterans Affairs (VA) Healthcare System patients with dementia (risperidone, olanzapine, quetiapine, and haloperidol). Based on evidence from our earlier work that anticonvulsants had similar mortality risks to antipsychotics [3], and that there was a small but significant increase in the use of valproic acid and its derivatives following the black box warning [10], these agents were also included for comparison.

METHOD

Study cohort

Data were provided by national VA registries maintained by the Serious Mental Illness Treatment, Resource, and Evaluation Center (SMITREC) in Ann Arbor, Michigan, USA. Patients included: 1) were ≥ 65 years old; 2) had a dementia diagnosis between October 1,1998–September 30, 2008 (ICD 9 diagnoses 290.0, 290.1x, 290.2x, 290.3, 290.4x, 291.2, 294.10, 294.11, 331.0, 331.1, and 331.82); and 3) began outpatient treatment with a study medication after a 12-month “clean period” without antipsychotic or anticonvulsant

exposure. Over 87% of patients in the sample had monotherapy (e.g. exposure to only the initial agent during 6-month follow-up). Given that switching to other antipsychotic agents might obscure risk profiles for individual antipsychotics, we restricted the final sample to these monotherapy patients. The final study sample included 33,604 patients.

This study was approved by the VA Ann Arbor Healthcare System IRB.

Medications

These included risperidone, olanzapine, quetiapine, and haloperidol, as well as valproic acid and its derivatives (an anticonvulsant group commonly used as a second-line treatment strategy for the neuropsychiatric symptoms of dementia). Patients taking valproic acid and its derivatives (sodium valproate or divalproex) who also had seizure disorders (n=337) were excluded from the sample as their anticonvulsant use would be less likely to be related to dementia.

Mortality

Data were obtained from the US National Death Index (National Center for Health Statistics, Hyattsville, MD).

Other variables

These included age, gender, ethnicity, marital status and indicators of psychiatric and medical comorbidity {the latter using a modified version of the Charlson comorbidity index [11] based on 18 medical comorbidities (excluding dementia) in the year prior to new medication start}. Also, as delirium occurs frequently among patients with dementia and is an independent mortality risk factor [12], and antipsychotics are often prescribed for delirium, we also assessed for the presence of a delirium diagnosis at the time of prescription, using a coding scheme for acute confusional states developed for a prior study [13]; this included the following codes: 290.3, 291.0, 292.0, 292.1, 292.2, 292.9, 293.0, 293.1, 293.9, 294.8, 294.9, 348.3, 437.2, 572.2, 290.11, 290.41, 292.81, 293.31, 293.82, 293.83, 293.89,349.82. To control for potential changes in health care, particularly given the impact of the black box warning [10], calendar time at the new medication start was included as a covariate. The model also included the following variables: inpatient and nursing home days in the year prior to new medication start; and size, rurality and academic affiliation of the VAMC where the medication was prescribed.

Statistical Analysis

Descriptive statistics were used to characterize patient characteristics by type of medication prescribed. A 180-day follow-up period was chosen based on the duration of trials in the FDA's analysis as well as the follow-up period used in prior studies [8, 14]. Analyses accounted for medication exposure days in two ways- "intent to treat" and exposure. For the intent to treat analyses, exposure-days were the length of time from the first filled prescription until death or 6 months, whichever was earlier. For the exposure analyses, exposure-days to a specific antipsychotic or valproic acid and its derivatives began on the date of the first fill; exposure was censored at the end of the exposure period, at 6 months, or at time of death, whichever was earlier. As in a prior study [2], the exposure period

continued for the number of days' supply of medication received plus 30 days. Any gaps in fills of less than 30 days were considered continued exposures. This accounts for some level of continued exposure and biological effect among patients who missed doses or used lower than prescribed doses.

For each of the medication types, mortality during 180-day follow-up was calculated as per 100 person years, and distribution of time to death since index prescription was estimated using the Kaplan-Meier survival analysis method.

We used a variety of approaches to deal with potential selection biases. Initially, we used multivariate analyses that included potential confounders available in administrative data. Additionally, we used propensity-weighted and propensity-stratified methods. Both methods attempt to control for "treatment by indication" in observational studies by adjusting for the predicted probability that a patient will receive a specific treatment conditional on the patient's baseline covariate values. The propensity-weighted analyses estimated hazard ratios using Cox's regression model with observations weighted inversely by the propensity estimates obtained using multinomial models, permitting comparisons across multiple medications based on the one model [15]. For the propensity-stratified analyses, comparisons were made between pairs of medications, with each medication compared against risperidone. For each pair-wise comparison, propensity scores were estimated using logistic regression, and hazard ratio estimates were obtained using Cox's regression model, stratified by the estimated propensity quintiles. In both propensity-weighted and propensity-stratified methods, models used to obtain propensity scores were optimally fit to be highly predictable without consideration for parsimony.

Secondary analyses included site of care examination (psychiatric vs. non-psychiatric) and adjustment for antipsychotic dose which was standardized to haloperidol equivalent dose [16]. After a visual inspection of the smoothed hazards revealed decreasing hazards in time for haloperidol, we also extended the Cox regression model to test for non-proportional hazards using logarithmically transformed time by medication indicator interaction terms. Upon finding significantly decreasing risks in time for haloperidol, we divided time since medication start into 30-day intervals and used a piece- wise exponential model to compare relative risks between medications at different time intervals.

To confirm that our conclusion was not biased by the inclusion of only monotherapy patients, we also did a true intent to treat analysis where patients who switched or augmented their initial medication were also included in the analysis and were analyzed as exposed to their initial medication.

Lastly, we did two additional analyses to further examine mortality risk differences: 1) an exploration of whether the relatively larger proportion of Parkinson's disease (PD) patients in the quetiapine cohort may have resulted in a lower mortality risk; and 2) an analysis where we sought to further confirm haloperidol's role as the agent with the highest mortality by comparing haloperidol and risperidone users after individually matching each haloperidol patient with up to two risperidone patients on a number of key variables.

RESULTS

Characteristics of the Study Population

Table 1 shows demographic and clinical characteristics of the individual medication groups. Haloperidol users were significantly older and sicker (as evidenced by the highest Charlson scores, highest rates of concurrent delirium, and having more inpatient days in the prior year) than users of the other study medications. A higher percentage of African-American patients used haloperidol as compared to the other agents. Those taking haloperidol also were significantly more likely to have used opiods or benzodiazepines and less likely to have used antidepressants during the year prior to the new antipsychotic start. Users of the various atypical agents had similar rates of medical and psychiatric comorbidities with the exception of significantly higher rates of Parkinson's disease in users of quetiapine. Users of valproic acid and derivatives tended to be younger, less likely to be African American, more likely to have comorbid bipolar disorder and other psychiatric illnesses than users of other agents.

Individual Medication Use and Mortality

The crude 6-month mortality rates were as follows: haloperidol 20.0%; olanzapine 12.6%; risperidone 12.5%; valproic acid and its derivatives 9.8%; and quetiapine 8.8% ($X^2 = 294.4$, df=4, $p<0.0001$). The mortality rate rankings were also consistent in the intent to treat and exposure analyses (Table 2).

Multivariate adjustment, as well as the propensity-weighted and propensity-stratified adjustments yielded similar results. Adjusted RRs (Table 3) averaged over 180-day period showed consistently that haloperidol had the highest mortality risk and quetiapine the lowest. In all but one analysis, valproic acid and its derivatives showed a risk higher than quetiapine, but lower than the other antipsychotics. Figure 1 shows covariate-adjusted survival function by days of exposure.

Secondary Analyses

Site of Care—Haloperidol users had the highest proportion of non-psychiatric visits associated with the prescription (77.6%) as compared to 52.4–57.8% of the other medications. An analysis stratified by script location produced results consistent with those from the main analyses, with haloperidol having the highest risk in both settings (propensity stratified results: non-psychiatric script RR 1.42, 95% CI 1.19–1.70, p< 0.001 and psychiatric script RR 1.41, 95% CI 0.93–2.13, p=.1068) and quetiapine the lowest (propensity stratified results: non-psychiatric script RR 0.75, 95% CI 0.64–0.88, p=0.0006; psychiatric prescription RR 0.71, 95% CI 0.55–0.91, p=0.006). Antipsychotic Dose Patients taking only "as needed" (PRN) antipsychotics (n=3,613) or valproic acid and its derivatives were not included in the analyses adjusting for dose. Table 4 shows summary statistics of initial prescribed doses and haloperidol equivalent doses. The majority of patients (81.6%) had initial haldol equivalent doses less than 1.5 mg, while 5.4% had prescribed doses ≥3 mg and 13.0% had prescribed doses between 1.5 to <3 mg. RR estimates adjusted for dose showed mortality risk order consistent with the main analyses.

Changes in Mortality Risks Over Time—Using a piece-wise exponential model, mortality risk was found to be on average 1.5 times higher in the first 120 days than for the subsequent 60 days across all medications, except haloperidol. Haloperidol risk was highest in the first 30 days (RR compared to risperidone in 150–180 day period was 2.24, $p<0.001$), and then the risk significantly decreased to no difference by 90–120 day period (RR=1.11 compared to risperidone in 150–180 day period, $p=0.65$). We note, however, that the exposure days were significantly shorter for haloperidol than for other medications (median of 60 days for haloperidol versus 111 days or longer for other medication groups). The RRs between olanzapine and risperidone and between valproic acid and its derivatives and risperidone were not significantly different during the 180-day period. Quetiapine risk was consistently lower than that of risperidone, with RRs of 0.67 ($p <0.001$) for 0–30 days, 0.76 ($p < 0.01$) for 30–60 days, 0.74 ($p = 0.02$) for 60–90 days, and 0.72 ($p = 0.02$) for 90–120 days, each relative to risperidone risk in 150–180 day period. After 120 days, there were no longer significant mortality risk differences between any of the medications.

Additional Sensitivity Analyses—Two additional analyses were performed to further understand mortality risk differences. First, we explored whether the relatively larger proportion of Parkinson's disease (PD) patients in the quetiapine cohort may have resulted in a lower mortality risk. Compared with non-PD patients taking quetiapine, PD patients tended to receive lower quetiapine doses, and also had less medical burden, but were more likely to have depression. However, after covariate adjustment, PD patients actually had higher mortality rates than non-PD patients in the quetiapine cohort (RR 1.39, 95% CI 1.18–1.64, $p< 0.001$).

Secondly, we sought to further confirm haloperidol's role as the agent with the highest mortality by comparing haloperidol and risperidone users after individually matching each haloperidol patient with up to two risperidone patients including age, site of care (psychiatric vs. non-psychiatric prescription), race and medical comorbidity (Charlson score, presence of delirium diagnosis, inpatient hospitalization in the prior year). This analysis based on 2,757 patients (n=1056 haloperidol patients and n=1691 matching risperidone patients) showed that haloperidol users were at higher risk of mortality than risperidone users with an adjusted RR of 1.45 ($p = 0.06$) for the exposure analysis and 1.57 ($p < 0.001$) for the intent to treat analysis.

Finally, a true intent to treat analysis (including patients who subsequently switched from their initial medication) did not yield different conclusions: haloperidol users had the highest covariate-adjusted mortality rates (RR 1.50, 95% CI 1.35–1.67) followed by olanzapine (RR 1.02, 95% CI 0.92–1.12), risperidone (reference), valproic acid and its derivatives (RR 0.95, 95% CI 0.82–1.10) and quetiapine (RR 0.76, 95% CI 0.70–0.82).

DISCUSSION

In this large US national sample of outpatients with dementia newly started on an antipsychotic or valproic acid and its derivatives, we examined differences in mortality among individual medications. Consistent across analyses was the finding that haloperidol had the highest mortality risk and quetiapine the lowest. Valproic acid and its derivatives,

included as a non-antipsychotic comparison, generally had morality 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.

Haloperidol's association with the highest mortality risks in this study is not surprising and is confirmatory of prior findings. A number of prior observational studies have reported that conventional antipsychotics are associated with higher mortality risks than atypical antipsychotics. [8,14] In addition, Schneider and colleagues' meta-analysis of atypical antipsychotics [2] showed haloperidol to have a higher relative risk of mortality compared to placebo (RR=1.68) than did atypicals antipsychotics (RR=1.54). The relationship between haloperidol and mortality may be confounded by selection issues and underlying user characteristics, particularly given secular trends in which atypical antipsychotics largely replaced conventionals in the 1990's.[10, 18, 19] The shift from conventional to atypical antipsychotics during this period is thought to be due to several factors: 1) efficacy evidence from early clinical trials; 2) perceived safety advantages; and 3) published expert consensus guidelines [20]. In this study, we found that patients receiving haloperidol were older, sicker (highest Charlson scores, most inpatient days and highest concurrent delirium diagnoses), and more likely to be African American than users of atypicals. After controlling for those confounding factors, the haloperidol- associated risks remained significant, although it should be noted that the main risk of mortality with this agent appeared to be in the first month of treatment with a rapid decrease in mortality over time. The majority of haloperidol users (approximately 78%) received their prescriptions at non-psychiatric visits; this result paired with likelihood that haloperidol is used for delirium in inpatient settings and therefore on discharge these could be picked up in observational data as "new prescriptions", might again suggest that the mortality difference could be influenced by unmeasured medical confounders such as unrecorded delirium episodes. However, our sensitivity analysis where we matched users of haloperidol to users of risperidone (chosen as the most relevant clinical comparison) using variables including age, race, medical comorbidities and site of prescription (psychiatric vs. non-psychiatric) did not corroborate this concern; here, although only marginally significant due to the reduction in sample size from matching, haloperidol showed increased mortality risk over risperidone (RR=1.45).

What about differences in risk among the atypicals? A recent case-control study [9] comparing information about antipsychotic users with non-users found that quetiapine was not associated with short-term increases in mortality, while the other atypical antipsychotics studied were. The study did not directly compare antipsychotics to each other to assess differential risk among these agents. Additionally the comparison of antipsychotic users to nonusers may have been problematic, as the underlying behavioral and frailty issues prompting medication use may be linked inextricably with mortality and may substantially overestimate the mortality risk of antipsychotics [21]. Using a variety of approaches to control for potential selection bias, our study focused on head-to-head antipsychotic comparisons to find differential risks among the atypical agents.

Notably, we found that quetiapine had the lowest risk of mortality across all analyses. Clinically, quetiapine is often prescribed in low doses by providers for sedation and hypnotic purposes, thus, we also performed analyses controlling for antipsychotic dose. In these analyses as well, quetiapine was associated with significantly lower risk. It is not entirely clear why quetiapine would have lower risk than the other atypicals. Some of the lower risk could have to do with quetiapine's receptor or side effect profile. A significantly higher proportion of quetiapine users had Parkinson's disease; however, our sensitivity analyses did not indicate that this was a likely explanation for quetiapine's lower mortality risk. An alternative explanation might be that quetiapine's lower mortality risk has more to do with the patients it is prescribed for, perhaps patients with milder dementia or behavioral disturbances. Notably, there is no rapid-acting form of quetiapine as there are for other atypicals, thus, this agent is likely used less in urgent situations.

In most analyses, valproic acid and its derivatives showed a risk higher than quetiapine but no different than that of risperidone or olanzapine. Thus, the use of valproic acid and its derivatives as an alternative to antipsychotics to address neuropsychiatric symptoms of dementia may not be without risks as well. Studies have linked anticonvulsant use in the elderly with fracture [22], somnolence and thrombocytopenia [23]. In addition, although valproic acid and its derivatives have been touted for behavioral stabilization and even as potentially neuroprotective, the evidence has been lacking for such efficacy [24, 25].

The greatest mortality risk for haloperidol was found to be within the first 30 days whereas for the other medications, mortality risk was higher in the first 120 days than the subsequent period. As noted above, the exposure period for haloperidol was considerably shorter than for the other agents, and thus, the haloperidol result may in part relate to its selection for older and sicker patients, a number of whom may have this agent started during an inpatient stay for delirium or in non-psychiatric settings. The clinical implications of increased mortality risk for atypical antipsychotics and valproic acid and derivatives in the first four months of treatment than the later period may be several-fold: 1) if these agents are prescribed then they should be used in conjunction with a risk-benefit approach [26, 27] with consideration of the established efficacy of each agent [2–4, 6, 20, 26]; 2) patients should be monitored during the acute treatment period for side effects and adverse reactions; and 3) periodic attempts at discontinuation should be attempted particularly in light of the DART-AD trial results. In the DART-AD trial [5], the investigators randomized patients with dementia taking antipsychotics to either continuation of antipsychotics {the majority taking risperidone (67%) or haloperidol (26%)} vs. antipsychotic discontinuation/placebo and found a significantly higher mortality rate for patients who continued antipsychotics. Difference in length of mortality risk for antipsychotics between DART-AD (>12 months) and our study (120 or less) may relate to exposure periods and differences in study samples.

The use of administrative data for pharmacoepidemiologic work has several limitations. Prescription fills can be an imprecise measure of actual drug exposure; medication fills may not reflect day-to-day usage. Data on dementia severity were also lacking, although not accounting for this confounder may actually contribute to an underestimation of the mortality risk of haloperidol [21]. Finally, while the large integrated VA health system offers us the opportunity to examine pharmacoepidemiologic changes, the findings may not

be completely generalizable. Consistent with the demographic characteristics of the VA patient population, the study cohort was primarily male. However, we note that there are striking similarities on many key variables that might affect provider antipsychotic prescribing practices (e.g. race mix, prevalence of key psychiatric and medical conditions) between our data and other national data [28, 29]. Finally, the issue of concurrent delirium in dementia is a key one, and as with other observational studies, we used diagnostic codes to denote the presence of delirium. Given the lack of recognition of delirium in many cases, underdiagnosis is a problem; however, we have no evidence to suggest that such underdiagnosis varies by antipsychotic agent. Despite these limitations, our results using various analytic methods consistently indicated differences in mortality risks among individual antipsychotic agents. Further, the use of valproic acid and its derivatives as alternative agents to address the neuropsychiatric symptoms of dementia may carry associated risks as well.

Acknowledgments

This research was supported by a grant from the National Institute of Mental Health, R01-MH081070. Resources were also contributed by the Serious Mental Illness Treatment, Resource, and Evaluation Center, Ann Arbor, MI.

References

1. Saha, S.; Robinson, S.; Bainco, T.; Schechtel, M.; Hickam, D. In A Summary for Clinicians and Policy Makers. Agency for Healthcare Research and Quality; 2007. Off-Label Use of Atypical Antipsychotic Drugs; p. 1-4.
2. 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(15):1934–1943. [PubMed: 16234500]
3. Kales HC, Valenstein M, Kim HM, McCarthy JF, Ganoczy D, Cunningham F, Blow FC. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. The American journal of psychiatry. 2007; 164(10):1568–1576. quiz 1623. [PubMed: 17898349]
4. Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, Bell CM, Lee PE, Fischer HD, Herrmann N, et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med. 2007; 146(11):775–786. [PubMed: 17548409]
5. Ballard C, Hanney M, Theodoulou M, Douglas S, McShane R, Kossakowski K, Gill R, Juszczak E, Yu L-M, Jacoby R. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow- up of a randomised placebo-controlled trial. Lancet neurology. 2009; 8(2):151–157.
6. FDA. Safety Labeling Changes for Antipsychotic Drugs. 2008.
7. Kryzhanovskaya L, Jeste D, Young C, Polzer J, Roddy T, Jansen J, Carlson J, Cavazzoni P. A review of treatment-emergent adverse events during olanzapine clinical trials in elderly patients with dementia. The Journal of clinical psychiatry. 2006; 67(6):933–945. [PubMed: 16848653]
8. 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(5):627–632. [PubMed: 17325327]
9. Rossom RC, Rector TS, Lederle FA, Dysken MW. Are All Commonly Prescribed Antipsychotics Associated with Greater Mortality in Elderly Male Veterans with Dementia? Journal of the American Geriatrics Society. 2010; 58(6):1027–1034. [PubMed: 20487081]
10. Kales HC, Zivin K, Kim HM, Valenstein M, Chiang C, Ignacio RV, Ganoczy D, Cunningham F, Schneider LS, Blow FC. Trends in Antipsychotic Use in Dementia 1999–2007. Arch Gen Psychiatry. 2010 In Press.

11. 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: 3558716]
12. Adamis D, Treloar A, Martin FC, Macdonald AJ. Recovery and outcome of delirium in elderly medical inpatients. Arch Gerontol Geriatr. 2006; 43(2):289–298. [PubMed: 16434113]
13. Kales HC, Kamholz BA, Visnic SG, Blow FC. Recorded delirium in a national sample of elderly inpatients: potential implications for recognition. Journal of geriatric psychiatry and neurology. 2003; 16(1):32–38. [PubMed: 12641371]
14. Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, Brookhart MA. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med. 2005; 353(22):2335–2341. [PubMed: 16319382]
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statistical Assoc. 1958; 53:457–481.
16. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983; 70(1):41–55.
17. Andreasen N, Pressler M, Nopoulos P, Miller D, Ho B-C. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biological psychiatry. 67(3):255–262. [PubMed: 19897178]
18. Lopez O, Becker J, Sweet R, Klunk W, Kaufer D, Saxton J, DeKosky S. Patterns of change in the treatment of psychiatric symptoms in patients with probable Alzheimer's disease from 1983 to 2000. The Journal of Neuropsychiatry and Clinical Neurosciences. 2003; 15(1):67–7. [PubMed: 12556574]
19. Rapoport M, Mamdani M, Shulman KI, Herrmann N, Rochon PA. Antipsychotic use in the elderly: shifting trends and increasing costs. International journal of geriatric psychiatry. 2005; 20(8):749–753. [PubMed: 16035128]
20. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006; 14(3):191–210. [PubMed: 16505124]
21. Schneeweiss S, Setoguchi S, Brookhart MA, Kaci L, Wang P. Assessing residual confounding of the association between antipsychotic medications and risk of death using survey data. CNS drugs. 2009; 23(2):171–180. [PubMed: 19173375]
22. Mezuk B, Morden N, Ganoczy D, Post E, Kilbourne A. Anticonvulsant use, bipolar disorder, and risk of fracture among older adults in the Veterans Health Administration. The American Journal of Geriatric Psychiatry. 18(3):245–255. [PubMed: 20224520]
23. Porsteinsson AP, Tariot PN, Erb R, Cox C, Smith E, Jakimovich L, Noviasky J, Kowalski N, Holt CJ, Irvine C. Placebo-controlled study of divalproex sodium for agitation in dementia. The American Journal of Geriatric Psychiatry. 2001; 9(1):58–66. [PubMed: 11156753]
24. Tariot P, Loy R, Ryan JM, Porsteinsson A, Ismail S. Mood stabilizers in Alzheimer's disease: symptomatic and neuroprotective rationales. Advanced Drug Delivery Reviews. 2002; 54(12): 1567–1577. [PubMed: 12453674]
25. Tariot P, Raman R, Jakimovich L, Schneider L, Porsteinsson A, Thomas R, Mintzer J, Brenner R, Schafer K, Thal L. Divalproex sodium in nursing home residents with possible or probable Alzheimer Disease complicated by agitation: a randomized, controlled trial. The American Journal of Geriatric Psychiatry. 2005; 13(11):942–949. [PubMed: 16286437]
26. US Food and Drug Administration. Public Health Advisory. US Department of Health and Human Services; 2005. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances.
27. Lyketsos, C.; Colenda, C.; Beck, C.; Blank, K.; Doriaswamy, M.; Kalunian, D.; Yaffe, K. Directors Bo: American Association for Geriatric Psychiatry. American Association for Geriatric Psychiatry Position Statement. 2005. Principles of Care for Patients With Dementia Resulting From Alzheimer Disease.
28. Langa K, Plassman B, Wallace R, Herzog AR, Heeringa S, Ofstedal M, Burke J, Fisher G, Fultz N, Hurd M, et al. The Aging, Demographics, and Memory Study: study design and methods. Neuroepidemiology. 2005; 25(4):181–191. [PubMed: 16103729]

29. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, Burke JR, Hurd MD, Potter GG, Rodgers WL, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007; 29(1–2):125–132. [PubMed: 17975326]

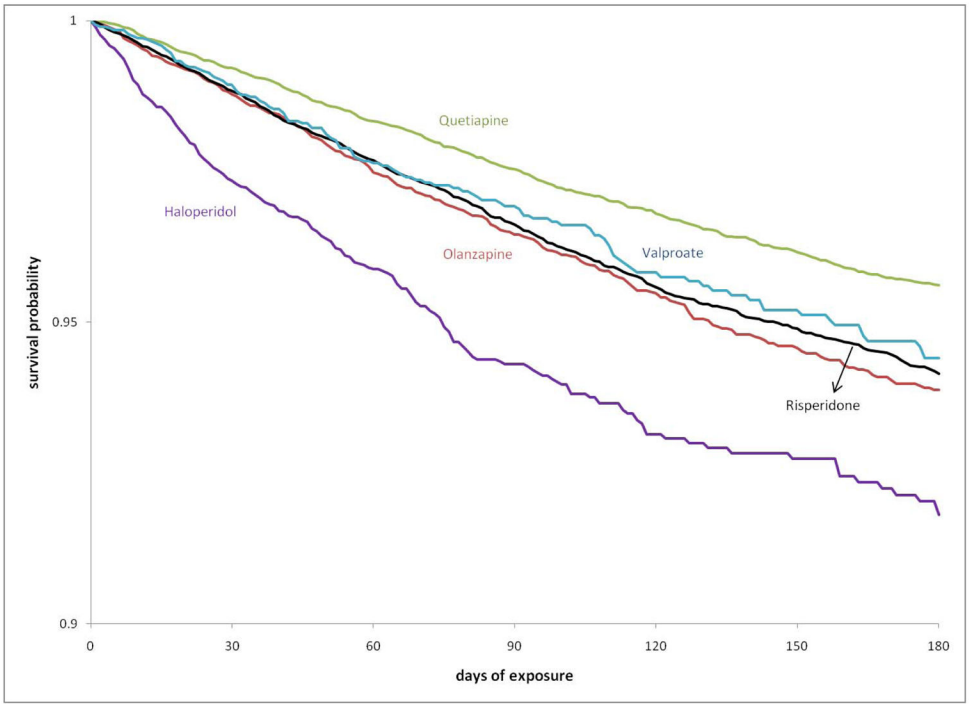

Figure 1.
Covariate Adjusted Survival Function by Days of Exposure

Table 1

Characteristics of Patients with Dementia who Started One of Five Psychotropic Medications

Variable Names	Haldol N=2855		Olanzapine N=4716		Quetiapine N=10651		Risperidone N=13356		Valproic acid and derivatives N=2026		
	N	%	N	%	N	%	N	%	N	%	p-value
Age											
65–69	138	4.8	288	6.1	559	5.2	755	5.7	192	9.5	<0.0001
70–74	368	12.9	648	13.7	1592	14.9	1827	13.7	303	15.0	
75–79	749	26.2	1303	27.6	2885	27.1	3756	28.1	546	27.0	
80–84	949	33.2	1571	33.3	3484	32.7	4342	32.5	601	29.7	
85+	651	22.8	906	19.2	2131	20.0	2676	20.0	384	19.0	
Female	66	2.3	134	2.8	222	2.1	370	2.8	37	1.8	0.0012
Race:											
White	1950	68.3	3232	68.5	7565	71.0	9024	67.6	1470	72.6	<0.0001
Black	431	15.1	397	8.4	974	9.1	1595	11.9	142	7.0	
Other	32	1.1	49	1.0	128	1.2	163	1.2	29	1.4	
Unknown	442	15.5	1038	22.0	1984	18.6	2574	19.3	385	19.0	
Married	1964	68.8	3170	67.2	7726	72.5	9130	68.4	1426	70.4	<0.0001
Benzodiazepine use	630	22.1	883	18.7	1971	18.5	2307	17.3	374	18.5	<0.0001
Antidepressant use	1184	41.5	2603	55.2	5708	53.6	6618	49.6	1161	57.3	<0.0001
Opioid use	889	31.1	1190	25.2	3119	29.3	3702	27.7	554	27.3	<0.0001
Delirium	1245	43.6	1735	36.8	4496	42.2	5408	40.5	870	42.9	<0.0001
Depression	578	20.2	1399	29.7	3199	30.0	3638	27.2	697	34.4	<0.0001
Schizophrenia spectrum*	55	1.9	145	3.1	179	1.7	307	2.3	17	0.8	<0.0001
Bipolar 1	10	0.4	66	1.4	68	0.6	102	0.8	100	4.9	<0.0001
Bipolar 2	0	0.0	18	0.4	19	0.2	38	0.3	39	1.9	<0.0001
Other psychoses	648	22.7	955	20.3	2372	22.3	3036	22.7	330	16.3	
Parkinsons Disease	132	4.6	339	7.2	1775	16.7	591	4.4	128	6.3	<0.0001
Psych Illnesses $^{\Psi}$											
0	2467	86.4	3894	82.6	8804	82.7	11184	83.7	1606	79.3	<0.0001
1	345	12.1	712	15.1	1621	15.2	1870	14.0	330	16.3	
≥2	43	1.5	110	2.4	236	2.1	302	2.2	90	4.4	

Variable Names	Haldol N=2855		Olanzapine N=4716		Quetiapine N=10651		Risperidone N=13356		Valproic acid and derivatives N=2026		
	N	%	N	%	N	%	N	%	N	%	p-value
Any Substance Abuse	159	5.6	240	5.1	464	4.4	641	4.8	95	4.7	0.0575
Alcohol Abuse	105	3.7	156	3.3	272	2.6	442	3.3	63	3.1	0.0025
Drug Abuse	98	3.4	148	3.1	289	2.7	386	2.9	60	3.0	0.2773
PTSD	82	2.9	206	4.4	559	5.2	551	4.1	105	5.2	<0.0001
Other Anxiety Disorders	177	6.2	375	8.0	917	8.6	1103	8.3	174	8.6	0.0010
Personality Disorder	8	0.3	41	0.9	60	0.6	73	0.5	24	1.2	0.0002
Charlson Comorbidities‡											
0	942	33.0	2064	43.8	4461	41.9	5281	39.5	763	37.7	
1	667	23.4	1107	23.5	2427	22.8	3136	23.5	546	27.0	<0.0001
>1	1246	43.6	1545	32.8	3763	35.3	4939	37.0	717	35.4	
Inpatient Days											
0	1857	65.0	3746	79.4	8441	79.3	10250	76.7	1593	78.6	
1–5	285	10.0	284	6.0	713	6.7	994	7.4	135	6.7	<0.0001
>5	713	25.0	686	14.5	1497	14.1	2112	15.8	298	14.7	
Nursing Home Days:											
0	2744	96.1	4562	96.7	10299	96.7	12777	95.7	1950	96.2	
1–30	68	2.4	89	1.9	224	2.1	378	2.8	50	2.5	0.0018
>30	43	1.5	65	1.4	128	1.2	201	1.5	26	1.3	
Fiscal Year											
2001	618	21.6	782	16.6	451	4.2	2018	15.1	212	10.5	
2002	416	14.6	968	20.5	852	8.0	2203	16.5	226	11.2	<0.0001
2003	296	10.4	950	20.1	1284	12.1	2116	15.8	188	9.3	
2004	275	9.6	787	16.7	1693	15.9	1872	14.0	222	11.0	
2005	275	9.6	448	9.5	1777	16.7	1617	12.1	253	12.5	
2006	343	12.0	311	6.6	1661	15.6	1371	10.3	299	14.8	
2007	319	11.2	245	5.2	1420	13.3	1148	8.6	295	14.6	
2008	313	11.0	225	4.8	1513	14.2	1011	7.6	331	16.3	
Urban facility	2507	87.8	4037	85.6	9761	91.6	11952	89.5	1781	87.9	<0.0001
Academic Affiliation:											
low	599	21.0	1150	24.4	2131	20.0	3447	25.8	467	23.1	

Am J Psychiatry. Author manuscript; available in PMC 2014 December 17.

Variable Names	Haldol N=2855		Olanzapine N=4716		Quetiapine N=10651		Risperidone N=13356		Valproic acid and derivatives N=2026		
	N	%	N	%	N	%	N	%	N	%	p-value
limited	1011	35.4	1432	30.4	3388	31.8	4519	33.8	724	35.7	<0.0001
high	1245	43.6	2134	45.3	5132	48.2	5390	40.4	835	41.2	
Facility Size (# beds)											
<=200	758	26.6	1182	25.1	2154	20.2	3001	22.5	491	24.2	
201–400	766	26.8	1060	22.5	2769	26.0	3552	26.6	618	30.5	<0.0001
401–600	752	26.3	1424	30.2	3511	33.0	3943	29.5	490	24.2	
>600	579	20.3	1050	22.3	2217	20.8	2860	21.4	427	21.1	

*includes Schizophrenia and Schizoaffective Disorder

ΨTotal number of psychiatric illnesses

‡Includes myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, COPD, rheumatologic disease, peptic ulcer disease, cirrhosis, hepatic failure, diabetes mellitus, diabetes mellitus with complications, hemiplegia, chronic renal disease, malignant neoplasm, leukemia, lymphomas, metastatic solid tumor, and AIDS.

All use and diagnoses data are based on one year prior to the initiation of the medication.

Table 2

Crude death rates for dementia patients with new medication starts after a 12-month clean period

Medication	Intent-to-Treat					Exposure			
	N	#Deaths within 180 days	Total person-years	Death rate per 100 person-years	95%CI	#Deaths in exposure	Total person-years	Death rate per 100 person-years	95%CI
haloperidol	2855	570	1245.0	45.8	(42.1–49.7)	294	710.9	41.4	(36.8–46.4)
olanzapine	4716	596	2169.4	27.5	(25.3–29.8)	371	1521.1	24.4	(22.0–27.0)
quetiapine	10651	933	5019.2	18.6	(17.4–19.8)	531	3484.9	15.2	(14.0–16.6)
risperidone	13356	1669	6162.4	27.1	(25.8–28.4)	935	4165.5	22.4	(21.0–23.9)
valproic acid and derivatives	2026	199	948.5	21.0	(18.2–24.1)	123	669.3	18.4	(15.3–21.9)

Table 3

Relative risks of 180-day mortality for dementia patients with new medication starts after a 12-month clean period

Intent to Treat	Adjusted, unweighted			Propensity-weighted			Propensity-stratified		
Medication	**Hazard Ratio**	**95%CI**	**P-VALUE**	**Hazard Ratio**	**95%CI**	**P-VALUE**	**Hazard Ratio**	**95%CI**	**P-VALUE**
risperidone	**1.0**			**1.0**			**1.0**		
haloperidol	1.54	(1.38–1.73)	<.0001	1.57	(1.39–1.78)	<.0001	1.54	(1.38–1.73)	<.0001
olanzapine	0.99	(0.89–1.10)	0.8748	1.03	(0.92–1.16)	0.6194	1.00	(0.90–1.12)	0.9941
quetiapine	0.73	(0.67–0.80)	<.0001	0.74	(0.67–0.81)	<.0001	0.74	(0.68–0.81)	<.0001
valproic acid and derivatives	0.91	(0.78–1.06)	0.2468	0.97	(0.83–1.14)	0.7220	0.93	(0.80–1.09)	0.3831
Exposure	**Adjusted, unweighted**			**Propensity-weighted**			**Propensity-stratified**		
risperidone	**1.0**			**1.0**					
haloperidol	1.59	(1.36–1.85)	<.0001	1.61	(1.37–1.89)	<.0001	1.56	(1.34–1.81)	<.0001
olanzapine	1.06	(0.93–1.22)	0.3954	1.10	(0.95–1.28)	0.2062	1.07	(0.93–1.23)	0.3347
quetiapine	0.74	(0.65–0.83)	<.0001	0.74	(0.65–0.85)	<.0001	0.74	(0.66–0.84)	<.0001
valproic acid and derivatives	0.96	(0.79–1.17)	0.6996	1.04	(0.84–1.29)	0.7057	0.99	(0.82–1.21)	0.9568

Note: All relative risks were based on Cox regression adjusted for gender, age, race, marital status, delirium, depression, schizophrenia, bipolar I, bipolar II, other psychoses, parkinson's disease, substance abuse, PTSD, other anxiety, personality disorder, use of benzodiazepine, antidepressent, opiod, days in hospitalization, days in nursing home, fiscal year of index drug use, rurality of facility, facility size, academic affiliation of facility, Charlson's comorbidity index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, COPD, rheumatologic disease, peptic ulcer disease, cirrhosis, hepatic failure, diabetes mellitus, diabetes mellitus with complications, hemiplegia, chronic renal disease, malignant neoplasm, leukemia, lymphomas, metastatic solid tumor, and AIDS.

Table 4

Prescribed initial daily dose and haloperidol equivalent daily dose of antipsychotic medications

Average Initial Dose								
Antipsychotic	**N**	**Mean**	**Min**	**25th Percentile**	**50th Percentile**	**75th Percentile**	**95th Percentile**	**Max**
haloperidol	1809	1.758	0.250	0.500	1.000	2.000	5.000	25.000
olanzapine	4446	4.715	0.625	2.500	5.000	5.000	10.000	40.000
quetiapine	9371	51.871	0.750	25.000	25.000	50.000	150.000	1600.000
risperidone	11962	0.818	0.100	0.500	0.500	1.000	2.000	8.000

Haloperidol Equivalent Average Initial Dose								
Antipsychotic	**N**	**Mean**	**Min**	**25th Percentile**	**50th Percentile**	**75th Percentile**	**95th Percentile**	**Max**
haloperidol	1809	1.758	0.250	0.500	1.000	2.000	5.000	25.000
olanzapine	4446	1.937	0.149	0.832	1.967	1.967	4.654	26.045
quetiapine	9371	0.585	0.002	0.201	0.201	0.486	1.966	39.957
risperidone	11962	1.096	0.088	0.584	0.584	1.319	2.979	15.188