Are All Commonly Prescribed Antipsychotics Associated with Increased Mortality in Elderly Male Veterans with Dementia?

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Abstract

Objective: Estimate mortality risk associated with individual commonly-prescribed antipsychotics.

Design: 5-year retrospective cohort study.

Setting: Veterans national health care data.

Participants: Predominantly male, 65 years or older with a diagnosis of dementia and no other known indication for an antipsychotic. Subjects who received an antipsychotic were compared to controls selected randomly from veterans with similar dates of dementia diagnosis and time elapsed from diagnosis to the start of antipsychotic therapy. Exposed and control cohorts were matched by their date of dementia diagnosis and time elapsed from diagnosis to the start of antipsychotic therapy.

Measurements: Mortality during incident antipsychotic use.

Results: Subjects who were exposed to haloperidol (n=2217), olanzapine (n=3384), quetiapine (n=4277) or risperidone (n=8249) had more co-morbidities than control cohorts. During the first 30 days, there was a significant increase in mortality in subgroups prescribed a daily dose of haloperidol>1mg (hazard ratio (HR) = 3.2, 95% confidence interval (CI): 2.2-4.5, $p<0.0001$), olanzapine>2.5 mg (HR=1.5, 95%CI: 1.1-2.0, p=0.01) or risperidone>1mg (HR=1.6, 95%CI: 1.1-2.2, p=0.01) adjusted for demographic, co-morbidity and medication history using Cox regression analyses. Increased mortality was not seen when quetiapine >50 mg (HR=1.2, 95%CI: 0.7-1.8, p=0.5) was prescribed, and there was no increased mortality associated with a dose

<50 mg (HR=0.7, 95%CI 0.5 to 1.0, p=0.03). No antipsychotic was associated with increased mortality after the first 30 days.

Conclusions: Commonly prescribed doses of haloperidol, olanzapine and risperidone, but not quetiapine, were associated with a short-term increase in mortality. Further investigations are warranted to determine causality and identify patient characteristics and antipsychotic dosage regimens that are not associated with an increased risk of mortality in elderly patients with dementia.

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INTRODUCTION

Behavioral and psychological symptoms associated with dementia, such as agitation, psychosis, dysphoria, apathy and disinhibition, occur in a majority of the more than 5 million people in the U.S. with Alzheimer's disease and other types of dementia.[1-4] There are no Food and Drug Administration (FDA)-approved treatments for behavioral symptoms of dementia; nevertheless, antipsychotic medications are widely prescribed for this indication. A recent study found that 60% of veterans who were prescribed antipsychotic medications had no FDA-approved indications for them, and 20% of veterans with organic brain syndrome or Alzheimer's disease were prescribed an antipsychotic.[5]

In 2005, the FDA issued a boxed warning based largely on unpublished data about an increased risk of mortality associated with the use of atypical antipsychotic medications in patients with dementia. This advisory was expanded to include conventional antipsychotics in 2008.[6] Several studies have indicated that the risk might be greater with conventional antipsychotics than with atypical antipsychotics.[7-11] Many studies regarding antipsychotics and mortality were short-term and indicated that the risk of mortality occurs shortly after initiation.[7, 9, 12] Information about the mortality risk posed by an individual atypical or conventional antipsychotic is scarce. Pharmacological differences and differences in how various antipsychotics are being used might make the use of some antipsychotics more risky than others. The purpose of this study was to examine the mortality risks associated with the use of individual antipsychotic

medications, including their time course, when prescribed for elderly veterans with dementia.

METHODS

Study Cohorts

We searched the Veterans Health Administration's (VHA) National Patient Care Database in Austin, Texas to identify veterans who had an inpatient or outpatient encounter record that listed a diagnosis of dementia from October, 1999 to September, 2005. Records were not available to determine whether subjects had dementia prior to this period. Dementia was defined as coding of 290 (dementia), 290.0 (senile dementia), 290.1 - 290.3 (dementia not otherwise specified), 290.4 (vascular dementia), 290.9 (unspecified senile psychotic conditions), 291.1 - 291.2 (alcohol-induced dementia), 294.1 (dementia in conditions classified elsewhere), 331.0 (Alzheimer's disease), 331.1 (frontotemporal dementia) and 331.82 (Lewy body dementia) according to the International Classification of Diseases, 9th Clinical Modification. Veterans younger than 65 years old were excluded, as were those with diagnostic codes for schizophrenia (292.0 - 295.9), bipolar affective disorder (296.0, 296.1, 296.4-296.8), delusional disorder (297 - 297.9) or other nonorganic psychosis (298 - 298.9) that could be indications for prescribing an antipsychotic.

Outpatient prescription records from October, 1998 to September, 2005 were obtained from the VHA Pharmacy Benefits Management Strategic Healthcare Group for subjects with the above diagnostic codes. These prescription files are extracted monthly from electronic prescription records at each VA medical center and include prescriptions from associated outpatient clinics. Subjects who had a prescription for any antipsychotic in the study period that was dispensed prior to their first recorded diagnosis of dementia

were excluded. The first VHA prescription for an antipsychotic medication dispensed concurrently or after each subject's dementia diagnosis was used to define the index date for each subject. Four cohorts of exposed patients [haloperidol (n=2,217), olanzapine (n=3,384), quetiapine (n=4,277) and risperidone (n=8,249)] were identified for further analysis. Those who had an outpatient prescription for any other antipsychotic (n=453) were excluded from the study, as were the small number (n=61) who had an outpatient prescription for an injectable antipsychotic.

Control subjects were selected from those who had a diagnosis of dementia and did not receive an antipsychotic prescription during the period of study. For each subject exposed to an antipsychotic, all potential control subjects with their first diagnosis of dementia in that same quarter of the same year and still at risk when the antipsychotic exposure began were identified, and four were randomly selected as control subjects to maximize power.[13] The date the index antipsychotic prescription was dispensed to the exposed subject was assigned as the index date for the four controls. The controls for each antipsychotic cohort were selected without replacement; however, some unexposed subjects were selected as a control for more than one antipsychotic.

Covariates

Baseline morbidity and utilization of VHA health care services measures were used to describe the study cohorts and to control for differences between the exposed and unexposed cohorts. VHA inpatient records (including acute, extended, observational, rehabilitation, and nursing home care provided by or paid for by the VHA) and VHA outpatient encounter records for a period of one year prior to each subject's index date

(inclusive) were searched for diagnosis codes to identify prior medical conditions using a previously described enhanced algorithm.[14] The diagnosis groups indicated whether or not subjects had a history of cerebrovascular disease, ischemic heart disease, peripheral vascular disease, heart failure, cancer, autoimmune deficiency syndrome, diabetes mellitus, chronic obstructive pulmonary disease, liver disease, renal disease, para- or hemiplegia, rheumatic disease or peptic ulcer disease. The subjects' age and gender were extracted from the encounter records along with the number of outpatient encounters during the baseline year (grouped as 0, 1, 2 to 12 or >12) and the days elapsed since the most recent discharge from an inpatient stay (grouped as 0, 1 to 90, 91 to 180, 181 to 365 and >365 days).

Outpatient prescriptions dispensed from a VHA pharmacy during the baseline year were used to define covariates as VHA formulary classifications (see Table 1). An additional 29 drug classes were examined but not reported because their use was not very prevalent or did not differ substantially between the antipsychotic and control cohorts.

Exposure

The initially prescribed daily doses of each antipsychotic were estimated by multiplying the total number of doses dispensed times their strength in milligrams and dividing by the days supply recorded on the electronic prescription record. Potential exposure to the initial antipsychotic was estimated as the total non-overlapping days of supply dispensed during each subject's follow-up period.

Follow-up

Dates of death were extracted from the national VHA Vital Status file that includes records of death collected from the Social Security Administration, Medicare, VHA beneficiary and inpatient discharge records.[15] Follow-up of survivors was censored when a subject's last prescription for his or her initial antipsychotic was presumably consumed, when a different antipsychotic was initiated, or on September 30, 2005, whichever occurred first.

Data Analysis

Study variables are summarized as means (standard deviations), medians (interquartile ranges) or percentages based on the level of measurement and distribution of the data. Given the large cohorts, nearly all comparisons of baseline characteristics were statistically significant even when seemingly inconsequential; thus, these p-values are not reported.

Life table methods were employed to estimate the unadjusted mortality hazards within several discrete time periods (0 to 30, 31 to 90, 91 to 180, 181 to 270 and 271 to 360 days) after the index date when exposed subjects were given their initial antipsychotic prescription. The estimated antipsychotic/control hazard ratios decreased with time. Therefore, the following Cox regression model of the natural logarithm of the hazard ratio was employed to estimate the effect of exposure to an antipsychotic during the same discrete time periods as the life table analysis and to adjust for covariates:

$$\text{Ln}\,[h(t_{ij})/h_o(t_j)] = \beta_1(X_1)D_{1ij} + \beta_2(X_1)D_{2ij} + \ldots \beta_6(X_1)D_{6ij} + \beta_p(X_p)$$

where X_1 denoted antipsychotic or control cohort, D_{kij} were dummy variables representing the k(6) discrete time periods, and X_p was a set of p covariates.[16] The

covariates in the Cox regression model included age, gender, type of dementia, and the medical conditions, medication classes and VHA health care utilization variables previously described in the covariates section. Hazard ratios for mortality among subjects who entered each discrete follow-up period were estimated using a stratified model, with strata defined by each exposed subject and his or her 4 matched controls.

To test the effects of different doses of each antipsychotic, the X_1 in the preceding equation was used to represent a dose subgroup and additional X_n terms were added to the equation to represent additional doses. The hazard ratios in groups defined by the 3 to 4 most commonly prescribed doses of each antipsychotic were examined first, and then dose groups that had similar risk estimates were combined. This approach resulted in the dose dichotomies presented herein that turned out to be defined by the median initially-prescribed dose of each antipsychotic.

Estimated p-values and 95% confidence intervals are reported without adjustment for multiple comparisons. Stata software (version 10) was used for all analyses. The Minneapolis VA Institutional Review Board reviewed and approved this study.

RESULTS

As summarized in Table 1, the mean age of the study cohorts was 77 years, and 98% were male. Diagnoses of Alzheimer's disease or dementia related to concurrent conditions were more frequent in all four of antipsychotic cohorts compared to their respective control cohorts.

Compared to their control cohorts, all of the exposed cohorts had higher percentages with diagnoses of heart failure, cerebrovascular accident, diabetes mellitus, chronic obstructive pulmonary disease and cancer. These differences in co-morbidity were notably larger in the haloperidol cohort. Only 4% to 5% of the antipsychotic cohorts did not have any of the prior conditions compiled for this analysis compared to 24% to 29% of the control cohorts. The exposed cohorts were more likely to be in a health care facility when the initial outpatient antipsychotic prescription was dispensed, particularly in the haloperidol cohort. All four of the exposed cohorts had more subjects with prior prescriptions for a benzodiazepine than their respective control cohorts. The olanzapine, quetiapine and risperidone cohorts had substantially greater baseline differences between exposed and controls in the percentages with prior prescriptions for an acetyl-cholinesterase inhibitor or an antidepressant, whereas the haloperidol cohort did not. A greater percentage of the quetiapine cohort had a prescription history for medications commonly used to treat Parkinson's disease. Other baseline medication comparisons that are not shown in Table 1 were unremarkable, and the percentages that did not have a prior VHA prescription for any one of the 50 drug classes examined were similar in the antipsychotic (16% to 22%) and the control (19%) cohorts.

The median time from the diagnosis of dementia to the first prescription for an antipsychotic was 60 days for haloperidol, 102 days for risperidone, and 120 days each for olanzapine and quetiapine (see Table 2). The most commonly prescribed initial daily doses were haloperidol 1 mg (30%), 0.5 mg (19%) and 2 mg (18%); olanzapine 2.5 mg (43%) and 5 mg (36%); quetiapine 25 mg (35%) and 50 mg (28%); and risperidone 0.5 (34%) and 1 mg (33%).

As shown in Table 3, substantial percentages of each cohort died, and a higher percentage died during the first 30-day period in the haloperidol cohort (5.4% vs. 1.7%; unadjusted hazard ratio = 3.1). An increase in the initial 30-day mortality was also seen in the olanzapine (2.7% vs. 1.7%; unadjusted hazard ratio = 1.6) and risperidone (2.8% vs. 2.0%; unadjusted hazard ratio = 1.4) cohorts. There was no apparent increase in the percentage dying in the quetiapine cohort (1.7% vs. 1.7%; unadjusted hazard ratio = 1.0). The percentage dying was not increased after the initial 30-day period in any of the cohorts exposed to the antipsychotics.

Adjusting for differences in baseline covariates, the hazard ratios representing all doses shown in Table 4 indicated that exposure to haloperidol and olanzapine continued to be associated with an increased mortality during the first 30 days. Quetiapine and risperidone were no longer associated with increased mortality. Like the unadjusted analyses shown in Table 3, none of the four antipsychotics were associated with a significantly increased adjusted risk of mortality in any of the time periods after the first 30 days of exposure (31 to 90, 91 to 180, 181 to 270 and 271 to 360 days; results not shown).

Also shown in Table 4, the lower doses of each antipsychotic were not associated with a statistically significant increase in risk, although the upper limit of the 95% confidence interval did not exclude some increase in risk except for the lower dose of quetiapine. Subgroups who were given the higher daily doses of haloperidol > 1mg (52%; n=1,166), olanzapine > 2.5mg (56%; n=1,889) or risperidone > 1mg (18%; n=1,490) had a significantly increased risk of death during the first 30 days. The 28% of subjects (n=1,181) who were prescribed the higher daily doses of quetiapine of 50 mg per day or more did not have a significantly increased mortality although the upper limit of the 95% confidence interval did not exclude a large increase in risk.

Secondary Analysis

After excluding inpatients and subjects discharged within 30 days and adjusting for any differences in baseline covariates, including time since previous discharge, prescriptions for haloperidol or olanzapine were still associated with an increased risk of mortality during the initial 30-days of exposure (see Table 4). The secondary estimate of the increased risk associated with risperidone changed little and was not statistically significant, but had an upper limit on the confidence interval that did not exclude a substantially increased risk (adjusted hazard ratio = 1.2; 95% confidence interval: 0.95-1.4; p-value =0.13). In this secondary analysis, prescriptions for quetiapine were associated with significantly reduced risk of mortality and the upper limit of the confidence interval excluded any increased risk (adjusted hazard ratio = 0.7; 95% confidence interval: 0.5-0.97; p-value =0.03).

DISCUSSION

The majority of studies published to date regarding the mortality associated with antipsychotic medications when prescribed for elderly patients with dementia have described the risk as a class effect, sometimes breaking this down further into typical versus atypical antipsychotics. Most[7, 9, 12, 17-19] but not all[8, 20, 21] have found that there is a higher risk of mortality associated with both classes of antipsychotics compared to unexposed cohorts. The FDA has issued a boxed warning for all antipsychotics. This study is consistent with the few investigations that reported some individual antipsychotics, including haloperidol and olanzapine, are associated with increased mortality.[11, 22, 23]

However, contrary to the general warnings that have been issued, one of the four commonly prescribed antipsychotics in our study was not associated with increased mortality in this study of an elderly veteran population with dementia. Being an observational cohort study, the observed increased risks could be related to baseline differences in risk between the exposed and unexposed cohorts including the unknown severity of the dementia. More severe dementia could prompt health care providers to prescribe antipsychotic medications (and higher doses), as patients are more likely to experience behavioral symptoms during moderate to severe dementia, and mortality is also associated with the severity of dementia.[24] Although adjustments were made by multivariable regression for all available baseline measures of co-morbidity, medication use and health care utilization, residual confounding cannot be ruled out for any of the observed associations.

Not surprisingly, the initial prescriptions were for the lower end of recommended daily doses for large percentages of each antipsychotic cohort. Nevertheless, this analysis could not rule out an increase in the 30-day mortality risk associated with haloperidol, olanzapine and risperidone, and confirmed an increased risk at higher doses of these antipsychotics. Risks that appear to increase with the dose generally support the notion that a medication rather than the characteristics of the patients being treated somehow increases the risk. An increased mortality risk was not observed in the quetiapine dose groups. However, this study cannot exclude the possibility that higher doses of quetiapine would be associated with an increased risk of mortality. In addition, the analyses of doses could be confounded by differences in baseline risk characteristics even though adjustments are made for all measured covariates.

Previous studies of quetiapine were not able to rule out a substantially increased risk of mortality. A study by Zhong had a small number of subjects and deaths and the confidence interval around the relative risk was very wide and inconclusive (relative risk 2.1 (95% CI 0.6 – 7.1)).[25] Another study of quetiapine, olanzapine and risperidone did not detect any differences in mortality compared to placebo, although again the number of subjects and deaths were small.[12] A meta-analysis of short-term randomized controlled trials also had wide inconclusive confidence intervals for the mortality risk associated with quetiapine (odds ratio 1.7 (95% CI 0.7-4.0)).[26] The present results from a larger cohort fall within the previously reported confidence intervals for the all-cause mortality risk associated with quetiapine.

A study of community-dwelling Medicaid enrollees did find that quetiapine was associated with an increased risk of sudden cardiac death (incidence-rate ratio 1.9 (95% CI 1.3-2.7)).[27] The incident rate of sudden cardiac death when these subjects were exposed to quetiapine was approximately 23 per 10,000 person-years versus the unexposed rate of 12 per 10,000 person-years. In contrast to the present study, subjects who had a high risk of non-cardiac death were excluded. Furthermore, less than 3% of the subjects in the study of Medicaid enrollees had a diagnosis of dementia and the majority of exposed subjects had mood disorders that were treated with other medications. Their average age was 46 years, and 65% of subjects were female. Together, these studies suggest that the mortality risk of quetiapine may vary in different patient populations. The effects of varying patient characteristics and dosage regimens on the mortality risk associated with quetiapine and other antipsychotics require further investigation.

The reason quetiapine's association with mortality might be different from the other antipsychotics' in this analysis is not obvious. The baseline characteristics of the subjects in the quetiapine cohort were similar to the other antipsychotic cohorts with the exception that a greater percentage of the quetiapine cohort had a diagnosis of Parkinson's disease (likely related to quetiapine's lower likelihood of exacerbating symptoms of Parkinson's, thought to be due to less avid binding at dopamine-2 receptors). While we did not have data regarding causes of death in this study, most deaths related to antipsychotic use in elderly demented patients are thought to be due to cardiovascular or infectious causes, although the mechanisms for the acute mortality

associated with the use of antipsychotics by patients with dementia have not been established.[28] In theory, sedation could lead to aspiration and pneumonia or to venous stasis and subsequent activation or pro-coagulant pathways. Additionally, orthostatic hypotension, QTc interval prolongation, and hyperprolactinemia associated with impaired endothelial function and increased platelet aggregation could theoretically contribute to heart attacks, strokes or arrhythmias.[29, 30] Given that quetiapine is active at nearly all the receptors thought to be involved in the above possible mechanisms, we do not have a ready explanation for why quetiapine in particular was not associated with an increased risk of mortality in this elderly veteran population.

The estimates of mortality hazards in discrete time periods indicated that the mortality risk was limited to approximately the first 30 days after the initial antipsychotic prescription. This apparently acute, transient risk could have been masked in previous studies that reported longer-term cumulative effects and is not noted in the FDA's boxed warning. The observation that the increased risk of mortality was limited to approximately the first 30 days of exposure suggests that much of the associated risk could be due to uncontrolled severity of illnesses rather than an antipsychotic per se. The exposure to antipsychotic medications could have been initiated during periods of acute illness and greater risk. Behavioral symptoms of dementia often occur when patients become delirious during acute illnesses. The exposed cohorts were more likely to be inpatients than the control cohorts, and inpatients might be more likely to die within a short period of time and covariate data to make proper adjustments for this risk are less available in administrative data when subjects are inpatients. Nevertheless, a secondary

analysis that excluded subjects who were inpatients or within 30 days of discharge at the time of exposure did not alter the results. Furthermore, the observed acute increase in mortality was positively associated with the prescribed dose although the reasons for prescribing different doses are not known. Thus this study cannot exclude the possibility that the initial exposure to some antipsychotics eliminates the small percentage at risk early on and surviving subjects are not at risk from continued use.

This study has several other limitations. The analysis relied on codes for clinical diagnoses that were recorded by clinicians during healthcare encounters. The completeness and accuracy of the diagnostic codes were not verified and could conceivably be different for the exposed versus control cohorts. Because veterans can and do receive non-VHA health care services, the VHA data can provide an incomplete assessment of co-morbidity and use of prescription medications. Based on the diagnoses recorded in the baseline year, the control cohorts in this analysis might have used (or needed) less VHA health care services than the exposed cohorts. If co-morbidity information was more incomplete for the control cohorts, the adjusted hazard ratios could be biased. Milder cases of dementia might have been missed, giving us a sample of patients that may be more demented than the population at large. Additionally, patients may not have taken the dispensed medications, so the prescription data may not accurately reflect how much exposure patients actually had to these medications or precisely when exposure occurred. These limitations most likely would not explain the lack of an increased mortality risk observed in the quetiapine cohort since an increased risk was observed for other antipsychotics and the quetiapine cohort did not differ greatly

from other exposed cohorts in regards to a number of covariates. As the older VHA population is largely male, our study results may not be applicable to other populations.

In summary, this study suggests that commonly prescribed doses of haloperidol, olanzapine and risperidone, but not quetiapine, were associated with a short-term increase in mortality in this sample of elderly veterans with dementia. Therefore, all antipsychotics might not pose the same degree of risk in all patient groups as implied by the general warnings that have been issued. Behavioral and personality changes associated with dementia are common and challenging for caregivers. Lacking approved medications or effective non-pharmacologic interventions for behavioral symptoms of dementia, antipsychotic medications continue to be prescribed despite the mortality risks.[31] Further research is needed to determine whether or under what circumstances each antipsychotic poses less or even no mortality risk.

Table 1. Baseline Characteristics of Study Cohorts.

	Haloperidol		Olanzapine		Quetiapine		Risperidone	
	Control	**Exposed**	**Control**	**Exposed**	**Control**	**Exposed**	**Control**	**Exposed**
Demographics								
Number	8867	2217	13536	3384	17109	4277	32996	8249
Age, mean(SD)	77(6)	78(6)	78(6)	78(6)	78(6)	78(6)	78(6)	78(6)
Female, (%)	2	2	3	2	3	2	2	2
Dementia Diagnosis (%)								
Senile	25	22	24	20	23	20	24	24
Vascular	18	18	17	14	17	16	17	17
Related to concurrent condition	24	33	23	30	22	31	23	31
Alzheimer's	39	54	40	51	41	49	40	51
Unspecified	9	10	9	10	8	9	9	11
Other*	4	4	4	3	4	5	4	3
Prior Conditions (%) †								
IHD	2	5	2	3	2	3	3	4
Heart failure	7	14	6	10	7	9	7	11
PVD	5	9	6	7	7	8	6	8
CVA	13	23	12	18	14	19	15	20
Diabetes	14	21	14	18	16	22	16	21
COPD	10	18	10	14	11	14	11	15
Cancer	6	15	6	11	9	11	8	11
Renal disease	3	6	3	4	3	4	3	5

Table 1. Baseline Characteristics of Study Cohorts (continued).

Prior Inpatient Stay (%)†								
None	83	63	87	82	88	79	85	75
On index date	2	18	2	7	2	9	2	12
Within 90 days	6	12	5	7	4	6	6	9
Within 91 to 365 days	8	6	6	4	6	6	7	5
Prior Prescriptions (%)†								
Cholinesterase inhibitor	29	31	31	37	35	44	30	38
Memantine	1	1	1	1	2	4	1	2
Benzodiazepine	11	18	10	18	9	18	10	16
Parkinson's drug	5	3	5	6	6	16	6	4
Anticonvulsant	9	9	9	9	9	10	9	8
Antidepressant	29	31	28	40	28	42	28	37
Opiate	12	14	12	11	12	11	12	12
NSAID	15	15	15	13	14	13	15	13
Other analgesic	38	40	33	29	28	28	34	33
Diuretic	29	29	29	25	30	28	29	27
ACEI or ARB	31	30	32	27	34	32	32	30
Beta-blocker	23	22	24	21	27	26	24	24
Calcium channel blocker	22	22	21	19	21	19	21	20
Digitalis	10	10	9	10	8	8	9	9

Table 1. Baseline Characteristics of Study Cohorts (continued).

Nitrate	15	17	15	14	14	14	15	15
Antiplatelet drug	8	8	9	9	10	10	9	9
Warfarin	8	6	7	7	8	7	8	7
Alpha blocker	19	17	18	14	18	16	18	16
Lipid reducer	26	21	30	24	35	32	30	25
Diabetes drug	17	15	17	13	17	16	17	16
Respiratory drug	13	13	13	11	13	11	13	12

* Alcohol-related, frontotemporal, Lewy body.

† During the year prior to the start of follow-up that began with the first prescription for an antipsychotic medication.

Abbreviations: IHD = ischemic heart disease, PVD = peripheral vascular disease, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, NSAID = nonsteroidal anti-inflammatory agent, ACEI =angiotensin converting enzyme inhibitor, ARB = Angiotensin II receptor blocker.

Table 2. Exposure to the Initial Antipsychotic.*

	Haloperidol	Olanzapine	Quetiapine	Risperidone
Days to first prescription after dementia diagnosis	60 (30 to 124)	120 (44 to 280)	120 (44 to 292)	102 (37 to 263)
Initially Prescribed Dose (mg/day)	1 (1 to 2)	5 (2.5 to 5)	50 (25 to 75)	1 (0.5 to 1)
Days to end of prescriptions	70 (30 to 204)	162 (47 to 405)	171 (50 to 409)	144 (42 to 395)
Fraction of days covered by dispensed days supply	1(0.76 to 1)	1(0.92 to 1)	1(0.91 to 1)	1(0.92 to 1)

* Data are summarized as the median (25^{th} to 75^{th} percentiles).

Table 3. Unadjusted Mortality Percentages within Specified Follow-up Intervals*

Follow-up Interval (days)	Haloperidol		Olanzapine		Quetiapine		Risperidone	
	Control	Exposed	Control	Exposed	Control	Exposed	Control	Exposed
0 to 30	1.7 (1.5-2.0) N=8867 D=153	5.4 (4.8-6.0) N=2217 D=120	1.7 (1.5-1.9) N=13536 D=227	2.7 (2.2-3.2) N=3384 D=91	1.7 (1.5-1.9) N=17109 D=296	1.7 (1.3-2.1) N=4277 D=73	2.0 (1.8-2.1) N=32996 D=645	2.8 (2.4-3.1) N=8249 D=229
31 to 90	1.4 (1.2-1.6) N=8650 D=242	1.3 (1.0-1.7) N=1919 D=51	1.4 (1.3-1.6) N=13172 D=379	1.5 (1.2-1.8) N=3197 D=96	1.4 (1.3-1.6) N=16296 D=469	1.0 (0.8-1.2) N=3991 D=82	1.6 (1.5-1.7) N=31964 D=1015	1.3 (1.1-1.6) N=7674 D=200
91 to 180	1.5 (1.4-1.6) N=8257 D=379	1.5 (1.2-1.8) N=1012 D=45	1.3 (1.2-1.4) N=12620 D=480	1.3 (1.1-1.6) N=2204 D=89	1.3 (1.2-1.4) N=15001 D=589	0.9 (0.8-1.1) N=2810 D=79	1.5 (1.4-1.6) N=30295 D=1365	1.1 (1.0-1.3) N=5167 D=176
181 to 270	1.4 (1.3-1.5) N=7699 D=323	1.6 (1.3-2.0) N=604 D=30	1.4 (1.3-1.5) N=11880 D=512	1.3 (1.1-1.6) N=1606 D=64	1.4 (1.3-1.5) N=13353 D=552	0.9 (0.7-1.1) N=2084 D=54	1.5 (1.4-1.5) N=27916 D=1244	1.1 (1.0-1.3) N=3659 D=124
271 to 360	1.4 (1.3-1.6) N=7217 D=313	1.1 (0.6-1.6) N=413 D=14	1.6 (1.5-1.7) N=11034 D=532	1.1 (0.6-1.6) N=1228 D=40	1.4 (1.3-1.5) N=11754 D=480	0.8 (0.6-1.0) N=1609 D=38	1.5 (1.4-1.6) N=25698 D=1158	0.9 (0.7-1.1) N=2835 D=79

* Percentage dying per 30 days among those who entered the specified follow-up interval. Values in parentheses are 95% confidence intervals.

N=number of subjects entering each time interval; D=number of subject deaths per interval

Table 4. Hazard Ratios (95% Confidence Intervals) for Mortality within the First 30 Days after an Antipsychotic Medication was Dispensed.

Analysis	Haloperidol	Olanzapine	Quetiapine	Risperidone
Any Prescribed Dose, Unadjusted	3.2 (2.5 to 4.1) P<0.0001	1.7 (1.3 to 2.2) P<0.0001	1.0 (0.7 to 1.2) P=0.80	1.4 (1.2 to 1.7) P<0.001
Any Prescribed Dose, Adjusted	2.2 (1.7 to 2.9) P<0.0001	1.3 (1.0 to 1.7) P=0.03	0.8 (0.6 to 1.1) P=0.14	1.2 (1.0 to 1.4) P=0.08
Any Prescribed Dose Excluding Recent Inpatients, Adjusted*	2.3 (1.6 to 3.3) P<0.0001	1.4 (1.0 to 1.9) P=0.03	0.7 (0.5 to 1.0) P=0.03	1.2 (1.0 to 1.4) P=0.13
Lower Prescribed Doses, Adjusted†	1.5 (1.0 to 2.2) P=0.07	1.0 (0.7 to 1.6) P=0.79	0.7 (0.5 to 1.0) P=0.03	1.1(0.9 to 1.3) P=0.47
Higher Prescribed Doses, Adjusted†	3.2 (2.2 to 4.5) P<0.0001	1.5 (1.1 to 2.0) P=0.01	1.1 (0.7 to 1.8) P=0.50	1.6 (1.1 to 2.2) P=0.01

Hazard ratios were estimated using the Cox regression models described under Data Analysis with unexposed cohorts as the reference group, and are rounded to the nearest decimal.

* Excludes all subjects who were in a health care facility within 30-days of the first prescription for an antipsychotic.

† Lower prescribed doses were haloperidol $\leq$ 1mg, olanzapine $\leq$ 2.5mg, quetiapine $\leq$ 50mg, and risperidone $\leq$1mg. Higher prescribed doses include all prescribed doses above these levels.

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