Original Investigation

Antipsychotics, Other Psychotropics, and the Risk of Death in Patients With Dementia
Number Needed to Harm

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IMPORTANCE Antipsychotic medications are associated with increased mortality in older adults with dementia, yet their absolute effect on risk relative to no treatment or an alternative psychotropic is unclear.

OBJECTIVE To determine the absolute mortality risk increase and number needed to harm (NNH) (ie, number of patients who receive treatment that would be associated with 1 death) of antipsychotic, valproic acid and its derivatives, and antidepressant 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 from October 1, 1998, through September 30, 2009. Participants included 90 786 patients 65 years or older with a diagnosis of dementia. Final analyses were conducted in August 2014.

EXPOSURES A new prescription for an antipsychotic (haloperidol, olanzapine, quetiapine, and risperidone), valproic acid and its derivatives, or an antidepressant (46 008 medication users).

MAIN OUTCOMES AND MEASURES Absolute change in mortality risk and NNH over 180 days of follow-up in medication users compared with nonmedication users matched on several risk factors. Among patients in whom a treatment with medication was initiated, mortality risk associated with each agent was also compared using the antidepressant group as the reference, adjusting for age, sex, years with dementia, presence of delirium, and other clinical and demographic characteristics. Secondary analyses compared dose-adjusted absolute change in mortality risk for olanzapine, quetiapine, and risperidone.

RESULTS Compared with respective matched nonusers, individuals receiving haloperidol had an increased mortality risk of 3.8% (95% CI, 1.0%-6.6%; $P < .01$) with an NNH of 26 (95% CI, 15-99); followed by risperidone, 3.7% (95% CI, 2.2%-5.3%; $P < .01$) with an NNH of 27 (95% CI, 19-46); olanzapine, 2.5% (95% CI, 0.3%-4.7%; $P = .02$) with an NNH of 40 (95% CI, 21-312); and quetiapine, 2.0% (95% CI, 0.7%-3.3%; $P < .01$) with an NNH of 50 (95% CI, 30-150). Compared with antidepressant users, mortality risk ranged from 12.3% (95% CI, 8.6%-16.0%; $P < .01$) with an NNH of 8 (95% CI, 6-12) for haloperidol users to 3.2% (95% CI, 1.6%-4.9%; $P < .01$) with an NNH of 31 (95% CI, 21-62) for quetiapine users. As a group, the atypical antipsychotics (olanzapine, quetiapine, and risperidone) showed a dose-response increase in mortality risk, with 3.5% greater mortality (95% CI, 0.5%-6.5%; $P = .02$) in the high-dose subgroup relative to the low-dose group. When compared directly with quetiapine, dose-adjusted mortality risk was increased with both risperidone (1.7%; 95% CI, 0.6%-2.8%; $P = .003$) and olanzapine (1.5%; 95% CI, 0.02%-3.0%; $P = .047$).

CONCLUSIONS AND RELEVANCE The absolute effect of antipsychotics on mortality in elderly patients with dementia may be higher than previously reported and increases with dose.

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Individual clinical trials and meta-analyses have suggested modest benefit from some antipsychotic agents over placebo for the treatment of psychosis and aggression in patients with dementia[1-3] and that these symptoms may return when a medication is discontinued.[4] Potential harms anticipated with use of these medications include known adverse effects such as metabolic changes and extrapyramidal symptoms.[1,5,6] However, evidence pooled across randomized, placebo-controlled trials (RCTs) of atypical antipsychotics, such as risperidone and olanzapine, demonstrated an increased risk of cerebrovascular adverse events for which the US Food and Drug Administration (FDA) issued a warning in 2003.[7] Subsequent analyses of published and unpublished clinical trial data on atypical antipsychotics by the FDA and a meta-analysis of 15 RCTs by Schneider et al[8] demonstrated an increased mortality risk. In April 2005, the FDA[9] issued a black box warning that the use of atypical antipsychotics leads to increased all-cause mortality when used for behavioral disturbances in patients with dementia. Additional observational analyses[10,11] have demonstrated that first-generation antipsychotic agents confer an even higher mortality risk than do the atypical agents, leading to another FDA[12] black box warning in 2008. However, at the time the warnings were issued, the available evidence described class-wide effects on mortality without clear delineation of the risks associated with individual medications.

Using a large national registry of Veterans Affairs (VA) patients with dementia, Kales et al[13] published the first analyses that provided estimates of the head-to-head mortality risk over 180 days, comparing individual antipsychotic agents and valproic acid and its derivatives (hereafter referred to as *valproic acid*), which are frequently used alternatives[14] for behavioral disturbances in dementia. Subsequent analyses of elderly community-dwelling[15] and nursing home[16] patients have generally confirmed the initial findings that individual antipsychotic agents vary in their mortality risk, ranging from quetiapine (lowest) to haloperidol (highest).

The decision to use any intervention in medicine requires balancing potential benefits with potential harms, but it can be difficult for clinicians to interpret the clinical significance of absolute changes in risk or benefit. The number needed to harm (NNH) is a useful metric for clinicians to understand a treatment's potential for harm, expressing the number of patients who have to receive treatment for a particular harmful outcome to occur with the intervention.[17] The *NNH* is formally defined as the reciprocal of the change in absolute risk. Two sets of meta-analyses of atypical RCTs by Schneider et al[1,8] provided key preliminary evidence for clinicians to help weigh the relative benefits and risks of using antipsychotics. First, this group demonstrated the increased mortality risk of atypical antipsychotics relative to placebo in patients with dementia,[8] showing an absolute mortality risk increase of 1% over 8 to 12 weeks of treatment, or an NNH of 100 (1/.01). The authors suggested that this degree of risk may be similar to that of other types of medications used in frail, elderly patients, although subsequent work[18] has demonstrated that the mortality risk associated with antipsychotic treatment is greater than that with other psychotropic medications. In a second set of analyses, Schneider et al[1] examined the potential benefits of treatment with antipsychotics. Depending on the outcome measure and criterion for improvement, the number needed to treat ranged from 5 to 14, in contrast to the NNH of 100.

Over the past several years, investigators have consistently demonstrated both class- and agent-specific associations with increased mortality risk when these agents are used to treat dementia-related behavioral disturbances. However, when faced with the clinical decision of whether to prescribe a given medication for a given patient, physicians may have difficulty quantifying and comparing the risk. Here, we build on previous observational analyses of a cohort of patients with dementia newly treated with an antipsychotic (haloperidol, olanzapine, quetiapine, and risperidone) to estimate the increased absolute mortality risk and corresponding NNH during 180 days of follow-up relative to no treatment. Similar analyses are included for valproic acid and antidepressants since they are commonly used as alternatives to antipsychotics for aggression/agitation in dementia.[14] Then, given the interest in antidepressant agents as more benign alternatives to antipsychotics[19,20] and their increased use following the FDA warnings,[14] we describe the mortality risk and NNH of antipsychotics and valproic acid relative to antidepressants. Finally, we provide estimates of the increased risk across atypical antipsychotics by agent and by dose.

Methods

Study Cohort

The data source and characteristics used here are similar to those previously published.[13] In brief, deidentified data were provided by national VA registries maintained by the Serious Mental Illness Treatment Resource and Evaluation Center in Ann Arbor, Michigan, and the study was approved, with waiver of informed consent, by the VA Ann Arbor Healthcare System. Patients potentially included were aged 65 years or older and had a dementia diagnosis for at least 1 inpatient or outpatient encounter (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 290.0, 290.1x, 290.2x, 290.3, 290.4x, 291.2, 294.10, 294.11, 331.0, 331.1, and 331.82) between October 1, 1998, and September 30, 2009. The cohort was then limited to patients who began outpatient treatment with a study medication following a period of at least 6 months without exposure to any antipsychotic, antidepressant, or anticonvulsant. Based on previous work demonstrating that 87% of VA patients with dementia received antipsychotic monotherapy,[13] we limited this cohort to monotherapy. In the event that patients had more than 1 treatment episode during the 11-year study period, the first episode was used. The final treatment group included 46 008 medication users.

Medications

We included the antipsychotics haloperidol, olanzapine, risperidone, and quetiapine; the anticonvulsant valproic acid and its derivatives; and antidepressants, excluding tricyclic antidepressants or monoamine oxidase inhibitors. Patients tak-

ing valproic acid who had a diagnosis of a seizure disorder were excluded from the sample.

Outcomes

The primary study outcome was 180-day mortality, with mortality data obtained from the US National Death Index (National Center for Health Statistics).[21] Secondary analyses compared dose-adjusted absolute change in mortality risk for olanzapine, quetiapine, and risperidone.

Clinical Characteristics

Variables included sex, age, race, marital status, active clinical diagnoses, and prescriptions for benzodiazepines and opioids during the 12 months before the index date when treatment began. Time since dementia diagnosis was used as a proxy for dementia severity. Because antipsychotics are frequently prescribed for treatment of delirium, and delirium itself is a risk factor for mortality, we used a coding scheme for acute confusional states developed for a previous study[22] to capture the presence of delirium. This scheme included the following *ICD-9* 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, and 349.82. A Charlson Comorbidity Index score[23] was calculated based on the presence of 18 medical comorbidities (excluding dementia) and then categorized as 0, 1, and greater than 1. We also included days in the hospital and in the nursing home during the 12 months before the index date, as well as urban vs rural location, academic affiliation, and size of the treating facility. The fiscal year of the prescription was also included as a variable to account for secular trends in the use of these medications.[14,24]

Study Design

Once the medication-user cohort was defined, to estimate the increased mortality risk difference and corresponding NNH relative to no treatment, we paired each medication user with a matching nonuser patient. First, we created a nonuser cohort of patients potentially eligible for matching: these individuals were aged 65 years or older, had a diagnosis of dementia (as described above), and had at least 6 months free of any antipsychotic, antidepressant, and anticonvulsant. For each medication-using patient, potential matching nonuser patients were first identified matching on the calendar year of the initial dementia diagnosis. Next, potential matching nonuser patients had a phantom fill date created that was the same number of days from the dementia diagnosis as for the corresponding medication-using patient. Using this phantom fill date, each medication-using patient was paired to an eligible nonuser patient selected randomly from the matching nonuser pool, and was matched further on additional patient characteristics at that time including age (±2.5 years), race, delirium diagnosis within the preceding 12 months, psychiatric hospitalization within the preceding 12 months, and 3-category Charlson Comorbidity Index score. Because medication users were limited to monotherapy, a potential nonuser was excluded if treatment with any antidepressant, antipsychotic, or anticonvulsant medication was started during the 180-day observation period.

Analytic Plan

The final study monotherapy cohort included 46 008 users; for the matched cohort, 45 393 of the monotherapy users were matched with nonusers. Descriptive statistics captured patient characteristics by medication prescribed (**Table 1**). A 180-day observation period was chosen based on previously published analyses.[10,11,13] The outcome was death within the observation period following a new prescription (or phantom fill date for the nonuser cohort).

Two primary analyses were done. First, we estimated the mortality risk difference for each medication relative to no treatment based on matched user and nonuser patients for each agent. We used a generalized linear model with logit link to fit a logistic regression model for the 180-day mortality risk associated with a given medication. We accounted for pairing between medication user and matched nonuser using a generalized estimating equation and adjusted for other clinical and demographic variables available in the administrative data (**Table 2** footnote provides full list of covariates). Based on this model, we calculated the absolute difference in mortality risk and the corresponding NNH for patients in each medication group relative to each matched nonuser cohort. Next, to estimate the 180-day mortality risk difference and NNH for each medication compared with antidepressants, we used a logistic regression model with data from the full monotherapy cohort. Primary predictors in the model were dummy indicators for each study medication, with antidepressants as the referent medication group.

As a secondary analysis, we compared the mortality risk difference across the 3 atypical antipsychotics (olanzapine, quetiapine, and risperidone) controlling for medication dosage. Among these patients, 14.7% (n = 1929) had missing dosage data; thus, missing dosages were multiply imputed using a multivariate normal model that included all covariates and study medications as well as mortality. Imputation was done using SAS, version 9.3 (SAS Institute Inc). Given evidence suggesting that mortality is associated with medication dosage,[15] we first grouped the 3 atypical antipsychotic users by haloperidol-equivalent dosage[25] (low [<1.5 mg/d], medium [1.5 to <3.0 mg/d], and high [≥3.0 mg/d]) to calculate dose-based absolute mortality risk differences, using the low-dose group as the reference. Lastly, mortality risk differences were calculated for olanzapine and risperidone relative to quetiapine, adjusting for haloperidol-equivalent prescribed dose and clinical and demographic variables. The risk difference estimates were pooled across 5 multiply-imputed data sets with the Rubin method[26] and were used to calculate the risk of death and NNH. As a sensitivity analysis, comparisons among the atypical antipsychotics by medication and by haloperidol-equivalent dosage were done only among medication users with valid dose information.

Results

Table 1 presents the clinical and demographic characteristics of the study population stratified by medication group. Patients who were receiving haloperidol were significantly sicker

Table 1. Characteristics of 46 008 Patients[a]

Characteristic	No. (%)					
	Haloperidol (n = 1958)	Olanzapine (n = 1952)	Quetiapine (n = 4700)	Risperidone (n = 6471)	Valproic Acid (n = 914)	Antidepressant (n = 30 013)
Died within 180 d	407 (20.8)	271 (13.9)	553 (11.8)	900 (13.9)	111 (12.1)	2499 (8.3)
Sex						
Female	48 (2.5)	57 (2.9)	83 (1.8)	166 (2.6)	18 (2.0)	778 (2.6)
Male	1910 (97.6)	1895 (97.1)	4617 (98.2)	6305 (97.4)	896 (98.0)	29 235 (97.4)
Age, y						
65-69	127 (6.5)	146 (7.5)	220 (4.7)	328 (5.1)	82 (9.0)	2338 (7.8)
70-74	256 (13.1)	251 (12.9)	616 (13.1)	837 (12.9)	137 (15.0)	4235 (14.1)
75-79	507 (25.9)	510 (26.1)	1211 (25.8)	1713 (26.5)	249 (27.2)	8054 (26.8)
80-84	630 (32.2)	638 (32.7)	1534 (32.6)	2122 (32.8)	261 (28.6)	9524 (31.7)
≥85	438 (22.4)	407 (20.9)	1119 (23.8)	1471 (22.7)	185 (20.2)	5862 (19.5)
Race						
White	1318 (67.3)	1296 (66.4)	3317 (70.6)	4233 (65.4)	658 (72.0)	21 885 (72.9)
African American	387 (19.8)	270 (13.8)	546 (11.6)	1089 (16.8)	101 (11.1)	3087 (10.3)
Other	21 (1.1)	23 (1.2)	67 (1.4)	100 (1.6)	6 (0.7)	469 (1.6)
Unknown	232 (11.9)	363 (18.6)	770 (16.4)	1049 (16.2)	149 (16.3)	4572 (15.2)
Married	1200 (61.3)	1217 (62.4)	3298 (70.2)	4023 (62.2)	614 (67.2)	20 172 (67.2)
Benzodiazepine use	397 (20.3)	328 (16.8)	735 (15.6)	969 (15.0)	137 (15.0)	4269 (14.2)
Opioid use	547 (27.9)	459 (23.5)	1315 (28.0)	1777 (27.5)	252 (27.6)	9102 (30.3)
Delirium	866 (44.2)	773 (39.6)	2010 (42.8)	2719 (42.0)	393 (43.0)	10 676 (35.6)
Depression	147 (7.5)	225 (11.5)	422 (9.0)	567 (8.8)	122 (13.3)	11 469 (38.2)
Schizophrenia	63 (3.2)	112 (5.7)	111 (2.4)	235 (3.6)	15 (1.6)	258 (0.9)
Bipolar I disorder	13 (0.7)	29 (1.5)	37 (0.8)	44 (0.7)	51 (5.6)	171 (0.6)
Bipolar II disorder	1 (0.1)	10 (0.5)	12 (0.3)	15 (0.2)	17 (1.9)	49 (0.2)
Other psychoses	414 (21.1)	431 (22.1)	1031 (21.9)	1553 (24.0)	144 (15.8)	4046 (13.5)
Parkinson disease	91 (4.7)	167 (8.6)	875 (18.6)	283 (4.4)	52 (5.7)	1950 (6.5)
Substance abuse	113 (5.8)	128 (6.6)	199 (4.2)	324 (5.0)	39 (4.3)	1384 (4.6)
Alcohol abuse	80 (4.1)	81 (4.2)	124 (2.6)	215 (3.3)	24 (2.6)	1047 (3.5)
Drug abuse	67 (3.4)	83 (4.3)	120 (2.6)	199 (3.1)	22 (2.4)	722 (2.4)
Posttraumatic stress disorder	29 (1.5)	55 (2.8)	140 (3.0)	148 (2.3)	23 (2.5)	1402 (4.7)
Other anxiety disorder	95 (4.9)	106 (5.4)	206 (4.4)	352 (5.4)	44 (4.8)	2656 (8.9)
Personality disorder	8 (0.4)	18 (0.9)	17 (0.4)	38 (0.6)	5 (0.5)	115 (0.4)
Charlson Comorbidity Index score						
0	650 (33.2)	852 (43.7)	1940 (41.3)	2505 (38.7)	352 (38.5)	10 143 (33.8)
1	463 (23.7)	465 (23.8)	1092 (23.2)	21 508 (3.3)	250 (27.4)	7270 (24.2)
>1	845 (43.2)	635 (32.5)	1668 (35.5)	2458 (38.0)	312 (34.1)	12 600 (42.0)
Days of hospitalization						
0	1277 (65.2)	1533 (78.5)	3748 (79.7)	4886 (75.5)	716 (78.3)	24 559 (81.8)
1-5	170 (8.7)	108 (5.5)	274 (5.8)	424 (6.6)	58 (6.3)	1777 (5.9)
>5	511 (26.1)	311 (15.9)	678 (14.4)	1161 (17.9)	140 (15.3)	3677 (12.3)
Days in nursing home						
0	1818 (92.9)	1848 (94.7)	4436 (94.4)	6031 (93.2)	859 (94.0)	28 561 (95.2)
1-30	80 (4.1)	44 (2.3)	157 (3.3)	243 (3.8)	31 (3.4)	755 (2.5)
>30	60 (3.1)	60 (3.1)	107 (2.3)	197 (3.0)	24 (2.6)	697 (2.3)
Fiscal year of index date						
2000	376 (19.2)	175 (9.0)	56 (1.2)	606 (9.4)	65 (7.1)	1965 (6.6)
2001	314 (16.0)	255 (13.1)	162 (3.5)	782 (12.1)	70 (7.7)	2417 (8.1)
2002	215 (11.0)	314 (16.1)	282 (6.0)	841 (13.0)	70 (7.7)	2921 (9.7)
2003	151 (7.7)	1328 (16.8)	473 (10.1)	824 (12.7)	63 (6.9)	3263 (10.9)
2004	144 (7.4)	274 (14.0)	505 (12.9)	823 (12.7)	82 (9.0)	3365 (11.2)
2005	132 (6.7)	179 (9.2)	726 (15.5)	698 (10.8)	92 (10.1)	3155 (10.5)

(continued)

Table 1. Characteristics of 46 008 Patients[a] (continued)

Characteristic	No. (%)					
	Haloperidol (n = 1958)	Olanzapine (n = 1952)	Quetiapine (n = 4700)	Risperidone (n = 6471)	Valproic Acid (n = 914)	Antidepressant (n = 30 013)
Fiscal year of index date						
2006	187 (9.6)	137 (7.0)	684 (14.6)	577 (8.9)	117 (12.8)	3357 (11.2)
2007	148 (7.6)	115 (5.9)	538 (11.5)	502 (7.8)	110 (12.0)	3188 (10.6)
2008	134 (6.8)	104 (5.3)	598 (12.7)	432 (6.7)	128 (14.0)	3185 (10.6)
2009	157 (8.0)	71 (3.6)	575 (12.2)	386 (6.0)	117 (12.8)	3197 (10.7)
Urbanicity	1789 (91.4)	1741 (89.2)	4403 (93.7)	5883 (90.9)	838 (91.7)	27 504 (91.6)
Academic affiliation[b]						
Low	460 (23.5)	469 (24.0)	1018 (21.7)	1741 (26.9)	228 (24.9)	7304 (24.3)
Limited	539 (27.5)	537 (27.5)	1311 (27.9)	1843 (28.5)	319 (34.9)	7983 (26.6)
High	959 (49.0)	946 (48.5)	2371 (50.5)	42 887 (4.6)	367 (40.2)	14 726 (49.1)
No. of beds in facility						
≤200	525 (27.3)	455 (23.3)	994 (21.2)	1536 (23.7)	223 (24.4)	6856 (22.8)
201-400	476 (24.3)	458 (23.5)	1197 (25.5)	1728 (26.7)	276 (30.2)	8029 (26.8)
401-600	544 (27.8)	612 (31.4)	1537 (32.7)	1812 (28.0)	227 (24.8)	8208 (27.4)
>600	370 (18.9)	400 (20.5)	933 (19.9)	1322 (20.4)	178 (19.5)	6624 (22.1)

[a] All risk factors were statistically significant at $P < .05$.

[b] Size of Veterans Affairs facilities are categorized as 3 equal groups based on the number of physician residency positions at each facility during the index year.

Table 2. Crude Death Rates During a 180-Day Observation Period Among Patients With Dementia Starting Therapy With a New Medication

Medication	No. of Pair[a]	Death, No. (%)		Risk Difference, % (95% CI)[b]	NNH (95% CI)[b]
		Users	Nonusers		
Haloperidol	1921	398 (20.7)	162 (8.4)	3.8 (1.0 to 6.6)[c]	26 (15 to 99)
Olanzapine	1908	265 (13.9)	187 (9.8)	2.5 (0.3 to 4.7)[d]	40 (21 to 312)
Quetiapine	4621	545 (11.8)	378 (8.2)	2.0 (0.7 to 3.3)[c]	50 (30 to 150)
Risperidone	6338	883 (13.9)	538 (8.5)	3.7 (2.2 to 5.3)[c]	27 (19 to 46)
Valproic acid	901	110 (12.2)	65 (7.2)	4.1 (−1.0 to 9.2)	NA[e]
Antidepressant	29 704	2472 (8.3)	2367 (8.0)	0.6 (0.3 to 0.9)[c]	166 (107 to 362)

Abbreviation: NA, not applicable; NNH, number needed to harm.

[a] A total of 45 393 pairs were evaluated. Users vs nonusers were matched on: calendar year of initial dementia diagnosis, days from dementia diagnosis to date of index drug start, age (±2.5 years), race, delirium diagnosis, psychiatric hospitalization, and 3-category Charlson Comorbidity Index group.

[b] Analyses were adjusted for sex, centered age and its quadratic term, marital status, depression, schizophrenia, bipolar I disorder, bipolar II disorder, other psychoses, Parkinson disease, substance abuse, posttraumatic stress disorder, other anxiety disorders, personality disorder, use of benzodiazepines, use of opioids, days of hospitalization, days in nursing home, fiscal year of index drug use, academic affiliation of facility, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, rheumatologic disease, peptic ulcer disease, cirrhosis, hepatic failure, type 1 or 2 diabetes mellitus, type 1 or 2 diabetes mellitus with complications, hemiplegia, chronic renal disease, malignant neoplasm, leukemia, lymphoma, metastatic solid tumor, human immunodeficiency virus without AIDS, and AIDS.

[c] $P < .01$.

[d] $P < .05$.

[e] The NNH was not calculable because the 95% CI for risk difference included 0.

than were those in the other medication groups, with a generally higher Charlson Comorbidity Index score, more days of hospitalization, and more nursing home days. This group was more likely to have received a delirium diagnosis within the prior 12 months and had the largest proportion also receiving benzodiazepines. The haloperidol group had a higher proportion of African American patients and a lower proportion of married patients than did the other medication groups. In addition, relative to the other groups, a larger proportion of patients receiving haloperidol were in facilities with fewer beds.

The valproic acid and antidepressant groups had the lowest proportions of African American patients, and the antidepressant group had the smallest proportion of patients who had received a benzodiazepine or a diagnosis of delirium within the prior 12 months. The antidepressant group had the highest proportion of patients with a comorbid diagnosis of depression, posttraumatic stress disorder, and other anxiety disorders; the valproic acid group included the highest proportion of patients with a comorbid bipolar disorder diagnosis. The olanzapine group had the smallest proportion of patients with a Charlson Comorbidity Index score greater than 1. Although the antidepressant group was second only to the haloperidol group for share of patients with Charlson Comorbidity Index score greater than 1, the antidepressant group had the largest proportions of patients with no hospital or nursing home days in the year before the index.

Table 2 presents the 180-day crude mortality for medication users and their matched nonuser counterparts. Haloperidol users had the highest mortality (20.7%) relative to nonusers, followed by risperidone (13.9%), olanzapine (13.9%), valproic acid (12.2%), quetiapine (11.8%), and antidepressants (8.3%). The crude mortality rates among matched nonusers ranged from 9.8% (matched nonusers for olanzapine) to 7.2% (matched nonusers for valproic acid).

The adjusted absolute mortality risk difference between medication users and matched nonusers is also presented in Table 2. The adjusted mortality risk was higher for haloperidol users relative to matched nonusers by 3.8% (95% CI, 1.0%-6.6%; $P < .01$). In terms of NNH, treatment with haloperidol was associated with 1 death for every 26 (1/.038; 95% CI, 15-99) patients who received treatment. Among the other antipsychotics, quetiapine had the lowest association with mortality relative to matched nonusers, with an adjusted risk difference of 2.0% (95% CI, 0.7%-3.3%; $P < .01$; NNH, 50; 95% CI, CI 30-150). The antidepressant group had only a slightly increased risk of death relative to matched nonusers; the risk difference for valproic acid and its derivatives was not significantly different from 0, providing no clear evidence for increased mortality. Including rurality and facility size as covariates did not impact the results.

Table 3 presents the adjusted mortality risk directly comparing the study psychotropic medications, using antidepressants as the reference group. Relative to other psychotropic monotherapy agents, haloperidol was associated with the greatest mortality risk, with an absolute risk of 12.3% higher (95% CI, 8.6%-16.0%; $P < .01$) than antidepressants, yielding an NNH of 8 (95% CI, 6-12) compared with antidepressant treatment. Quetiapine use had the lowest effect on mortality, with a 3.2% (95% CI, 1.6%-4.9%; $P < .01$) higher mortality risk relative to antidepressants (NNH, 31; 95% CI, 21-62).

Table 3. Adjusted Mortality Risk Differences in Death Rates During the 180-Day Observation Period Between Medication Users and Antidepressant Users[a]

Medication	Risk Difference, % (95% CI)	NNH (95% CI)
Antidepressant	[Reference]	NA
Haloperidol	12.3 (8.6-16.0)[b]	8 (6-12)
Olanzapine	7.0 (4.2-9.8)[b]	14 (10-24)
Quetiapine	3.2 (1.6-4.9)[b]	31 (21-62)
Risperidone	6.1 (4.1-8.2)[b]	16 (12-25)
Valproic acid	5.1 (1.8-8.4)[b]	20 (12-56)

Abbreviations: NA, not applicable; NNH, number needed to harm.

[a] Analyses in the 46 008 patients adjusted for calendar year of first dementia diagnosis, days from dementia diagnosis to date of index drug start, centered age and its quadratic term, sex, race, delirium diagnosis, psychiatric hospitalization, marital status, depression, schizophrenia, bipolar I disorder, bipolar II disorder, other psychoses, Parkinson disease, substance abuse, posttraumatic stress disorder, other anxiety disorders, personality disorder, use of benzodiazepines, use of opioids, days of hospitalization, days in nursing home, fiscal year of index drug use, academic affiliation of facility, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, rheumatologic disease, peptic ulcer disease, cirrhosis, hepatic failure, type 1 or 2 diabetes mellitus, type 1 or 2 diabetes mellitus with complications, hemiplegia, chronic renal disease, malignant neoplasm, leukemia, lymphoma, metastatic solid tumor, human immunodeficiency virus without AIDS, and AIDS.

[b] $P < .01$.

Secondary Analyses

Dosage information for olanzapine, quetiapine, and risperidone is presented in **Table 4**. Compared with the low-dose haloperidol-equivalent group, mortality for the medium-dose group was nonsignificantly higher (1.3%; 95% CI, −0.1% to 2.7%; $P = .07$), but the high-dose group had significantly increased mortality (3.5%; 95% CI, 0.5% to 6.5%; $P = .02$; NNH, 29; 95% CI, 15-200). Controlling for dose, the 3 second-generation antipsychotics differed in mortality risk when compared directly. Relative to quetiapine, olanzapine increased the risk by 1.5% (95% CI, 0.02% to 3.0%; $P = .047$; NNH, 67; 95% CI, 33 to 5000) and risperidone increased the risk by 1.7% (0.6% to 2.8%, $P = .003$; NNH, 59; 95% CI, 36 to 167). Sensitivity analyses evaluating only medication users with valid dose information also demonstrated increased mortality risk among the high-dose group and the risperidone group. However, the increased risk associated with olanzapine relative to quetiapine was no longer statistically significant.

Discussion

Building on previous work in this large national sample of outpatients with dementia, we examined the mortality risk associated with newly prescribed antipsychotics, valproic acid, and antidepressants. Compared with the matched cohort of medication nonusers, the mortality risk associated with haloperidol was the highest overall among the study medications, and risperidone was the highest among the atypical antipsychotics. Antidepressant use was associated with a small, but statistically significant, increase in mortality. This finding is of note in light of the recent RCT[20] suggesting that citalopram significantly reduced agitation but may also carry adverse cognitive and cardiac effects. Our findings suggest that, during a 180-day

Table 4. Initially Prescribed Mean Daily Dose and Haloperidol-Equivalent Dosage Groups of Atypical Antipsychotic Medications

	Overall		Haloperidol-Equivalent Dosage, mg/d					
			Low (<1.5)		Medium (1.5 to <3.0)		High (≥3.0)	
Medication	No. of Users	Mean (Range) Dosage, mg/d	No. of Users	Range	No. of Users	Range	No. of Users	Range
Olanzapine	1776	4.63 (1.25-40.00)	875	1.25-3.75	629	5.00-6.00	272	7.50-40.00
Quetiapine	3945	52.15 (0.75-1600.00)	3686	0.75-112.50	178	125.00-200.00	81	225.00-1600.00
Risperidone	5473	0.84 (0.13-9.00)	4741	0.13-1.00	575	1.25-2.00	157	2.50-9.00

period, starting haloperidol therapy for a patient with dementia may be associated with 1 additional death for every 26 patients receiving treatment. For the atypical antipsychotics, the NNH ranged from 27 to 50 relative to the NNH in matched nonusers. When directly comparing other medication users with patients receiving antidepressants, haloperidol had the largest associated mortality risk and quetiapine had the least risk. Comparing the atypical antipsychotics directly and controlling for dose, both risperidone and olanzapine increased mortality relative to quetiapine, although the increased risk with olanzapine was no longer significant in the sensitivity analysis limited to nonimputed data. Lastly, the analyses suggested a dose-response relationship between atypical antipsychotics and risk of mortality.

The increased risk of mortality is higher than that previously reported, although prior estimates were from RCTs, which are less subject to confounding by indication. In 2005, Schneider et al[8] originally reported an NNH for death of 100 for the second-generation agents from clinical trials of 10 to 12 weeks. A more recent Agency for Healthcare Research and Quality Comparative Effectiveness Review found a slightly lower NNH for a mortality of 87 for patients with dementia.[27] The results of the present study confirm previous findings that have demonstrated that haloperidol has the highest associated mortality risk, followed by atypical antipsychotics and valproic acid.[10,13,15,16,18] Even quetiapine, which was consistently found to be less harmful than other antipsychotics, had an increased mortality risk of 2.0% (95% CI, 0.7-3.3; $P < .01$) relative to matched nonusers, yielding an NNH of 50 (95% CI, 30-150). Although quetiapine appears to have the least association with mortality, it also has less evidence of benefit than olanzapine or risperidone.[1,3]

Our findings suggest that the mortality risk for the least harmful antipsychotic studied (quetiapine) is double that of the initial estimate of Schneider et al[8]; for risperidone the mortality risk is nearly 4-fold higher. In addition, our secondary analyses demonstrated a mortality dose response, suggesting that a strategy using a high dose rather than a low dose (eg, risperidone, 3.0 mg rather than 0.5 mg) may be associated with additional mortality. Although the prior estimates were based on RCTs completed during 6 to 12 weeks,[3,8] the longer period of analysis in the present study is likely a more accurate reflection of how these medications are used in the community and therefore may more fully capture the association with mortality.

The primary limitations of this study stem from the use of an administrative, claims-based database lacking information on dementia severity and behavioral or psychiatric symptoms. Although the analyses were adjusted for a wide range of clinical characteristics, the clinical complexity of these patients, who were not randomly assigned to treatment, may not have been captured. Some analyses[28-30] have found an association between certain neuropsychiatric symptoms and mortality, so 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 addition, our analyses were limited to episodes of medication monotherapy during the first treatment episode, which potentially limits the generalizability.

Conclusions

The balance of benefit to risk of antipsychotic treatment in dementia continues to shift, as our findings suggest that use of these medications may be associated with increased mortality of a greater magnitude than previously described. The present analyses provide critical information that can help physicians minimize potential harms at multiple decision points. If an antipsychotic or alternative psychotropic is prescribed, how much may this increase the patient's risk of mortality? If a second-generation antipsychotic is prescribed, which agent is most associated with increased mortality? Is dose of an antipsychotic associated with mortality? The decision to use these medications is generally in response to profoundly distressing and potentially dangerous behaviors of patients. Prescribing a medication that increases mortality risk seems contrary to the tenet "first, do no harm," yet for patients who pose a danger to themselves and others and are in profound distress, use of such medications may still be appropriate.[31,32] These new data can help physicians minimize the potential harm associated with antipsychotic treatment.

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REFERENCES

1. 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.

2. Sultzer DL, Davis SM, Tariot PN, et al; CATIE-AD Study Group. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. *Am J Psychiatry*. 2008;165(7):844-854.

3. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA*. 2011;306(12):1359-1369.

4. Devanand DP, Mintzer J, Schultz SK, et al. Relapse risk after discontinuation of risperidone in Alzheimer's disease. *N Engl J Med*. 2012;367(16):1497-1507.

5. Schneider LS, Tariot PN, Dagerman KS, et al; CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355(15):1525-1538.

6. Jeste DV. Tardive dyskinesia rates with atypical antipsychotics in older adults. *J Clin Psychiatry*. 2004;65(suppl 9):21-24.

7. US Food and Drug Administration. Risperdal (risperidone) dear healthcare professional letter Apr 2003. http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm168933.htm. Published April 16, 2003. Accessed February 2, 2014.

8. 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.

9. US Food and Drug Administration. Public health advisory: deaths with antipsychotics in elderly patients with behavioral disturbances. US Department of Health and Human Services. http://www.fda.gov/Drugs/DrugSafety/ucm053171.htm. Accessed February 2, 2014.

10. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med*. 2005;353(22):2335-2341.

11. 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.

12. US Food and Drug Administration. Information for healthcare professionals: information on conventional antipsychotics. US Department of Health and Human Services. http://www.fda.gov/Drugs/DrugSafety/ucm124830.htm. Accessed February 2, 2014

13. Kales HC, Kim HM, Zivin K, et al. Risk of mortality among individual antipsychotics in patients with dementia. *Am J Psychiatry*. 2012;169(1):71-79.

14. Kales HC, Zivin K, Kim HM, et al. Trends in antipsychotic use in dementia 1999-2007. *Arch Gen Psychiatry*. 2011;68(2):190-197.

15. Gerhard T, Huybrechts K, Olfson M, et al. Comparative mortality risks of antipsychotic medications in community-dwelling older adults. *Br J Psychiatry*. 2014;205(1):44-51.

16. Huybrechts KF, Gerhard T, Crystal S, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. *BMJ*. 2012;344:e977.

17. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ*. 1995;310(6977):452-454.

18. Kales HC, Valenstein M, Kim HM, et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. *Am J Psychiatry*. 2007;164(10):1568-1576.

19. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA*. 2005;293(5):596-608.

20. Porsteinsson AP, Drye LT, Pollock BG, et al; CitAD Research Group. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA*. 2014;311(7):682-691.

21. Fillenbaum GG, Burchett BM, Blazer DG. Identifying a National Death Index match. *Am J Epidemiol*. 2009;170(4):515-518.

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.

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.

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.

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.

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

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.

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.

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.

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

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.