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Research Article

Association Between Antipsychotics and All-Cause Mortality Among Community-Dwelling Older Adults

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Abstract

Background: Antipsychotics are prescribed to treat various symptoms in older adults, however, their safety in this context has not been fully evaluated. The objective was to evaluate mortality risks associated with off-label use of antipsychotics among older adults with no preexisting mental illness or dementia relative to those with diagnosis of dementia.

Methods: Data (2007–2015) were derived from Department of Veterans Affairs registries for 730,226 patients (≥65 years) with no baseline serious mental illness, dementia). We estimated the cumulative incidence of antipsychotics prescription and 10-year all-cause mortality. The extended Cox models were used to estimate Hazard Ratios (HRs) associated with antipsychotics prescription, adjusted for time-varying covariates, dementia diagnosis, comorbidity index score, and age at time of first exposure to antipsychotics.

Results: The study included 98% males, 13% African Americans, and 81% Caucasian. Patients with dementia and antipsychotics had the highest risk of mortality (78.0%), followed by (73.0%) for patients with dementia alone and compared with patients without dementia or antipsychotics exposure who had the lowest mortality risk (42.0%). Exposure to typical antipsychotics was associated with (HR: 2.1, confidence interval [CI] 2.0–2.2) compared with atypical antipsychotics (HR: 1.5, CI 1.4–1.5, p = <.0001).

Conclusion: In a large cohort of older adults, antipsychotics were associated with an increased risk of all-cause mortality. While significant increase in mortality was attributable to the diagnosis of dementia, the addition of antipsychotics resulted in added mortality risk among all patients. Antipsychotic medications should be used cautiously in all older adults, not only those with dementia.

Keywords: Cognition, Drug related, Primary care

Typical and atypical antipsychotic medications are approved by the U.S. Food and Drug Administration (FDA) to treat a range of serious mental illnesses, including schizophrenia, bipolar disorder, and depression under specific circumstances (1,2). Unlike the older typical medications, several atypical antipsychotics have a broader spectrum of action and are used to treat bipolar disorder and/or depression that did not respond to antidepressant medication alone (3,4).

Recent studies have found that nearly 58% of Medicaid patients and 60% of veterans have been prescribed antipsychotic medications for an off-label use (ie, not specifically approved by the FDA) (5–7), much of this off-label uptake in atypical antipsychotics prescriptions for older adults were seen in the United States, Canada, and Europe (8–10). Antipsychotics are often prescribed for challenging behavior rather than for diagnosed mental illness (11–15). And they are associated with serious adverse effects, particularly in older adults with

dementia (5,16–18). Despite the limited evidence that antipsychotics have behavioral and psychological symptoms of dementia (19), their safety has been challenged by an increase in cerebrovascular adverse side effects and mortality.

Several pooled studies and meta-analyses have demonstrated increased risk of cerebrovascular events and mortality with the use of antipsychotics among persons with dementia (11,17,20,21). This was shown in older adults residing nursing homes, which might be due to advanced dementia; hence, higher baseline mortality risk (22–28).

The American Geriatric Society's 2015 Beers criteria for safe medication use in older adults recommend avoiding antipsychotics to treat the neuropsychiatric symptoms of dementia because of the increased mortality and stroke risk (29). While the risk associated with the use of antipsychotics in patients with dementia is well established, their safety in the absence of dementia or mental illness is not well studied. In this study, we attempted to evaluate the mortality risks associated with the use of antipsychotics among community-dwelling older adults with or without dementia. We hypothesized that dementia and/or exposure antipsychotic medications, in the absence of preexisting mental illness, is associated with increased risk of mortality

Methods

Study Design

This was a retrospective cohort study of community-dwelling older U.S. veterans. Data were identified and extracted from the Veterans Affairs (VA) Informatics and Computing Infrastructure Corporate Data Warehouse (VINCI), which houses a national repository and is composed of data from several Veterans Health Administration (VHA) sources, including clinical and health utilization data.

Study Population

Veterans ages ≥65 years between January 1, 2007 and January 1, 2015, were identified (730,226 patients). At baseline, patients are classified as having dementia if they were diagnosed as such or if they were prescribed treatment for dementia. The diagnosis is defined by the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes [ICD9] for dementia (ICD9:290.0-290.4,294.20,331.1,331.8), schizophrenia (ICD9: 292.0–295.9), schizoaffective disorder and bipolar disorder (ICD9: 296.0, 296.1, 296.4–296.8), delusional disorder (ICD9: 297–297.9), or other non-organic psychosis (ICD9: 298–298.9). Patients residing in a nursing home or hospice prior to or during the study were excluded. To determine whether patients received care through VHA, they were included only if they had at least two outpatient VHA encounters during the study.

Exposure

Outpatient prescription records were obtained from the VHA Pharmacy Benefits Management Strategic Healthcare Group and were reviewed from January 2007 to January 2015. These prescription files are extracted monthly from electronic prescriptions at each VA medical center and clinic. Patients who had been prescribed any antipsychotic prior to study entry were excluded. To control for length of exposure, we defined exposure as the period between date of first antipsychotics medication prescription and last date of antipsychotics prescription. The atypical antipsychotic medications included were aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. The typical antipsychotic medications included were chlorpromazine, fluphenazine, haloperidol, perphenazine, thioridazine, and trifluoperazine. In this cohort, 37,110 patients were identified as first taking antipsychotic medication during the study based on two or more prescriptions for antipsychotics.

Thirteen thousand three hundred and eighty-five patients developed dementia and/or were prescribed donepezil, galantamine, rivastigmine, or memantine during the study. 683,072 had no dementia and no antipsychotics exposure during the study.

Outcome Variables

The primary endpoint for this study was mortality after age 65 years. Date of death was extracted from the national VHA Vital Status File (VSF), which includes records of death for veterans who have received care from the VHA since 1992 and were enrolled in VHA or received compensation or pension benefits from the Veterans Benefit Administration since 2002. Multiple VHA and non-VHA data sources contribute to the VHA VSF, including the Beneficiary Identification Records Locator Subsystem Death File, VHA Medicare VSF, Social Security Administration Death Master File, and inpatient discharge records (30).

Baseline Covariates

Baseline demographic information such as gender, race, ethnicity, marital status, and rurality was extracted. Rurality was defined according to a custom map based on the Goldsmith Modification of the Office of Management and Budget definition urban, rural, and highly rural land areas (31).

Urban is any land area that the Census Bureau formally defines as an urbanized area (UA). All areas that are not classified as urban are classified as rural. Those areas in counties with a population density of less than seven persons per square mile. These areas are designated as highly rural.

Comorbidities

To control for the presence of comorbidities, we calculated a time-varying comorbidity index score at each age interval based on the Elixhauser comorbidity index, which includes 18 medical comorbidities (excluding dementia) (30).

Statistical Analysis

Bivariate analyses were conducted using chi-square tests, Fisher's Exact Test, and t tests to examine the association of baseline characteristics with survival.

Kaplan–Meier method was used to estimate the probability of each end point according to the age of the patient, and differences between the antipsychotics medication and the control group were tested using two-sided log-rank tests and stratified according to dementia.

The extended Cox model was used to generate hazard ratios and confidence intervals for antipsychotic use versus no antipsychotic use (time-varying covariate), and dementia versus no dementia (time-varying covariate), age at first exposure to antipsychotics, and Elixhauser comorbidity index (time-varying covariate).

Left Truncation

For incidence of antipsychotic use, data for each patient was left truncated at age 65.

For incidence of all-cause mortality, data for patients was left censored at time of first antipsychotic prescription or at age 65 for patients not prescribed antipsychotics.

Right Censoring

For incidence of antipsychotic use, each patient was right censored at time of first exposure to an antipsychotic. Patients who were not prescribed antipsychotics were censored at time of last encounter.

For incidence of all-cause mortality, patients were right censored at time of death or administratively censored at end of follow-up period.

Results

Of the 730,226 veterans who met inclusion criteria, 98% were male, 81% were Caucasian, and 13% were African American (Table 1). During the study period, of the 716,841 veterans identified for this study, 13,385 (1.8%) were diagnosed with dementia, of which 48.8% were prescribed antipsychotic medications (10-year cumulative incidence of 51.5%, N = 6,538). Antipsychotics use among patients who were not diagnosed with dementia was approximately 4.7%.

Patients with dementia generally had significantly higher prevalence of comorbid conditions as compared with the patients without dementia. Diabetes was the most prevalent condition amongst patients with dementia at 43 versus 60% in patients without dementia. Cerebrovascular disease was the second most prevalent (37 vs 14%), and chronic kidney disease at (19 vs 13%) (Table 2).

Kaplan–Meier curves demonstrated that patients without dementia or antipsychotics exposure had the lowest mortality risk (51.0%), followed by patients without dementia who were prescribed antipsychotics (55.0%), then patients with dementia and antipsychotics prescription had the highest risk of mortality (78.0%), while patients with dementia alone (73.0%) (log rank p-value = <.0001) (Figure 1; Table 3).

Overall, exposure to typical antipsychotic medications was associated with an adjusted (hazard ratio [HR]: 2.12; confidence interval [CI] 2.00–2.24) compared with no exposure, and exposure to atypical antipsychotic medications was associated with an adjusted HR of 1.46 (CI 1.41–1.51) compared with no exposure (Table 4). A diagnosis of dementia was associated with an (HR: 2.26; CI 2.19–2.34) compared with no dementia (Table 4).

Discussion

This study demonstrated that in a large cohort of community-dwelling older veterans, antipsychotic use was associated with an increased risk of all-cause mortality in patients with and without dementia and without preexisting serious mental illness. A significant increase in mortality risk was attributable to dementia, and the addition of antipsychotics increased that risk. To the best of our knowledge, this is the largest sample to date of this cohort and the first study to explore the association between antipsychotics and all-cause mortality in older veterans without dementia or serious mental illness.

In the last several decades, antipsychotics have been frequently prescribed as a psychopharmacologic treatment for a variety of symptoms in older adults (32). These medications are frequently prescribed to treat delusions, hallucinations, aggression, and agitation in older adult patients with dementia. Antipsychotics have a small but statistically significant effect in treating agitation, psychosis, and behavioral symptoms associated with dementia (11,33).

Furthermore, atypical antipsychotics have been found to be effective as an adjuvant medication in major depressive disorder in patients with inadequate responses to selective serotonin reuptake inhibitors/serotonin and norepinephrine reuptake inhibitors, and quetiapine has been found to be effective as a monotherapy for major depressive disorder (34). Limited data suggest possible efficacy in other conditions, such as obsessive-compulsive disorder and posttraumatic stress disorder (35), but in general these medications

Table 1. Baseline Characteristics of Community-Dwelling Older Adult U.S. Veterans

	No Dementia (N = 716,841) N (%)			Dementia (N = 13,385) N (%)		
	No Meds (N = 683,072)	Meds (N = 33,769)	p Value*	No Meds (N = 6,847)	Meds (N = 6,538)	p Value*
Gender						
Male	671,437 (98.3%)	33,007 (97.7%)	.535	6,745 (98.5%)	6,415 (98.1%)	.533
Race						
African American/Black	87,681 (12.8%)	5,260 (15.6%)	<.001	1,229 (17.9%)	1,080 (16.5%)	.076
Caucasian/White	552,001 (80.8%)	26,403 (78.2%)	<.001	5,217 (76.2%)	5,095 (77.9%)	.043
American Indian/Native Alaskan	5,491 (0.8%)	281 (0.8%)	.574	40 (0.6%)	47 (0.7%)	.193
Asian	4,463 (0.7%)	139 (0.4%)	<.001	25 (0.4%)	24 (0.4%)	1
Ethnicity						
Hispanic	31,483 (4.6%)	1,530 (4.5%)	.515	280 (4.1%)	350 (5.4%)	<.001
Marital Status						
Married	430,713 (63.1%)	18,817 (55.7%)	<.001	4,049 (59.1%)	4,052 (62%)	.003
Divorced	152,750 (22.4%)	9,141 (27.1%)	<.001	1,627 (23.8%)	1,502 (23%)	.398
Separated	15,496 (2.3%)	1,050 (3.1%)	<.001	177 (2.6%)	176 (2.7%)	.895
Single	665 (0.1%)	27 (0.1%)	.369	12 (0.2%)	10 (0.2%)	.412
Widow	32,318 (4.7%)	1,771 (5.2%)	<.001	402 (5.9%)	286 (4.4%)	.073
Rurality	35,631 (5.2%)	1,557 (4.6%)	<.001	296 (4.3%)	236 (3.6%)	.111

Note: *Fisher's test, Significant difference (p < .05).

Table 2. Distributing of Comorbidities Among Community-Dwelling Older Adult U.S. Veterans

	No Dementia (*N* = 716,841) *N* (%)				Dementia (*N* = 13,385) *N* (%)			
	Controls (*N* = 683,072)	Meds (*N* = 33,769)	All (*N* = 716,841)	*p* Value*	Controls (*N* = 6,847)	Meds (*N* = 6,538)	All (*N* = 13,385)	*p* Value*
Cerebrovascular Disease	98,075 (14.4%)	2594 (7.7%)	100,669 (14%)	<.001	2,776 (40.5%)	2140 (32.7%)	4,916 (36.7%)	<.001
Heart Failure	45,770 (6.7%)	1138 (3.4%)	46,908 (6.5%)	<.001	850 (12.4%)	552 (8.4%)	1,402 (10.5%)	<.001
Chronic Kidney Disease	88,075 (12.9%)	2256 (6.7%)	90,331 (12.6%)	<.001	1,391 (20.3%)	1087 (16.6%)	2,478 (18.5%)	<.001
Connective Tissue Disease	378 (0.1%)	16 (0%)	394 (0.1%)	.634	5 (0.1%)	3 (0%)	8 (0.1%)	.671
Diabetes	418,985 (61.3%)	7,892 (23.4%)	426,877 (59.5%)	<.001	3,105 (45.3%)	2,600 (39.8%)	5,705 (42.6%)	<.001
Cancer	91,199 (13.4%)	1,962 (5.8%)	93,161 (13%)	<.001	700 (10.2%)	646 (9.9%)	1,346 (10.1%)	.483
Peptic Ulcer Disease	30,995 (4.5%)	830 (2.5%)	31,825 (4.4%)	<.001	362 (5.3%)	300 (4.6%)	662 (4.9%)	.178
Liver Disease	24,380 (3.6%)	728 (3.2%)	25,108 (3.5%)	<.001	408 (6.0%)	307 (4.7%)	715 (5.3%)	.011

*Fisher's test, Significant difference ($p < .05$).

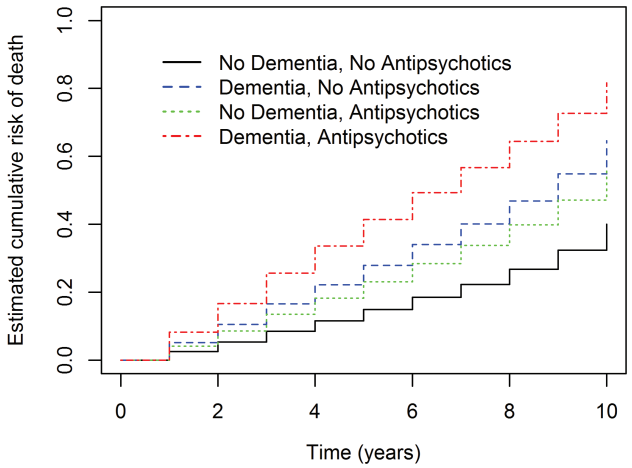

Figure 1. Kaplan–Meier estimates of the cumulative risk of death by 10 years. Shown is the probability of death among patients who no exposure to antipsychotics or diagnosis of dementia (black curve), among patients who were exposed to antipsychotics with no dementia diagnosis (green curve), among patients who were not exposed to antipsychotics with dementia diagnosis (blue curve), and among patients who were exposed to antipsychotics with dementia diagnosis (red curve). Rates were compared with the use of the log-rank test. Full color version is available within the online issue.

tend to be used frequently for off-label conditions and nonspecific symptoms in a variety of contexts, including insomnia (6,36). Widespread use of atypical antipsychotics is of concern given the observed risk for adverse outcomes and mortality, particularly in older adults (5,28,37).

Given that research has mostly focused on the use of antipsychotic medications in the context of dementia, it has been difficult to separate the baseline mortality risk that may be attributed to dementia itself (7,8). However, one study that examined the behavioral symptoms of dementia separately found that they independently increased mortality risk (9). When samples of patients with dementia are further categorized as those receiving and not receiving antipsychotics, it is likely that underlying differences in the severity of the dementia may partly account for the mortality risk between the groups.

Vulnerable groups, including older adults, are often prescribed off-label use of antipsychotics, and this use has occurred in the absence of clear efficacy data (10). However, older adults, including those without dementia, may be at increased risk for serious adverse events when exposed to antipsychotics. Older adults are more sensitive to many of the known side effects of these medications, such as their anticholinergic effects. Older adults also are more likely to have preexisting comorbidities that interact negatively with complications associated with these medications, such as weight gain, metabolic syndrome, and hyperlipidemia. Older persons with cardiovascular disease, hypercholesterolemia, or diabetes mellitus are predisposed to worsening of these conditions as a result of antipsychotic use. Furthermore, the prescription of these medications in an older population may be a proxy for more serious underlying illness, and thus a harbinger of increased risk.

The management of late-life behavioral disorders is clinically complex and must include assessment of the risks versus benefits of the use of antipsychotic medications. In its recent practice guidelines, the American Psychiatric Association recommended prescribing antipsychtics to patients with dementia (11,38) only when behavioral problems are severe, potentially harmful to self or others, or resulting in significant distress. Clinicians should be made aware of that potential for adverse outcomes in such patients are increased with the use of psychotropic medications. Given the absence of prospective studies, guideline-based clinical judgment in prescribing must be patient-centered and focused on quality of life. It is essential to understand that dementia itself is a life-limiting illness. Medications should be used in the lowest effective dose, for the shortest clinically indicated duration. Medications are only one part of a comprehensive care plan that emphasizes quality and compassionate care. In older adults without dementia, the off-label use of antipsychotic medications should receive even more caution. Clinicians should recognize the increased risk for mortality that is associated with the use of these agents in this population.

This study was limited by several factors; the cohort was predominantly male and while representative of the VA population may not be generalizable to nonveteran groups. Additionally, the retrospective design relied on data that had already been collected, and not all pertinent risk factors may have been identified. For example, dementia was based on clinician diagnosis, which is likely to be

Table 3. Incidence of Mortality Among Community-Dwelling Older Adult U.S. Veterans by Dementia Diagnosis and Antipsychotics Use

	Controls			Meds			Dementia			Dementia and Meds		
Age	Number at Risk	Number of Events	Risk	Number at Risk	Number of Events	Risk	Number at Risk	Number of Events	Risk	Number at Risk	Number of Events	Risk
66	683,072	16,286	0.02	40,307	325	0.01	6,847	140	0.02	6,538	34	0.01
67	532,764	17,280	0.06	21,266	422	0.03	4,912	205	0.07	1,704	53	0.04
68	456,823	16,553	0.09	19,968	640	0.06	4,582	286	0.13	1,625	84	0.09
69	369,935	14,789	0.13	17,734	728	0.10	4,055	353	0.20	1,477	110	0.15
70	280,598	12,616	0.17	14,897	747	0.14	3,384	342	0.28	1,257	102	0.22
71	194,872	9,921	0.21	11,614	687	0.19	2,518	286	0.36	994	124	0.32
72	124,492	7,009	0.26	8,589	572	0.25	1,769	234	0.45	694	104	0.42
73	71,157	4,784	0.31	6,057	508	0.31	1,065	173	0.54	430	87	0.54
74	28,276	2,609	0.37	3,806	408	0.38	450	108	0.65	204	61	0.68
75	2,917	229	0.42	1,629	257	0.48	34	8	0.73	19	6	0.78

Table 4. The Extended Cox Model Hazard Modelling Prescription for Incidence of Death Among Community-Dwelling Older Adult U.S. Veteran

		95%	95%			95%	95%	
	Unadjusted HR	LCL	UCL	*p* Value	Adjusted HR[a]	LCL	UCL	*p* Value
Elixhauser comorbidity index Score 3 vs 0	2.75	2.69	2.84	<.001	2.98	2.92	3.03	<.001
Elixhauser comorbidity index Score 2 vs 0	1.71	1.7	1.73	<.001	1.55	1.53	1.58	<.001
Dementia	2.91	2.814	2.998	<.001	2.26	2.19	2.34	<.001
Conventional Antipsychotics	2.54	2.41	2.68	<.001	2.12	2	2.24	<.001
Atypical Antipsychotics	1.48	1.44	1.51	<.001	1.46	1.41	1.51	<.001
Age (at time of antipsychotics exposure)	1.13	1.12	1.14	<.001	1.06	1.05	1.07	<.001

Note: LCL = Lower confidence limit; UCL = Upper confidence limit.

[a]Adjusted for Elixhauser comorbidity index (time-varying), Dementia (time-varying), Conventional Antipsychotics (time-varying), Atypical Antipsychotics (time-varying), Age (at time of antipsychotics exposure).

*Significant difference ($p < .05$).

under-recognized in the clinical setting. Consequently, some of the patients receiving antipsychotic medication may have been receiving treatment for early symptoms of undiagnosed dementia or subclinical delirium; these conditions would be independently associated with mortality regardless of antipsychotic exposure (39,40).

In conclusion, in this large cohort of community-dwelling U.S. veterans, off-label antipsychotics exposure after age 65, in the absence of baseline serious mental illness or dementia, was associated with an increased risk of all-cause mortality. Although the association between antipsychotic medication and all-cause mortality was significant in patients with dementia, the increased risk was independent of the dementia. Future prospective studies should be conducted to validate the current results and test generalizability outside the VA population.

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Conflict of Interest

None reported.

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