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Association of atypical antipsychotics and mortality for patients hospitalised with pneumonia

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ABSTRACT

Introduction: Atypical antipsychotics are commonly used in patients with psychiatric conditions and dementia. They are also frequently used in patients being admitted with pneumonia; however, there are few safety data. The purpose of this study was to examine whether atypical antipsychotic use prior to admission is associated with increased mortality in patients with pneumonia.

Methods: We conducted a retrospective cohort study of hospitalised patients with pneumonia over a 10-year period. We included patients 65 years or older and hospitalised with pneumonia. For our primary analysis, we used propensity score matching to balance confounders between atypical antipsychotic users and nonusers.

Results: There were 102 897 patients and 5977 were taking atypical antipsychotics. After matching there were 5513 users and 5513 nonusers. Atypical antipsychotic use was associated with increased odds of 30-day (OR 1.20, 95% CI 1.11–1.31) and 90-day mortality (1.19, 1.09–1.30).

Conclusion: In patients 65 years or older that are hospitalised with pneumonia, we found an association between atypical antipsychotic use and increased odds of mortality. This was particularly pronounced for patients with pre-existing psychiatric or cardiac conditions. We suggest closely monitoring patients who use these medications and minimising their use in older adult patients.

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When hospitalised with pneumonia, older patients who use atypical antipsychotics should be monitored closely and their use of these drugs should be minimised as much as possible http://bit.ly/2JEevHV

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Introduction

Pneumonia continues to be a leading cause of death in the United States [1, 2]. The vast majority of deaths due to pneumonia occur in patients over 65 years of age. In addition, this condition is responsible for a high financial burden with over US$10 billion spent caring for patients with pneumonia [1].

Antipsychotics are used to treat psychiatric diseases such as psychosis, schizophrenia, and dementia, and are also used for the management of delirium and agitation. There are two categories of antipsychotic medications, typical and atypical antipsychotics. One of the main differences between the two groups is the safety profile. Typical antipsychotics have been shown to increase cardiac events, whereas atypical antipsychotics were designed to reduce that risk [3]. Although there have been studies demonstrating an association between the use of antipsychotics and increased mortality in older adult patients with dementia [4], there have been few studies that examine the association between typical antipsychotic medications and outcomes for patients with pneumonia [3–5]. One study examined the association of atypical antipsychotics with pneumonia and found no significant association with increased mortality [5]. Examining the safety of atypical antipsychotics will help physicians to make informed decisions about the continuation of atypical antipsychotic medications for patients hospitalised with pneumonia, who are at increased risk for cardiac events due to the infection as well as the antibiotics used [6–13].

The primary aim of this study was to examine the association between prior atypical antipsychotic use and 90-day all-cause mortality in patients 65 years and older that were hospitalised with pneumonia using data from the Department of Veterans Affairs (VA) Health Care System. Our *a priori* hypothesis was that being prescribed atypical antipsychotic medications would be associated with an increase in the odds of 90-day mortality in patients hospitalised with pneumonia.

Materials and methods

We conducted a retrospective cohort study using the clinical and administrative databases of the Department of VA Health Care System. These databases are the repositories of clinical data from all of the national VA hospitals and outpatient clinics [14]. This study was approved by the VA North Texas Institutional Review Board.

Inclusion criteria

We included patients who met the following criteria:

a) Hospitalisation between October 1, 2001 and September 30, 2012.
b) 65 years or older on the date of admission.
c) Discharged with a diagnosis of pneumonia defined as either a primary diagnosis of pneumonia (ICD-9 codes 480.0–483.99 or 485.0–487.0) or a secondary diagnosis of pneumonia with a primary diagnosis of respiratory failure (ICD-9 code 518.81) or sepsis (ICD-9 code 0.38xx).
d) Had at least one dose of antimicrobial therapy within the first 48 h of admission.
e) Had at least three or more VA outpatient clinic visits in the year preceding admission.
f) Received at least one outpatient medication from a VA pharmacy within 90 days prior to admission, thereby ensuring that the patients were receiving medications from VA pharmacies.

We excluded those who received typical antipsychotics from further analyses due to these medications' clear associations with increased mortality. For patients who had multiple pneumonia-related hospitalisations during the study period, we included only their first hospitalisation.

Data sources and definitions

Atypical antipsychotics included risperidone, olanzapine, clozapine, quetiapine, ziprasidone, aripiprazole, amisulpride, paliperidone and sertindole [4, 5, 15].

We controlled for race and ethnicity categories (white, black, and Hispanic), tobacco use (ICD-9 codes 305.1 and V15.82, smoking cessation clinic use, and/or use of medications for the treatment of nicotine dependence such as Zyban, nicotine replacement, or varenicline), alcohol abuse (ICD-9 codes 291, 303, 305.0), and illicit drug use (ICD-9 codes 292, 304, 305, excluding 305.0–0.1). We also used the Charlson–Deyo comorbidity system to identify pre-existing comorbid conditions [16], and the VA priority status for socioeconomic status [17]. Psychiatric conditions, including depression, bipolar disorder, post-traumatic brain disorder (PTSD) and schizophrenia, were identified using the method described by Selim *et al.* [18, 19].

Potential confounding medications were controlled for by using a count of unique drugs in each of the following classes for outpatient prescriptions filled within 90-days prior to presentation: antidepressants, lithium, statins, beta blockers, calcium channel blockers, oral antidiabetic agents, lipid-lowering agents, other antihypertensive agents, antiarrhythmic agents, inhaled beta agonists, other bronchodilators and theophylline.

Outcomes

The primary outcomes of this study were all-cause mortality within 30- and 90-days of admission. Death was identified using the VA Vital Status file, which has an 98% accuracy in identifying mortality [20].

Statistical analysis

For the primary analyses, we used propensity score matching to balance measured confounders between groups (atypical antipsychotic users *versus* nonusers). Logistic regression was used to create the propensity score and then nearest-number matching with a calliper of 0.001 with no replacement was performed [21]. We selected candidate variables that we believed would be potentially associated with severity of illness (*e.g.* intensive care unit admission, use of mechanical ventilation), outcomes (*e.g.* age, nursing home residence), or with prescription of antipsychotics (*e.g.* dementia, psychiatric conditions.) Variables included in the propensity score are displayed in table 1. Odds ratios were calculated to determine the association between atypical antipsychotic use and the outcomes using conditional logistic regression.

To analyse the time-to-event for mortality and cardiovascular outcomes by receipt of antipsychotics, we used Kaplan–Meier plots to display the survivor functions and assessed statistical significance using the log rank test.

For secondary analyses, we used generalised linear mixed effect models to examine the association of atypical antipsychotic use on 90-day mortality in the following pre-defined subgroups: dementia, psychiatric conditions (PTSD, schizophrenia, bipolar disorder and depression), pre-existing cardiac conditions (myocardial infarction, heart failure and cardiac arrhythmias), and intensive care unit admission. These models were adjusted for all of the covariates in the propensity score as well as adjusted for the admitting hospital.

Statistical significance was defined as a two-tailed p-value $\leqslant 0.05$. All analyses were performed using STATA 15 (College Station, TX, USA).

Results

There was a total of 102 897 patients who met the inclusion criteria. Overall, the mean age was 77.8 years (SD 7.4), 101 118 (98.3%) were male, 53 252 (51.7%) were married, 83 529 (81.2%) were white, and 6414 (6.3%) were Hispanic. In this cohort, 23 717 (23.1%) died within 90 days.

There were 5977 patients on atypical antipsychotics prior to hospitalisation. These included: 2212 patients on quetiapine, 2205 patients on risperidone, 1375 patients on olanzapine, 361 on aripiprazole, 101 patients on ziprasidone, 46 patients on clozapine and 2 patients on paliperidone. Patients could be on more than one atypical antipsychotic during the exposure period.

Propensity-matched analysis

The propensity-matched group consisted of 11 026 patients: 5513 atypical antipsychotic users and 5513 nonusers. Table 1 shows the balance between key variables after propensity matching. There were no significant differences between groups for any of the key characteristics.

In the propensity-matched cohort, 30-day mortality was 16.5% for atypical antipsychotic users *versus* 14.2% for nonusers (p=0.0001) and 90-day mortality was 26.7% *versus* 23.9% (p=0.001). In the regression analyses, atypical antipsychotic use was associated with increased 30-day mortality (OR1.20, 95% CI1.11–1.31) and 90-day mortality (OR 1.19, 95% CI 1.09–1.30). Figure 1 shows mortality and demonstrates that those who received atypical antipsychotics had significantly higher mortality than nonusers (p<0.001).

Secondary analyses

Table 2 shows the results of the secondary analyses. In the entire cohort, the use of atypical antipsychotics was associated with increased odds of 90-day mortality (OR 1.31, 95% CI 1.22–1.40). For those with pre-existing psychiatric conditions, the use of atypical antipsychotics was associated with increased odds of 90-day mortality (OR 1.21, 95% CI 1.12–1.30). For those with pre-existing cardiac conditions, atypical antipsychotics use was associated with increased odds of 90-day mortality (OR 1.22, 95% CI 1.09–1.36). For those admitted to the intensive care unit and for those with dementia there were no statistically significant associations between atypical antipsychotic use and 90-day mortality.

Discussion

In this study, we found that there was an association between the use of atypical antipsychotics and mortality, after adjusting for potential confounders, in patients with pneumonia. While many patients hospitalised with pneumonia are receiving atypical antipsychotics, there has been a dearth of research data

TABLE 1 Comparison of propensity-matched atypical antipsychotic users and nonusers hospitalised with pneumonia

Variables	Atypical antipsychotics (N=5513)	No atypical antipsychotics (N=5513)	p-value	Standardised difference
Age groups			0.6	0.02
65–74 years	2024 (36.7%)	2011 (36.5%)		
75–84 years	2427 (44.0%)	2382 (43.2%)		
85–94 years	1031 (18.7%)	1085 (19.7%)		
95 years and above	31 (0.6%)	35 (0.6%)		
Men	5404 (98.0%)	5399 (97.9%)	0.7	−0.006
White	4485 (81.4%)	4454 (81.0%)	0.5	−0.01
Black	641 (11.6%)	678 (12.3%)	0.3	0.02
Hispanic	685 (12.4%)	684 (12.4%)	0.9	−0.0005
Nursing home residence	165 (3.0%)	153 (2.8%)	0.5	−0.01
VA priority group			0.4	−0.02
Group 1	1876 (34.0%)	1895 (34.4%)		
Groups 2–6	3303 (60.0%)	3318 (60.2%)		
Groups 7–8	334 (6.0%)	300 (5.4%)		
Primary care visits in the year prior	5.4±5.1	5.4±4.6	0.6	−0.01
Intensive care unit admission	867 (15.7%)	837 (15.2%)	0.4	−0.02
Invasive mechanical ventilation	333 (6.0%)	341 (6.2%)	0.8	0.006
Vasopressors	275 (5.0%)	280 (5.1%)	0.8	0.004
Inpatient guideline concordant antibiotics[#]	4334 (78.6%)	4343 (78.8%)	0.8	0.004
Tobacco use/cessation	2330 (42.3%)	2278 (41.3%)	0.3	−0.02
Alcohol abuse	504 (9.1%)	499 (9.1%)	0.9	−0.003
Illicit drug abuse	219 (4.0%)	203 (3.7%)	0.4	−0.02
Myocardial infarction	375 (6.8%)	395 (7.2%)	0.5	0.01
Heart failure	1221 (22.2%)	1251 (22.7%)	0.5	0.01
Peripheral vascular disease	737 (13.4%)	756 (13.7%)	0.6	0.01
COPD	2567 (46.6%)	2515 (45.6%)	0.3	−0.01
Stroke	1367 (24.8%)	1406 (25.5%)	0.4	0.01
Rheumatologic disease	93 (1.7%)	102 (1.9%)	0.5	0.002
Mild liver disease	47 (0.9%)	40 (0.7%)	0.5	−0.003
Peptic ulcer disease	178 (3.2%)	180 (3.3%)	0.9	0.002
Dementia	1146 (21.0%)	1111 (20.1%)	0.4	−0.01
Diabetes	1827 (33.1%)	1845 (33.5%)	0.7	0.007
Diabetes with complications	554 (10.1%)	572 (10.4%)	0.6	0.01
Moderate liver disease	21 (0.4%)	20 (0.4%)	0.9	−0.01
Renal disease	782 (14.2%)	804 (14.6%)	0.6	−0.009
Any prior malignancy	996 (18.1%)	977 (17.7%)	0.6	−0.009
Metastatic solid tumour	148 (2.7%)	250 (2.7%)	0.9	0.002
Hematologic malignancy	77 (1.4%)	73 (1.3%)	0.7	−0.006
HIV	4 (0.1%)	4 (0.1%)	1.0	0.00
Psychiatric conditions[¶]	1.09±0.98	1.10±1.0	0.33	0.02
Prior outpatient antibiotics	1445 (26.2%)	1458 (26.5%)	0.8	0.005
Antidepressants	3049 (55.3%)	2922 (53.0%)	0.1	−0.04
Lithium	49 (0.9%)	46 (0.8%)	0.8	−0.006
Statins	1935 (35.0%)	1968 (35.5%)	0.4	0.01
ARB	226 (4.1%)	220 (4.0%)	0.99	−0.004
ACE inhibitors	1745 (31.6%)	1768 (32.0%)	0.9	0.009
Antiarrhythmics	133 (2.4%)	137 (2.5%)	0.6	0.006
Β-blockers	1910 (34.6%)	1851 (33.6%)	0.4	−0.02
Calcium channel blockers	1255 (22.8%)	1261 (22.9%)	0.7	0.002
Oral antidiabetics	654 (11.9%)	608 (11.0%)	0.2	−0.02
Other lipid-lowering medications	244 (0.05%)	252 (0.05%)	0.8	0.007
Other antihypertensive medications	1206 (21.9%)	1207 (21.9%)	0.8	−0.002
Inhaled β-agonists	1670 (30.2%)	1603 (29.0%)	0.1	−0.008
Other inhaled medications	1617 (29.3%)	1575 (28.1%)	0.4	−0.0003
Theophylline	93 (1.7%)	89 (1.6%)	0.8	−0.006

Data are presented as mean±SD or n (%) unless otherwise stated. VA: Dept of Veterans Affairs; ARB: angiotensin II receptor blocker; ACE: angiotensin-converting enzyme. [#]: concordant with 2007 American Thoracic Society/Infectious Diseases Society of America clinical practice guideline for community-acquired pneumonia [26]. [¶]: Selim psychiatric conditions.

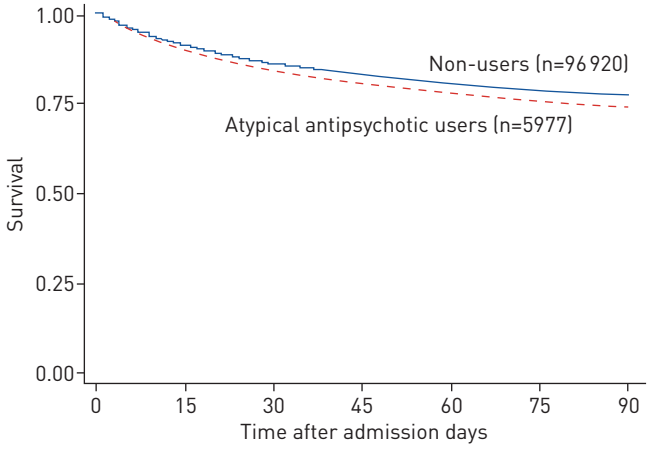

FIGURE 1 Survival curves demonstrating a statistically significant (p=0.001) association with increased mortality in those receiving atypical antipsychotics in the entire cohort.

to inform clinical decision making. In addition, most research to date has focused on the differences in outcomes between typical and atypical psychotics rather than between those who use atypical antipsychotics *versus* nonusers. We believe our results support the need to minimise the use of these medications for older adult hospitalised patients [22].

We hypothesise that the increased odds of mortality seen for those using atypical antipsychotics may be due to an increased QT interval arrhythmia resulting in torsades de pointes. Multiple studies [23–25] have suggested that the mechanism is a torsade de pointes associated with a prolonged QT interval, which can both lead to sudden cardiac death. Glassman *et al.* [24] found different risk levels of sudden cardiac death among antipsychotics, even within the same class (typical or atypical). We suggest that the increased mortality risk seen with atypical antipsychotic patients is the result of arrhythmias caused by a prolonged QT interval.

Other studies found no significant association between the use of atypical antipsychotics and mortality. Barnett *et al.* [5] found no increased mortality risk for patients with pneumonia taking atypical antipsychotics. The study consisted of 14 057 patients hospitalised in the VA system with a primary diagnosis of pneumonia. They found no significant association between atypical antipsychotic use with in-hospital mortality of veterans (OR 1.20, 95% CI 0.96–1.50). We believe that our results differ as they did not control for significant confounding variables such as smoking and socioeconomic status, both of which could have significantly affected their outcomes. In addition, our study examined both in-hospital and outpatient mortality, had a larger population, and a more representative race profile.

Our study has several limitations. We studied the VA population, which may not be representative of the general population. Our sample was predominantly men, and further research is needed to examine these issues in women. Our study was restricted to those ⩾65 years of age as the source dataset was focused on that age group, so additional research is needed for other age groups. Also due to the retrospective study design and inability to examine ECGs obtained during the hospitalisation, we were unable to identify QT prolongation, torsades de pointes, or the outcome of sudden cardiac death, which we believe would be the ideal outcome for this study. That is why we focused on mortality. Unfortunately, we know of no way to adjudicate sudden cardiac death in a valid manner retrospectively. Also, for this analysis we only examined prior outpatient use of atypical antipsychotics; however, we hypothesise that most patients would have these medications continued as inpatients and after discharge. Finally, as in a nonrandomised study, we

TABLE 2 Results of the adjusted multilevel regression models for secondary analyses

Subgroup	Patients	90-day mortality OR (95% CI)
Entire cohort	102 976	1.31 (1.22–1.40)
Dementia	5156	0.96 (0.82–1.12)
Psychiatric conditions[#]	26 006	1.21 (1.12–1.30)
Pre-existing cardiac conditions[¶]	36 379	1.22 (1.09–1.36)
Intensive care unit admission	17 738	0.96 (0.82–1.12)

[#]: post-traumatic stress disorder, schizophrenia, bipolar disorder and depression; [¶]: myocardial infarction, heart failure and cardiac arrhythmias.

cannot assert causality between the exposure and outcome; however, we believe that our findings still have importance for those who care for patients with pneumonia.

In conclusion, in older adult veterans admitted with pneumonia we found an association between prior atypical antipsychotic use and mortality. This was particularly pronounced for patients with pre-existing psychiatric or cardiac conditions. We believe that physicians should be aware of this association and should use this to make informed decisions when using this family of drugs in adults over 65 years old. Further studies should be performed to better characterise the associations we have presented.

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Conflict of interest: None declared.

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