Association of Antipsychotic Use With Mortality Risk in Patients With Parkinson Disease

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Abstract

IMPORTANCE—As many as 60% of patients with Parkinson disease (PD) experience psychosis, 80% develop dementia, and the use of antipsychotics (APs) in the population with PD is common. The use of APs by patients with dementia in the general population is associated with increased mortality, but whether this risk extends to patients with PD remains unknown.

OBJECTIVE—To determine whether AP use in patients with PD is associated with increased mortality.

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DESIGN, SETTING, AND PARTICIPANTS—This retrospective matched-cohort study used data from a Veterans Health Administration database from fiscal years 1999 to 2010 to examine the risk associated with AP use in a cohort of patients with idiopathic PD and recent stable physical health. The rates of 180-day mortality were compared in 7877 patients initiating AP therapy and 7877 patients who did not initiate AP therapy (matched for age ±2.5 years, sex, race, index year, presence and duration of dementia, PD duration, delirium, hospitalization, Charlson Comorbidity Index, and new nonpsychiatric medications). Data were analyzed from October 19, 2012, to September 21, 2015.

MAIN OUTCOMES AND MEASURES—Mortality rates at 180 days in those patients who initiated AP therapy compared with matched patients who did not use APs. Cox proportional hazards regression models were used with intent-to-treat (ITT) and exposure-only analyses.

RESULTS—The study population included 7877 matched pairs of patients with PD (65 women [0.8%] and 7812 men [99.2%] in each cohort; mean [SD] age, 76.3 [7.7] years for those who initiated AP therapy and 76.4 [7.6] years for those who did not). Antipsychotic use was associated with more than twice the hazard ratio (HR) of death compared with nonuse (ITT HR, 2.35; 95% CI, 2.08–2.66; *P* < .001). The HR was significantly higher for patients who used typical vs atypical APs (ITT HR, 1.54; 95% CI, 1.24–1.91; *P* < .001). Among the atypical APs used, HRs relative to nonuse of APs in descending order were 2.79 (95% CI, 1.97–3.96) for olanzapine, 2.46 (95% CI, 1.94–3.12) for risperidone, and 2.16 (95% CI, 1.88–2.48) for quetiapine fumarate.

CONCLUSIONS AND RELEVANCE—Use of APs is associated with a significantly increased mortality risk in patients with PD, after adjusting for measurable confounders. This finding highlights the need for cautious use of APs in patients with PD. Future studies should examine the role of nonpharmacologic strategies in managing psychosis in PD. In addition, new pharmacologic treatments that do not increase mortality in patients with neurodegenerative diseases need to be developed.

A range of nonmotor symptoms, including psychosis and dementia, are common in Parkinson disease (PD).[1] Psychosis occurs in as many as 60%[2,3] and dementia in as many as 80% of patients with long-term PD.[4,5] Further, dementia is a known correlate of psychosis in PD.[6]

Use of antipsychotics (APs) in PD is common. One study reported that approximately one-third of patients with newly diagnosed PD were prescribed an AP within 7 years,[7] and another reported a 6-year cumulative probability of initiating AP treatment at 50%.[8] In an examination of approximately 2600 patients with PD and psychosis (using Veterans Affairs [VA] data from fiscal year 2008),[9] 50% were prescribed an AP during a 1-year period, with dementia significantly associated with increased AP use.

In 2005, the US Food and Drug Administration issued a public health advisory that the treatment of behavioral disorders in elderly patients with dementia with atypical AP medications is associated with increased mortality.[10] A similar US Food and Drug Administration alert for typical APs followed in 2008,[11] with evidence that typical (or conventional) APs may be more harmful than atypical APs for morbidity[12] and mortality.[13] Since then, Kales et al[14] have demonstrated a differential risk among AP classes and specific APs.

Specific features of PD (eg, rigidity, gait and balance impairment, orthostatic hypotension, dysphagia, and autonomic system cardiac changes) may place these patients at even higher risk of morbidity and mortality than patients with general dementia. For example, patients with PD are already at a nearly 3-fold increased risk for hip fracture owing to gait and balance impairment.[15]

Little research has examined the risks associated with AP use in PD. A study using Medicaid data[16] found that the use of quetiapine fumarate, risperidone, or olanzapine was associated with a higher rate of fracture in patients with a diagnosis of parkinsonism. Another study using Canadian health care administrative data[17] compared deceased with matched living patients with PD; the investigators found that individuals exposed to APs had higher odds of death and that typical APs were associated with an increased odds of death compared with atypical APs. However, the investigators could not control for confounding by indication, and only 242 AP-treated patients with PD were included.

Using methods similar to what Kales et al[14,18] used to document the increased risk for mortality associated with AP use in patients with general dementia, we used national VA health system administrative data to examine 180-day mortality risks associated with AP use in a large cohort of patients with PD. We compared patients who initiated AP treatment (exposed) with those who did not (unexposed) while controlling for a wide array of potential confounding factors. We hypothesized that AP-exposed patients with PD would have increased mortality compared with matched non–AP-exposed patients with PD.

Methods

Study Design

This retrospective, matched-cohort study used VA data from fiscal years 1999–2010. For every unique patient with PD who filled a new AP prescription, we randomly selected 1 individual from the risk set with replacement of matched non–AP-exposed patients. Matching (as outlined below) was performed to identify the day the exposed patient with PD filled the AP prescription as a phantom start date for the non–AP-exposed patients with PD so that the observation periods were matched by calendar time and comparisons would be unaffected by secular trends and other selection biases. We only included the first new AP prescription for each unique patient, which was defined as no AP exposure in the prior 6 months, which was a matching factor. We used National Death Index data[19] to assess mortality. Typical APs included haloperidol, chlorpromazine hydrochloride, fluphenazine, loxapine, mesoridazine besylate, molindone hydrochloride, perphenazine, thioridazine hydrochloride, thiothixene hydrochloride, and trifluoperazine hydrochloride; atypical APs included olanzapine, quetiapine, risperidone, aripiprazole, clozapine, and ziprasidone. This study was approved by the VA Central institutional review board, which waived the need for informed consent.

Participants

As in the VA research study of patients with PD, psychosis, and dementia by Weintraub et al,[9] patients with idiopathic PD were identified using code 332.0 from the *International*

Classification of Diseases, Ninth Revision, Clinical Modification (*ICD-9-CM*). Psychosis diagnoses included *ICD-9-CM* codes 293.81, 293.82, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298.0, 298.1, 298.2, 298.3, 298.4, 298.8, 298.9, 368.16, and 780.1; patients with schizophrenia and bipolar disorder were excluded. Because patients with PD constituted the population of interest, patients with a diagnosis of dementia with Lewy bodies *ICD-9-CM* code 331.82) were excluded. A patient was counted as having PD with dementia and included in the study if the dementia diagnosis followed the PD diagnosis by at least 1 year, to match the exclusion criteria for dementia with Lewy bodies.[20] Dementia diagnoses included *ICD-9-CM* codes 290.0, 290.1, 290.11, 290.12, 290.13, 290.2, 290.21, 290.3, 290.4, 290.41, 290.42, 290.43, 291.2, 294.1, 294.11, 331.0, 331.1, 331.11, 331.19, and 331.2.

Inclusion and Exclusion Criteria, Matching Variables, and Covariates

Inclusion and Exclusion Criteria—Patients with an *ICD-9-CM* diagnosis of idiopathic PD were included. We excluded patients with (1) a diagnosis of dementia with Lewy bodies; (2) a dementia diagnosis preceding or within 1 year of the PD diagnosis; (3) a hospitalization or an emergency department visit within 14 days of the index new AP prescription (to ensure medical stability); (4) AP exposure in the preceding 180 days; (5) initiation of AP therapy before the PD diagnosis; (6) younger than 50 years at initiation of AP therapy; (7) more than 1 type of AP included on the same fill date; (8) a diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, or Huntington disease; and (9) an AP index prescription that occurred during a nursing home or inpatient stay. For every unique patient with PD who filled a new AP prescription, the AP fill date was defined as the index date, and we constructed a risk set of matched patients not treated with APs on the index date.

Matching Variables and Covariates—We matched patients by (1) age (±2.5 years); (2) sex; (3) race (white, black, other, and unknown); (4) index year; (5) comorbid dementia diagnosis within the year before the index date; (6) time from PD diagnosis to index date (±180 days); (7) delirium diagnosis within the year before the index date; (8) hospitalization in the prior year; (9) 3-category Charlson Comorbidity Index[21] based on prior 1-year data (0, 1, or >1, where >1 could be >1 condition or a single condition with weighted score >1; the following conditions were weighted [weight]: hepatic failure [3], diabetes mellitus with complications [2], hemiplegia [2], chronic renal disease [2], malignant neoplasm [2], leukemia [2], lymphomas [2], metastatic solid tumor [6], human immunodeficiency virus without AIDS [2], and AIDS [6]); and (10) prescription of new nonpsychiatric medications within 14 days before and including the index date, to help ensure medical stability. For patients with comorbid dementia, an additional matching variable was time from dementia diagnosis to index date (±180 days), because longer duration of dementia is associated with mortality. For patients without comorbid dementia, additional matching variables were comorbid post-traumatic stress disorder and substance abuse diagnoses due to between-group differences in the distribution of these variables for patients without dementia.

Covariates included (1) marital status; (2) use of any new psychiatric medications within 14 days before the index date; (3) number of psychiatric and nonpsychiatric outpatient visits

within 180 days before the index date; (4) medication use within the previous 1 year (separately for antidepressants, opioids, benzodiazepines, and cholinesterase inhibitors); (5) psychiatric diagnoses (separately for depression, other psychoses, alcohol abuse, other drug abuse, posttraumatic stress disorder, personality disorders, and other anxiety disorders); (6) number of days in the hospital in the year before the index date; (7) number of days in a nursing home in the year before the index date; (8) having an outpatient visit with a neurologist for PD within the year before the index date; (9) individual diseases from the Charlson Comorbidity Index[21] (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, rheumatologic disease, peptic ulcer disease, cirrhosis, hepatic failure, diabetes mellitus with and without complications, hemiplegia, chronic renal disease, malignant neoplasm, leukemia, lymphomas, metastatic solid tumor, and human immunodeficiency virus with and without AIDS); (10) academic affiliation of the facility; (11) urban vs rural facility; and (12) size of the facility. In subanalyses that include only those patients with AP exposure, matching variables were also entered as covariates.

Statistical Analysis

Data were analyzed from October 19, 2012, to September 21, 2015. We used intention-to-treat (ITT) analysis and exposure-only analysis approaches to measure the exposure period. For the ITT analysis, exposure period for the initial exposure status continued until 180 days after the index date (or the phantom fill date for unexposed participants) or death, whichever occurred first, regardless of any changes in exposure status (ie, stopping or switching AP treatments for the AP-exposed group or starting an AP treatment for the non–AP-exposed group). In the exposure-only analysis, the exposure period continued until the end of 180 days or to the time of switch, stop, or death, whichever occurred first.

Time to death since the index date was used to compare mortality risks during the 180-day period by baseline AP treatment status (exposed vs nonexposed), across baseline AP classes, and across different APs. Cox proportional hazards regression models stratified by the matched pairs using the robust sandwich estimate of Lin and Wei[22] were used to adjust for covariates and to obtain adjusted hazard ratios (HRs). Comparisons across the different APs used only those patients exposed to an AP on the index date. Covariate-adjusted survival function for an average patient in the cohort by baseline AP exposure group was generated based on the predicted survival functions from the Cox proportional hazards regression without accounting for matching.

Results

Characteristics of Study Cohort

The demographic characteristics of the 7877 matched pairs (65 women [0.8%] and 7812 men [99.2%] in each cohort; mean [SD] age, 76.3 [7.7] years for those who initiated AP therapy and 76.4 [7.6] years for those who did not) are given in eTable 1 in the Supplement. A total of 905 AP-exposed patients were not included in the matched analyses because a matched non–AP-exposed participant could not be found. For the analyses comparing mortality rates in patients with typical vs atypical AP exposure, we included 8782 AP-

exposed patients with or without a matched unexposed participant. Despite matching, AP-exposed and non–AP-exposed patients differed in a number of characteristics measuring mental health, including psychoses other than bipolar disorder or schizophrenia, alcohol abuse, other drug abuse, other anxiety disorders, personality disorders, and use of other psychiatric medications, so these variables were included as covariates in the models.

AP Classes and Specific Medications Prescribed

Among the 7877 AP-exposed patients, 422 (5.4%) were prescribed a typical (or conventional/traditional) AP, with haloperidol (282 [3.6%] of all AP prescriptions) being the most commonly prescribed typical AP. For atypical APs, the most commonly prescribed medication was quetiapine (5270 [66.9%]), followed by risperidone (1155 [14.7%]), olanzapine (837 [10.6%]), and other atypical APs (193 [2.5%]).

Unadjusted Mortality Rates by AP Class and Specific Medication

For AP-exposed patients, the unadjusted mortality rates (per 100 person-years) in the ITT analysis were highest for haloperidol, followed by other typical APs, risperidone, olanzapine, and quetiapine. In the exposure-only analysis, the rates were highest for haloperidol, followed by risperidone, other typical APs, olanzapine, and quetiapine (Table 1).

Mortality Rates in AP-Exposed vs Non–AP-Exposed Groups

After we adjusted for covariates, AP-exposed patients had greater than 2-fold higher hazards for mortality in the 180-day period after AP exposure in the ITT and exposure-only analyses compared with nonexposed patients (Table 2). This finding applied to patients exposed to typical and atypical APs, with an HR in the ITT analysis of 2.26 (95% CI, 1.98–2.57) in atypical AP-exposed vs non–AP-exposed patients and an HR in the exposure-only analysis of 3.65 (95% CI, 2.47–5.39) in typical AP-exposed vs non–AP-exposed patients. Survival probability graphs are presented for ITT analyses in the Figure and for exposure-only analyses in the eFigure in the Supplement. The HR was significantly higher for patients who used typical vs atypical APs (ITT HR, 1.54; CI, 1.24–1.91; $P < .001$).

Because patients at imminent risk for mortality might be prescribed an AP as part of palliative care, we ran additional analyses excluding those patients who died within 4 weeks of the index date (eTable 2 in the Supplement). Excluding those patients who died within 4 weeks of the index date, the elevated mortality HR associated with AP exposure vs no exposure (HR, 2.30; 95% CI, 2.01–2.64), for typical AP exposure vs no exposure (HR, 3.98; 95% CI, 2.50–6.34), and atypical AP exposure vs no exposure (HR, 2.20; 95% CI, 1.90–2.55) were similar to the HRs presented for the entire cohort.

Mortality Risk by Specific AP

Increased mortality risk (compared with non–AP-exposed patients) was seen, in descending order, with use of haloperidol, olanzapine, risperidone, and quetiapine (Table 3). These results were seen for the ITT and exposure-only analyses. When we ran similar additional analyses excluding those patients who died within 4 weeks of the index data, an elevated HR

associated with AP exposure remained for haloperidol, olanzapine, risperidone, and quetiapine specifically (eTable 3 in the Supplement).

Relative AP-Related Mortality Risks

In a subanalysis that included AP-exposed patients only and that used quetiapine exposure as a referent group (because quetiapine is the most commonly prescribed AP in patients with PD), increased mortality risks relative to quetiapine were seen (in descending order) for haloperidol, other typical APs, olanzapine, and risperidone (Table 4).

Causes of Death

The leading causes of death in AP-exposed and non–AP-exposed patients (all causes of death in the ITT population) are given in eTable 4 in the Supplement. The leading cause of death in AP-exposed patients was PD (listed in 443 of 832 [53.2%] as a cause of death), 38% higher compared in non–AP-exposed patients (165 of 427 [38.6%]). The other causes of death that were listed in more than 10% of AP-exposed patients and more common in this group vs non–AP-exposed patients were influenza or pneumonia (127 of 832 [15.3%] vs 57 of 427 [13.3%]) and pneumonitis (85 of 832 [10.2%] vs 29 of 427 [6.8%]).

Discussion

Use of APs in patients with dementia is associated with an increased risk for morbidity and mortality,[10,12,13] with differential risk among AP classes and specific APs.[12,14] Our results extend this increased mortality risk to patients with PD and confirm preliminary research.[17] We found a differential risk for typical vs atypical APs and among the atypical APs. Of particular note, the increased risk is not specific to dementia in this case because less than 10% of the patients studied herein were diagnosed as having dementia.

Some differences between patients with general dementia and PD preclude generalization. First, patients with PD have disease-related risk symptoms that may predispose them to or overlap with AP-associated adverse events (eg, falls, sedation, orthostatic hypotension, and parkinsonism). Second, the APs studied in dementia clinical trials (risperidone and olanzapine) are different than the most commonly used AP in patients with PD (quetiapine). Third, some general dementia studies have enrolled patients with broadly defined agitation or psychosis, whereas AP studies in PD have enrolled patients with psychosis specifically. Finally, psychosis in PD has a higher overall prevalence rate and presents differently than in general dementia; psychosis in patients with PD is associated with dopamine replacement therapy and is characterized by higher rates of hallucinations and less frequent delusions.[2,23]

The HR for mortality associated with any AP exposure was 2.35 (95% CI, 2.08–2.66), indicating a 6-month mortality rate 135% higher in AP-exposed patients compared with non–AP-exposed patients. Patients treated with atypical AP had an HR 62% higher than patients treated with an atypical AP. Given that two-thirds of typical AP exposure in this cohort was for haloperidol, this finding may suggest that APs that are potent dopamine receptor antagonists or have a high ratio of dopamine to serotonin receptor blocking[24] pose the greatest risk to patients with PD.

Approximately 30% of treated patients were prescribed a high-potency AP (eg, risperidone, olanzapine, or haloperidol). These APs are most likely to worsen parkinsonism and potentially to increase mortality risks in patients with PD. Consistently, mortality rates were higher for haloperidol, risperidone, and olanzapine compared with lower-potency quetiapine.

Approximately 70% of APs prescribed in PD were quetiapine.[9] Because no placebo-controlled studies demonstrate quetiapine's efficacy for PD psychosis,[25] clinicians often make it the first-line AP in PD based on clinical impressions of effectiveness, good tolerability compared with other APs, and complexities associated with use of the single AP approved by the US Food and Drug Administration that is efficacious for this condition (ie, clozapine). The concept of relatively good tolerability is supported by the finding that quetiapine had a lower mortality rate compared with all other commonly used APs, similar to what has been reported in patients with general dementia.[26]

We aimed to discern how AP exposure increases mortality in patients with PD. The most common cause of death in AP-exposed patients and the second most common cause of death in non–AP-exposed patients was PD, a nonspecific diagnosis in terms of determining the direct cause of death. However, patients treated with an AP were 38% more likely to have PD listed as their cause of death, and one possible explanation is that AP exposure was associated with worsening parkinsonism that led to serious adverse events subsumed under a diagnosis of PD.

Strengths of the research include our experience with analyzing VA pharmacoepidemiologic data, the exposure-matched design, the large sample size, and careful attention to inclusion and exclusion criteria and covariates. Limitations include our inability to verify the accuracy of medical record diagnoses (eg, not having a PD diagnosis made by a movement disorders neurologist, although a secondary analysis restricting the analyses to patients seen by a neurologist in the year before the index date yielded a similar result (HR, 2.61; 95% CI, 1.67–4.09; P < .001) and possible confounding by indication despite the inclusion and exclusion criteria, extensive matching, and inclusion of covariates (ie, patients prescribed an AP may have had more severe PD that predisposed to mortality, and we were unable to examine directly the severity of disease with this data set). As an additional measure to account for this latter possibility, additional analyses that excluded those patients who died within 4 weeks of initiation of AP treatment still showed a similar, elevated mortality HR associated with AP exposure in 180 days.

Future research should examine whether AP exposure is also associated with excess morbidity, compare risks in patients with PD vs Alzheimer disease and dementia with Lewy bodies, and determine whether clinical and demographic moderators of mortality exist. The latter analyses will help to inform clinical care as clinicians weigh the potential benefits and risks associated with AP prescribing to patients with PD. As new APs are introduced for PD psychosis, such as pimavanserin,[27] whether they have a different mortality and morbidity risk profile needs to be determined. If newer APs with significantly different mechanisms of action are not similarly associated with increased mortality, this finding would more strongly implicate existing APs as associated with the observed increased mortality.

Conclusions

Given the more than 2-fold increased mortality risk during 6 months of AP exposure and limited evidence of their efficacy, APs need to be used cautiously in patients with PD. Evaluation for treatable comorbid medical conditions should be performed, and attempts to decrease use of PD medications that may contribute to psychosis should be considered.[28] Off-label use of APs (eg, for insomnia) should be discouraged. Prescribing typical APs to patients with PD should be avoided. Research efforts are needed to develop APs that are efficacious but do not increase mortality risk in vulnerable patients, to test cognition-enhancing medications for AP properties (eg, cholinesterase inhibitors[29,30]), and to evaluate structured nonpharmacologic approaches to manage psychosis as has been done for behavioral symptoms in Alzheimer disease.[31–33] Given that the incidence of PD is increasing worldwide and that psychosis is very common[2] and distressing to patients and caregivers,[34] the development of informed and improved treatment strategies for this condition remains a priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Key Points

Question

Is an increased mortality risk associated with antipsychotic (AP) use in Parkinson disease (PD)?

Findings

In this retrospective cohort study of 7877 matched pairs of veterans with PD, AP use was associated with more than twice the hazard of death compared with nonuse. The hazard ratio was significantly higher for typical compared with atypical AP use.

Meaning

Because AP use is associated with significantly increased mortality risk in patients with PD, this medication class needs to be used cautiously in this population.
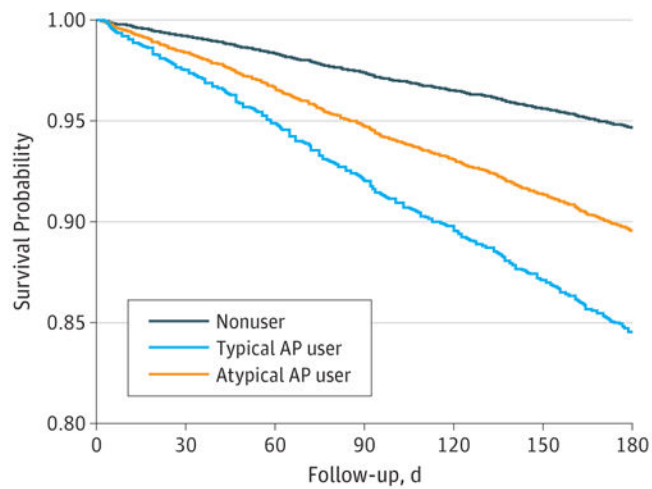
Figure. Mortality Rates in Antipsychotic (AP)-Exposed vs Non–AP-Exposed Patients
Covariate-adjusted 180-day survival estimates by baseline AP treatment status (intention-to-treat analysis) are shown. Graph is based on Cox proportional hazards regression modeling without pairing.

Table 1

Unadjusted Mortality Rates by AP Exposure

Antipsychotic	No. Patients Died/Total (%)	Total Person-years	Mortality Rate per 100 Person-years (95% CI)
Intention-to-treat analysis			
Haloperidol	60/282 (21.3)	122.5	49.0 (37.4–63.0)
Other typical AP	20/140 (14.3)	64.0	31.3 (19.1–48.3)
Olanzapine	113/837 (13.5)	386.3	29.3 (24.1–35.2)
Quetiapine fumarate	462/5270 (8.8)	2488.8	18.6 (16.9–20.3)
Risperidone	164/1155 (14.2)	529.5	31.0 (26.4–36.1)
Other atypical AP	13/193 (6.7)	91.3	14.2 (7.6–24.3)
Exposure-only analysis			
Haloperidol	35/282 (12.4)	68.7	50.9 (35.5–70.9)
Other typical AP	8/140 (5.7)	32.5	24.6 (10.6–48.5)
Olanzapine	54/837 (6.5)	240.1	22.5 (16.9–29.3)
Quetiapine	268/5270 (5.1)	1754.2	15.3 (13.5–17.2)
Risperidone	96/1155 (8.3)	340.8	28.2 (22.8–34.4)
Other atypical AP	7/193 (3.6)	59.1	11.8 (4.8–24.4)

Abbreviation: AP, antipsychotic.

Table 2

Adjusted HRs for 180-Day Mortality in AP-Exposed vs Non–AP-Exposed Patients

Group	HR (95% CI)	*P* Value[a]
Intention-to-treat analysis		
No AP exposure	1 [Reference]	NA
AP exposure	2.35 (2.08–2.66)	<.001
AP exposure by type		
No AP exposure	1 [Reference]	NA
Atypical AP exposure	2.26 (1.98–2.57)	<.001
Typical AP exposure	3.65 (2.47–5.39)	<.001
Exposure-only analysis		
No AP exposure	1 [Reference]	NA
AP use	2.15 (1.82–2.55)	<.001
AP exposure by type		
No AP exposure	1 [Reference]	NA
Atypical AP exposure	2.09 (1.75–2.49)	<.001
Typical AP exposure	3.11 (1.72–5.60)	<.001

Abbreviations: AP, antipsychotic; HR, hazard ratio; NA, not applicable.

[a]Obtained from testing for the significance of the covariate estimates obtained from the corresponding Cox proportional hazards regression model.

Table 3

Adjusted HRs for 180-Day Mortality by AP

Group	HR (95% CI)	P Value[a]
Intention-to-treat analysis		
No AP exposure	1 [Reference]	NA
Haloperidol	5.08 (3.16–8.16)	<.001
Other typical AP	1.82 (0.94–3.50)	.07
Olanzapine	2.79 (1.97–3.96)	<.001
Quetiapine fumarate	2.16 (1.88–2.48)	<.001
Risperidone	2.46 (1.94–3.12)	<.001
Other atypical AP	1.19 (0.60–2.37)	.62
Exposure-only analysis		
No AP exposure	1 [Reference]	NA
Haloperidol	4.80 (2.41–9.57)	<.001
Other typical AP	0.82 (0.35–1.88)	.63
Olanzapine	2.76 (1.58–4.84)	<.001
Quetiapine	1.93 (1.59–2.33)	<.001
Risperidone	2.62 (1.83–3.76)	<.001
Other atypical AP	1.14 (0.41–3.18)	.80

Abbreviations: AP, antipsychotic; HR, hazard ratio; NA, not applicable.

[a]Obtained from testing for the significance of the covariate estimates obtained from the corresponding Cox proportional hazards regression model.

Table 4

Individual AP Risks Relative to Quetiapine in AP-Exposed Patients

Group	HR (95% CI)	P Value[a]
Intention-to-treat analysis		
Quetiapine fumarate	1 [Reference]	NA
Haloperidol	1.85 (1.41–2.43)	<.001
Other typical AP	1.54 (1.01–2.36)	.047
Olanzapine	1.47 (1.20–1.79)	<.001
Risperidone	1.30 (1.08–1.56)	.006
Other atypical AP	1.23 (0.69–2.19)	.49
Exposure-only analysis		
Quetiapine	1 [Reference]	NA
Haloperidol	2.33 (1.62–3.36)	<.001
Other typical AP	1.39 (0.70–2.79)	.35
Olanzapine	1.36 (1.01–1.83)	.04
Risperidone	1.42 (1.11–1.82)	.005
Other atypical AP	1.30 (0.58–2.89)	.52

Abbreviations: AP, antipsychotic; HR, hazard ratio; NA, not applicable.

[a]Obtained from testing for the significance of the covariate estimates obtained from the corresponding Cox proportional hazards regression model.