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Antipsychotics and the Risk of Mortality or Cardiopulmonary Arrest in Hospitalized Adults

Matthew Basciotta, MD[1,2,3], **Wenxiao Zhou, MSc**[1], **Long Ngo, PhD**[1,4], **Michael Donnino, MD**[4,5], **Edward R. Marcantonio, MD, MSc**[1,4], **Shoshana J. Herzig, MD, MPH**[1,4]

[1]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

[2]Department of Hospital Medicine, North Shore Medical Center, Salem, MA

[3]Tufts University School of Medicine, Boston, MA

[4]Harvard Medical School, Boston, MA

[5]Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA

Abstract

Background/Objectives: Prior studies in outpatient and long-term care settings have demonstrated increased risk for sudden death with typical and atypical antipsychotics. To date, there are no studies investigating this association in a general hospitalized population.

We sought to evaluate the risk of death or non-fatal cardiopulmonary arrest in hospitalized adults exposed to antipsychotics.

Design: Retrospective cohort study.

Setting: Large academic medical center in Boston, Massachusetts.

Participants: All hospitalizations between 2010-2016 were eligible for inclusion. We excluded those admitted directly to the Intensive Care Unit, Obstetric and Gynecologic or Psychiatric services, or with a diagnosis of a psychotic disorder.

Corresponding author info: Matthew Basciotta, Department of Hospital Medicine, North Shore Medical Center, Salem, MA, 100 Heard St Unit 313, Chelsea, MA 02150, Matt.Basciotta@gmail.com, Twitter handles: @MattBasciotta@ShaniHerzig.

Author's Contributions:

All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. No additional persons besides those listed as authors have made any substantial contribution to the work.

Individual author contributions:

Study concept and design: Basciotta, Zhou, Ngo, Donnino, Marcantonio, Herzig.

Acquisition of data: Basciotta, Donnino, Herzig.

Analysis and interpretation of data: Basciotta, Zhou, Ngo, Donnino, Marcantonio, Herzig.

Drafting of the manuscript: Basciotta, Herzig.

Critical revision of the manuscript for important intellectual content: Basciotta, Zhou, Ngo, Donnino, Marcantonio, Herzig.

Statistical Analysis: Zhou, Ngo.

Study Supervision: Herzig.

Conflict of Interest:

To the best of our knowledge, no conflict of interest, financial, personal or otherwise, exists.

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Exposures: Typical and Atypical antipsychotic administration, defined by pharmacy charges.

Measurements: The primary outcome was death or non-fatal cardiopulmonary arrest during hospitalization (composite).

Results: Of 150,948 hospitalizations in our cohort, there were 691 total events (515 deaths, 176 cardiopulmonary arrests). After controlling for comorbidities, ICU time, demographics, admission type and other medication exposures, typical antipsychotics were associated with the primary outcome (hazard ratio [HR] = 1.6, 95% confidence interval [CI] 1.1-2.4, p = 0.02), while atypical antipsychotics were not (HR = 1.1, 95% CI 0.8-1.4, p = 0.5). When focusing on adults age 65 and older, however, both typical and atypical antipsychotics were associated with increased risk of death or cardiopulmonary arrest (HR 1.8, 95% CI 1.1-2.9, and HR 1.4, 95% CI 1.1-2.0, respectively). Sensitivity analyses using a propensity score approach and a cohort of only patients with delirium both yielded similar results.

Conclusion: In hospitalized adults, typical antipsychotics were associated with increased mortality or cardiopulmonary arrest, while atypical antipsychotics were only associated with increased risk among adults age 65 and older. Providers should be thoughtful when prescribing antipsychotic medications, especially to older adults in settings where data regarding benefit are lacking.

Keywords

Antipsychotics; Mortality; Pharmacopeidemiology

Introduction

Prior studies in varied outpatient settings have demonstrated that typical antipsychotics are associated with sudden death[1,2,3]. This association is thought to be mediated by increased risk of QT prolongation and polymorphic ventricular tachycardia[1]. More recently, studies have identified risks associated with atypical antipsychotics as well, including falls[4], pneumonia[5,6], and death[2]. A large retrospective study in a cohort of outpatients identified a dose-dependent increase in sudden cardiac death with both typical and atypical antipsychotics[2]. In patients hospitalized with acute myocardial infarction (MI), another study demonstrated that typical antipsychotic use was associated with increased mortality when compared to atypical antipsychotics[3].

Despite these known risks, atypical antipsychotics are frequently used in hospitalized patients. One recent retrospective analysis of patients at our medical center found that antipsychotics were prescribed in 9% of all non-psychiatric adult hospitalizations[7]. Often these medications are used in the prevention or treatment of delirium[7], despite lack of evidence of efficacy for these indications. While individual RCTs have had conflicting results, a large recent meta-analysis found that antipsychotic use for prevention or treatment of delirium was not associated with lower mortality, less-severe or shorter duration of delirium, shorter intensive care unit (ICU) time, or hospital length of stay[8]. When compared against placebo in a randomized controlled trial for the treatment of delirium in the palliative care setting, patients receiving antipsychotics actually had significantly worse delirium

severity scores[9]. In another randomized controlled trial in ICU patients, neither typical nor atypical antipsychotics reduced the duration of delirium[10].

From a physician perspective, the treatment of delirium is difficult. It is a common condition, occurring in 15 to 26 percent of hospitalized older adults[11-13], with limited existing evidence-based treatments once it develops, other than trying to correct the underlying medical problem. Patients with hyperactive delirium are often a risk to themselves or providers by interfering with medical care or directly harming themselves or others. Besides behavioral interventions and physical restraints, antipsychotics represent one of the few therapeutic alternatives in this scenario.

Despite widespread use, to date there are no existing studies examining whether antipsychotic use increases mortality risk among inpatients, outside of the context of acute MI[5]. Such evidence might tip the balance on the risk-benefit scale physicians consider when prescribing these medications. Additionally, better understanding the danger posed by these medications when not carefully prescribed could mobilize resources towards alternative methods of delirium prevention and/or management. Using a cohort of admissions to a large, academic medical center, we sought to investigate our hypothesis that exposure to antipsychotics during hospitalization is associated with increased risk of death or cardiopulmonary arrest.

Methods

This study included data from hospitalized patients at a single large academic medical center in Boston, Massachusetts. Data were collected from electronic medical information databases maintained at the medical center and supplemented by chart review where noted. These electronic databases, collected prospectively for clinical and administrative purposes, contain patient-specific information related to each admission during the study time period, including demographics, pharmacy charge records, and discharge diagnoses.

All adult admissions (aged ≥ 18 years old) from 2010-2016 were eligible for inclusion. We excluded hospitalizations of patients admitted to the ICU within the first 24 hours to achieve more homogeneous comparison groups with respect to initial severity of illness. We excluded admissions to the OB/GYN service since these are generally young and healthy patients not representative of the general hospitalized patient. We also excluded admissions to the Psychiatry service and admissions with a diagnosis of a psychotic disorder since we wanted to avoid patients who were taking antipsychotics long term for FDA-approved indications. Finally, we excluded hospitalizations with receipt of comfort-focused care since antipsychotics are often used in this setting for palliation, which could result in a spurious association with mortality. This was achieved by excluding hospitalizations with a palliative care consult, a “comfort measures only” order, or where patients received comfort care medications (concentrated oral morphine, scopalamine or glycopyrrolate). We reviewed the charts of all hospitalizations with an outcome event and antipsychotic exposure to ensure patients receiving antipsychotics as part of comfort focused care were excluded.

Antipsychotic Exposure

In-hospital antipsychotic use was ascertained from pharmacy charges, reflecting each medication dispensed during the hospitalization. We categorized antipsychotic medications as typical and atypical based on classification by the Food and Drug Administration[14-15]. We excluded prochlorperazine (Compazine) from our typical antipsychotic definition, as this medication is almost exclusively used as an anti-emetic.

Outcomes

Our primary outcome was death or non-fatal cardiopulmonary arrest during hospitalization (composite). A composite outcome was chosen to capture cardiopulmonary arrests that do not result in death. Cardiopulmonary arrest events were identified using a prospectively collected registry of “code blue” events at BIDMC over the study period. Code blue events at our institution can represent different scenarios including cardiopulmonary arrest, respiratory arrest, first aid or “other”. Only code blue events characterized as cardiopulmonary arrest were included as outcome events in our analysis. We reviewed the charts of all hospitalizations with death or cardiopulmonary arrest in the group with antipsychotic exposure to ensure the correct temporal relationship between exposure and outcome, and to exclude any patients receiving comfort focused care. Hospitalizations were censored at discharge or at hospitalization day 50 (impacted <1% of all hospitalizations).

Covariates

We included variables thought to represent potential confounders of the association between antipsychotic administration and death or cardiopulmonary arrest, selected a priori based on clinical grounds. These included: 1) demographics: age, gender and race (white, black, other); 2) admission characteristic variables, including admitting department (medicine versus non-medicine), and time spent in ICU; 3) potential indications for use, including delirium (included delirium superimposed upon dementia), dementia (without delirium), and insomnia; 4) comorbidities, identified via *ICD-9-CM* and *ICD-10-CM* secondary diagnosis codes and Diagnosis Related Groups using Healthcare Cost and Utilization Project Comorbidity Software based on the work of Elixhauser et al.;[16-18] and 5) other medication exposures (benzodiazepines, opioids, acid-suppressive medications).

Statistical Analysis

We considered a patient exposed for 7 days after a charge for a given medication. For example, if antipsychotic exposure occurred on hospital day 2, they were considered exposed through hospital day 8. This period was chosen due to the long half-life of some of these medications and to account for any lag time between exposure and adverse event. See Supplemental Figure S1 for a schematic of exposure status categorization.

Our primary analysis used a Cox-Proportional Hazards model with time-dependent covariates and a robust variance estimator[19] to determine the association between antipsychotic exposure and death or cardiopulmonary arrest. To obtain the unadjusted hazard ratio (HR), we first fit a model where our time-varying antipsychotic variables (typical exposure alone, atypical exposure alone, and exposure to both typical and atypical) were the only independent variables. To obtain the adjusted HR we fit another Cox-proportional

hazards model accounting for all potential confounders, where all medication exposures and ICU time were included as time-varying covariates (i.e., could vary by hospital day) and all other variables were fixed (i.e., if present, a patient was considered to have had that condition for the entire hospitalization). The proportionality assumption of the Cox model was examined by checking Kaplan-Meier survival curves and log(-log(S)) for all main baseline covariates.

To further address confounding by indication, we performed a secondary analysis using a three-way propensity match of hospitalizations with typical antipsychotic exposure alone, atypical antipsychotic exposure alone, and no antipsychotic exposure. In this approach, we excluded hospitalizations with exposure to both typical and atypical antipsychotics to create mutually exclusive groups and avoid having more than three treatment groups. We used a previously described approach for propensity matching in cohort studies with three treatment groups[20]. We first ran one multinomial logistic regression model where exposure to typical alone, atypical alone, or no antipsychotic (as the reference) was the outcome, and each of the covariates, with the exception of the other medication variables, were included as independent variables. In this manner, the propensity for each patient to have been exposed to typical antipsychotics, atypical antipsychotics, or neither was calculated. We subsequently used a previously published match algorithm[20] that creates matches without replacement and performs “within-trio” greedy matching in a two-dimensional space, the goal of which is to find the trios of patients (one from each of our three treatment groups) with the smallest within-trio distance. This approach results in trios of patients, all of whom, on average, will have similar covariate vectors. Following the three-way propensity match, we assessed covariate balance using the standardized mean difference. We then ran a Cox Proportional Hazard model in our matched cohort where death or code blue was the dependent variable and our antipsychotic exposure categories (typical, atypical, neither) and the other medication exposures were included as time-varying independent variables. The matched nature of this dataset was accounted for by applying a marginal Cox model with a robust sandwich-type standard error estimator[19].

Subgroup Analyses

Due to changes in the pharmacokinetics and pharmacodynamics of medications in older adults, we hypothesized that the association between antipsychotics and mortality or cardiopulmonary arrest could differ by age. To investigate this possibility, we re-ran our primary analysis separately in hospitalizations age 65 and older, and in hospitalizations younger than age 65.

Sensitivity Analysis

We performed a sensitivity analysis in which we reran our primary Cox Proportional Hazards model in the subset of patients with an *ICD-9-CM or ICD-10*-CM code for delirium. We did this to address confounding from unmeasured (i.e. not coded) delirium, which could independently increase risk of exposure to antipsychotics and mortality. All analyses were performed in SAS 9.4, Cary N.C.

Results

There were a total of 236,093 admissions from 2010-2016. We excluded 4,918 psychiatric hospitalizations, 41,032 OB-GYN hospitalizations, and 31,021 hospitalizations that were admitted to the ICU on hospital day 1. An additional 8,174 were identified as receiving palliative care or comfort-focused care during hospitalization and excluded, resulting in a final analytic cohort of 150,948 hospitalizations. See Supplemental Figure S2 for the study consort diagram.

Cohort Characteristics and Antipsychotic Exposure

Table 1 shows the cohort characteristics, stratified by exposure status. Supplemental Table S1 includes the full cohort characteristics with all 31 possible comorbid conditions. The average age of the cohort was 61.2 years, with 67,758 (44.9%) age 65 and older. Typical antipsychotic exposure occurred in 2,681 (1.8%) hospitalizations, atypical antipsychotic exposure occurred in 10,431 (6.9%); 1,262 (0.8%) had exposure to both. Compared to hospitalizations without antipsychotic exposure, hospitalizations with exposure to either typical or atypical antipsychotics tended to be older, had higher rates of comorbidities, were more likely to have been admitted to a medicine service and to have spent time in the ICU, were more likely to have received benzodiazepines, and were more likely to have dementia and/or delirium.

Antipsychotic medications were usually started within the first 48 hours of hospitalization, with an average of 1.8 (standard deviation [sd] 3.7) days between admission and first exposure. For hospitalizations with antipsychotic exposure and an outcome event, the mean time between exposure and event was 1.3 (sd 3.8) days. Haloperidol accounted for 72.7% of all typical antipsychotic pharmacy charges (table 2). Atypical antipsychotic prescription was more distributed, with quetiapine (38.5%), olanzapine (25.8%) and risperidone (16.2%) accounting for 80.5% of all atypical antipsychotic charges (table 2).

Outcomes

There were a total of 691 outcome events (0.5% of total hospitalizations), comprised of 515 deaths and 176 cardiopulmonary arrests. Events were more common among each exposure group relative to unexposed, with 543 (0.4%) events in the unexposed group, 36 (2.5%) events in the typical antipsychotic group, 83 (0.9%) events in the atypical antipsychotics group and 28 (2.2%) events in the group exposed to both (Table 3). There were 0.15 events per 100 hospitalization-days in the group exposed to antipsychotics, compared to 0.08 events per 100 hospitalization-days in the unexposed group.

Table 3 shows the results of the primary analysis. After adjusting for time-dependent and fixed variables via a Cox Proportional Hazards model, hospitalizations with receipt of typical antipsychotics were significantly more likely to experience death or cardiopulmonary arrest compared to unexposed hospitalizations (HR 1.6, 95% CI 1.1-2.4). Exposure to atypical antipsychotics was not associated with death or cardiopulmonary arrest (HR = 1.1, 95% CI 0.8-1.4). Full Cox-Proportional model with all included variables is shown in Supplemental Table S2.

Subgroup Analyses

Antipsychotic exposure occurred in 6,838 (10.1%) hospitalizations age 65 and older, and 7,536 (9.1%) hospitalizations less than 65 years of age. Death or cardiopulmonary arrest occurred in 475 (0.7%) of hospitalizations age 65 and older, and 216 (0.3%) of hospitalizations less than 65 years of age. Among hospitalizations less than 65 years of age, typical antipsychotics were not associated with increased risk of death or cardiopulmonary arrest (HR 1.4, 95% CI 0.7-2.6) and atypical antipsychotics were associated with lower risk (HR 0.6, 95% CI 0.3-1.0). In hospitalizations age 65 years and older, both typical (HR 1.8, 95% CI 1.1-2.9) and atypical antipsychotics (HR 1.4, 95% CI 1.1-2.0) were associated with increased risk of death or cardiopulmonary arrest.

Propensity-Matched Analysis

We were able to match 1,411 out of 1,419 (99%) hospitalizations with typical antipsychotic exposure to a hospitalization with atypical exposure and a hospitalization with no exposure, for a total of 4,233 hospitalizations in our propensity-matched cohort. Following matching, baseline characteristics of exposed and unexposed groups were much more similar, with all standardized mean differences less than 0.1 (see Table 4). See Table 3 for the results of our Cox Proportional Hazards model within our propensity-matched cohort, controlling for other medication exposures as time-varying covariates. We again found a significant association between typical antipsychotic exposure and death or cardiopulmonary arrest (HR = 1.8, 95% CI 1.1 - 3.0), but not atypical antipsychotic exposure (HR = 1.2, 95% CI 0.7 - 2.0).

Sensitivity Analysis

In the analysis restricted to hospitalizations with diagnosis of delirium, the results were similar to our primary analysis, with typical but not atypical antipsychotics associated with increased risk (see Table 3).

Discussion

In this cohort of adult hospitalizations from a large academic medical center, typical antipsychotics were associated with increased mortality or cardiopulmonary arrest, while atypical antipsychotics were only associated with increased risk among adults age 65 and older. The observed associations persisted after adjusting for demographics, comorbidities, other medication exposures, and time spent in the intensive care unit, and were robust to different analytic approaches and sensitivity analyses. While associations between typical and atypical antipsychotics and death have been demonstrated previously in the ambulatory and long-term care settings, our study adds to newly emerging data on the risks of antipsychotics in the inpatient setting.

Our finding of risk with typical but not atypical antipsychotics in the overall cohort is consistent with the findings of a recent study by Park et al., which demonstrated increased risk of death within seven days of initiating haloperidol compared with initiating an atypical antipsychotic in hospitalized patients with acute MI. Our study extends their findings to a more diverse hospitalized patient population[5]. Notably, similar to the findings in our overall cohort, Park et al. found no association between atypical antipsychotics and death or

cardiopulmonary arrest. Studies in the outpatient setting have generally demonstrated greater risk of death with typical compared to atypical antipsychotics, but nonetheless have demonstrated a small increased risk of death with atypical antipsychotics compared to no exposure[4,21-25]. There are several possible explanations for the observed lack of association with atypical antipsychotics in our overall cohort and in the Park et al. study, both of which focused on the inpatient setting. First, it is possible that the risk with atypical antipsychotics is more time dependent and brief inpatient use poses less of a hazard than longer-term use. Second, the results of our subgroup analysis by age suggest that risk from antipsychotics, including atypical antipsychotics, may be specific to adults age 65 and older. Notably, the outpatient studies on this topic all focused on older adults, while our study and the study by Park et al. included all hospitalized patients regardless of age. Older adults are known to be more susceptible to medication-related adverse events, owing to changes in body composition, declining renal function, altered drug metabolism, and greater poly-pharmacy, all of which result in alterations in the pharmacokinetics and pharmacodynamics.

It is important to recognize that although the risk of death or cardiopulmonary arrest with atypical antipsychotics seemed to be restricted to older adults, atypical antipsychotics have other previously demonstrated risks in hospitalized patients, including aspiration pneumonia and falls, and should not be considered without risk even in younger adults[27-28].

The reason for a reduced risk of cardiopulmonary arrest or death with atypical antipsychotic exposure in younger patients is unclear, but could be due to differences in indications for use or residual confounding.

Because our study was observational, and thus prone to confounding by severity of illness and indication, we performed several sensitivity analyses. Our propensity matching approach was designed to address confounding by indication through more homogeneous comparator groups. After matching, characteristics were well balanced between those hospitalizations with and without antipsychotic exposure. We conducted our sensitivity analysis in the subpopulation of patients with delirium because we anticipated that documentation of this diagnosis might be incomplete and this could confound our results since antipsychotic use and death or cardiopulmonary arrest are both expected to be more common among patients with delirium. In both of these analyses, the association between typical antipsychotics and our primary outcome remained statistically significant. This is important as delirious patients are some of the most likely to be prescribed antipsychotics, despite the limited evidence of any clinical benefit for this indication[8,29]. Although our results may be subject to residual confounding, the persistence of our findings across multiple analytic approaches supports the existence of a relationship between typical antipsychotics and the primary outcome.

Exposure to both typical and atypical antipsychotics within the same 7 day window was not associated with greater risk than that for typical antipsychotics alone, consistent with our finding of lack of an association between atypical antipsychotics and the primary outcome. Although the association between exposure to both types of antipsychotics and the outcome was not statistically significant, the sample size of patients exposed to both is quite small, at <1% of the overall cohort, resulting in wide confidence limits and limiting the ability to

draw firm conclusions about the comparative magnitude of the association relative to typical antipsychotics alone.

Limitations

There are several additional limitations to our analysis. Since this was a retrospective cohort study, we are unable to infer causality or rule out confounding or bias in our results. In the matched cohort, the characteristics of unexposed and exposed patients are strikingly similar. Despite this, it is still possible that our results could be confounded by indication, severity of illness, or other variables not included in our model. Another limitation is that this analysis is from a single, large academic center. Use of antipsychotics has been demonstrated to vary substantially across different hospitals, both in frequency and dosing[30]. Additionally factors such as nursing ratios, vital sign monitoring frequency and hospital specific safety measures could have affected these results. Our results should be validated at other hospitals.

Conclusions

In a cohort of hospitalized adults from a large academic medical center, typical antipsychotic exposure was significantly associated with in-hospital death or cardiopulmonary arrest. This association persisted after controlling for 39 comorbidities and other risk factors. This association remained present when selecting for patients with a diagnosis of delirium and in a propensity-matched cohort. Atypical antipsychotic exposure was not associated with increased risk in our overall cohort, but was associated with increased risk among adults age 65 and older. Although the risks of death or cardiopulmonary arrest with atypical antipsychotics in hospitalized patients may be specific to older adults, given that prior analyses have demonstrated other risks of these medications, including pneumonia and falls, atypical antipsychotic medications should continue to be used with caution regardless of age. Inpatient providers should be thoughtful when prescribing antipsychotic medications, especially in settings where there are few data regarding benefit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Impact statement: We certify that this work is novel and highlights important risks that should be considered when prescribing antipsychotic medications to hospitalized patients, particularly those age 65 and older.

Table 1:

Cohort characteristics overall and by exposure group (N = 150,948)

	Unexposed	**Typical**	**Atypical**	**Both**
Hospitalizations	139,098	1,419	9,169	1,262
	n (%)	n (%)	n (%)	n (%)
Age				
< 65	76,660 (55.1%)	739 (52.1%)	5,288 (57.7%)	503 (39.9%)
65 - 79	40, 339 (29.0%)	399 (28.1%)	2,228 (24.3%)	343 (27.2%)
> 79	22,099 (15.9%)	281 (19.8%)	1,653 (18.0%)	416 (33.0%)
Race				
Black	17,530 (12.6%)	192 (13.5%)	1,160 (12.7%)	177 (14.0%)
White	92,583 (66.6%)	1,011 (71.3%)	6,577 (71.7%)	886 (70.2%)
Gender				
Female	69,282 (49.8%)	612 (43.1%)	5,008 (54.6%)	611 (48.4%)
Internal Medicine Service	60,714 (43.7%)	794 (56.0%)	5,660 (61.7%)	803 (63.6%)
Intensive Care Unit Exposure	5,629 (4.1%)	258 (18.2%)	710 (7.7%)	263 (20.8%)
Delirium	4,871 (3.5%)	324 (22.8%)	1,390 (15.2%)	611 (48.4%)
Dementia	3,502 (2.5%)	145 (10.2%)	1,191 (13.0%)	304 (24.1%)
Insomnia	3,357 (2.4%)	47 (3.3%)	430 (4.7%)	38 (3.0%)

Table 2:

Type of antipsychotic exposure across all hospitalizations

Typical Antipsychotics	Number of Pharmacy Charges	Percentage
Haloperidol	35353	72.7%
Chlorpromazine	5110	10.5%
Perphenazine	3845	7.9%
Fluphenazine	2837	5.8%
Thiothixene	591	1.2%
Trifluoperazine	438	0.9%
Loxapine	251	0.5%
Thioridazine	208	0.4%
Pimozide	13	0.03%
Molindone	3	0.01%
Total	48649	100.0%
Atypical Antipsychotics		
Quetiapine	64858	38.5%
Olanzapine	43446	25.8%
Risperidone	27217	16.2%
Aripiprazole	13642	8.1%
Ziprasidone	9787	5.8%
Clozapine	7864	4.7%
Paliperidone	652	0.4%
Asenapine	384	0.2%
Lurasidone	296	0.2%
Iloperidone	157	0.1%
Total	168303	100.0%

Table 3:

Unadjusted and adjusted* outcomes by exposure status (N = 150,948)

	Unexposed	Typical	Atypical	Both
Hospitalizations	139,098	1,419	9,169	1,262
Death or cardiopulmonary arrest – n (%)	543 (0.4%)	36 (2.5%)	83 (0.9%)	28 (2.2%)
Unadjusted HR (95%CI)	Reference	2.9 (2.0 - 4.2)	1.1 (0.9 - 1.4)	2.1 (1.3 - 3.3)
Cox-Proportional Hazards Model Adjusted HR (95%CI)	Reference	1.6 (1.1 - 2.4)	1.1 (0.8 - 1.4)	1.3 (0.8 - 2.0)
Propensity Matched Analysis (n=4,233) HR (95%CI)	Reference	1.8 (1.1 - 3.0)	1.2 (0.7 - 2.0)	N/A
Delirium-only Cohort (n=7196) HR (95% CI)	Reference	1.9 (1.1 - 3.2)	0.9 (0.6 - 1.4)	1.4 (0.7 - 2.5)

*All models adjusted for: demographics (age, gender, race); admission characteristic variables, including admitting department (medicine versus non-medicine), and time spent in the intensive care unit (ICU); delirium, dementia, insomnia; 28 additional medical comorbidities identified via *ICD-9-CM* and *ICD-10-CM* secondary diagnosis codes and Diagnosis Related Groups using Healthcare Cost and Utilization Project Comorbidity Software based on the work of Elixhauser et al.;[12-14]; and other medication exposures (benzodiazepines, opioids, acid-suppressive medications).

Table 4:

Cohort characteristics after three-way propensity matching

	Unexposed	**Typical**	**Atypical**	**Average Standardized Mean Differences**
Hospitalizations	1,411	1,411	1,411	N/A
	n (%)	n (%)	n (%)	
Age				
< 65	742 (52.6%)	734 (52.0%)	694 (49.2%)	0.06
65 - 79	365 (25.9%)	396 (28.1%)	411 (29.1%)	0.06
> 79	304 (21.6%)	281 (19.9%)	306 (21.7%)	0.06
Race				
Black	198 (14.0%)	215 (15.2%)	211 (15.0%)	0.03
White	1,025 (72.6%)	1,005 (71.2%)	1,014 (71.9%)	0.03
Gender				
Female	618 (43.8%)	611 (43.3%)	615 (43.6%)	0.00
Internal Medicine Service	798 (56.6%)	788 (55.9%)	766 (54.3%)	−0.01
ICU Exposure	263 (18.6%)	251 (17.8%)	249 (17.7%)	−0.01
Delirium	299 (21.2%)	322 (22.8%)	325 (23.0%)	0.03
Dementia	154 (10.9%)	145 (10.3%)	165 (11.7%)	−0.01
Insomnia	36 (2.6%)	47 (3.3%)	42 (3.0%)	0.03