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Mortality Risk with Use of Atypical Antipsychotics in Later-Life Bipolar Disorder

Sachin Bhalerao, DO¹, Lisa S. Seyfried, MD¹, Hyungjin Myra Kim, ScD^{1,2,3,4}, Claire Chiang, PhD^{1,2,3}, Janet Kavanagh, MS¹, and Helen C. Kales, MD^{1,2,3}

¹Department of Psychiatry, University of Michigan, Ann Arbor, Michigan

²Department of Veterans Affairs, Center for Clinical Management Research (CCMR), Ann Arbor, Michigan

³Serious Mental Illness Treatment, Resource, and Evaluation Center (SMITREC), Ann Arbor, Michigan

⁴Center for Statistical Consultation and Research, University of Michigan, Ann Arbor, Michigan

Abstract

Introduction—In recent years, concerns about use of antipsychotic medications in dementia have grown. There is limited data on mortality risk of atypical antipsychotics for other psychiatric disorders of later life such as bipolar disorder.

Methods—Data were derived from national Department of Veterans Affairs registries for older patients with bipolar disorder (≥ 65 years) with a new start of an atypical antipsychotic (risperidone, olanzapine or quetiapine) or valproic acid and derivatives during fiscal years 2001–2008. Six-month mortality rates were compared for individual drug groups.

Results—The sample included 4717 patients. The risperidone cohort had the highest mortality rate (11.8 per 100 person-years) with the quetiapine and valproic acid cohorts having the lowest (5.3 and 4.6 per 100 person-years respectively). Various methods to adjust for baseline differences including propensity models showed similar patterns.

Conclusions—Among older patients with bipolar disorder, there may be differences in mortality risks among individual antipsychotic agents.

Introduction

Bipolar disorder is a chronic, relapsing psychiatric condition with significant negative impact on overall general health and quality of life. Generally, symptoms of this disorder persist into later-life and necessitate long-term treatment [1]. Thus, among the elderly, bipolar disorder is a significant public health problem, often leading to functional impairment and substantial utilization of health care resources [2–4]. A recent large-scale review of national Veterans Affairs (VA) data examining the impact of age on outcomes of bipolar disorder showed that older bipolar patients utilize greater inpatient and outpatient

healthcare resources and require more chronic medication interventions than do younger patients [5].

Despite its importance, the evidence-base for the treatment of later-life bipolar disorder is limited [6]. While traditional mood stabilizers continue to be used frequently in acute mania and maintenance therapy, there has been a rise in the use of atypical antipsychotics as first-line treatments. In fact, a recent Expert Consensus Panel recommended the first-line use of these agents in the treatment of geriatric mania with prominent psychosis [7]. A recent study using national VA data with a sample of bipolar patients aged 60 or over found that nearly 35% were receiving an antipsychotic as part of their treatment for bipolar disorder, with a majority of these being atypical agents [8]. Notably, however, because randomized controlled trials of the atypical antipsychotics with elderly patient samples are lacking, efficacy data has largely been extrapolated from mixed-aged populations [6].

Given the FDA warnings regarding increased risk of mortality associated with the use of typical and atypical antipsychotics for management of dementia-related neuropsychiatric behaviors [9, 10], there is logical concern related to mortality risk of antipsychotics in other later-life psychiatric conditions. However, none of the clinical trials on which the FDA based these meta-analyses involved older patients with bipolar disorder. Review of the literature, also shows a paucity of information regarding mortality risk of antipsychotics in later-life bipolar disorder.

The goal of this study was to utilize national VA data to examine the risks of mortality with commonly used individual atypical antipsychotic agents, with a focus on older patients with bipolar disorder starting a new atypical antipsychotic prescription. Additionally, we included older patients with bipolar disorder newly starting valproic acid or its derivatives as 1) a type of treatment control; 2) valproic acid and derivatives are the most commonly used mood stabilizers in older patients with bipolar disorder; and 3) our prior work has also indicated increased mortality risk with this agent in older patients with dementia as compared to quetiapine [11].

Methods

Study cohort

Data were provided by national VA registries maintained by the Serious Mental Illness Treatment, Resource, and Evaluation Center (SMITREC) in Ann Arbor, Michigan, USA. Cohort eligibility criteria included: 1) age of at least 65 years; 2) a diagnosis of bipolar disorder (296.0X; 296.1X; 296.4X; 296.5x,296.6x,296.7x 296.8x); 3) initiation of an antipsychotic (risperidone, olanzapine or quetiapine) or valproic acid derivatives in fiscal years 2001–2008 after a prior 12 month “clean period” without exposure to any antipsychotics or mood stabilizers; and 4) no additional use of mood stabilizers or antipsychotics from the initial fill date to 180 days in follow up. The last condition was included as over 80% of patients in the sample had monotherapy (e.g. exposure to only the initial agent during 6-month follow-up). Given that switching to other antipsychotic agents might obscure risk profiles for individual antipsychotics, we restricted the final sample to these monotherapy patients. Finally, although they are also used for bipolar disorder, we did

not include aripiprazole, ziprasidone and clozapine in our analyses due to low rates of use in the VA older bipolar population (patients using these agents during the study period and meeting other cohort criteria: aripiprazole n=265, ziprasidone n=75 and clozapine n=8).

This study was approved by the VA Ann Arbor Healthcare System Institutional Review Board.

Medications

These included risperidone, olanzapine, quetiapine, as well as valproic acid and its derivatives (an anticonvulsant group commonly used as a first-line treatment strategy for later-life bipolar disorder). Patients taking valproic acid and its derivatives (sodium valproate or divalproex) who also had seizure disorders (n=80) were excluded from the sample as their anticonvulsant use would be less likely to be related to bipolar disorder.

Mortality

Data were obtained from the US National Death Index (National Center for Health Statistics, Hyattsville, MD).

Other variables

These included age, gender, ethnicity, marital status and indicators of psychiatric and medical comorbidity {the latter using a modified version of the Charlson comorbidity index [12] based on 19 medical comorbidities}. Indicators of psychiatric and medical comorbidity were assessed in the year prior to new medication start. Also, as delirium occurs frequently among older patients, is an independent risk factor for mortality [13], and is often treated with antipsychotics, we also assessed for the presence of a delirium diagnosis at the time of prescription, using a coding scheme for acute confusional states developed for a prior study [14]. This included the following codes: 290.3, 291.0, 292.0, 292.1, 292.2, 292.9, 293.0, 293.1, 293.9, 294.8, 294.9, 348.3, 437.2, 572.2, 290.11, 290.41, 292.81, 293.31, 293.82, 293.83, 293.89, 349.82. To control for potential changes in health care, particularly given the temporal impact of the black box warning [15], calendar year at the new medication start was included as a covariate. The model also included the following variables: inpatient and nursing home days in the year prior to new medication start; and size, rurality and academic affiliation of the VAMC where the medication was prescribed.

Statistical Analysis

Descriptive statistics were used to illustrate patient characteristics by type of medication prescribed. A 180-day follow-up period was chosen based on the duration of trials in the FDA's analysis, as well as the follow-up period used in prior studies [16, 17]. Analyses accounted for medication exposure days in two ways - "intent-to-treat" and exposure. For the "intent-to-treat" analyses, exposure-days were the length of time from the first filled prescription until death or 180 days, whichever occurred earlier. For the exposure analyses, the exposure-period to a specific medication began on the date of the first fill and was censored at the end of the actual exposure period, at 6 months, or at time of death, whichever occurred earlier. As in a prior study [18], the exposure period included the number of days' supply of last prescription received plus 30 days. Any gaps in fills of less

than 30 days were treated as continued exposures. This accounts for some level of continued exposure and biological effect among patients who missed doses or used lower than prescribed doses.

For each of the medication types, mortality during 180-day follow-up was calculated as per 100 person years; distribution of time to death since index prescription was estimated using the Kaplan-Meier survival analysis method.

We used a variety of approaches to deal with potential selection biases. Initially, we used multivariate Cox regression that included all potential confounders available in administrative data. Additionally, we used propensity-weighted and propensity-stratified Cox regression. Both propensity-based methods attempt to control for “treatment by indication” in observational studies by using the propensity scores. The goal of the propensity scores is to create balance between treatment groups on the baseline characteristics included in the propensity score model. For the propensity-weighted method, propensity score estimates (the predicted probability that a patient will receive a specific treatment conditional on the patient's baseline covariate values) were obtained using multinomial models. The propensity-weighted analyses then estimated hazard ratios using Cox's regression model with observations weighted inversely by the propensity estimates obtained using multinomial models, permitting comparisons across multiple medications based on the one model [19]. We examined the weights to assess the influence of various observations. For the propensity-stratified analyses, comparisons were made between pairs of medications, with each medication compared against risperidone. For each pair-wise comparison, propensity scores were estimated using logistic regression, and hazard ratio estimates were obtained using Cox's regression model, stratified by the estimated propensity quintiles. The idea is to make the within propensity quintile stratum comparisons where patients are as similar as possible and then to pool across the hazard ratio estimates obtained within each propensity quintile. Balance between the medication groups was checked by assessing the differences in the distributions of potential confounders between medication groups among propensity score strata. In both propensity-weighted and propensity-stratified methods, models used to obtain propensity scores were optimally fit to be highly predictable without consideration for parsimony. The final Cox models were further adjusted for covariates that remain significant predictors of mortality after propensity adjustment. To confirm that our conclusion was not biased by the inclusion of only monotherapy patients, we also did a true intent to treat analysis where patients who switched or augmented their initial medication were also included in the analysis and were analyzed as exposed to their initial medication.

Results

Characteristics of the Study Population

The study sample included 4717 older bipolar patients meeting the eligibility criteria. In terms of individual antipsychotic cohorts, this included: 868 olanzapine patients, 1027 risperidone patients, 1119 quetiapine patients and 1703 patients taking valproic acid derivatives. For each patient, only first antipsychotic or valproic acid derivative initiations were included.

Table 1 shows the demographic and clinical characteristics for each of the study groups. The group of patients taking risperidone tended to have a higher proportion of African-American patients, more patients with schizophrenia spectrum disorders, as well as more patients with medical comorbidity, delirium, dementia and the highest number of inpatient days. On the other hand, users of valproic acid and derivatives tended to: be younger, have a lower proportion of African-American patients, more married patients, less antidepressant and benzodiazepine use, lower rates of delirium, dementia or other comorbid psychiatric disorders (including depression, schizophrenia spectrum illnesses, PTSD and other anxiety disorders) and the fewest number of inpatient days as compared to the groups of patients taking antipsychotics. Quetiapine users also had a few noteworthy characteristics, with the highest rates of antidepressant and benzodiazepine use, depression, comorbid psychiatric illnesses, PTSD and other anxiety disorders, and Parkinson's disease.

Individual Medication Use and Mortality

Table 2 shows 6-month mortality rates for each study group. Examining crude death rates ("intent to treat"), the highest mortality rate (11.8 per 100 person-years) occurred in the risperidone group, followed by the olanzapine group (10.3 per 100 person-years), and the quetiapine (5.3 per 100 person-years) and the valproic acid and derivative groups (4.6 per 100 person-years). The crude estimates from the exposure analysis were similar with the highest risk in the risperidone group (death rate of 11.7 per 100 person-years) and the lowest risks in the quetiapine (4.0 per 100 person-years) and the valproic acid and derivatives groups (death rate of 3.1 per 100 person-years).

Table 3 shows the results of multivariate adjustment, as well as the propensity-weighted and propensity-stratified analyses. Covariate-adjusted "intent to treat" and exposure analyses revealed the same patterns as the unadjusted analyses where the risperidone group had the highest mortality rates while the quetiapine and valproic acid groups consistently had the lowest mortality rates. The results of propensity-weighted and propensity-stratified analyses were similar. The hazard ratio estimates were not significantly different for risperidone and olanzapine in all propensity analyses, while both quetiapine and valproic acid groups showed significantly lower risks than risperidone across the different analytic approaches.

Figure 1 shows covariate-adjusted survival function by days of exposure.

Secondary Analyses

Antipsychotic Dose—Patients taking only "as needed" (PRN) antipsychotics (n=187) or valproic acid and its derivatives were not included in the analyses adjusting for dose (mean dose of valproic acid and derivatives=776.8 mg per day with a range of 50–3000 mg per day). Table 4 shows the summary statistics for initial prescribed doses and haloperidol equivalent doses. The majority of patients (66.8%) had initial haloperidol equivalent doses less than 1.5 mg, while 15.0% had prescribed doses ≥ 3 mg and 18.2% had prescribed doses between 1.5 to <3 mg. The group receiving olanzapine received higher average haloperidol equivalent doses than the other antipsychotic groups and the group receiving quetiapine received lower haloperidol equivalent doses. The relative risk estimates adjusted for dose showed mortality risk order consistent with the main analyses

(risperidone>olanzapine>quetiapine). Although the risk associated with olanzapine treatment was not significantly different in most analyses than the risk for risperidone, the propensity-stratified estimate based on exposure analysis showed olanzapine to have significantly lower risk than risperidone after adjusting for dose. The hazard ratio estimates associated with quetiapine showed consistently lower risk than risperidone after adjusting for dose.

Inclusion of Non-monotherapy Patients—Because an argument could be made that excluding the approximately 20% of non-monotherapy patients biased the estimates of association in some way, a true intent to treat analysis was also performed. Here, patients who switched or augmented their initial medication were also included in the analysis; these patients were analyzed as exposed to their initial medication. In the true intent to treat analysis, the relative risk estimates showed a mortality risk order consistent with the main analyses (highest risk for risperidone, lowest risks for quetiapine and valproic acid and derivatives).

Discussion

Given the rising use of atypical antipsychotics to treat bipolar disorder in older adults, the FDA warnings regarding antipsychotic use in dementia, and the paucity of information regarding potential associations between mortality and antipsychotic use in bipolar disorder, an examination of these issues is critical. The goal of this study was to assess the overall risk of mortality in older bipolar patients associated with the use of common individual atypical antipsychotic agents. Similar to our recent work in patients with dementia [20], risperidone had the highest risk among the individual atypical antipsychotic agents and quetiapine had the lowest risk. Notably, the quetiapine risk was similar to that of valproic acid and its derivatives.

It should be noted that the relationships between these individual agents and mortality are likely partly confounded by selection issues. Our prior work in patients with dementia has indicated that certain patient characteristics are predictive of provider choice of agent [21]. In this study, we indeed found a number of key differences between users of individual agents. For example, the agent with the highest mortality association, risperidone, appears to be used with a “sicker” population than the other agents, e.g. patients who are more likely to have significant medical comorbidity, delirium, dementia and greater inpatient hospitalization utilization. Conversely, the agent with the lowest mortality rate association, valproic acid and derivatives, had a very different profile. The latter group tended to be younger and with lower rates of delirium, dementia or other comorbid psychiatric disorders (including depression, schizophrenia spectrum illnesses, PTSD and other anxiety disorders) and the fewest number of inpatient days as compared to the groups of patients taking antipsychotics. While such user differences might impact the crude mortality rates, even after controlling for the impact of such confounding with a variety of methods, the differences between agents remained. We additionally controlled for antipsychotic dose; both choice of a particular atypical antipsychotic and dose given may relate to patient characteristics including disease severity and predominant symptom types. The group receiving olanzapine received higher average haloperidol equivalent doses than the other

antipsychotic groups while the group receiving quetiapine received lower average haloperidol equivalent doses. Notably, while risperidone and olanzapine showed similar risks in most analyses, in the propensity-stratified exposure analysis adjusting for dose, olanzapine showed significantly lower risk than risperidone, possibly indicating that some of the mortality risk was attributable to higher dose received by these patients on average. Other the other hand, hazard ratio estimates for quetiapine showed consistently lower risk than risperidone after adjusting for dose. Finally, differences between atypical antipsychotics' risk of mortality could also relate to differences in side effect profile or receptor affinity (e.g. anticholinergic or sedative properties).

While a growing body of evidence suggests that antipsychotics increase mortality risk in both elderly dementia and non-dementia populations, the exact mechanism of the increased mortality risk associated with the use of antipsychotics in older adults is still unknown. The FDA warning for atypical agents in dementia suggested that there were higher rates of deaths from infection and cardiovascular causes among atypical users. However, in our prior work using administrative data linked to the National Death Index [11,20], we have found no significant differences in causes of death between users of the various individual agents. The link to mortality in these conditions may have less to do with the particular psychiatric condition or underlying brain pathology (e.g. in dementia) and more to do with age and associated medical comorbidity. Thus, more work will need to be done to fully elucidate the pathways involved in the connection between antipsychotics and mortality.

Only a randomized controlled trial (RCT) can reliably exclude the possibility of bias due to unmeasured confounders. However, conducting RCTs with samples of sufficient size to address serious but relatively uncommon adverse events like mortality is generally not feasible. Observational cohort studies, particularly retrospective cohort studies, have important advantages when studying serious adverse events associated with atypical antipsychotics, including allowing the study of antipsychotic treatments as delivered in the community, the study of patient deaths, and the ability to follow large groups of patients for extended periods of time. The sophisticated information technology possessed by large organized healthcare systems such as the VA has created new opportunities for following large samples of patients with detailed treatment information for long periods. No observational study can completely exclude the possibility of bias due to unmeasured confounders; nevertheless, we attempted to adjust for this bias in our analyses by controlling for a variety of potential confounders using different analytic approaches and sensitivity analyses.

Using administrative data for pharmacoepidemiologic work has several additional limitations. Prescription fills can be an imprecise measure of actual drug exposure and may not reflect day-to-day usage. Additionally, we had no information on bipolar disease severity which could impact mortality. Although we did adjust for inpatient days in the year prior to prescription, such adjustment may not have fully controlled for severity of disease. Finally, while the large integrated VA health system offers us the opportunity to examine pharmacoepidemiologic changes, the findings may not be completely generalizable. Consistent with the demographic characteristics of the VA patient population, the study cohort was primarily male.

While our findings suggest differential mortality among atypical antipsychotics used in later-life bipolar disorder, we believe that a translation of these findings to clinical recommendations that suggest the use of one agent over another would be premature. The findings should be replicated in other samples. In the meantime, evidence related to increased mortality risk with atypical agents as well as other associated risks (cerebrovascular events, metabolic syndrome, changes in cognition [22], etc.) would suggest a cautious approach to the use of any atypical antipsychotic in older adults. Although antipsychotics are FDA-approved for use in bipolar disorder (unlike with the neuropsychiatric symptoms of dementia), they should be used judiciously when traditional mood stabilizers and psychosocial interventions and psychotherapies do not fully address the patient's needs. If these agents are prescribed, then they should be used in conjunction with a risk-benefit approach [9,23]. Additionally, patients should be carefully monitored during the acute treatment period for side effects and adverse reactions. Finally, periodic attempts at discontinuation should be attempted [24].

Conclusions

There may be differences in mortality risks among individual antipsychotic agents. We suggest the use of risk-benefit ratios in a provider's decision-making process when choosing the best treatment regimen for later-life bipolar patients.

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Figure 1.
Covariate Adjusted Survival Function by Days of Exposure

Table 1
 Characteristics of Patients with Bipolar who Started One of Five Psychotropic Medications

Variable Names		Olanzapine N=868		Quetiapine N=1,119		Risperidone N=1,027		Valproic acid and derivatives N=1,703		p-value	
		N	%	N	%	N	%	N	%		
Age	65–69	252	29.0	365	32.6	297	28.9	651	38.2	<0.0001	
	70–74	222	25.6	256	22.9	235	22.9	461	27.1		
	75–79	198	22.8	234	20.9	248	24.1	367	21.6		
	80–84	140	16.1	183	16.4	167	16.3	172	10.1		
	85+	56	6.5	81	7.2	80	7.8	52	3.1		
Female		39	4.5	39	3.5	35	3.4	40	2.3	0.030	
Race	White	713	82.1	903	80.7	817	79.6	1368	80.3	<0.0001	
	Black	58	6.7	94	8.4	121	11.8	59	3.5		
	Other	13	1.5	19	1.7	15	1.5	22	1.3		
	Unknown	84	9.7	103	9.2	74	7.2	254	14.9		
		395	45.5	537	48.0	446	43.4	935	54.9	<0.0001	
Married		249	28.7	369	33.0	294	28.6	354	20.8	<0.0001	
Benzodiazepine use		532	61.3	842	75.2	721	70.2	1005	59.0	<0.0001	
Antidepressant use		100	11.5	161	14.4	124	12.1	193	11.3	0.088	
Opioid use		135	15.6	238	21.3	236	23.0	184	10.8	<0.0001	
Delirium		409	47.1	658	58.8	565	55.0	741	43.5	<0.0001	
Depression		104	12.0	102	9.1	172	16.7	54	3.2	<0.0001	
Schizophrenia spectrum*		108	12.4	148	13.2	197	19.2	77	4.5		
Other psychoses		32	3.7	65	5.8	36	3.5	48	2.8	0.007	
Parkinsons Disease		579	66.7	616	55.0	599	58.3	1229	72.2	<0.0001	
Psych Illnesses ψ_0		1	239	27.5	383	34.2	331	32.2	372	21.8	
	>=2	50	5.8	120	10.7	97	9.4	102	6.0		
Any Substance Abuse		75	8.6	130	11.6	119	11.6	149	8.7	0.013	
Alcohol Abuse		63	7.3	99	8.8	93	9.1	123	7.2	0.196	
Other Abuse		30	3.5	78	7.0	59	5.7	64	3.8	<0.0001	

Variable Names	Olanzapine N=868		Quetiapine N=1,119		Risperidone N=1,027		Valproic acid and derivatives N=1,703		p-value
	N	%	N	%	N	%	N	%	
PTSD	96	11.1	212	18.9	155	15.1	140	8.2	<0.0001
Other Anxiety Disorders	143	16.5	259	23.1	212	20.6	242	14.2	<0.0001
Personality Disorder	31	3.6	40	3.6	50	4.9	52	3.1	0.109
Charlson Comorbidities [‡]	0	37.3	349	31.2	300	29.2	733	43.0	<0.0001
	1	228	26.3	322	28.8	260	25.3	435	25.5
	>1	267	30.8	448	40.0	467	45.5	535	31.4
Dementia	105	12.1	149	13.3	187	18.2	105	6.2	<0.0001
Inpatient Days	0	659	75.9	832	74.4	695	67.7	1411	82.9
	1-5	51	5.9	93	8.3	97	9.4	117	6.9
	>5	158	18.2	194	17.3	235	22.9	175	10.3
Nursing Home Days:	0	857	98.7	1096	97.9	997	97.1	1681	98.7
	1-30	4	0.5	10	0.9	19	1.9	12	0.7
	>30	7	0.8	13	1.2	11	1.1	10	0.6
Fiscal Year 2001	137	15.8	41	3.7	109	10.6	260	15.3	<0.0001
2002	160	18.4	78	7.0	138	13.4	242	14.2	
2003	143	16.5	121	10.8	153	14.9	224	13.2	
2004	159	18.3	185	16.5	163	15.9	220	12.9	
2005	93	10.7	180	16.1	132	12.9	199	11.7	
2006	60	6.9	161	14.4	128	12.5	203	11.9	
2007	57	6.6	174	15.5	115	11.2	182	10.7	
2008	59	6.8	179	16.0	89	8.7	173	10.2	
Urban facility	783	90.2	1020	91.2	933	90.8	1518	89.1	0.50
Academic Affiliation:	low	200	23.0	260	23.2	243	23.7	376	22.1
	limited	264	30.4	291	26.0	302	29.4	601	35.3
	high	404	46.5	568	50.8	482	46.9	726	42.6
Facility Size (# beds) <=200	213	24.5	237	21.2	209	20.4	348	20.4	<0.0001
201-400	214	24.7	253	22.6	255	24.8	506	29.7	

Variable Names	Olanzapine N=868		Quetiapine N=1,119		Risperidone N=1,027		Valproic acid and derivatives N=1,703		p-value
	N	%	N	%	N	%	N	%	
	401–600	245	28.2	379	33.9	340	33.1	437	25.7
	>600	196	22.6	250	22.3	223	21.7	412	24.2

* includes Schizophrenia and Schizoaffective Disorder

ψ Total number of psychiatric illnesses

‡ Includes dementia, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, COPD, rheumatologic disease, peptic ulcer disease, cirrhosis, hepatic failure, diabetes mellitus, diabetes mellitus with complications, hemiplegia, chronic renal disease, malignant neoplasm, leukemia, lymphomas, metastatic solid tumor, and AIDS.

All use and diagnoses data are based on one year prior to the initiation of the medication.

Table 2

180-day crude death rates for bipolar patients with new medication starts after a 12-month clean period

Medication	Intent-to-Treat					Exposure*			
	N	#Deaths within 180 days	Total person-years	Death rate per 100 person-years	95%CI	#Deaths in exposure	Total person-years	Death rate per 100 person-years	95%CI
Olanzapine	868	43	417.4	10.3	(7.5–13.9)	21	288.9	7.3	(4.5–11.1)
Quetiapine	1119	29	544.2	5.3	(3.6– 7.7)	14	347.4	4.0	(2.2– 6.8)
Risperidone	1027	58	490.6	11.8	(9.0–15.3)	37	316.6	11.7	(8.2–16.1)
Valproic acid and derivatives	1703	38	830.8	4.6	(3.2– 6.3)	18	584.0	3.1	(1.8– 4.9)

* The exposure period to a specific medication began on the date of the first fill and was censored either at the end of the actual exposure period (6 months), or at time of death, whichever occurred first. The exposure period included the number of days' supply of last prescription received plus 30 days. Any gaps in fills of less than 30 days were treated as continued exposures.

Table 3

Hazard ratios of 180-day mortality for bipolar patients with new medication starts after a 12-month clean period

Intent to Treat	Adjusted, unweighted ^a			Propensity-weighted ^b			Propensity-stratified ^c		
	Hazard Ratio	95%CI	P-VALUE	Hazard Ratio	95%CI	P-VALUE	Hazard Ratio	95%CI	P-VALUE
Medication									
risperidone	1.0			1.0			1.0		
olanzapine	0.98	(0.62–1.55)	0.9371	0.95	(0.58–1.56)	0.8507	0.99	(0.61–1.60)	0.9522
quetiapine	0.46**	(0.28–0.76)	0.0027	0.39**	(0.23–0.65)	0.0004	0.45**	(0.27–0.77)	0.0034
valproic acid and derivatives	0.48**	(0.29–0.80)	0.0046	0.49**	(0.30–0.82)	0.0063	0.52*	(0.31–0.89)	0.0165
Exposure									
risperidone	1.0			1.0			1.0		
olanzapine	0.68	(0.37–1.23)	0.2021	0.67	(0.36–1.25)	0.2073	0.64	(0.34–1.23)	0.1797
quetiapine	0.32**	(0.16–0.65)	0.0017	0.27**	(0.13–0.55)	0.0003	0.31**	(0.14–0.70)	0.0046
valproic acid and derivatives	0.31**	(0.15–0.66)	0.0023	0.36**	(0.17–0.75)	0.0061	0.32**	(0.14–0.71)	0.0052

^aThe hazard ratios were based on Cox regression adjusted for gender, age, race, marital status, delirium, depression, schizophrenia, other psychoses, Parkinson's disease, alcohol abuse, PTSD, other anxiety, personality disorder, use of benzodiazepine, antidepressant, opioid, days in hospitalization, days in nursing home, fiscal year of index drug use, rurality of facility, facility size, academic affiliation of facility, and Charlson's comorbidity index which is a composite score based on the weights of dementia, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, COPD, rheumatologic disease, peptic ulcer disease, cirrhosis, hepatic failure, diabetes mellitus with complications, hemiplegia, chronic renal disease, malignant neoplasm, leukemia, lymphomas, metastatic solid tumor, HIV+ without AIDS, and AIDS.

^bThe hazard ratios were further adjusted for use of benzodiazepines, opioids, schizophrenia, other psychoses, Parkinson's disease, alcohol abuse, and Charlson's comorbidity index.

^cThe hazard ratios were further adjusted for delirium, use of opioids, academic affiliation of facility, and Charlson's comorbidity index for olanzapine vs. risperidone comparison; schizophrenia, inpatient days, days in nursing home, and Charlson's comorbidity index for quetiapine vs. risperidone comparison; Parkinson's disease and Charlson's comorbidity index for valproate acid and derivatives vs. risperidone comparison.

* p<0.05

** p<0.01

Table 4
Prescribed initial daily dose and haloperidol equivalent daily dose of antipsychotic medications

Average Initial Dose									
	Antipsychotic	N	Mean	Min	25th Percentile	50th Percentile	75th Percentile	95th Percentile	Max
	olanzapine	838	6.615	1.250	2.500	5.000	10.000	20.000	40.000
	quetiapine	968	72.691	6.250	25.000	50.000	100.000	250.000	1000.000
	risperidone	963	1.082	0.125	0.500	1.000	1.000	3.000	8.000
Haloperidol Equivalent Average Initial Dose									
	Antipsychotic	N	Mean	Min	25th Percentile	50th Percentile	75th Percentile	95th Percentile	Max
	olanzapine	838	2.991	0.352	0.832	1.967	4.654	11.010	26.045
	quetiapine	968	0.929	0.034	0.201	0.486	1.174	3.766	21.973
	risperidone	963	1.550	0.115	0.584	1.319	1.319	4.797	15.188