Journal of Medical Economics

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: informahealthcare.com/journals/ijme20

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To cite this article: Yonghua Jing, Stephen S. Johnston, Robert Fowler, John A. Bates, Robert A. Forbes & Tony Hebden (2011) Comparison of second-generation antipsychotic treatment on psychiatric hospitalization in Medicaid beneficiaries with bipolar disorder, Journal of Medical Economics, 14:6, 777-786, DOI: 10.3111/13696998.2011.625066

To link to this article: https://doi.org/10.3111/13696998.2011.625066

Published online: 29 Sep 2011.

Journal of Medical Economics Vol. 14, No. 6, 2011, 777–786

1369-6998
doi:10.3111/13696998.2011.625066

Article 0061.R1/625066

Original article

Comparison of second-generation antipsychotic treatment on psychiatric hospitalization in Medicaid beneficiaries with bipolar disorder

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Keywords:
Second-generation antipsychotics – Bipolar disorder – Hospitalization – Medicaid

Accepted: 14 September 2011; published online: 29 September 2011
Citation: J Med Econ 2011; 14:777–86

Abstract

Objective:
To compare second-generation antipsychotics on time to and cost of psychiatric hospitalization in Medicaid beneficiaries with bipolar disorder.

Methods:
Retrospective study using healthcare claims from 10 US state Medicaid programs. Included beneficiaries were aged 18–64, initiated a single second-generation antipsychotic (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone) between 1/1/2003–6/30/2008 (initiation date = index), and had a medical claim with an ICD-9-CM diagnosis code for bipolar disorder. A 360-day post-index period was used to measure time to and costs of psychiatric hospitalization (inpatient claims with a diagnosis code for a mental disorder [ICD-9-CM 290.xx–319.xx] in any position). Cox proportional hazards models and Generalized Linear Models compared time to and costs of psychiatric hospitalization, respectively, in beneficiaries initiating aripiprazole vs each other second-generation antipsychotic, adjusting for beneficiaries' baseline characteristics.

Results:
Included beneficiary characteristics: mean age 36 years, 77% female, 80% Caucasian, aripiprazole ($n = 2553$), mean time to psychiatric hospitalization or censoring = 85 days; olanzapine ($n = 4702$), 81 days; quetiapine ($n = 9327$), 97 days; risperidone ($n = 4377$), 85 days; ziprasidone ($n = 1520$), 82 days. After adjusting for baseline characteristics, time to psychiatric hospitalization in beneficiaries initiating aripiprazole was longer compared to olanzapine (hazard ratio [HR] = 1.52, $p < 0.001$), quetiapine (HR = 1.40, $p < 0.001$), ziprasidone (HR = 1.33, $p = 0.032$), and risperidone, although the latter difference did not reach significance (HR = 1.18, $p = 0.13$). The adjusted costs of psychiatric hospitalization in beneficiaries initiating aripiprazole were significantly lower compared to those initiating quetiapine (incremental per-patient per-month difference = $42, 95% CI = $16–66, $p < 0.05$), but not significantly lower for the other comparisons.

Limitations:
This study was based on a non-probability convenience sample of the Medicaid population. Analyses of administrative claims data are subject to coding and classification error.

Conclusions:
Medicaid beneficiaries with bipolar disorder initiating aripiprazole had significantly longer time to psychiatric hospitalization than those initiating olanzapine, quetiapine, or ziprasidone, and significantly lower adjusted costs for psychiatric hospitalization than those initiating quetiapine.

Introduction

Bipolar disorder is a chronic and disabling psychiatric illness that is associated with a wide range of comorbid psychiatric and medical conditions[1,2]. Estimates of the lifetime prevalence of bipolar disorder depend on the spectrum of illnesses that the condition is said to encompass and range from 1% for bipolar I disorder to 5% or more for bipolar spectrum disorder[3–5].

The burden of bipolar disorder includes productivity losses and direct medical costs, family and caregiver burden, costs borne by employers and payers, and personal challenges faced by individuals with this mental disorder[6]. In the US, Medicaid is the single largest payer for mental health services[7]. The economic burden of Medicaid beneficiaries with bipolar disorder is substantial, with per-patient estimates of annual all-cause healthcare costs ranging from $8567 (2000 year dollars) to $11,641 (2002 year dollars)[1,8]. Similar to the general population of individuals with bipolar disorder, one of the primary drivers of healthcare costs within Medicaid beneficiaries with bipolar disorder is inpatient care, accounting for 35–44% of total healthcare costs in such patients[1,9].

In the acute treatment of severe manic or mixed bipolar episodes, the recommended first-line pharmacological treatment is initiation of a mood stabilizer in combination with a second-generation (atypical) antipsychotic[10]. Three recent US retrospective observational studies focusing on commercially-insured patients with bipolar disorder found that treatment with aripiprazole was associated with longer time to psychiatric hospitalization and lower psychiatric treatment costs than various other second-generation antipsychotics[11–13]. However, US commercially-insured individuals with bipolar disorder may differ substantially from Medicaid beneficiaries with bipolar disorder in terms of important comorbid and socioeconomic factors that may affect their clinical outcomes and health-related behaviors.

State Medicaid programs are increasingly facing budgetary pressures from a rise in healthcare costs and other economic factors. Therefore, it is important for them to gain a better understanding of the comparative economic value of available therapeutic options in their own covered populations. Thus, this retrospective observational study compared second-generation antipsychotics on time to and cost of psychiatric hospitalization in Medicaid beneficiaries with bipolar disorder.

Methods

Data

This study used Medicaid claims data extracted from the 2002–2009 years of the *Thomson Reuters MarketScan®* *Multi-State Medicaid (Medicaid) Database*, which comprises covered inpatient medical, outpatient medical, and outpatient pharmaceutical claims and encounter data for Medicaid beneficiaries covered under the Medicaid programs in 10 states of varying sizes and industrial composition across the US. The Medicaid database also includes detailed patient demographic information such as age, sex, and race. Further identifying information about the states that contribute Medicaid claims data to the Medicaid database is restricted due to confidentiality agreements between the states and Thomson Reuters. The data contained in the Medicaid database are statistically de-identified and fully-compliant with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Regulations; as such, Institutional Review Board approval and written informed consent were not required for this study.

Study sample

Patients were included in the study if they met the following criteria: at least one prescription claim for a second-generation antipsychotic during the period from 1/1/2003 to 6/30/2008 (first prescription claim = the index event); aged 18–64 at index, continuous enrollment for at least 180 days before (designated the 'baseline period') and 360 days after (designated the 'follow-up period') index, at least one inpatient or outpatient claim with an *International Classification of Diseases, Clinical Modification, Ninth Revision* (ICD-9-CM) diagnosis code for bipolar disorder (ICD-9-CM 296.0x, 296.1x, 296.4x, 296.6x, 296.7x, 296.8x) in any diagnosis position during either the baseline or follow-up period; and, since some Medicaid plans provide coverage of mental health and substance abuse-related services through third-party vendors (also commonly known as 'carve-out' plans), mental health and substance abuse coverage as a part of their Medicaid plan.

In order to focus on beneficiaries who were initiating a single second-generation antipsychotic therapy as opposed to being treated with multiple second-generation antipsychotics or being non-naïve to treatment, beneficiaries with multiple second-generation antipsychotics at index or any baseline use of second-generation antipsychotics were excluded. Since Medicare Part D data and some medical claims are unavailable for Medicaid beneficiaries who are dually-eligible for Medicare coverage within the study data source, these beneficiaries were excluded to ensure complete capture of data. In order to focus on a population that was not at high initial probability of hospitalization (i.e., they had the opportunity to stabilize on treatment) or without already being in a residential care facility, beneficiaries who were residents in a nursing homes, hospice, or another type of care facility as well as beneficiaries who were in a psychiatric hospital at index or who had a

psychiatric hospitalization within 7 days following index were excluded. Since some analyses used drug exposure periods to determine the length of follow-up (described below), beneficiaries with at least one prescription for a second-generation antipsychotic having a 90-day or greater supply of medication were excluded. Beneficiaries with any inpatient or outpatient diagnosis for schizophrenia (ICD-9-CM 295.xx) in any diagnosis position during either the baseline or follow-up periods were also excluded to eliminate individuals who may have been treated with a second-generation antipsychotic for multiple reasons. Finally, for the analyses of psychiatric hospitalization costs only, beneficiaries who had their claims paid under capitated payment arrangements were excluded to ensure complete capture of cost data; these patients were not excluded from the analyses of time to psychiatric hospitalization because the Medicaid database captures hospitalization claims from capitated plans and, therefore, the pertinent outcome information could be collected.

Study outcome variables

The study focused on two outcome variables: (1) time to psychiatric hospitalization and (2) costs of psychiatric hospitalization. Psychiatric hospitalizations were defined as medical claims for inpatient admissions with a diagnosis code for a mental disorder (ICD-9-CM 290.xx–319.xx) in any position. Time to psychiatric hospitalization was defined as the number of days from index to the first occurrence of a psychiatric hospitalization, with censoring imposed at the first occurrence of any of the following censoring events: non-psychiatric hospitalization, a 16-day or longer gap in index second-generation antipsychotic therapy, addition of a non-index second-generation antipsychotic, or end of the 360-day follow-up period. A gap in therapy was measured as the duration of time between the exhaustion of the days' supply of a given prescription and the refilling of a subsequent prescription.

Costs of psychiatric hospitalizations were calculated as the gross covered payments associated with the hospital stay. Costs of psychiatric hospitalization were measured using an intent-to-treat design in which costs accrued over the entire 360-day follow-up period regardless of the occurrence of non-psychiatric hospitalizations, therapy gaps, switches. Costs of psychiatric hospitalization are expressed as per-patient per-month in 2008 constant dollars, adjusted using the Medical Care component of the Consumer Price Index[14].

Study explanatory variables

The primary explanatory variables of interest were the second-generation antipsychotic treatment comparison groups, defined by the type of second-generation antipsychotic initiated: aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone. The remaining explanatory variables of interest were all measured during the baseline period and included beneficiaries' age, sex, race (black, Hispanic, white, other, or unknown), health plan type (capitation vs fee-for-service), index year, de-identified indicators for Medicaid state, baseline psychiatric hospitalization, diabetes diagnosis, glucose screening, hyperlipidemia diagnosis, lipid screening, the Deyo-Charlson Comorbidity Index[15], antidepressant exposure (binary indicators for tricyclic, tetracyclic, selective serotonin reuptake inhibitor, serotonin/norepinephrine reuptake inhibitors, miscellaneous antidepressant), and mood stabilizer exposure (binary indicators for carbamazepine, lamotrigine, lithium, oxcarbazepine, topiramate, valproate).

Statistical analyses

For the analysis of time to psychiatric hospitalization, multivariate Cox proportional hazards models were used to compare the time to psychiatric hospitalization in aripiprazole vs each other second-generation antipsychotic, separately, adjusting for all explanatory variables listed above. For the analysis of costs of psychiatric hospitalization, a two-stage multivariate modeling approach was used combining logistic regression, generalized linear models, and bootstrapping with 200 repetitions, all to account for the fact that many beneficiaries had no psychiatric hospitalizations and therefore incurred no costs for psychiatric hospitalizations. All models employed backwards stepwise selection to retain variables with a p-value of 0.05 or less, with forced inclusion of the treatment comparison group indicators, age, sex, race, de-identified indicators for Medicaid state, and index year.

A sensitivity analysis was conducted in which a propensity score match was performed to construct treatment comparison groups that were balanced with respect to important demographic and clinical characteristics. Beneficiaries were matched 1:1 utilizing propensity scoring, through nearest neighbor matching with calipers of 0.25 SD of the logit of the propensity score. In total, four matches were performed, one for each comparison of aripiprazole vs each of the four treatment comparison groups. Additionally, a second sensitivity analysis was conducted to reflect the primary cost analysis follow-up period, in which time to psychiatric hospitalization was measured, but without censoring imposed at the first occurrence of a non-psychiatric hospitalization, a 16-day or longer gap in index second-generation antipsychotic therapy, or the addition of a non-index second-generation antipsychotic.

All analyses were conducted with SAS, version 9.2.

Table 1. Sample inclusion and exclusion criteria and sample sizes.

	n	%
Inclusion criteria		
Initiate second generation antipsychotic between 1/1/2003 and 6/30/2008	1,102,270	
One and only one SGA at index (within 30 days)	1,035,766	94.0%
Aged 18–64 at index	623,562	56.6%
180 days continuous enrollment before (designated the 'baseline period') index	277,118	25.1%
360 days after (designated the 'follow-up period') index	209,568	19.0%
Bipolar disorder diagnosis	50,422	4.6%
Mental Health and Substance Abuse services coverage	45,196	4.1%
*Exclusion criteria**		
Medicare eligibility	0	0.0%
Use of any SGA during the baseline period	16,026	35.5%
$\geq$90-day supply prescription for a second-generation antipsychotic	45	0.1%
Schizophrenia diagnosis	5447	12.1%
Residence in nursing homes, hospice, or other type of long-term care facilities	287	0.6%
Patients with a psychiatric hospitalization within 7 days following index	349	0.8%
Patients with capitated payments on their claims (Healthcare cost analyses only)	8385	18.6%
Hospitalization analysis patients	22,479	49.7%
Aripiprazole at index†	2553	5.6%
Olanzapine at index	4702	10.4%
Quetiapine at index	9327	20.6%
Risperidone at index	4377	9.7%
Ziprasidone at index	1520	3.4%
Cost analysis patients	14,094	31.2%
Aripiprazole at index‡	1622	11.5%
Olanzapine at index	3058	21.7%
Quetiapine at index	5746	40.8%
Risperidone at index	2705	19.2%
Ziprasidone at index	963	6.8%

*Each criterion is applied in order from the remaining patients not excluded above. The percentages are out of the final number of included patients.
†Percentages for SGAs at index are out of the total number of hospitalization analysis patients.
‡Percentages for SGAs at index are out of the total number of cost analysis patients.

Results

Characteristics of sample

Initially, the database contained 1,102,270 beneficiaries who had initiated a second-generation antipsychotic between 1/1/2003 and 6/30/2008. Table 1 presents the impact of applying all inclusion and exclusion criteria on the sample sizes for the treatment comparison groups. The final sample sizes for the treatment comparison groups were: 2553 aripiprazole, 4702 olanzapine, 9327 quetiapine, 4377 risperidone, and 1520 ziprasidone beneficiaries.

Tables 2 and 3 present the demographic and pre-index clinical characteristics, respectively, of the study cohort. As shown in Table 2, the average age of beneficiaries was similar across the treatment comparison groups. The majority of beneficiaries were female and most beneficiaries were Caucasian. As shown in Table 3, baseline clinical characteristics varied significantly between the treatment comparison groups. Beneficiaries initiating quetiapine, risperidone, and ziprasidone had a higher percentage of beneficiaries with a pre-period psychiatric hospitalization compared to the beneficiaries initiating aripiprazole.

Time to psychiatric hospitalization

Table 4 presents descriptive results for the second-generation antipsychotic treatment measures as well as the post-index incidence of psychiatric hospitalization. The number of days of therapy (SD) prior to psychiatric hospitalization or censoring was relatively similar across the cohorts, ranging from 82 days [97] in beneficiaries initiating ziprasidone to 97 days [104] in beneficiaries initiating quetiapine. In each cohort, starting and maximal doses did not vary greatly, indicating minimal titration over the course of treatment.

Beneficiaries initiating aripiprazole had 234 incidences of psychiatric hospitalization per 1000 patient years at risk compared to 321 (Log-rank/chi-square $(\chi^2) = 9.08$, degrees of freedom [DF] = 1, $p = 0.0026$) for olanzapine, 349 (Log-rank/$\chi^2 = 20.45$, DF = 1, $p < 0.0001$) for quetiapine, 288 (Log-rank/$\chi^2 = 3.75$, DF = 1, $p = 0.053$) for risperidone, and 315 (Log-rank/$\chi^2 = 5.52$, DF = 1, $p = 0.019$) for ziprasidone (Table 4).

Table 5 presents the results of the multivariate Cox proportional hazards models that compare the time to psychiatric hospitalization in aripiprazole vs each other second-generation antipsychotic. After adjusting for differences in demographic and clinical characteristics, the

Table 2. Demographic characteristics of the study sample.

	Aripiprazole ($n=2553$)		Olanzapine ($n=4702$)		p	Quetiapine ($n=9327$)		p	Risperidone ($n=4377$)		p	Ziprasidone ($n=1520$)		p
Age (mean, SD)	35.3	10.9	36.4	11.1	<0.0001	36.3	10.7	<0.0001	36.1	11.0	0.0032	35.8	10.6	0.14
Female (*n*, %)	2062	81%	3430	73%		7361	79%		3321	76%		1217	80%	
Race (*n*, %)					0.12			0.20			<0.0001			0.023
Caucasian	2078	81%	3792	81%		7653	82%		3367	77%		1200	79%	
African American	291	11%	597	13%		1093	12%		673	15%		226	15%	
Hispanic	24	1%	33	1%		53	1%		45	1%		11	1%	
Other	52	2%	116	2%		182	2%		106	2%		27	2%	
Unknown	108	4%	164	3%		346	4%		186	4%		56	4%	
Insurance type (*n*, %)					0.20			0.075			0.15			0.91
Capitated	931	36%	1644	35%		3581	38%		1672	38%		557	37%	
Fee-for-service	1622	64%	3058	65%		5746	62%		2705	62%		963	63%	
Index year (*n*, %)					<0.0001			<0.0001			<0.0001			<0.0001
2003	515	20%	2623	56%		2482	27%		1506	34%		355	23%	
2004	612	24%	1258	27%		2520	27%		1336	31%		367	24%	
2005	487	19%	400	9%		1838	20%		680	16%		322	21%	
2006	339	13%	155	3%		890	10%		365	8%		187	12%	
2007	346	14%	179	4%		1025	11%		316	7%		199	13%	
2008	254	10%	87	2%		572	6%		174	4%		90	6%	

Note: p-value corresponds to aripiprazole vs comparator to left of p-value column.

hazard ratio (HR) for psychiatric hospitalization was 1.52 ($\chi^2=13.78$, model DF = 25, $p=0.0002$) for olanzapine, 1.40 ($\chi^2=13.78$, model DF = 25, $p=0.0003$) for quetiapine, 1.18, ($\chi^2=2.29$, model DF = 25, $p=0.13$) for risperidone, and 1.33 ($\chi^2=4.58$, model DF = 25, $p=0.032$) for ziprasidone when compared to beneficiaries initiating aripiprazole. Within every model, baseline hospitalization was a statistically significant predictor of higher hazard of psychiatric hospitalization. The Charlson Comorbidity Index and indicators for pre-index use of antidepressants were almost always statistically significant predictors of higher hazard of psychiatric hospitalization. The indicators for index year were never statistically significant predictors of psychiatric hospitalization and there was no notable or consistent pattern of higher or lower hazards for any given year across the models, suggesting minimal evidence of secular trends affecting the study outcomes.

Costs of psychiatric hospitalization

Calculation of cost of psychiatric hospitalization required exclusion of patients with capitated payment arrangements (see Methods), reducing sample size for each group to 1622 for aripiprazole, 3058 for olanzapine, 5746 for quetiapine, 2705 for risperidone, and 963 for ziprasidone beneficiaries. Patients' demographics and clinical characteristics were similar to those of the larger sample, with the exception of payer type, since all included patients were covered under fee-for-service arrangements.

Table 6 presents the proportions of beneficiaries with a psychiatric hospitalization during the follow-up period, as well as the unadjusted costs of such hospitalizations. The proportion of beneficiaries with psychiatric hospitalization was lowest for those initiating aripiprazole ($n=344$ or 21.2%), followed closely by those initiating ziprasidone ($n=213$ or 22.1%). Compared to aripirazole, psychiatric hospitalization was significantly greater in olanzapine ($n=760$ or 24.9%, $\chi^2=7.810$, DF = 1, $p=0.0052$), risperidone ($n=692$ or 25.6%, $\chi^2=10.652$, DF = 1, $p=0.0011$), and quetiapine ($n=1566$ or 27.3%, $\chi^2=24.074$, DF = 1, $p<0.001$) treated beneficiaries.

As shown in Table 6, the mean [SD] unadjusted psychiatric hospitalization costs were $226 [$881] for beneficiaries initiating aripiprazole, which was significantly less than those treated with olanzapine ($330 [$1490], $t=2.9988$, DF = 4624, $p=0.0027$), quetiapine ($431 [$1807], $t=6.3360$, DF = 5545, $p<0.0001$), risperidone ($350 [$1575], $t=3.3325$, DF = 4306, $p=0.0009$), and ziprasidone ($351 [$1499], $t=2.3564$, DF = 1363, $p=0.019$).

After adjusting for differences in demographic and clinical characteristics, the adjusted costs of psychiatric hospitalization in beneficiaries initiating aripiprazole were significantly lower compared to those initiating quetiapine

Table 3. Clinical characteristics of the study sample.

	Aripiprazole ($n=2553$)		Olanzapine ($n=4702$)		*p*	Quetiapine ($n=9327$)		*p*	Risperidone ($n=4377$)		*p*	Ziprasidone ($n=1520$)		*p*
Psychiatric hospitalization *(n, %)*	376	15%	684	15%	0.84	1735	19%	< 0.0001	749	17%	0.0094	269	18%	0.012
Diabetes *(n, %)*	258	10%	281	6%	<0.0001	797	9%	0.014	400	9%	0.19	154	10%	0.98
Hyperlipidemia *(n, %)*	205	8%	258	5%	<0.0001	730	8%	0.74	311	7%	0.16	108	7%	0.28
Lipid screening *(n, %)*	467	18%	540	11%	<0.0001	1377	15%	<0.0001	588	13%	<0.0001	259	17%	0.31
Glucose screening *(n, %)*	153	6%	214	5%	0.0075	519	6%	0.41	234	5%	0.26	95	6%	0.74
DCI* (M, SD)	0.4	0.9	0.4	1.0	0.79	0.5	1.0	0.035	0.5	1.1	0.020	0.4	1.0	0.46
Total expenditures (M, SD)	$7788	$12,263	$8237	$25,268	0.41	$8894	$18,667	0.0048	$8697	$16,663	0.040	$7954	$18,710	0.81
Antidepressants (n, %)														
Any	1724	68%	2792	59%	<0.0001	6274	67%	0.80	2733	62%	<0.0001	927	61%	<0.0001
Tricyclics	214	8%	494	11%	0.0036	941	10%	0.0099	363	8%	0.90	132	9%	0.74
Tetracyclics	118	5%	270	6%	0.043	590	6%	0.0013	228	5%	0.28	72	5%	0.87
SSRIs†	1127	44%	1922	41%	0.0071	4214	45%	0.35	1905	44%	0.62	622	41%	0.044
SNRIs‡	438	17%	618	13%	<0.0001	1587	17%	0.87	581	13%	<0.0001	225	15%	0.049
Miscellaneous	655	26%	914	19%	<0.0001	2488	27%	0.30	987	23%	0.0034	383	25%	0.75
Mood stabilizers (n, %)														
Any	783	31%	814	17%	<0.0001	2365	25%	<0.0001	973	22%	<0.0001	424	28%	0.061
Carbamazepine	65	3%	117	2%	0.88	261	3%	0.49	143	3%	0.090	55	4%	0.050
Lamotrigine	239	9%	112	2%	<0.0001	571	6%	<0.0001	218	5%	<0.0001	118	8%	0.081
Lithium	209	8%	334	7%	0.094	728	8%	0.53	320	7%	0.19	121	8%	0.80
Oxcarbazepine	150	6%	156	3%	<0.0001	464	5%	0.069	168	4%	<0.0001	71	5%	0.10
Topiramate	214	8%	186	4%	<0.0001	652	7%	0.017	247	6%	<0.0001	122	8%	0.69
Valproate	4	0%	15	0%	0.20	25	0%	0.31	21	0%	0.030	5	0%	0.26

Note: *p*-value corresponds to aripiprazole vs comparator to left of *p*-value column.
*DCI = Charlson Comorbidity Index, Deyo Version.
†SSRIs = Selective serotonin reuptake inhibitors.
‡SNRIs = Serotonin norepinephrine reuptake inhibitors.

Table 4. Second-generation antipsychotic treatment measures and incidence of psychiatric hospitalization.

	Aripiprazole ($n=2553$)		Olanzapine ($n=4702$)		p	Quetiapine ($n=9327$)		p	Risperidone ($n=4377$)		p	Ziprasidone ($n=1520$)		p
Second-generation antipsychotic treatment measures (M, SD)														
Days on therapy prior to psychiatric hospitalization or censoring	85	96	81	90	0.11	97	104	<0.0001	84	94	0.88	82	97	0.39
Starting dose	11.8	6.3	8.2	5.1		149	146		1.4	1.0		80.4	45.5	
Maximum dose	13.7	7.2	9.6	5.8		194	184		1.7	1.1		94.4	50.2	
Incidence of psychiatric hospitalization														
Time to hospitalization														
Person time at risk (M, SD)	85	96	81	90	0.11	97	104	<0.0001	85	94	0.87	82	97	0.40
Person time at risk (median)	34		35			51			34			30		
Reason for end of follow-up (n, %)														
Medical hospitalization	34	1%	79	2%	0.25	203	2%	0.0068	70	2%	0.38	19	1%	0.82
≥16 day gap in therapy	2109	83%	3748	80%	0.0028	7104	76%	<0.0001	3495	80%	0.0048	1210	80%	0.017
Addition of non-index second-generation antipsychotic	108	4%	296	6%	0.0002	393	4%	0.97	257	6%	0.0032	79	5%	0.15
Psychiatric hospitalization	139	5%	337	7%	0.0047	865	9%	<0.0001	292	7%	0.041	108	7%	0.032
Psychiatric hospitalization IR*	234		321		0.0026	349		<0.0001	288		0.053	315		0.019

Note: p-value corresponds to aripiprazole vs comparator to left of p-value column.
*IR = Incidence rate, reported as the number of events per 1000 patient years at risk.

(incremental per-patient per-month difference = $42, 95% CI = $16–66; Table 5), but non-significantly lower for the other comparisons.

Sensitivity analyses

In the propensity-score matched sensitivity analysis, when compared to beneficiaries initiating aripiprazole, the HR for psychiatric hospitalization was 1.41 ($\chi^2 = 6.66$, model DF = 23, $p = 0.0099$) for olanzapine, 1.39 ($\chi^2 = 8.97$, model DF = 23, $p = 0.0027$) for quetiapine, 1.11 ($\chi^2 = 0.67$, model DF = 23, $p = 0.41$) for risperidone, and 1.30 ($\chi^2 = 3.14$, model DF = 23, $p = 0.077$) for ziprasidone. Beneficiaries initiating aripiprazole had lower adjusted psychiatric hospitalization costs than those initiating olanzapine, quetiapine, risperidone, or ziprasidone, this difference reaching statistical significance with quetiapine (incremental per-patient per-month cost difference = $80, 95% CI = $24–129) (data not shown).

In the time to psychiatric hospitalization sensitivity analysis that did not use censoring events, when compared to beneficiaries initiating aripiprazole, the HRs for psychiatric hospitalization were: *non-matched analysis* 1.30 ($\chi^2 = 18.94$, $p < 0.0001$ for olanzapine, 1.26 ($\chi^2 = 21.69$, $p < 0.0001$) for quetiapine, 1.14 ($\chi^2 = 5.09$, $p = 0.024$) for risperidone, and 1.08 ($\chi^2 = 1.00$, $p = 0.32$) for ziprasidone; *matched analysis* 1.30 ($\chi^2 = 13.39$, $p = 0.0003$) for olanzapine, 1.29 ($\chi^2 = 17.73$, $p < 0.0001$) for quetiapine, 1.06 ($\chi^2 = 0.92$, $p = 0.34$) for risperidone, and 1.09 ($\chi^2 = 1.14$, $p = 0.28$) for ziprasidone (data not shown).

Discussion

This is the first study to compare second-generation antipsychotic treatment on time to and costs of psychiatric hospitalization in a Medicaid population with bipolar disorder. Our findings are in general agreement with three prior studies that examined commercially-insured patients with bipolar disorder: Kim *et al.*[11] compared time to psychiatric hospitalization in commercially-insured patients with bipolar disorder treated with a mood stabilizer and adjunctive second generation antipsychotic therapy (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone). They found that after multivariate adjustment for differences in baseline characteristics, aripiprazole was associated with a significantly longer time to hospitalization over a 90-day period after initiating therapy compared to all other second-generation antipsychotics. Jing *et al.*[12] compared healthcare costs in commercially-insured bipolar disorder patients treated with a mood stabilizer and adjunctive aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone, and found that after multivariate adjustment for differences in baseline characteristics across the cohorts, aripiprazole was associated with

Table 5. Results of the multivariate analyses.

Time to psychiatric hospitalization				Costs of psychiatric hospitalization				
Comparison	Hazard ratio	95% CI		Adjusted mean costs		Difference	95% CI	
Aripiprazole vs Olanzapine	1.52	1.22	1.89	Aripiprazole = $127	Olanzapine = $155	$27	−$2	$50
Aripiprazole vs Quetiapine	1.40	1.17	1.68	Aripiprazole = $153	Quetiapine = $195	$42	$16	$66
Aripiprazole vs Risperidone	1.18	0.95	1.46	Aripiprazole = $150	Risperidone = $168	$18	−$13	$45
Aripiprazole vs Ziprasidone	1.33	1.02	1.73	Aripiprazole = $161	Ziprasidone = $177	$16	−$20	$51

Note: Cost measures are reported on a per-patient per-month basis.

significantly lower psychiatric costs (including inpatient and outpatient costs) over the 90-day period after initiating therapy compared to all of the other second generation antipsychotic. In a similar study, Kim *et al.*[13] compared time to psychiatric hospitalization and healthcare costs in commercially-insured patients with bipolar disorder treated with aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone, but looked over a 1-year period after initiating therapy. It was found that after multivariate adjustment for differences in baseline characteristics, aripiprazole was associated with significantly lower risk of psychiatric hospitalization than ziprasidone, quetiapine, and olanzapine, and significantly lower healthcare costs than quetiapine, but not other second generation antipsychotics.

Similar to the study of Kim *et al.*[13], the current study measured costs over a 360-day follow-up period after initiating therapy. We noted that during this time many patients experienced a gap in therapy, while others switched to a different second generation antipsychotic. Thus, it is possible that changes in the management of patients over a full year may have somewhat reduced the cost benefit observed with aripiprazole in the shorter studies described above[11,12]. In order to explore this hypothesis, we conducted a post-hoc investigation focusing on the 90-day period after initiating therapy only. The results of this post-hoc investigation were in closer agreement to those studies that used a 90-day period, in that beneficiaries initiating aripiprazole had significantly lower adjusted psychiatric hospitalization costs than those initiating olanzapine (incremental per-patient per-month cost = $51, 95% CI = $25–66), quetiapine (incremental per-patient per-month cost = $57, 95% CI = $28–78), and ziprasidone (incremental per-patient per-month cost = $50, 95% CI = $8–76).

In the three studies described above[11–13], it was observed that mean second generation antipsychotic dose tended to be at the lower end of the label-recommended dosing range, a finding that was confirmed in the current study. Interestingly, further analysis of our data demonstrated that this phenomenon was particularly profound in the quetiapine-treated beneficiaries, where the mean dose increased from 149 mg at initiation to 194 mg at maximum dose, despite the label-defined therapeutic window being 400–800 mg/daily in this population. This finding may go some way to explaining why differences in the study outcomes were most pronounced between aripiprazole and quetiapine. While this treatment pattern cannot be explained by the information that is available within an administrative claims database, it is plausible that physicians may have initiated beneficiaries on low dose quetiapine to avoid tolerability or safety issues. An alternative explanation for this finding is that physicians may have initiated beneficiaries on low dose quetiapine to address sleeping problems. Whatever the reason for the low dose, it is noteworthy that the study outcomes were most pronounced between aripiprazole and quetiapine.

Several sensitivity analyses on various aspects of the study design and statistical methods yielded results that were generally in line with the results to the primary analyses. In all of the sensitivity analyses, aripiprazole was still associated with a numerically lower hazard of psychiatric hospitalization for all comparisons and numerically lower adjusted psychiatric hospitalization costs. The sensitivity analyses yielded some slight differences with respect to the comparisons that were statistically significant, which were likely driven by (1) the reductions in sample size for the matched sensitivity analysis and (2) that changes in the management of patients—such as switching and discontinuation—that occur over a full year were captured in the psychiatric hospitalization sensitivity analyses that did not incorporate censoring.

This study was subject to limitations. Although the database covers several heterogeneous Medicaid states, the data come from a non-probability convenience sample of the Medicaid population, and thus our findings are not necessarily generalizable to the entire population of individuals covered under state Medicaid programs. Identification of study-eligible beneficiaries, comorbidities, and the study outcomes was based on ICD-9-CM diagnosis codes, which are recorded by physicians to support claims for reimbursement and are subject to classification error. Non-randomized studies are limited in their ability to establish causal relationships, and thus our findings are subject to residual confounding. Exposure to second-generation antipsychotics and other medications was based on records of prescriptions fills and the number of days supply obtained; these records do not

Table 6. Costs of psychiatric hospitalization.

Psychiatric hospitalization	Aripiprazole ($n = 1622$)		Olanzapine ($n = 3058$)		p	Quetiapine ($n = 5746$)		p	Risperidone ($n = 2705$)		p	Ziprasidone ($n = 963$)		p
Costs (*M*, SD)	$226	$881	$330	$1490	0.0027	$431	$1807	<0.0001	$350	$1575	0.0009	$351	$1499	0.019
Patients with psychiatric hospitalization (*n*, %)	344	21.2%	760	24.9%	0.0052	1566	27.3%	<0.0001	692	25.6%	0.0011	213	22.1%	0.59
Number of hospitalizations (*M*, SD)	0.3	0.8	0.4	0.9	0.0040	0.5	1.0	<0.0001	0.4	0.9	0.0031	0.4	1.0	0.24
Total days in hospital (*M*, SD)	1.6	5.4	2.2	11.8	0.026	2.4	6.8	<0.0001	2.2	6.3	0.0031	1.8	5.8	0.40
1 day (*n*, %)	34	2.1%	75	2.5%	0.44	132	2.3%	0.63	64	2.4%	0.56	22	2.3%	0.75
2–4 days (*n*, %)	122	7.5%	281	9.2%	0.053	503	8.8%	0.12	231	8.5%	0.24	78	8.1%	0.59
5–7 days (*n*, %)	87	5.4%	161	5.3%	0.89	367	6.4%	0.13	139	5.1%	0.75	41	4.3%	0.21
8+days (*n*, %)	101	6.2%	243	7.9%	0.032	564	9.8%	<0.0001	258	9.5%	0.0001	72	7.5%	0.22

Notes: p-value corresponds to aripiprazole vs comparator to left of p-value column; cost measures are reported on a per-patient per-month basis; utilization measures are reported for the entire follow-up period.

necessarily reflect actual medication-taking behavior. This study focused on the costs of psychiatric hospitalization only and did not address the overall cost of care across the treatment comparison groups. Future research examining this issue would be informative to State Medicaid programs. Additionally, future studies examining whether there are difference in outcomes across patients with bipolar 1 vs bipolar 2 disorder would be useful as these groups may be subject to differing risks of psychiatric hospitalization. Finally, although in the first year of the analysis (2003) all of the second-generation antipsychotics were available on the market for the bipolar indication, it is possible that, because of the varying amount of time for which they had already been available, their patterns of use may have been different from one another.

Conclusions

In this real-world study of Medicaid beneficiaries with bipolar disorder newly initiating a second-generation antipsychotic, those initiating aripiprazole had a significantly longer time to psychiatric hospitalization than beneficiaries initiating olanzapine, quetiapine, and ziprasidone, although this difference did not reach significance for risperidone. The unadjusted costs of psychiatric hospitalization in beneficiaries initiating aripiprazole were significantly lower compared to all other atypical antipsychotics. Following adjustment for demographic and clinical characteristics, cost of psychiatric hospitalization for patients initiating aripiprazole remained significantly lower than for those initiating quetiapine, but was not significantly lower for the other comparators. It is possible that the continued significant increase in cost for quetiapine may be explained, at least in part, by the prevalence of sub-therapeutic dosing of quetiapine, the reason for which is unknown. Medicaid programs may use the information from this and other studies[11–13] to gain further insight into the comparative economic value of these therapies in their own covered populations.

Transparency

Declaration of funding

Supported by funding from Bristol-Myers Squibb Company and Otsuka Pharmaceutical Co., Ltd. Thomson Reuters was paid by Bristol-Myers Squibb Company and Otsuka Pharmaceutical Co., Ltd to conduct this research.

Declaration of financial/other relationships

Dr Jing: employee of Bristol-Myers Squibb Company; Mr Johnston: employee of Thomson Reuters; Mr Fowler employee of Thomson Reuters; Dr Bates: employee of Bristol-Myers Squibb Company; Dr Forbes: employee of Otsuka Pharmaceutical

Development & Commercialization; Dr Hebden: employee of Bristol-Myers Squibb Company.

Acknowledgments

The authors would like to thank Greg Lenhart and Katy Pan, employees of Thomson Reuters, for their support in the study activities.

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