

Bipolar Disorder Healthcare Costs for Quetiapine Extended-Release Versus Aripiprazole

Elise Pelletier, MS; Mariam Hassan, PhD; Berhanu Alemayehu, DrPh; Daniel Smith, MA; and Jennifer Kim, PharmD

Bipolar disorder affects approximately 2.6% (5.7 million) of adult Americans annually and is the most costly mental health disorder.¹⁻³ Patients with bipolar disorder suffer from recurrent episodes of mania and depression, and the chronic relapsing course of the disease results in substantial use of direct medical resources.^{4,5}

The total costs associated with bipolar disorder were estimated to be around \$45.2 billion based on 2001 values.⁶ Hospitalizations in patients with bipolar disorder are common and represent the major cost driver.⁷⁻⁹ Among the different phases of bipolar disorder, bipolar depression has the highest rate of hospitalizations and overall medical costs within 12 months after diagnosis.¹⁰

There is limited research on the healthcare utilization and costs of patients treated with atypical antipsychotics for bipolar disorder.¹¹⁻¹⁷ Extended-release quetiapine (quetiapine XR) and aripiprazole are 2 atypical antipsychotics approved for the treatment of bipolar disorder. The bipolar indication profiles for quetiapine XR and aripiprazole differ. Quetiapine XR is indicated for the acute treatment of bipolar I manic and mixed episodes, both as monotherapy and as an adjunct to lithium or divalproex; for the acute treatment of bipolar depressive episodes; and for maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex.¹⁸ Aripiprazole is indicated for acute and maintenance treatment of bipolar I manic and mixed episodes, both as monotherapy and as an adjunct to lithium or divalproex; however, it is not indicated for the treatment of acute bipolar depressive episodes.¹⁹ Because economic data are scant in the published literature on the use of quetiapine XR or aripiprazole for the management of bipolar disorder in real-world settings, the objective of this retrospective study was to assess any differences in all-cause and mental health-related costs after initiation of treatment with quetiapine XR or aripiprazole among patients with bipolar disorder in a managed care population.

METHODS

This retrospective cohort study extracted medical and pharmacy claims data from the IMS PharMetrics Database

ABSTRACT

Objectives: To compare changes in all-cause and mental health-related costs after initiation of extended-release quetiapine (quetiapine XR) or aripiprazole among patients with bipolar disorder enrolled in managed care plans.

Study Design: Retrospective cohort study.

Methods: The cohort consisted of adults with at least 2 prescriptions for quetiapine XR or aripiprazole from June 1, 2007, to June 30, 2008, and at least 2 diagnoses of bipolar disorder within 6 months before the first prescription (index date). The difference in all-cause and mental health-related costs (6 months after index date minus 6 months before index date) and their components (ie, inpatient, outpatient, pharmacy) were compared between treatments using Wilcoxon rank-sum tests.

Results: A total of 287 bipolar disorder patients initiated therapy with quetiapine XR and 4554 initiated therapy with aripiprazole. There were significantly greater reductions in mean costs per patient with quetiapine XR compared with aripiprazole for total all-cause healthcare costs ($P = .029$), all-cause hospitalizations ($P = .006$), total mental health-related costs ($P < .001$), and mental health-related hospitalizations ($P = .003$).

Conclusions: In patients with bipolar disorder, greater reductions in all-cause and mental health-related costs were seen after treatment initiation with quetiapine XR than with aripiprazole.

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PRACTICAL IMPLICATIONS

Extended-release quetiapine (quetiapine XR) and aripiprazole are 2 atypical antipsychotics approved for the treatment of bipolar disorder.

- Quetiapine XR provided greater reductions in all-cause and mental health-related costs from 6 months before to 6 months after treatment initiation compared with aripiprazole.
- Patients with bipolar disorder also had greater reductions in inpatient healthcare costs (after adjustment for inflation) with quetiapine XR than with aripiprazole.

(IMS Lifelink Health Plan Claims Database) for the period from January 2007 through December 2008. This retrospective database includes fully adjudicated claims from more than 100 health plans across the United States. Patients in the database are representative of the national commercially insured population on a variety of demographic measures including age and sex. The data also are longitudinal, with an average member enrollment time of 2 years. Inpatient and outpatient diagnoses (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* format), procedures (*Current Procedural Terminology, 4th Edition*, Healthcare Common Procedure Coding System), and standard and mail order prescription records are included in the data set. Reimbursed payments and charged amounts are available for all services rendered, as well as dates of service for all claims. Additional data elements include demographic variables (age, sex, geographic region), plan type (eg, health maintenance organization [HMO], preferred provider organization [PPO]), payer type (eg, commercial, self-pay), provider specialty, and start and stop dates for plan enrollment.

Inclusion and Exclusion Criteria

Patients were included in the study if they had at least 2 prescriptions for quetiapine XR or aripiprazole from June 1, 2007, to June 30, 2008, were at least 18 years of age on the date of the first quetiapine XR or aripiprazole prescription (index date), were continuously enrolled in the same health plan for at least 6 months prior to and 6 months after the index date, and had at least 2 diagnoses of bipolar disorder based on *ICD-9-CM* codes (296.0x-296.8x) on 2 separate days within the 6 months prior to or on the index date. Patients were excluded if they were members of a health plan that carved out mental health services (complete utilization and cost data were unavailable for these members), had invalid data on days of supply, or if they were 65 years or older with incomplete claims records.

Demographic information along with claim information for hospitalizations, outpatient services, and prescription medications were extracted for patients in the cohort. All data conformed to Health Insurance Portability and Accountability Act patient privacy standards.

Measurement of Cost

The “allowed amount,” a predetermined amount of the billed charge that the insurance company has agreed to pay to the provider, was used as a proxy for medical (inpatient, outpatient, and pharmacy) costs.

The allowed amount was chosen in this study, as it reflects the real-world cost of services to the insurer. All costs were expressed in 2008 US dollars and were adjusted, as necessary, using the medical care component of the US Consumer Price Index. All-cause healthcare costs included all inpatient and outpatient services and prescriptions. Mental health-related healthcare costs included inpatient and outpatient services with an *ICD-9-CM* code for a mental health disorder (290.xx-316.xx) and pharmacy costs for psychiatric medications.

All-cause and mental health-related costs per patient were calculated for each treatment group during the 6 months prior to the index date and the 6 months following the index date. These 2 time periods were compared to determine the change in cost per patient after initiating therapy with quetiapine XR or aripiprazole.

Statistical Analyses

Unadjusted changes in all-cause and mental health-related total costs as well as component costs (inpatient services, outpatient services, and pharmacy services) per patient during the 6 months before and 6 months after the index date were compared between treatments using Wilcoxon rank-sum tests. All analyses were conducted using SAS versions 8.2 and 9.1 (SAS Institute Inc, Cary, North Carolina), and findings with a *P* value of <.05 were considered statistically significant.

RESULTS

During the index period, 287 patients with bipolar disorder were treated with quetiapine XR and 4554 patients were treated with aripiprazole (Table 1). Most patients were between 18 and 64 years of age, enrolled in a commercial plan, and had a Charlson Comorbidity Index²⁰ score of 0 or 1. Of the baseline characteristics, only sex and geographic region were significantly different between the 2 treatment groups. The quetiapine XR group included a greater proportion of males compared with aripiprazole-treated patients (41.1% vs 31.0%,

Table 1. Patient Demographics and Clinical Characteristics

Characteristic, n (%)	Quetiapine XR (n = 287)	Aripiprazole (n = 4554)	P
Age, y			
Mean (SD)	43.1 (12.4)	42.0 (12.8)	
Median	43	44	.166
Sex			
Male	118 (41.1)	1413 (31.0)	<.001
Geographic region			
Northeast	118 (41.1)	1670 (36.7)	<.001
Midwest	105 (36.6)	1795 (39.4)	
South	50 (17.4)	573 (12.6)	
West	14 (4.9)	516 (11.3)	
Health plan type			
Consumer directed	0 (0.0)	7 (0.2)	.940
Health maintenance organization	81 (28.2)	1335 (29.3)	
Indemnity	15 (5.2)	199 (4.4)	
Preferred provider organization	130 (45.3)	2034 (44.7)	
Point of service	56 (19.5)	914 (20.1)	
Unknown	5 (1.7)	65 (1.4)	
Payer type			
Commercial	255 (88.9)	4130 (90.7)	.406
Medicaid	17 (5.9)	176 (3.9)	
Medicare Risk	6 (2.1)	120 (2.6)	
Self-insured	7 (2.4)	111 (2.4)	
Unknown	2 (0.7)	17 (0.4)	
Charlson Comorbidity Index score			
0	198 (69.0)	3335 (73.2)	.282
1	49 (17.1)	724 (15.9)	
2	28 (9.8)	319 (7.0)	
3+	12 (4.2)	176 (3.9)	

SD indicates standard deviation; XR, extended release.

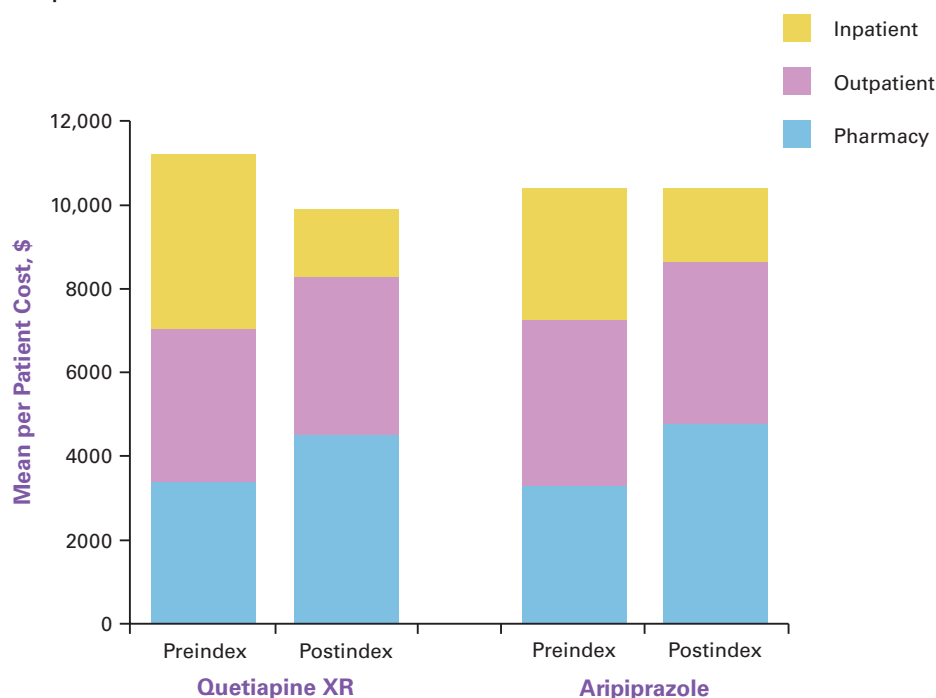
respectively; $P < .001$). Although there was a statistically significant difference between the 2 treatment groups in geographic region ($P < .001$), with the largest difference being for patients from the West, the overall distributions were similar (ie, greater proportions of patients from the Northeast and Midwest).

All-Cause Healthcare Costs

During the 6-month preindex period, the mean (standard deviation, median) total all-cause healthcare costs per patient were \$11,213 (\$12,942, \$6967) for the quetiapine XR group and \$10,395 (\$14,491, \$6331) for the aripiprazole group. For both treatments, all-cause total costs and inpatient costs were reduced in the 6 months after treatment initiation compared with the 6 months

before treatment initiation, but to a significantly greater extent in quetiapine XR patients versus aripiprazole patients (Figure 1; Table 2). The mean per patient reduction in costs for all-cause total health services was \$1368 for quetiapine XR and \$8 for aripiprazole ($P = .029$), while the reduction for all-cause hospitalizations was \$2577 for quetiapine XR and \$1395 for aripiprazole ($P = .006$) (Table 2). The proportion of patients with at least 1 admission decreased by 16.4% in the quetiapine XR group and 11.3% in the aripiprazole group, while the mean length of stay decreased by 1.4 days in quetiapine XR patients and 0.2 days in aripiprazole patients. The time to first hospitalization postindex was longer with quetiapine XR than with aripiprazole (93.4 vs 77.3 days, respectively). Pharmacy costs increased in the 6-month postindex period

Figure 1. Mean Costs per Patient for All-Cause Healthcare Services



XR indicates extended release.

for both cohorts, but aripiprazole patients had a significantly greater mean per patient cost increase compared with quetiapine XR patients ($P = .022$) (Table 2). In the 6-month postindex period, the mean number of quetiapine XR prescriptions in the quetiapine XR cohort was 4.7 and the mean number of aripiprazole prescriptions in the aripiprazole cohort was 4.6.

Mental Health-Related Healthcare Costs

The mean per patient reduction in costs for all mental health-related services was \$1303 for quetiapine XR compared with an increase of \$302 per patient with aripiprazole ($P < .001$) (Table 3). Mean per patient inpatient costs for mental health-related services were lowered with both treatments, while mean per patient outpatient mental health-related costs were not significantly different. The reduction in inpatient costs was significantly greater in the quetiapine XR patients than in the aripiprazole patients (Figure 2; Table 3). The mean per patient reduction in costs for mental health-related hospitalizations was \$2195 for quetiapine XR and \$1038 for aripiprazole ($P = .003$). The proportion of patients with at least 1 admission decreased by 16% in the quetiapine XR group and 10.8% in the aripiprazole group. The mean length of stay decreased by 1.3 days in quetiapine XR patients and increased by 0.5 days in aripiprazole patients. The

time to first hospitalization in the postindex period was longer with quetiapine XR than with aripiprazole (83.8 vs 74.7 days, respectively). The mean increase in mental health-related pharmacy costs was higher in the aripiprazole group (\$1451) compared with the quetiapine XR group (\$1163) ($P = .004$) (Table 3).

DISCUSSION

This study compared the healthcare costs of quetiapine XR and aripiprazole, 2 atypical antipsychotics used in the treatment of patients with bipolar disorder. Although quetiapine XR and aripiprazole are approved for the treatment of bipolar disorder, they have different US Food and Drug Administration-approved bipolar indications.^{18,19} Although previous studies have compared other second-generation antipsychotics,¹¹⁻¹⁷ there are no data on the comparative healthcare costs of quetiapine XR and aripiprazole in bipolar disorder.

In this study of patients with bipolar disorder, we found that despite increased pharmacy costs, both all-cause and mental health-related total costs decreased when initiating therapy with quetiapine XR and that significantly greater reductions were seen with quetiapine XR than with aripiprazole. The cause of the increased pharmacy costs is likely to be multifaceted, and as costs rose in both cohorts, it is likely that common factors contributed

Table 2. Per Patient Change in Medical Costs for All-Cause Healthcare Services in Patients With Bipolar Disorder

Costs	Change in Cost (Postindex minus Preindex), Mean (SD), Median, \$		
	Quetiapine XR (n = 287)	Aripiprazole (n = 4554)	P (Wilcoxon)
Total	-1368 (13,524), 39	-8 (15,065), 687	.029
Pharmacy	1229 (2149), 1187	1543 (2291), 1319	.022
Outpatient	-20 (5956), -127	-156 (7112), -159	.268
Inpatient hospitalization	-2577 (11,593), 0	-1394 (13,092), 0	.006

SD indicates standard deviation; XR, extended release.

Table 3. Per Patient Change in Medical Costs for Mental Health–Related Healthcare Services in Patients With Bipolar Disorder

Costs	Change in Cost (Postindex minus Preindex), Mean (SD), Median, \$		
	Quetiapine XR (n = 287)	Aripiprazole (n = 4554)	P (Wilcoxon)
Total	-1303 (9987), 470	302 (9306), 840	<.001
Pharmacy	1163 (1574), 1042	1451 (1657), 1279	.004
Outpatient	-271 (3328), -64	-112 (4617), -67	.700
Inpatient hospitalization	-2195 (8875), 0	-1038 (7855), 0	.003

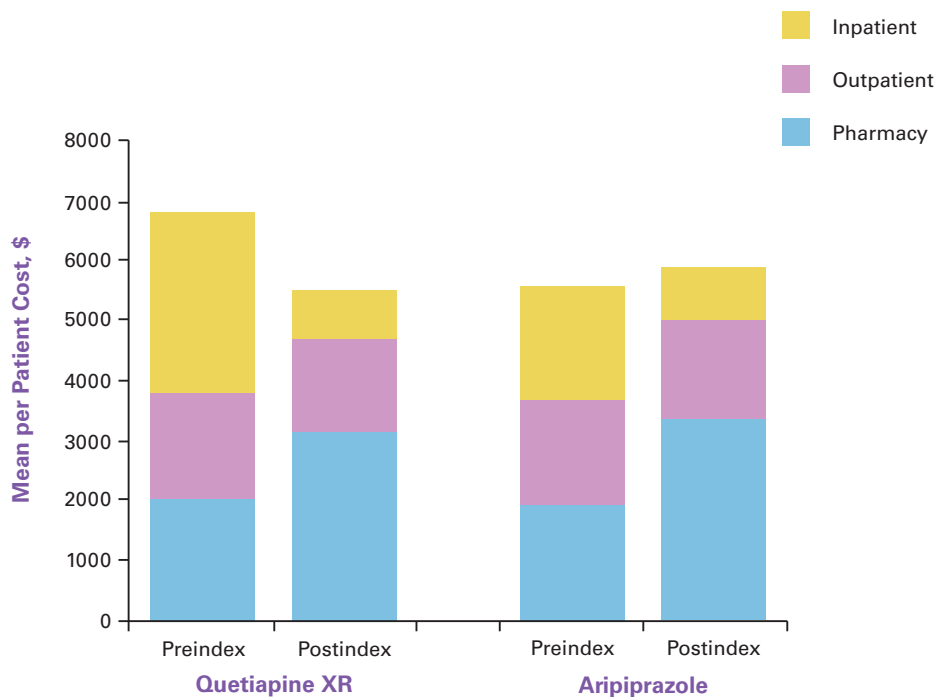
SD indicates standard deviation; XR, extended release.

to the increases. However, the claims database does not allow the causes of the increases, or indeed the factors behind the significantly greater pharmacy cost increase in the aripiprazole cohort, to be determined. The reductions in total all-cause and mental health–related costs with quetiapine XR should be viewed in the context of the higher, albeit not statistically different, total all-cause pre-index costs compared with aripiprazole. Even taking this initial difference into account, total postindex costs were still lower with quetiapine XR. The significant decrease in total cost seen with quetiapine XR was due primarily to the reduced cost of hospitalization. Both all-cause and mental health–related hospitalization costs were reduced almost \$1200 more in the quetiapine XR group than in the aripiprazole group. The greater reduction in hospitalization costs with quetiapine XR may well be due to the smaller proportion of patients admitted to hospital and the shorter length of hospital stay compared with aripiprazole. These results are especially noteworthy as inpatient care has been shown to be the single greatest contributor to overall costs and accounts for about 50% to 70% of the total direct cost for bipolar disorder.^{21,22} Hospitalization is a significant risk for patients with bipolar disorder, as more than 75% of bipolar patients experience at least 1 hospital admission related to the disease.⁶ Readmission also is prevalent in patients with bipolar disorder. In a study of a bipolar patient registry, 44% of patients had at least 1 readmission during 5 years of follow-up.²³ In addition to having adverse economic consequences, hospitalization may serve as an indicator of relapse as well as poor patient functioning.^{24–27}

Limitations

There are several limitations to consider when interpreting the results of this study. First, the accuracy of bipolar disorder diagnoses relied on correct coding of *ICD-9-CM*, which is used for administrative purposes. Physicians may have prescribed therapy based on patient characteristics that were not studied. In particular, the data set used in this study did not contain data on the severity, duration, and type of episodes (manic, depressed, mixed, or interepisodic) when the medication was initiated, or on prior treatment history beyond the 6-month preindex period. Because quetiapine XR is indicated for the treatment of manic, mixed, and depressive episodes and the maintenance treatment of bipolar I disorder, while aripiprazole is not indicated for the treatment of bipolar depressive episodes, there may have been differences in the phase of illness when treatment was initiated. While patient characteristics may have had an impact on the results, it is important to note that there were no significant differences in the Charlson Comorbidity Index scores and total preindex all-cause healthcare costs prior to initiating therapy with 1 of the 2 atypical antipsychotics. The Charlson Comorbidity Index has been shown to correlate with healthcare costs in patients with depression.²⁸ Also, because patients might have been taking concomitant psychotropic medications that could have affected healthcare utilization and outcomes, the results might not have been solely due to the 2 medications studied. Only 6 months of data were evaluated in the postindex period; therefore, it was not possible to predict the long-term healthcare cost implications of these treatments, which will reflect both

Figure 2. Mean Costs per Patient for Mental Health–Related Healthcare Services



XR indicates extended release.

the beneficial effects of a therapy on bipolar disorder and the therapy's particular side effect and tolerability profile. Finally, this study looked at only direct costs; indirect costs (eg, lost productivity) are unknown.

CONCLUSIONS

In patients with bipolar disorder, greater reductions were observed in all-cause and mental health–related costs from 6 months before to 6 months after treatment initiation with quetiapine XR compared with aripiprazole. Additionally, inpatient healthcare costs were significantly lower in patients with bipolar disorder who initiated therapy with quetiapine XR rather than aripiprazole.

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Author Affiliations: Health Economics and Outcomes Research (EP, DS), IMS Health, Inc, Watertown, MA; AstraZeneca Pharmaceuticals LP (MH, BA, JK), Wilmington, DE.

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Address correspondence to: Berhanu Alemayehu, DrPH, AstraZeneca, 1800 Concord Pike, Wilmington, DE 19850. E-mail: berhanu@umich.edu.

REFERENCES

1. National Institute of Mental Health. Statistics. <http://www.nimh.nih.gov/statistics/index.shtml>. Accessed April 12, 2011.
2. Brook RA, Rajagopalan K, Kleinman NL, Smeeding JE, Brizee TJ, Gardner HH. Incurring greater health care costs: risk stratification of employees with bipolar disorder. *Prim Care Companion J Clin Psychiatry*. 2006;8(1):17–24.
3. Peele PB, Xu Y, Kupfer DJ. Insurance expenditures on bipolar disorder: clinical and parity implications. *Am J Psychiatry*. 2003;160(7):1286–1290.
4. National Institute of Mental Health. Bipolar disorder. <http://www.nimh.nih.gov/health/publications/bipolar-disorder/complete-index.shtml#pub9>. Revised 2008. Accessed April 12, 2011.
5. Kleinman NL, Brook RA, Rajagopalan K, Gardner HH, Brizee TJ, Smeeding JE. Lost time, absence costs, and reduced productivity output for employees with bipolar disorder. *J Occup Environ Med*. 2005;47(11):1117–1124.
6. Kleinman L, Lowin A, Flood E, Gandhi G, Edgell E, Revicki D. Costs of bipolar disorder. *Pharmacoeconomics*. 2003;21(9):601–622.
7. Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996–2004. *Biol Psychiatry*. 2007;62(2):107–114.
8. Ling DCY, Bresnahan BW, White AS, Neslusan CA, Crown WH. Risk of hospitalization for patients with bipolar disorder. *Value Health*. 2001;4(2):144.
9. Dean BB, Gerner D, Gerner RH. A systematic review evaluating health-related quality of life, work impairment, and healthcare costs and utilization in bipolar disorder. *Curr Med Res Opin*. 2004;20(2):139–154.
10. Ohsfeldt RL, Lage MJ, Rajagopalan K. Medication use, service utilization, and medical costs associated with new episodes of bipolar disorder: evidence

- from a retrospective claims database. *Prim Care Companion J Clin Psychiatry*. 2007;9(4):280-286.
11. Qiu Y, Christensen DB, Fu AZ, Liu GG. Cost analysis in a Medicaid program for patients with bipolar disorder who initiated atypical antipsychotic monotherapy. *Curr Med Res Opin*. 2009;25(2):351-361.
 12. Zhu B, Kulkarni PM, Stensland MD, Ascher-Svanum H. Medication patterns and costs associated with olanzapine and other atypical antipsychotics in the treatment of bipolar disorder. *Curr Med Res Opin*. 2007;23(11):2805-2814.
 13. Fleurence RL, Chatterton ML, Dixon JM, Rajagopalan K. Economic outcomes associated with atypical antipsychotics in bipolar disorder: a systematic review. *Prim Care Companion J Clin Psychiatry*. 2007;9(6):419-428.
 14. Brook RA, Kleinman NL, Rajagopalan K. Employee costs before and after treatment initiation for bipolar disorder. *Am J Manag Care*. 2007;13(4):179-186.
 15. Kim E, You M, Pikalov A, Van-Tran Q, Jing Y. One-year risk of psychiatric hospitalization and associated treatment costs in bipolar disorder treated with atypical antipsychotics: a retrospective claims database analysis. *BMC Psychiatry*. 2011;11:6.
 16. Jing Y, Kim E, You M, Pikalov A, Tran QV. Healthcare costs associated with treatment of bipolar disorder using a mood stabilizer plus adjunctive aripiprazole, quetiapine, risperidone, olanzapine or ziprasidone. *J Med Econ*. 2009;12(2):104-113.
 17. Zhang Y. Cost-saving effects of olanzapine as long-term treatment for bipolar disorder. *J Ment Health Policy Econ*. 2008;11(3):135-146.
 18. Seroquel XR [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2011.
 19. Abilify [prescribing information]. Tokyo, Japan: Otsuka Pharmaceutical Co, Ltd; 2012.
 20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
 21. Bryant-Comstock L, Stender M, Devercelli G. Health care utilization and costs among privately insured patients with bipolar I disorder. *Bipolar Disord*. 2002;4(6):398-405.
 22. Stender M, Bryant-Comstock L, Phillips S. Medical resource use among patients treated for bipolar disorder: a retrospective, cross-sectional, descriptive analysis. *Clin Ther*. 2002;24(10):1668-1676.
 23. Osby U, Tiainen A, Backlund L, et al. Psychiatric admissions and hospitalization costs in bipolar disorder in Sweden. *J Affect Disord*. 2009;115(3):315-322.
 24. Buckley PF. Update on the treatment and management of schizophrenia and bipolar disorder. *CNS Spectr*. 2008;13(2)(suppl 1):1-10.
 25. Colom F, Vieta E, Martinez-Aran A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Arch Gen Psychiatry*. 2003;60(4):402-407.
 26. Keck PE Jr, McElroy SL, Strakowski SM, et al. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. *Am J Psychiatry*. 1998;155(5):646-652.
 27. Dickerson F, Origoni A, Stallings C, Khushalani S, Dickinson D, Medoff D. Occupational status and social adjustment six months after hospitalization early in the course of bipolar disorder: a prospective study. *Bipolar Disord*. 2010;12(1):10-20.
 28. Unützer J, Schoenbaum M, Katon WJ, et al. Healthcare costs associated with depression in medically ill fee-for-service Medicare participants. *J Am Geriatr Soc*. 2009;57(3):506-510. [ajpb](#)