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Effect of Second-Generation Antidepressants on Mania- and Depression-Related Visits in Adults with Bipolar Disorder: A Retrospective Study

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ABSTRACT

Objective: To assess the effect of second-generation antidepressants on mania-related and depression-related office visits for adults with bipolar disorder.

Methods: Using a national managed-care claims database, we retrospectively identified continuously enrolled patients with bipolar disorder who had a new antidepressive prescription treatment between January 1998 and December 2002. Patients were followed for at least 12 months after the date of initial use of antidepressant monotherapy, mood stabilizer monotherapy, or antidepressant–mood stabilizer combination therapy. Logit models with propensity score matching were used to identify the relationship between treatment types and the likelihood of having mania-related visits within 12 months. Negative binomial models and Cox proportional hazard models were used to predict the number of depression-related visits and time to first mania- or depression-related visit.

Results: Patients on antidepressant monotherapy and combination therapy did not have different likelihoods of mania-related visits compared with those on mood stabilizer monotherapy (with odds ratios (ORs) 0.67 (95% confidence interval (CI) 0.42–1.04) and 0.99 (95% CI 0.69–1.43), respectively). The numbers of depression-related visits for the same comparisons were significantly lower, with incidence rate ratios of 0.68 (95% CI 0.56–0.82) and 0.65 (95% CI 0.52–0.81), respectively. The results of time to first mania- or depression-related visit provided similar indications.

Conclusions: Second-generation antidepressant was associated with a decreased number of depression-related visits but was not associated with an increased risk of mania-related visits within a 1-year period. Although more work is needed to establish the safety and efficacy of second-generation antidepressants in treating bipolar depression, the evidence from this study supports a favorable risk–benefit profile.

Keywords: bipolar depression, bipolar disorder, manic-switching, propensity score, second-generation antidepressant.

Introduction

Bipolar disorder, also referred to as manic-depressive illness, is a severe psychiatric recurrent mood disorder characterized by both depressive and manic or hypomanic episodes with intervening periods of euthymia (a return to normal functioning) [1]. Bipolar disorder is ranked as one of the most costly mental-health diseases [2] in terms of both the direct medical costs of managing the condition and the indirect costs associated with loss of work productivity and disruption of daily activities of both the sufferers themselves and their family members and caregivers [3]. It is a major cause of disability worldwide. The World Health Organization identified bipolar disorder as the sixth leading cause of disability-adjusted life years in the world among people aged 15 to 44 years, above osteoarthritis, HIV, diabetes, and asthma [4].

Although mania and hypomania historically have received extensive attention from medical researchers, the depressed phase of bipolar disorder is a more significant cause of suffering, disability, and mortality. Bipolar patients are estimated to spend more than three times as long suffering from depressive symptoms than manic symptoms [5]. Compared with manic phases, episodes of bipolar depression are more frequent and last longer [6]. Depressive symptoms are the primary determinant of health-related quality of life in bipolar disorder [7]. Additionally, recovery from depression is slower and less complete than recovery from mania [8]. The lifetime risk of completed suicide during bipolar depression is 30 times higher than that of mania [9].

Most treatments for bipolar depression are based on unsupported extrapolation from the treatment of

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unipolar depression or guidelines derived largely from the clinical practice experience of experts in this field [10,11]. No sufficient evidence was available to verify the appropriateness of treatment guidelines in adults on a large population basis. Specifically, current American Psychiatric Association (APA) practice guidelines recommend that antidepressant (AD) monotherapy not be considered for bipolar depression given the potential risk of induced manic-switching and rapid-cycling [11]. The combined use of mood stabilizer (MS) drugs and ADs can be considered if the illness is severe. Nevertheless, the risk associated with second-generation ADs is not certain because not enough information has been provided regarding this newer group of medications.

Moller and Grunze from Germany [12] suggested that modern ADs should be used as a first-line treatment for bipolar depression, which is contradictory to the current APA guidelines. Although Europe might have different treatment guidelines than the United States, this controversy has inspired more discussion [13], and additional research would provide more information to determine whether second-generation AD therapies are appropriate to use.

The aim of this study is to assess the effects of different types of medication treatment—including second-generation ADs—on mania-related and depression-related office visits as outcomes. We used an intent-to-treat approach to evaluate three different types of pharmacotherapy: AD monotherapy, MS monotherapy, and AD–MS combination therapy.

Methods

Conceptual Framework

We developed our conceptual framework by following the Andersen behavioral model for health service utilization [14]. This conceptual framework guided our choice of variables for the explanatory regression models. The Andersen model indicates that in order to make a policy change, mutable variables such as enabling factors should be the focus of attention. We assessed the effects of prescribing behavior (types of treatment with or without AD) on health outcomes while simultaneously considering the influence of other mutable enabling factors, including insurance plan, type of medical providers, and geographic regions as well as other enabling factors, including clinical-related variables (e.g., concurrent use of other medications or psychotherapy).

The model for this study seeks to evaluate the extent to which enabling factors (e.g., prescribing behavior) affect consequential health service utilization and health outcomes with simultaneous consideration of previous-period health status (comorbidities), which is indicated by need variables in the Andersen model.

Data Source

Data were derived from the Integrated Healthcare Information Services database, which is aggregated from more than 30 managed-care health plans in the United States. The data are organized into the following five files: 1) member demographics and enrollment information; 2) medical service utilization; 3) inpatient confinement utilization; 4) pharmacy claims; and 5) laboratory results. All service utilization files provide insurance claims-level account of health-care services received by a patient, including visits with a physician, medical procedures, inpatient stays, diagnostic tests, and prescription drugs.

Medications of Interest

Medication treatments for bipolar depression were classified as second-generation AD monotherapy, MS monotherapy, or second-generation AD–MS combination therapy. To be consistent with the APA national practice guidelines, AD monotherapy was defined as the use of ADs without MSs [11]. Patients were still considered using AD monotherapy if they switched/augmented to another brand of AD prescriptions. Table 1 lists the second-generation ADs that were included in the study. Anticonvulsants were categorized as MS. Patients with antipsychotic use as an initial treatment were excluded because the focus of this study is only AD without the case-mix of the antipsychotics. Combination of antipsychotic use with ADs might confound the results of a treatment type. Use of benzodiazepines, sometimes added as ancillary treatment for bipolar mania [10], was noted and treated as a covariate. National Drug Codes codes were used to identify all medications in the pharmacy file.

Inclusion and Exclusion Criteria

Subjects (aged 18–64 years) were included in the study if they had at least one medical claim for bipolar disorder (International Classification of Diseases, 9th Edition (ICD-9): 296.4x–296.8x) between January 1, 1998 and December 31, 2002. Each subject must have received at least one prescription for an MS or a second-generation AD during the period. Patients were required to have continuous prescription drug benefit and full mental-health information reported in the database. Members with a comorbid diagnosis of epi-

Table I Second-generation antidepressants included in the study for bipolar disorder

Subclass and name of the medications
• Selective serotonin reuptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
• Serotonin–norepinephrine reuptake inhibitors: venlafaxine
• Serotonin reuptake inhibitor: nefazodone, trazodone
• Dopamine reuptake inhibitor: bupropion
• Noradrenergic antagonist: mirtazapine

lepsy (ICD-9: 345.xx) and/or schizophrenia (ICD-9: 295.xx) were excluded so that we would have reasonable assurance that the prescriptions were used to treat bipolar disorder [15].

To guard against false negative coding within the claim database (i.e., bipolar depression coded as major depression disorder (MDD)), any patient with a diagnosis of MDD (ICD-9: 296.2, 296.3, 311) that occurred after the pure bipolar-related diagnosis (296.0, 296.1, 296.4–296.8) or earlier but no more than 90 days before the pure bipolar-related diagnosis were deemed miscoded and considered bipolar depression.

We attempted to identify a cohort of patients receiving a new episode of prescription drug treatment for bipolar depression. The index date was defined as the first dispensing date of either a second-generation AD or an MS coupled with a depression-related diagnosis. The MS with a depression-related diagnosis ensured that such an MS was used for treating bipolar depression rather than bipolar mania. Patients were excluded if they had one or more visits for a depression-related diagnosis (296.82, 296.5, or miscoded 296.2, 296.3, 311 without remission) and/or received a prescription claim for a second-generation AD within the 3-month period before the index date. Patients must have had at least 12 months of continuous enrollment after the index date. As an intent-to-treat approach, the treatment cohort was defined by the first 30-day use of ADs and/or MSs after the index date.

Outcome Measures

Outcome variables were observed over the 12 months after treatment was initiated. Based on the variable distribution, the primary outcomes of the study included whether a patient had any mania-related visits and the number of depression-related visits within 12 months after the index date. Mania-related visits were identified by ICD-9 codes 296.0x, 296.1x, 296.4x, or 296.81 using both the medical service and inpatient confinement utilization data. Depression-related visits were identified by ICD-9 codes 296.5x, 296.82, or miscoded 296.2x, 296.3x, 311 (i.e., bipolar depression was coded as MDD). Secondary outcome variables included time from index to the first mania-related visit and time to the first depression-related visit.

Explanatory Variables

In addition to the medication use as interventional variable, other explanatory variables were grouped into demographic, clinical-related, and health-related following the conceptual framework. Demographic variables (i.e., age, sex) were used to define predisposing characteristics. Enabling resources were conceptualized as insurance type and geographic region. Insurance type was categorized into health maintenance organization, preferred provider organization, and point of service as data provided.

Clinical-related variables included use of antipsychotics, benzodiazepines, tricyclics, and monoamine oxidase inhibitors in the 12 month follow-up period; use of electroconvulsive therapy (ECT) and psychotherapy identified by Current Procedural Terminology codes; and type of medical provider, categorized as psychiatrist, internal medicine specialist, general/family practitioner, and other. Health-related variables included presence of selected comorbidities and the Charlson Comorbidity index score [16]. The Charlson Comorbidity index is a validated method to predict future mortality from medical records, and it was used as a surrogate measure for general health status.

Bipolar patients have a significantly higher prevalence of diabetes mellitus than the average population [17]. Therefore, diabetes was considered a comorbid condition. Other comorbidities of interest included substance abuse and other mental-health conditions.

Econometric Modeling

Our modeling strategy begins with a logistic regression model to predict the likelihood of having mania-related visits over the 12-month follow-up period, controlling for the type of treatment, observed individual demographics, clinical-related variables, health-related variables during the treatment, and the baseline disease severity of bipolar disorder. Because the baseline disease severity of bipolar disorder cannot be truly observed and the rating measures to assess the disease severity (e.g., the Clinical Global Impression for Bipolar Disorder (CGI-BP) scale) were unavailable in the database, we used a proxy to control for disease severity—whether the patient had any mania-related visits in the pre-index period. This proxy variable, however, is simply a lagged dependent variable, which is endogenous and also a function of the true disease severity. As a result, it could potentially lead to a biased estimation.

To better balance the background characteristics between groups, a propensity score approach was used to predict the propensity to be in the AD-related treatment groups (comparison 1: AD monotherapy vs. MS monotherapy; comparison 2: AD–MS combination therapy vs. MS monotherapy). Variables in the predictive equation included individual demographics, clinical-related variables, health-related variables, quarter of the year when initiating the treatment, miscoding of bipolar depression, and bipolar severity variables, which included the number of mania-related visits, number of any bipolar-related visits (mixed and unspecified types also included), natural logarithm of bipolar-related costs, and natural logarithm of total health-care costs in the pretreatment period. After achieving covariate balancing, the greedy matching algorithm [18] was used with matching from best to

next-best. Best matches were defined as those with the highest digit match (0.00001) on propensity score in the study. The algorithm proceeded sequentially to the lower digit match. The lowest allowable digit match for the study was 0.1. The matched subsamples were used as the analytic data set.

Based on the variable distribution, negative binomial models were used when the outcome was the number of depression-related visits. Cox proportional hazard models were used when the outcomes were time to first mania- or depression-related visit. Both the Cox proportional hazard model and the negative binomial model were used with propensity score matching after the control of potential confounding variables described earlier.

Results

Descriptive Statistics

Of the 3737 patients in the final sample, 2096 patients were receiving AD monotherapy, 504 were receiving MS monotherapy, and 1137 were receiving AD–MS combination therapy at the index date. The proportion of patients receiving AD monotherapy, MS monotherapy, and AD–MS combination therapy stayed approximately the same over the 5-year analytic period (i.e., 1998–2002). AD monotherapy accounted for 40% to 51% of patients at any given year during the study.

The percentages of patients having at least one mania-related visit within 1 year after treatment initiation were 12%, 22%, and 21% for AD monotherapy, MS monotherapy, and AD–MS combination therapy, respectively. The average numbers of depression-related visits within the same period were 3.2, 4.6, and 3.1, respectively.

Explanatory Results

Table 2 shows the baseline characteristics of bipolar patients who had AD monotherapy and MS monotherapy before and after the propensity score matching. The matching resulted in more balanced groups in terms of the measured covariates. All of the variables that showed statistically significant differences before matching had no significant differences after matching. The same procedure was carried out for the propensity score matching between patients with AD–MS combination therapy and MS monotherapy. The balancing was achieved as well.

The full logistic regression results are reported in Table 3 with propensity score-matched sample for the two comparison pairs. The original coefficient estimates were exponentiated to derive odds ratios (ORs) to characterize the effect of a unit change of each independent variable on the probability of having mania-related visits within the observed 12 months while holding all other covariates constant. Table 3 indicates that the odds of having mania-related visits for patients with AD monotherapy were not significantly different from the odds for the patients on MS monotherapy (OR 0.67; 95% confidence interval (CI) 0.42–1.04). The indication was the same for the comparison between combination therapy and MS monotherapy. In addition, patients were more likely to have mania-related visits after the index date if they had visits before the index date with statistically significant ORs of 34.6 and 1.77 for comparison 1 and comparison 2, respectively. Among clinical-related variables, use of antipsychotics, psychotherapy, and ECT in the 12-month follow-up period were all strong positive predictors of the likelihood of mania-related visits, with ORs ranging from 1.85 to 2.94.

The negative binomial model (Table 4) showed that patients on AD monotherapy and AD–MS combination therapy had significantly lower rates of depression-related visits within 12-months after the index date than the patients on MS monotherapy, with incidence rate ratios of 0.68 (95% CI 0.56–0.82) and 0.65 (95% CI 0.52–0.81), respectively. To test the effect of treatment on time to first mania- or depression-related visit in the secondary analysis, we used Cox proportional hazard models with propensity score matching (Table 4). Patients on AD monotherapy and AD–MS combination therapy did not have significantly different time to first mania-related visits compared with patients with MS monotherapy, with hazard ratios of 0.83 (95% CI 0.60–1.16) and 1.08 (95% CI 0.82–1.41), respectively. On the other side, time to first depression-related visit for those on AD monotherapy and AD–MS combination therapy were significantly longer than the patients with MS monotherapy, with hazard ratios of 0.55 (95% CI 0.44–0.68) and 0.59 (95% CI 0.48–0.73).

Discussion

Bipolar disorder is a severe, lifelong chronic illness for which optimal treatment requires long-term management. The depressed phase of bipolar disorder is a more significant cause of suffering, disability, and mortality, but it has been understudied and most treatments are based on unsupported extrapolation from the treatment of unipolar depression [19,20]. This article adds to the literature of bipolar depression treatment by providing additional empirical evidence. Recent debate and discussion revealed that the risk of manic-switching with second-generation ADs is uncertain for the treatment of bipolar depression [12,13]. This study, which consisted of an insured population, indicated that second-generation AD (including monotherapy and AD–MS combination therapy) was not related with a higher likelihood of manic-switching compared with MS monotherapy.

Table 2 Propensity score matching results for comparison between antidepressant monotherapy and mood stabilizer monotherapy

	Prematching			Postmatching		
	AD only (n = 2096)	MS only (n = 504)	*P*-value	AD only (n = 347)	MS only (n = 347)	*P*-value
Age at treatment initiation (years, %)						
Age 1: 18–24	10.6	8.3		9.2	9.2	
Age 2: 25–34	25.8	20.0		21.6	23.6	
Age 3: 35–44	31.2	25.6		26.5	28.0	
Age 4: 45–54	22.9	29.6		27.7	25.4	
Age 5: 55–64	9.6	16.5	<0.001	15.0	13.8	0.92
Sex (%)						
Female	61.8	55.4	<0.01	56.5	58.5	0.59
Insurance plan type (%)						
PPO	51.2	42.7		45.2	47.6	
HMO	32.4	36.3		33.3	32.9	
POS	8.0	9.5		10.1	9.8	
Others	8.4	11.5	<0.01	11.5	9.8	0.87
Geographic region (%)						
Mid Atlanta	36.2	31.0		30.0	33.7	
New England	30.8	41.3		38.9	36.6	
Others	33.0	27.8	<0.001	31.1	29.7	0.57
Use of tricyclics and MAOIs (%)	7.8	12.1	<0.01	10.4	11.0	0.81
Use of antipsychotics (%)	15.8	12.9	0.10	12.1	14.7	0.32
Use of benzodiazepines (%)	30.2	24.8	<0.05	26.2	24.2	0.54
Use of psychotherapy or ECT (%)	50.3	72.0	<0.001	67.4	70.0	0.46
Type of medical provider (%)						
General/family practitioner	14.1	6.8		8.4	8.4	
Internal medicine specialist	15.7	8.3		9.5	9.2	
Psychiatrist	21.1	34.3		33.7	35.7	
Others	49.1	50.6	<0.001	48.4	46.7	0.95
Selected comorbidities (%)						
Neurotic disorders	44.5	23.4	<0.001	26.2	29.1	0.40
Personality disorder	6.8	5.6	0.32	5.8	6.6	0.64
Alcohol abuse/dependence	9.2	5.8	<0.05	6.3	7.5	0.55
Drug abuse/dependence	6.7	6.2	0.67	5.2	6.6	0.42
Other mental disorders	32.0	23.6	<0.001	25.4	28.0	0.44
Diabetes	5.6	4.4	0.26	5.2	4.9	0.86
Charlson comorbidity index score	0.492	0.399	0.05	0.452	0.427	0.75
Miscoding-related variables (%)						
Without pure bipolar codes*	65.5	13.9	<0.001	18.2	18.7	0.84
With bipolar depressive codes*	6.8	45.4	<0.001	23.6	28.2	0.17
Quarter of treatment initiation (%)						
Quarter 1	25.1	24.4		21.3	24.8	
Quarter 2	29.6	31.2		33.4	31.7	
Quarter 3	23.7	23.0		24.2	24.2	
Quarter 4	21.7	21.4	0.93	21.0	19.3	0.73
Preindex bipolar severity						
Number of mania-related visits	0.07	0.46	<0.001	0.29	0.28	0.90
Number of any bipolar visits	0.50	1.31	<0.001	1.18	1.22	0.81
Log of bipolar-related costs	1.76	4.39	<0.001	4.08	4.06	0.91
Log of total health-care costs	5.90	6.20	<0.01	6.21	6.28	0.60

*Pure bipolar codes: 296.0, 296.1, 296.4–296.8; pure bipolar depressive codes: 296.5, 296.82.

Notes: AD only, antidepressant monotherapy; MS only, mood stabilizer monotherapy; AD–MS, antidepressant–mood stabilizer combination therapy. Chi-square tests were calculated for categorical variables and *t*-tests were calculated for continuous variables.

AD, antidepressant; ECT, electroconvulsive therapy; HMO, health maintenance organization; MAOIs, monoamine oxidase inhibitors; POS, point of service; PPO, preferred provider organization.

The analysis of time to first postindex mania-related visit found no difference between AD monotherapy or AD–MS combination therapy and MS monotherapy, which further supports the primary results of the logistic regression with the likelihood of mania-related visits in the 12 months as an outcome. Furthermore, both AD monotherapy and AD–MS combination therapy were found to be more effective than MS monotherapy in reducing the number of depression-related visits and lengthening the time to first depression-related visit. This is clinically justifiable because AD is used primarily for the purpose of treating depressive symptoms.

The propensity score method in the study included more variables to better represent the disease severity of bipolar disorder in the first-stage predictive model (Table 2) without the problem of overparameterization in the second-stage outcome model. These variables were included also to further balance the disease severity between the comparison groups to further control for the potential prescribing bias. In addition, quarters of treatment initiation were included in the first-stage predictive model to balance the seasonal variation, which is a common phenomenon for psychiatric disorders [21,22].

Table 3 Logit models on probabilities of having mania-related visits with propensity score matching, odds ratios (with 95% confidence intervals)

	Comparison one: AD only vs. MS only (n = 694)	Comparison two: AD–MS vs. MS only (n = 756)
AD only (or AD–MS)	0.67 (0.42, 1.04)	0.99 (0.69, 1.43)
MS only (reference)		
Mania-related visits before index	34.58 (18.02, 66.37)***	1.77 (1.03, 3.02)*
Age categories		
Age 1: 18–24 (reference)		
Age 2: 25–34	1.01 (0.35, 2.92)	0.92 (0.44, 1.94)
Age 3: 35–44	0.69 (0.23, 2.00)	0.89 (0.44, 1.81)
Age 4: 45–54	1.48 (0.53, 4.17)	1.36 (0.68, 2.72)
Age 5: 55–64	1.19 (0.39, 3.71)	1.44 (0.65, 3.18)
Female (reference: male)	0.95 (0.57, 1.59)	0.93 (0.63, 1.36)
Insurance plan type		
HMO	1.16 (0.62, 2.14)	0.90 (0.56, 1.44)
POS	0.82 (0.29, 2.28)	1.22 (0.61, 2.46)
PPO (reference)		
Other insurance	0.75 (0.32, 1.78)	0.85 (0.42, 1.71)
Geographic region		
Middle Atlantic	2.43 (1.19, 4.99)*	1.32 (0.79, 2.23)
New England	1.77 (0.90, 3.51)	1.31 (0.81, 2.12)
All other regions (reference)		
Use of tricyclics and MAOIs	1.44 (0.64, 3.23)	1.19 (0.68, 2.10)
Use of antipsychotics	2.13 (1.13, 4.00)*	1.85 (1.16, 2.94)**
Use of benzodiazepines	1.23 (0.70, 2.18)	1.06 (0.69, 1.64)
Use of psychotherapy or ECT	2.44 (1.27, 4.68)**	2.94 (1.65, 5.24)***
Type of medical provider		
General/family practitioner	1.17 (0.45, 3.03)	1.05 (0.49, 2.27)
Internal medicine specialist	1.70 (0.66, 4.39)	0.63 (0.28, 1.41)
Psychiatrist (reference)		
Others	0.82 (0.46, 1.47)	1.02 (0.68, 1.54)
Selected comorbidities		
Neurotic disorders	0.71 (0.39, 1.31)	0.81 (0.53, 1.24)
Personality disorder	0.59 (0.17, 2.02)	1.33 (0.64, 2.78)
Alcohol abuse/dependence	0.42 (0.09, 2.01)	1.13 (0.51, 2.50)
Drug abuse/dependence	0.81 (0.22, 3.03)	1.20 (0.54, 2.68)
Other mental disorders	1.39 (0.80, 2.43)	1.21 (0.80, 1.84)
Diabetes	1.92 (0.70, 5.25)	0.88 (0.33, 2.38)
Charlson comorbidity index score	1.07 (0.87, 1.31)	1.08 (0.94, 1.24)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Notes: AD only, antidepressant monotherapy; MS only, mood stabilizer monotherapy; AD–MS, antidepressant–mood stabilizer combination therapy.

AD, antidepressant; ECT, electroconvulsive therapy; HMO, health maintenance organization; MAOIs, monoamine oxidase inhibitors; PPO, preferred provider organization; POS, point of service.

A recently published article [23] based on the elderly patients provided similar clinical indications for AD. Second-generation ADs, however, were not differentiated from the first-generation tricyclics in that study. The reference arm were patients who did not receive an AD, which could comprise patients with any other types of treatment, including no treatment. Having MS monotherapy as the reference group and focusing on adults between the age of 18 and 64 years, the results of the present study provide important information on the impact of second-generation AD medication use for bipolar depression. Nonetheless, the results are limited by the study design. First, this study used an intent-to-treat approach for which the treatment type was defined based on patients' first month of prescriptions. It is possible that patients may have discontinued the initial treatment and/or switched to other treatment type in the follow-up period, although such a phenomenon happens in randomized clinical trials too. As a sensitivity analysis, types of treatment

Table 4 Summary of second-generation antidepressant effects with propensity score matching (95% confidence intervals)

	Comparison One: AD only vs. MS only (n = 694)	Comparison Two: AD–MS vs. MS only (n = 756)
Logit models on probabilities of having mania-related visits, odds ratios	0.67 (0.42, 1.04)	0.99 (0.69, 1.43)
Negative binomial models on number of depression-related visits, incidence rate ratios	0.68 (0.56, 0.82)*	0.65 (0.52, 0.81)**
Cox models on time to first mania-related visit, hazard ratios	0.83 (0.60, 1.16)	1.08 (0.82, 1.41)
Cox models on time to first depression-related visit, hazard ratios	0.55 (0.44, 0.68)**	0.59 (0.48, 0.73)**

*$P < 0.01$, **$P < 0.001$.

Notes: AD only, antidepressant monotherapy; MS only, mood stabilizer monotherapy; AD–MS, antidepressant–mood stabilizer combination therapy. Controlled variables included demographic, clinical-related, and health-related covariates. Please see Appendices for a detailed list of controlled variables and coefficients.

were redefined according to patients' first 2 to 6 months of prescriptions. Similar study results were achieved but with a much smaller sample size. Second, this study used a 3-month washout period to provide some reasonable assurance of the start of a medication treatment. A 3-month period was used because the existing literature recognizes that bipolar depression episodes generally last for at least 2 to 3 months [24]. A longer washout period of, say, 6 months was considered, but it would have decreased the sample size dramatically. Third, the index date was defined by either the first MS use coupled with a depressive diagnosis or the first second-generation AD use after the washout period. There could potentially be dissimilarities between the patients having depressive diagnosis as index and those having AD use as index, as patients with MS monotherapy would never have an AD use as index by design. Nonetheless, because all the characteristics between the comparison groups were balanced after propensity score matching, we are confident that the study results should be valid. Fourth, although we included variables to better represent the disease severity of bipolar disorder during propensity score matching, the absence of better ratings, such as CGI-BP scale, could still limit our study results.

Based on the definition of bipolar disorder, if one manic or hypomanic episode has been observed in a patient, any depression-related diagnosis after such an episode should definitively be bipolar depression rather than MDD [1]. In fact, before the recognition of manic or hypomanic symptoms, a depressive symptom could be either bipolar depressive or major depressive. The literature indicated that, on average, a correct diagnosis of bipolar disorder is made 8 to 10 years after the onset of symptoms [25]. Knowing that bipolar depression is often underdiagnosed or miscoded as MDD, we developed an algorithm to guard against a false negative coding (i.e., bipolar depression coded as MDD). Any MDD diagnoses (296.2, 296.3, 311) that occurred after a bipolar or mania-related diagnosis (296.0, 296.1, 296.4–296.8) or earlier but no more than 90 days [24] before the bipolar or mania-related diagnosis were deemed a miscoding and considered bipolar depression [26].

For the same reason, our sample consisted of more patients on AD monotherapy than the usual treatment pattern in the United States. Many patients in our sample were treated with AD monotherapy after a miscoded MDD diagnosis (71% of the diagnosis-indexed patients with AD monotherapy and 57% with MS monotherapy), which would be truly bipolar depression based on our miscode guarding algorithm. This group of patients is less severe with bipolar symptoms as their descriptive statistics indicated. This reason could also contribute to the slightly better results of the AD monotherapy than the AD–MS combination therapy, although it is not the purpose of the study to compare these two. Less severe bipolar patients have lower symptomatic frequency, which makes it more difficult to identify dual depressive and manic features. Hence, these patients are more likely to receive a diagnosis of MDD rather than bipolar depression. Without arguing too much of the correctness of such an algorithm, we must acknowledge that with its purpose to guard against the miscoding, this algorithm might be a limitation of the study design itself, too.

We used 1:1 greedy matching for the propensity score method. The advantage is its simplicity and intuitive appeal. It is robust to the functional form of the conditional expectations and hence allows arbitrary heterogeneity of the effects in the population. A simulation suggests that matching on the propensity score is best when there are more than 20 covariates [27]. Practically, 1:1 greedy matching usually reduces the original sample size considerably, like the case in our study. Such a phenomenon can be conceived as applying the selection criteria in a randomized clinical trial. Internal validity is considered first rather than external validity. Avoiding bias is more important and should be given priority over efficiency of the estimates [28]. Nonetheless, it should be noted that the matched samples are different from the unmatched ones. In our study, less-severe patients with AD monotherapy were left out because of the propensity score matching. The study results were more applicable for the relatively severe patients.

This study focused only on the group effect of second-generation ADs. It is possible that the prescription distributions of ADs are not similar between treatment types, which may lead to skewed conclusions. For example, if most of the ADs in AD monotherapy were bupropion and most of the ADs in combination therapy were venlafaxine, the comparison would be meaningless. Therefore, we further checked the second-generation AD distributions in different treatment types (Table 5) and found that they are quite comparable for most medications.

Table 5 Second-generation antidepressants included in the study according to treatment types

	Treatment types	
Antidepressant medications	AD only (%)	AD–MS (%)
Bupropion	18.7	25.4
Citalopram	14.5	15.2
Fluoxetine	15.3	12.8
Fluvoxamine	0.8	1.1
Mirtazapine	1.9	3.6
Nefazodone	3.8	3.8
Paroxetine	19.0	14.5
Sertraline	19.9	13.0
Trazodone	9.4	15.4
Venlafaxine	6.4	8.9

Notes: AD only, antidepressant monotherapy; AD–MS, antidepressant–mood stabilizer combination therapy.

The study is based on a claims database, in which the disease symptoms are recognized and recorded by ICD-9 diagnosis codes rather than symptom descriptive texts in medical charts. It is possible that physicians or psychiatrists may not have assigned ICD-9 codes correctly and it would have been preferred if the ICD-9 codes could be validated by medical chart reviews.

Because of the available data and the follow-up time limitation, it is likely that our study included bipolar patients with relatively rapid symptomatic cycles. Patients whose symptoms occur less frequently, say, once every 2 years, would have been less likely to be observed in the data and less likely to be included in the study. In addition, although administrative databases provide a readily available source of information on large patient populations, there may be problems with the generalizability of the results because of the homogeneity of the insured population in the study.

Conclusion

This study presents empirical evidence on the relationship between second-generation AD medication use and mania- and depression-related health outcomes for patients with bipolar depression in a national sample of insured patients. Monotherapy with second-generation ADs was not found to be associated with either a higher likelihood of having mania-related visits or shorter time to next mania-related visit in bipolar depressed patients. This relationship also held for AD–MS combination therapy. Thus, our study does not support a risk of induced manic-switching with second-generation AD treatment. In addition, both second-generation AD monotherapy and AD–MS combination therapy were shown to decrease the number of depression-related visits, further supporting the efficacy of this type of treatment. Although the evidence from the study supports a favorable risk–benefit profile, more evidence from other populations including randomized clinical trials is needed to further establish the safety and efficacy of second-generation ADs in treating bipolar depression.

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