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ORIGINAL RESEARCH

Treatment Patterns Among Patients with Bipolar Disorder in the United States: A Retrospective Claims Database Analysis

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ABSTRACT

Introduction: Bipolar disorder is a chronic and complex disorder that can be difficult to treat. The objective of this retrospective study was to describe treatment patterns among patients with bipolar disorder.

Methods: Adults newly diagnosed with bipolar disorder from 2016 to 2018 were identified using the IBM® MarketScan® Commercial claims database. Patients were enrolled for at least 12 months prior to and 6 months after initial diagnosis. Lines of therapy (LOTs) were continuous treatment periods based on filled prescriptions; medications, such as antidepressants, mood stabilizers, atypical antipsychotics, benzodiazepines, stimulants, and off-label prescriptions, were recorded. All data were analyzed descriptively.

Results: A total of 40,345 patients met criteria. The most common initial episode types were bipolar II (38.1%), and bipolar I depression (29.8%), mania (12.8%), and mixed features (12.0%). Among all episode types, approximately 90% of patients received treatment (LOT1) and approximately 80% of these patients received at least one additional LOT. Across all episode types, the most common medication classes in LOT1 (n = 36,587) were mood stabilizers (43.8%), antidepressants (42.3%; 12.9% as monotherapy), atypical antipsychotics (31.7%), and benzodiazepines (20.7%); with subsequent LOTs, antidepressant (51.4–53.8%) and benzodiazepine (26.9–27.4%) usage increased. Also in LOT1, there were 2067 different regimens. Treatment patterns were generally similar across episode type.

Conclusions: Antidepressants and benzodiazepines were frequently prescribed to treat bipolar disorder despite guidelines recommending against use as frontline therapy. These results highlight the considerable heterogeneity in care and suggest that many clinicians treating bipolar disorder are not using evidence-based prescribing practices.

Keywords: Bipolar disorder; Treatment patterns; Atypical antipsychotic

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Key Summary Points

Why carry out this study?

There are limited published studies that describe how patients with bipolar disorder are treated in clinical practice.

This retrospective analysis was conducted to evaluate real-world treatment patterns among patients with bipolar disorder and assess how treatment patterns aligned with clinical practice guidelines.

What was learned from the study?

The most common medications used for patients with bipolar disorder were antidepressants, mood stabilizers, and atypical antipsychotics.

Antidepressants and benzodiazepines were commonly prescribed to patients with bipolar I depression, despite guidelines specifically recommending against use of these medications for this episode type.

Few patients were treated with guideline-recommended therapy during their first line of therapy for a first bipolar I depression or mania episode, indicating that there is an opportunity to improve care for patients with bipolar I disorder.

INTRODUCTION

Bipolar I and II disorders affect an estimated 4.5% of the adult population in the USA each year [1]. Bipolar I disorder is characterized by alternating or intertwining manic, hypomanic, and depressive episodes between periods of euthymia [2]. Bipolar II disorder, on the other hand, is defined by a pattern of depressive and hypomanic phases without the full manic episodes typical of bipolar I disorder [2]. Further, it has been reported that patients with bipolar II disorder spend more time in the depressive versus hypomanic/manic phase compared with bipolar I disorder [3]. Bipolar disorder is associated with significant functional disability and reduced quality of life (QoL) [4, 5] and imposes a substantial economic burden on the American healthcare system [6].

Guideline-recommended initial treatments for bipolar I depression are atypical antipsychotics (e.g., lurasidone and cariprazine), mood stabilizers (e.g., lamotrigine and lithium), or adjunctive therapy (i.e., a mood stabilizer and an atypical antipsychotic) [7]. In bipolar I depression, antidepressant therapy is only recommended as a fourth-line therapeutic option adjunctive to mood stabilizers [7]. For bipolar I mania, guideline-recommended treatments do not include antidepressants [7]. Instead, the recommended initial treatments are mood stabilizers and atypical antipsychotics as monotherapy or a combination of both for severe cases or those requiring hospitalization; in addition, electroconvulsive therapy is also recommended for severe cases, such as medical emergency or if pharmacotherapy is insufficient [7]. There are fewer studies that provide quality evidence (e.g., studies adequately powered, studies that assess only patients with bipolar II) to support treatment for bipolar II disorder compared with bipolar I disorder, but the 2018 International Society for Bipolar Disorders (ISBD) guidelines [8] provide some recommendations on bipolar II disorder. For acute bipolar II depression, quetiapine is recommended as first-line treatment, with lithium, lamotrigine, bupropion, sertraline, and venlafaxine recommended as second-line treatment options. The ISBD guidelines offer no specific suggestions for the acute treatment of hypomania episodes, but state that clinical evidence suggests antimanic medications are also efficacious in hypomanic episodes. First-line maintenance treatment options for bipolar II disorder include quetiapine, lithium, and lamotrigine [8].

There are many challenges associated with the management of bipolar disorder. Studies indicate that bipolar disorder is often treated inappropriately [9–11]. For example, up to 20% of patients with bipolar I disorder in the past 20 years have been prescribed antidepressant therapy without a concomitant mood stabilizer or atypical antipsychotic [9]. Additionally, an analysis of the Systematic Treatment

Enhancement Program for Bipolar Disorder (STEP-BD) study showed that antidepressants and sedatives are commonly used in bipolar disorder [11]. These practice patterns do not adhere to current guidelines. Moreover, some of the same treatments that can alleviate depression can cause mania, and some treatments that reduce mania or hypomania may cause depressive episodes [12, 13]. The use of antidepressants in bipolar disorder remains controversial. Some studies suggest that antidepressants may be safe and efficacious for the treatment of acute bipolar depression [14, 15] and for relapse prevention of bipolar II major depressive episodes [16]. Other studies [17–21] suggest that the use of antidepressant monotherapy in bipolar I disorder may be ineffective and potentially induce a switch to agitation or mania, especially with prolonged use in bipolar I depression. Further, many patients with bipolar disorder have comorbid conditions or may be at high risk for consequences of medication side effects, both of which further complicate the appropriate treatment for each individual [22]. In some cases, such as comorbid anxiety, antidepressants in combination with atypical antipsychotics or mood stabilizers may be warranted in patients with bipolar disorder [23]; however, international guidelines [8, 23, 24] consistently recommend using antidepressants with caution and avoiding monotherapy antidepressants in bipolar I disorder because of the potential risk for mood switching and rapid cycling.

This study was conducted to understand current treatment patterns for bipolar disorder in clinical practice and how they compare to recommended treatment guidelines. As such, the objective of this study was to examine real-world treatment patterns across multiple episodes and lines of therapy (LOTs) in patients who were newly diagnosed with bipolar disorder in the USA.

METHODS

Data Source

Patients newly diagnosed with bipolar I or bipolar II disorder were identified using administrative healthcare claims data from the IBM® MarketScan® Commercial Database, which included medical and outpatient pharmacy (retail and mail order) claims for services from March 16, 2015 to September 30, 2018. This study was exempt from ethics committee approval and institutional review because it is a retrospective analysis which used anonymized and de-identified data certified as fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Allergan (prior to its acquisition by AbbVie) obtained permission to access and use the IBM® MarketScan® data used in the analysis through licensing agreements.

Study Design

This retrospective, observational analysis characterized treatment patterns across multiple episodes and LOTs within each episode (Fig. 1). The baseline period was a 12-month period of continuous insurance enrollment without any bipolar disorder diagnosis. The index date was the date of bipolar disorder diagnosis (administrative medical claim) after the baseline period. The follow-up period included at least 6 months of continuous insurance enrollment following the index date.

Patient Selection

Selected patients had at least one inpatient claim with a primary diagnosis or one outpatient non-diagnostic medical claim with an International Classification of Diseases, Tenth Edition (ICD-10) diagnosis code for bipolar I or bipolar II disorder and were continuously enrolled for at least 12 months prior to (baseline period) and at least 6 months after diagnosis (follow-up period). Additionally, patients were at least 18 years of age at index and had mental health/substance abuse coverage during the variable post-index period. Patients were excluded if they had one or more inpatient or outpatient non-diagnostic medical claim(s) with an ICD-9-CM or ICD-10-CM diagnosis code for schizoaffective disorder (SAD) during the variable post-index period.

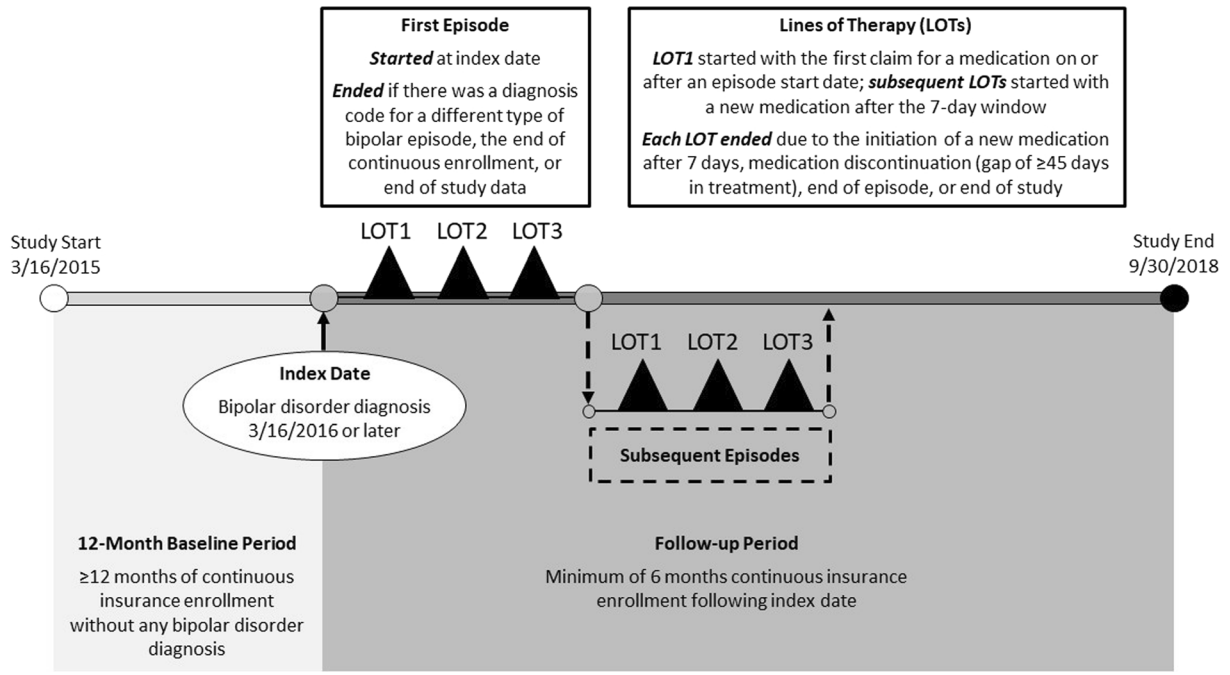

Fig. 1 Study design

Episodes

Episodes in this study were reported per the following criteria: (1) the first episode started on the index date and ended if there was a diagnosis code for a different type of bipolar episode (including codes for active disease or remission), the end of continuous enrollment, or end of study data; (2) episodes were classified into different types based on diagnosis codes: bipolar I depression, mania, mixed, depression with psychosis, mania with psychosis, mixed with psychosis, remission-depression, remission-mania, and remission-mixed; or bipolar II disorder; (3) a subsequent episode started with the observation of a bipolar disorder diagnosis different from the prior diagnosis; (4) patients were required to have active disease on the index date; therefore, a remission episode could not be classified as the first episode (but remission episodes were allowed for episodes 2 and 3); and (5) patients could not have bipolar II disorder as episode 2 or 3 following bipolar I disorder as episode 1 because clinically, a patient could not have bipolar I disorder and then be diagnosed with bipolar II disorder. Up to three mood episodes were captured for a person throughout the follow-up period.

Lines of Therapy (LOTs)

Up to three LOTs were reported for each episode. The first claim for a medication on or after an episode's start date was considered LOT1 (first line of therapy). Subsequent LOTs started with a new medication initiated after a 7-day window following the start of the previous LOT. Each LOT consisted of all medications within 7 days of the first observed treatment. A LOT was considered ended as a result of initiation of a new medication after 7 days, discontinuation (gap of at least 45 days in treatment), end of bipolar episode as defined earlier, or end of study. Overlapping days' supply of medication were appended and applied to the next LOT/episode.

Study Measures and Analyses

Demographics and Clinical Characteristics

Patient demographics at the index date included age, sex, insurance plan type, and geographical region. Clinical characteristics measured during the 12 months prior to each

episode (baseline period) included the Deyo–Charlson comorbidity index, baseline diagnoses, and baseline medication use. Length of diagnosis of bipolar disorder episodes was also recorded.

Bipolar Disorder Treatment Use

Outpatient prescription fills for the following medications were captured and used to define LOTs: atypical antipsychotics (by generic name), mood stabilizers (by generic name), antidepressants (by type), typical antipsychotics (by class), benzodiazepines (by class), stimulants (by class), and off-label prescriptions (i.e., pimavanserin, tamoxifen; by generic name). Inpatient medication use was not available in this database.

Descriptive Analyses

Categorical variables were presented as the count and proportion of patients, and continuous variables were presented as mean and standard deviation (SD). Episodes were presented overall and stratified by type; up to three episodes were presented. The episode types included bipolar I depression, mania, or mixed features (active, remission [only episodes 2 and 3]); bipolar I disorder with psychosis (active); and bipolar II disorder active (only applied to first bipolar II episode because, per DSM-5 guidelines [25], a previously defined bipolar I episode could not be classified as bipolar II episode 2 or 3). When we reported combination therapy by medication class, patients were counted for each combination; for example, a patient on an atypical antipsychotic and antidepressant combination therapy would be counted as using an atypical antipsychotic combination therapy as well as an antidepressant combination therapy. All data were analyzed descriptively; no statistical comparisons were conducted.

RESULTS

Patients

A total of 40,345 patients meeting criteria were identified from the IBM® MarketScan® Commercial database (Fig. 2).

Table 1 describes the patient demographics and baseline clinical characteristics of first episodes; the average age of all patients was 37.5 years, and the majority (63.9%) were female. In the 12-month period prior to first bipolar diagnosis, the most common baseline diagnoses were major depressive disorder (MDD; 46.4%), anxiety (44.2%), and substance use disorder (24.4%). Other baseline diagnoses included attention deficit hyperactivity disorder (ADHD), borderline personality disorder, cardiovascular disease, diabetes, overweight/obesity, and schizophrenia. The most common medications used during the year before initial bipolar disorder diagnosis were antidepressants (64.2%), mood stabilizers (43.6%), benzodiazepines (41.0%), and atypical antipsychotics (32.3%). Other baseline medications included stimulants, sedatives, anti-addiction medications, antidiabetic medications, antihyperlipidemics, antihypertensives, and other cardiac medications.

Compared to all episode types, demographics and baseline characteristics were similar for patients with bipolar II disorder (Table S1 in the supplementary material) and bipolar I depression, mania, and mixed (Table 1).

Episodes and LOTs

Episode types and mean episode length, measured as time between the start of an episode and coding change, end of continuous enrollment, or end of study data are described in Table 2. For first episodes, the most common types were bipolar II disorder (38.1%), bipolar I depression (29.8%), bipolar I mania (12.8%), and bipolar I mixed features (12.0%); these four types accounted for 93% of all first episodes. Bipolar I depression, bipolar I mania, and bipolar I mixed were the most common episode types for episodes 2 and 3. Remission episodes were uncommon. Mean episode length ranged from 333 to 441 days for all first episodes and decreased for subsequent episodes.

Among all bipolar disorder episode types, approximately 90% of patients received at least one LOT during episode 1, and approximately 80% of these patients received a second LOT

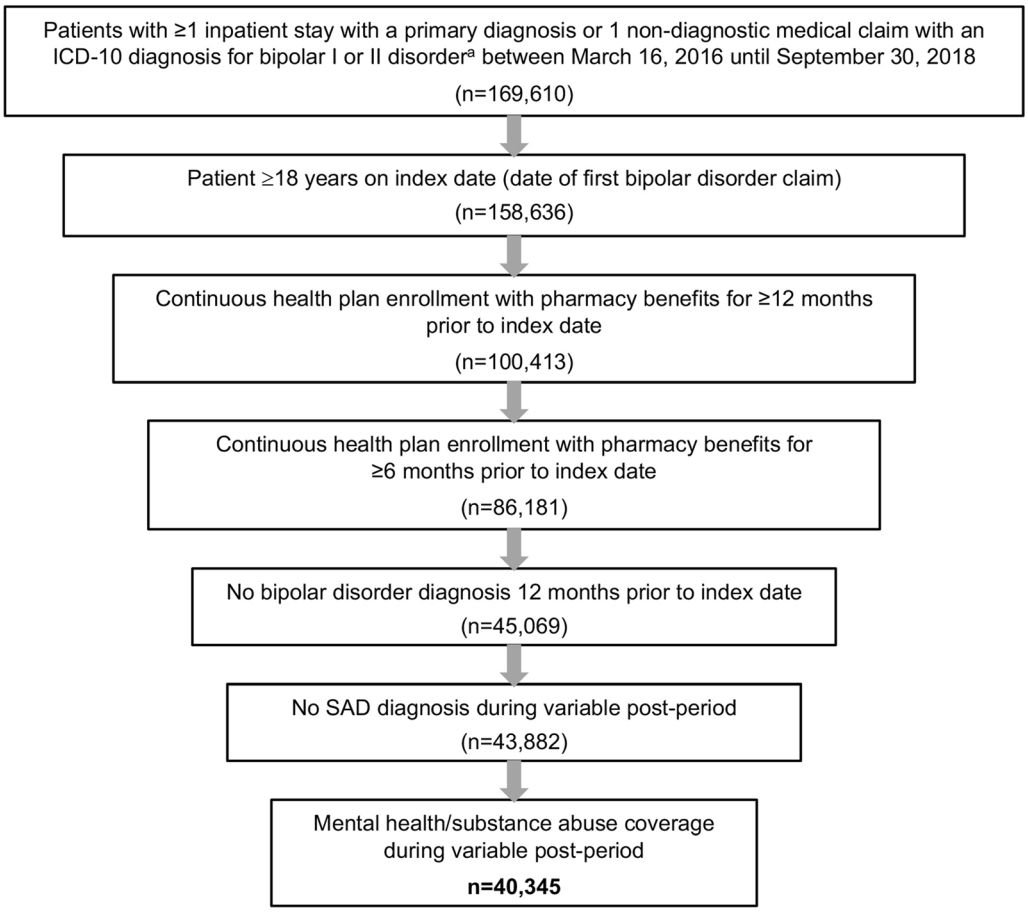

Fig. 2 Patient selection. [a]Excludes bipolar I remission (maintenance) ICD-10-CM codes. *ICD-10* International Classification of Diseases, 10th Edition, *SAD* schizoaffective disorder

(LOT2). This pattern of medication usage in the first episode (e.g., proportion of patients receiving subsequent LOTs decreased by 10–30% compared with LOT1) was generally similar for all the different episode types (Fig. S1 in the supplementary material).

Episode 1

All Bipolar Disorder Types

Of the 36,587 (90.7%) patients who received treatment for any type of initial bipolar episode, there were 2067 different individual regimens, with the top 10 accounting for 43.0% of the regimens (Table S2 in the supplementary material). Of the top 10 regimens, the most common treatments were monotherapies: lamotrigine (9.6%), selective serotonin reuptake inhibitors (SSRIs; 6.9%), and benzodiazepines (6.9%). Among all patients, the most common medication classes in LOT1 were mood stabilizers (43.8%; 16.0% for monotherapy, 27.8% in combination), antidepressants (42.3%; 12.9% for monotherapy, 29.4% in combination), atypical antipsychotics (31.7%; 10.3% for monotherapy, 21.4% in combination), and benzodiazepines (20.7%; 6.2% for monotherapy, 14.5% in combination). With subsequent LOTs, antidepressant (LOT2, 51.4%; LOT3, 53.8%) and benzodiazepine (LOT2, 26.9%; LOT3, 27.4%) usage increased (Fig. 3a).

Bipolar I Depression

Of the 11,005 (91.4%) treated patients with bipolar I depression as their first episode, there

Table 1 Patient demographics and baseline clinical characteristics of first episodes

Characteristic	All patients[a] *n* = 40,345	Bipolar I depression *n* = 12,037	Bipolar I mania *n* = 5175	Bipolar I mixed *n* = 4845
Age, mean (SD), years	37.5 (13.9)	38.4 (14.1)	38.0 (13.9)	37.5 (13.8)
18–24, *n* (%)	11,581 (28.7)	3256 (27.1)	1430 (27.6)	1368 (28.2)
25–34, *n* (%)	6713 (16.6)	1886 (15.7)	831 (16.1)	821 (17.0)
35–44, *n* (%)	7880 (19.5)	2303 (19.1)	1038 (20.1)	951 (19.6)
45–54, *n* (%)	7941 (19.7)	2531 (21.0)	1047 (20.2)	975 (20.1)
55–64, *n* (%)	6230 (15.4)	2061 (17.1)	829 (16.0)	730 (15.1)
Sex, *n* (%)				
Female	25,791 (63.9)	7752 (64.4)	3074 (59.4)	3054 (63.0)
Male	14,554 (36.1)	4285 (35.6)	2101 (40.6)	1791 (37.0)
Geographical region, *n* (%)				
South	18,410 (45.6)	5661 (47.0)	2362 (45.6)	2358 (48.7)
North Central	8799 (21.8)	2779 (23.1)	1035 (20.0)	1162 (24.0)
Northeast	7389 (18.3)	2076 (17.3)	1133 (21.9)	798 (16.5)
West	5621 (13.9)	1498 (12.4)	629 (12.2)	505 (10.4)
Unknown	126 (0.3)	23 (0.2)	16 (0.3)	22 (0.5)
Insurance plan, *n* (%)				
PPO	22,686 (56.2)	6742 (56.0)	2908 (56.2)	2761 (57.0)
CDHP	4710 (11.7)	1474 (12.3)	609 (11.8)	524 (10.8)
HMO	4182 (10.4)	1199 (10.0)	499 (9.6)	429 (8.9)
HDHP	3139 (7.8)	880 (7.3)	430 (8.3)	364 (7.5)
POS	2619 (6.5)	826 (6.9)	332 (6.4)	349 (7.2)
Comprehensive	1819 (4.5)	564 (4.7)	231 (4.5)	272 (5.6)
Other[b]	750 (1.9)	223 (1.9)	88 (1.7)	92 (1.9)
Unknown	440 (1.1)	129 (1.1)	78 (1.5)	54 (1.1)
Length of follow-up,[c] mean (SD), days	490.4 (209.4)	490.3 (207.6)	499.7 (212.9)	484.8 (210.0)
Deyo–Charlson comorbidity index, mean (SD)	0.4 (1.0)	0.5 (1.1)	0.4 (1.0)	0.4 (0.9)
Baseline diagnoses, *n* (%)				
MDD	18,709 (46.4)	5782 (48.0)	2132 (41.2)	2153 (44.4)
Anxiety	17,827 (44.2)	5249 (43.6)	2197 (42.5)	2191 (45.2)
Substance use disorder	9842 (24.4)	3069 (25.5)	1332 (25.7)	1337 (27.6)
Overweight/obesity	7475 (18.5)	2502 (20.8)	886 (17.1)	953 (19.7)

Table 1 continued

Characteristic	All patients[a] *n* = 40,345	Bipolar I depression *n* = 12,037	Bipolar I mania *n* = 5175	Bipolar I mixed *n* = 4845
ADHD	4901 (12.2)	1369 (11.4)	632 (12.2)	603 (12.5)
Diabetes	3294 (8.2)	1148 (9.5)	403 (7.8)	401 (8.3)
Cardiovascular disease	1388 (3.4)	492 (4.1)	189 (3.7)	169 (3.5)
Schizophrenia[d]	421 (1.0)	96 (0.8)	73 (1.4)	55 (1.1)
Schizoaffective disorder	377 (0.9)	100 (0.8)	54 (1.0)	62 (1.3)
Schizophreniform disorder	37 (0.1)	7 (0.1)	5 (0.1)	4 (0.1)
Borderline personality disorder	46 (0.1)	14 (0.1)	6 (0.1)	6 (0.1)
Baseline medication use, *n* (%)				
Antidepressants	25,890 (64.2)	7994 (66.4)	3014 (58.2)	3095 (63.9)
Mood stabilizers	17,570 (43.6)	5419 (45.0)	2070 (40.0)	2126 (43.9)
Benzodiazepines	16,535 (41.0)	5195 (43.2)	2066 (39.9)	2036 (42.0)
Atypical antipsychotics	13,045 (32.3)	4169 (34.6)	1615 (31.2)	1702 (35.1)
Antihypertensive drugs	9937 (24.6)	3244 (27.0)	1262 (24.4)	1211 (25.0)
Anti-addiction drugs	9791 (24.3)	3146 (26.1)	1096 (21.2)	1168 (24.1)
Antihyperlipidemic drugs	5458 (13.5)	1906 (15.8)	693 (13.4)	638 (13.2)
Sedatives	5029 (12.5)	1692 (14.1)	595 (11.5)	588 (12.1)
Antidiabetic agents (oral, injectable, insulin)	3313 (8.2)	1114 (9.3)	394 (7.6)	412 (8.5)
Stimulants	3062 (7.6)	867 (7.2)	386 (7.5)	379 (7.8)
Other cardiac drugs	1429 (3.5)	490 (4.1)	192 (3.7)	174 (3.6)
Typical antipsychotics	909 (2.3)	265 (2.2)	137 (2.7)	119 (2.5)

Demographic characteristics were measured on the first date of the first diagnosis episode. Clinical characteristics were captured during the 12-month period prior to the start date of the first episode

ADHD attention deficit hyperactivity disorder, *CDHP* consumer-driven health plan, *EPO* exclusive provider organization, *HDHP* high-deductible health plan, *HMO* health maintenance organization, *MDD* major depressive disorder, *POS* point-of service, *PPO* preferred provider organization, *SD* standard deviation

[a]Includes patients with bipolar I depression, mania, mixed, depression-psychosis, mania-psychosis, mixed-psychosis, and bipolar II episodes

[b]Other insurance plans includes EPO and POS with capitation

[c]Length of follow-up was calculated from index date to end of continuous enrollment

[d]Excludes schizoaffective disorder and schizophreniform disorder

Table 2 Episode types and lengths across all episodes

	Episode 1 *n* = 40,345	Episode 2 *n* = 7304	Episode 3 *n* = 2904
Episode type, *n* (%)			
Bipolar I depression	12,037 (29.8)	2722 (37.3)	1041 (35.9)
Bipolar I mania	5175 (12.8)	1563 (21.4)	614 (21.1)
Bipolar I with mixed features	4845 (12.0)	1422 (19.5)	613 (21.1)
Bipolar I psychosis with depression	957 (2.4)	425 (5.8)	169 (5.8)
Bipolar I psychosis with mania	1468 (3.6)	503 (6.9)	257 (8.9)
Bipolar I psychosis with mixed features	490 (1.2)	230 (3.2)	93 (3.2)
Bipolar I remission with depression	N/A	192 (2.6)	59 (2.0)
Bipolar I remission with mania	N/A	176 (2.4)	42 (1.4)
Bipolar I remission with mixed features	N/A	71 (1.0)	16 (0.6)
Bipolar II disorder	15,373 (38.1)	N/A	N/A
Length of episode, mean (SD), days			
Bipolar I depression	441.3 (230.1)	253.4 (222.0)	176.1 (192.8)
Bipolar I mania	414.1 (247.9)	222.9 (221.3)	158.9 (181.1)
Bipolar I with mixed features	406.2 (239.0)	210.2 (207.5)	154.2 (178.7)
Bipolar I psychosis with depression	349.4 (255.1)	178.6 (191.6)	124.9 (155.6)
Bipolar I psychosis with mania	346.9 (257.7)	208.5 (220.2)	158.2 (200.9)
Bipolar I psychosis with mixed features	332.9 (249.5)	203.7 (220.5)	85.1 (121.2)
Bipolar I remission with depression	N/A	237.5 (210.1)	166.5 (163.7)
Bipolar I remission with mania	N/A	235.8 (219.9)	153.5 (144.5)
Bipolar I remission with mixed features	N/A	221.8 (182.5)	189.6 (222.1)
Bipolar II disorder	438.5 (228.5)	N/A	N/A

N/A not applicable, *SD* standard deviation

were 1141 different individual regimens, with the top 10 accounting for 42.5% of the regimens (Table S2 in the supplementary material). Of the top 10 regimens, monotherapy with SSRIs (7.7%), lamotrigine (7.5%), and benzodiazepines (7.3%) were most common. Among all patients in LOT1, 14.5% of patients with bipolar I depression were treated with monotherapy antidepressants; with subsequent LOTs, monotherapy antidepressant usage slightly decreased to less than 10% of patients (Fig. 3b). For patients with acute bipolar depression (bipolar I depression or depression with psychosis), only 11.8% of patients were treated with guideline-recommended therapy [19] in LOT1 in their first episode, 9.3% in LOT2, and 55.8% in LOT3 (Table 3).

Bipolar I Mania

Of the 4503 treated patients with bipolar I mania as their first episode, there were 637 different individual regimens, with the top 10

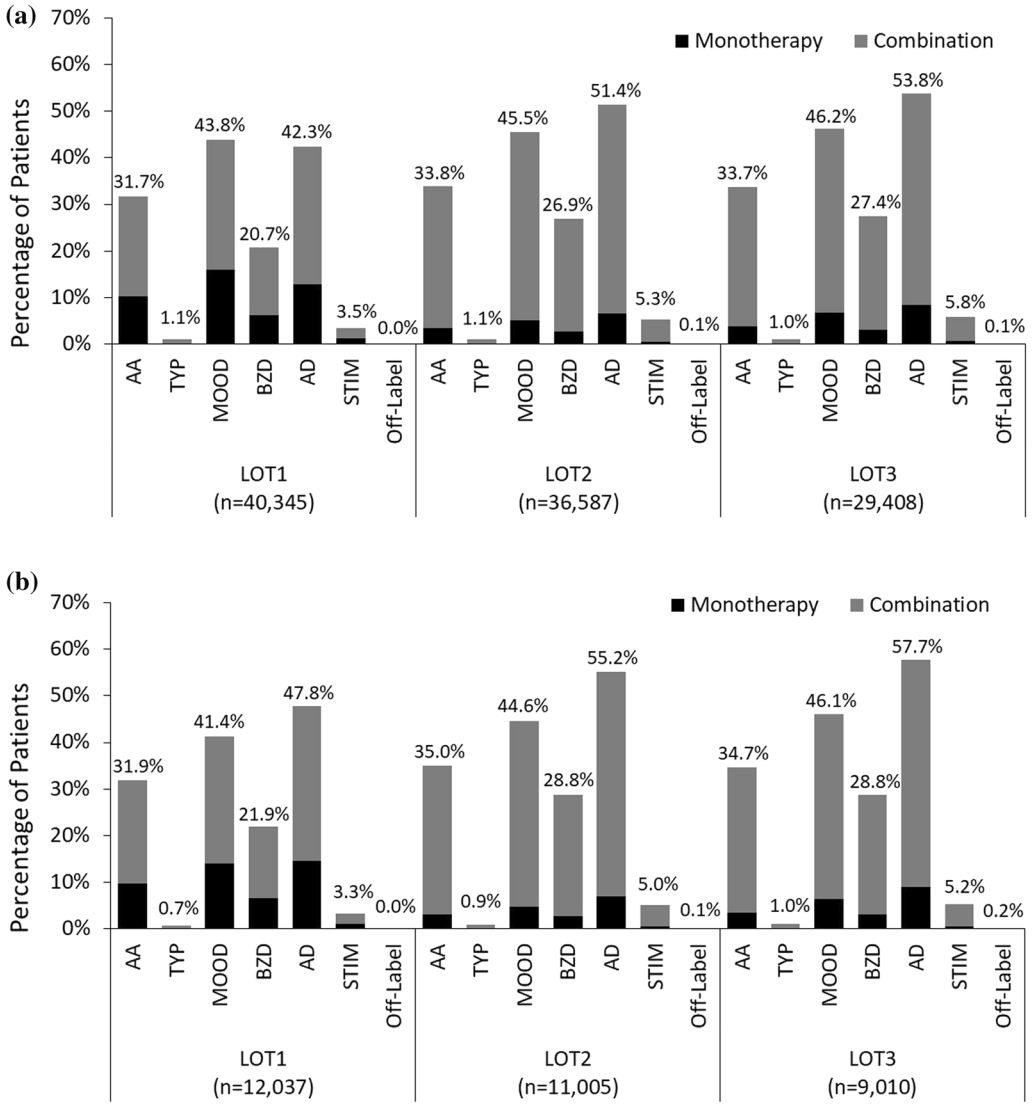

Fig. 3 Monotherapy and combination therapy[a] medications during first episodes for **a** all patients, **b** patients with bipolar I depression, **c** patients with bipolar I mania, and **d** patients with bipolar I mixed. [a]For combination therapy by medication class, patients may be counted more than once. *AA* atypical antipsychotics, *AD* antidepressants, *BZD* benzodiazepines, *LOT* line of therapy, *MOOD* mood stabilizers, *STIM* stimulants, *TYP* typical antipsychotics

accounting for 43.5% of the regimens (Table S2 in the supplementary material). Of the top 10 regimens, the most common treatments were benzodiazepines (8.8%), SSRIs (7.6%), and lamotrigine (6.2%). Among all patients in LOT1, 12.4% of patients with bipolar I mania were treated with antidepressant monotherapy, which is not recommended for the treatment of manic symptoms [19]; with subsequent LOTs, monotherapy antidepressant usage slightly decreased to less than 10% of patients (Fig. 3c). For patients with bipolar I mania or mania with psychosis, only 21.6% of patients were treated with guideline-recommended therapy [19] in LOT1 in their first episode, 4.4% in LOT2, and 0.0% in LOT3 (Table 3).

Bipolar I Mixed Features

Of the 4424 treated patients with bipolar I mixed as their first episode, there were 666 different

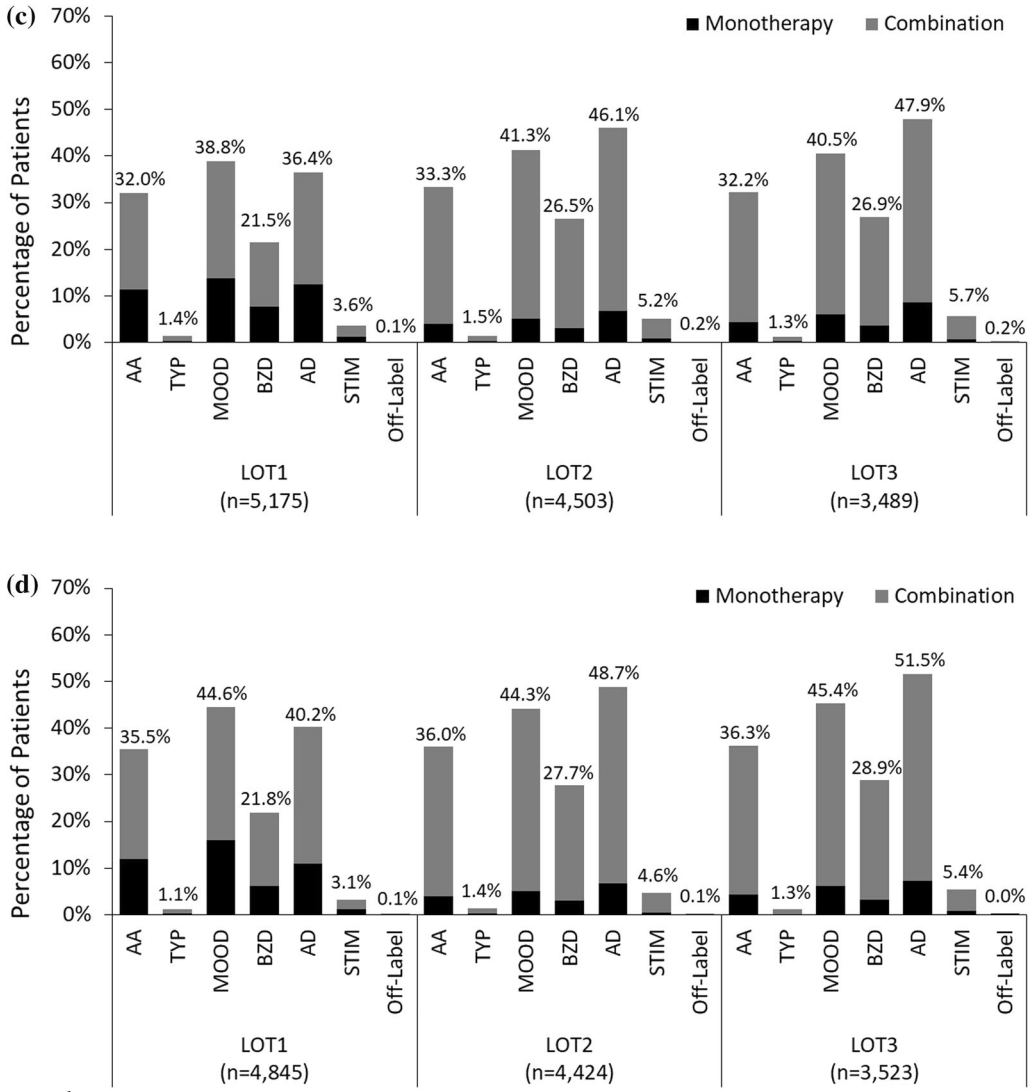

Fig. 3 continued

individual regimens, with the top 10 accounting for 40.7% of the regimens (Table S1 in the supplementary material). Among the top 10 regimens, the most common treatments were monotherapy with lamotrigine (7.7%), benzodiazepines (6.8%), and SSRIs (6.0%). Among all patients in LOT1, 20.7% of patients were treated with an SSRI as monotherapy or in combination and 19.5% were treated with another antidepressant, which increased to 26.2% and 25.4%, respectively, by LOT3 (Fig. 3d).

Bipolar II Disorder

Of the 14,106 (91.8%) treated patients with bipolar II disorder as their first episode, there were 987 different individual regimens, with the top 10 accounting for 47.9% of the regimens (Table S2 in the supplementary material). Of the top 10 regimens, the most common treatments were also monotherapies: lamotrigine (14.3%), SSRIs (7.0%), and benzodiazepines (6.3%). The most common medication classes in LOT1 were mood stabilizers (47.9%; 20.0% for monotherapy, 27.9% in combination), antidepressants (42.0%; 13.4% for monotherapy, 28.6% in combination), atypical antipsychotics (26.2%; 9.1% for monotherapy, 17.1% in combination), and benzodiazepines (19.3%; 5.8% for monotherapy, 13.5% in combination). With subsequent LOTs, atypical antipsychotic (LOT2, 30.1%; LOT3, 30.6%), antidepressant

Table 3 Medication use in episode 1 among patients with bipolar I depression and bipolar I mania compared to Florida Medicaid treatment guidelines

Medications for bipolar I depression and bipolar I mania	*n* (%)
Bipolar I depression or depression with psychosis	
LOT1 (*n* = 11,849)	
Treated with guideline-recommended LOT1	1399 (11.8)
Lurasidone or cariprazine monotherapy	245 (2.1)
Lamotrigine	846 (7.1)
Lithium	258 (2.2)
Lithium or divalproex + (lurasidone or lamotrigine)	48 (0.4)
Lithium or divalproex + cariprazine	2 (0.0)
Treated with non-guideline-recommended LOT1	10,450 (88.2)
Antidepressants	6153 (51.9)
LOT2 (*n* = 9641)	
Treated with guideline-recommended LOT2	898 (9.3)
Divalproex + lurasidone	4 (0.0)
Olanzapine + fluoxetine	0 (0)
Two LOT1 recommended drugs[a]	898 (9.3)
Treated with non-guideline-recommended LOT2	8743 (90.7)
LOT3 (*n* = 7943)[b,c]	
Treated with guideline-recommended LOT3	4432 (55.8)
Any FDA-approved bipolar medication + conventional antidepressant	802 (10.1)
Any 3 drug combination[d]	3630 (45.7)
Treated with non-guideline-recommended LOT3	3511 (44.2)
Bipolar I mania or mania with psychosis	
LOT1 (*n* = 5764)	
Treated with guideline-recommended LOT1[e]	1247 (21.6)
Lithium	141 (2.5)
Aripiprazole, asenapine, cariprazine, divalproex, quetiapine, risperidone, or ziprasidone monotherapy	784 (13.6)
Olanzapine[f]	143 (2.5)
Lithium or divalproex + (aripiprazole, asenapine, quetiapine, or risperidone)	179 (3.1)
Treated with non-guideline-recommended LOT1[e]	4517 (78.4)
LOT2 (*n* = 4390)	
Treated with guideline-recommended LOT2[e]	191 (4.4)

Table 3 continued

Medications for bipolar I depression and bipolar I mania	*n* (%)
Olanzapine[f]	49 (1.1)
Divalproex + lithium	3 (0.1)
Lithium or divalproex + second-generation antipsychotic (besides clozapine)	132 (3.0)
Carbamazepine	7 (0.2)
Treated with non-guideline-recommended LOT2[d]	4199 (95.6)
LOT3 (*n* = 3365)	
Treated with guideline-recommended LOT3	0 (0)
Clozapine + (lithium or divalproex)	0 (0)
Lithium + carbamazepine	0 (0)
Divalproex + carbamazepine	0 (0)
Treated with non-guideline-recommended LOT3	3365 (100)

FDA Food and Drug Administration, *LOT* line of therapy
[a]Does not include two antipsychotic medications
[b]Treatment reflects level 4 in guidelines as level 3 is only electroconvulsive therapy
[c]Includes observed drugs in study and does include racemic ketamine/esketamine, pramipexole, modafinil, stimulants or thyroid 3 hormone
[d]Only among observed drugs in study
[e]Only includes observed drugs in study, does not include haloperidol
[f]Level 1B in guidelines (between levels 1A and 2)

(LOT2, 53.1%; LOT3, 54.5%), and benzodiazepine (LOT2, 26.1%; LOT3, 26.4%) treatment increased, while mood stabilizer treatment (LOT2, 49.3%; LOT3, 49.0%) remained largely the same (Fig. S2a in the supplementary material).

Subsequent Episodes

Bipolar I Depression, Mania, and Mixed

For episodes 2 and 3, generally similar treatment trends were observed across episode types and LOTs. There was an increase in the percentage of patients using atypical antipsychotics, mood stabilizers, and antidepressants in LOT1 of each episode type in the second and third episodes (Figs. S3 and S4, respectively, in the supplementary material) relative to LOT1 of the first episode (Fig. 3). In addition, a higher proportion of patients were on combination therapy with these classes in subsequent episodes compared with the first episode.

Remission (Episode 2)

Similar to the first active bipolar disorder episode, the most commonly observed monotherapy or combination treatment in first remission episodes (episode 2) for bipolar I depression, bipolar I mania, and bipolar I mixed were mood stabilizers (66.7%, 60.8%, and 59.2%, respectively), antidepressants (57.3%, 35.2%, and 39.4%, respectively), and atypical antipsychotics (45.8%, 52.8%, and 39.4%, respectively) in LOT1; patterns were similar for LOTs 2 and 3 (Fig. S2b to d in the supplementary material). Few patients (n = 59, 42, and 16 for bipolar I depression, mania, and mixed features, respectively) experienced a second remission episode (episode 3).

DISCUSSION

This retrospective claims study examined real-world treatment patterns across multiple LOTs in patients who were newly diagnosed with bipolar disorder in the USA. Certain mood episodes in bipolar disorder were more common than others; for example, bipolar I depression, bipolar I mania, bipolar I mixed features, and bipolar II disorder constituted 93% of all first episodes. Medications and medication combinations were heterogenous among patients with bipolar disorder. There was substantial variability in the number of treatment patterns for LOT1 through LOT3. Across LOTs, the most commonly observed prescription fills prior to and after bipolar diagnosis were antidepressants, mood stabilizers, and atypical antipsychotics, with antidepressants being the most common. Although treatment guidelines and recommendations for bipolar II disorder are limited, the treatment patterns for bipolar II disorder were similar to those of bipolar I disorder. The main difference was the lack of lithium prescribed in the top 10 medications/combinations. Interestingly, there were very few patients who were in remission (less than 3% in all remission episodes), which may be attributed to less inclination of these patients to seek out care and, therefore, a lack of documented clinician visits. Though remission was rare overall, similar treatment patterns were seen for the patients who were in remission—most patients were also on mood stabilizers, antidepressants, and atypical antipsychotics, but mood stabilizers were the most common class instead of antidepressants.

When comparing the episode 1 results to bipolar I treatment guidelines [7], only a small portion of patients were treated with recommended regimens. In LOT1 of their first episode, only 12% of patients with bipolar I depression and 22% of patients with bipolar I mania were treated with guideline-recommended therapy. In particular, antidepressants and benzodiazepines were frequently prescribed despite current guidelines. Our study results were compared with US (Florida) guidelines [7], which are in agreement with international bipolar treatment guidelines [8, 23, 24] that consistently recommend caution with antidepressant use and avoiding antidepressant monotherapy use in bipolar I depression. However, monotherapy and combination antidepressant use in this study was high regardless of the patient population. In patients with bipolar I depression, approximately 50% were prescribed antidepressants and approximately 15% were on monotherapy antidepressant therapy in LOT1. Similarly, in patients with bipolar I mania, over 36% of patients were prescribed antidepressants and approximately 12% of patients were on antidepressant monotherapy in LOT1. The use of antidepressants is not recommended as a first-line treatment or as monotherapy in bipolar I depression and specifically not recommended for the treatment of bipolar I mania. Benzodiazepines may be used as adjunctive treatment for acute mania but are otherwise not recommended [7]; however, they were frequently prescribed and filled in all patient populations (approximately 20% in LOT1, with more than 5% as monotherapy, and more than 25% in subsequent LOTs). In contrast, guidelines commonly highlight the value of atypical antipsychotics in the treatment of bipolar disorder [7, 8]; however, only about one-third of patients, regardless of patient population (bipolar I depression, bipolar I mania, or bipolar I mixed), were prescribed atypical antipsychotics. Given these results, there appears to be a large gap in current prescribing patterns and guideline recommendations, indicating that many patients with bipolar I disorder may not be receiving adequate or appropriate care.

The results of this study are consistent with previous studies that demonstrate bipolar disorder is often treated inappropriately [9, 10]. In the claims database analysis by Rhee and colleagues (2020) [9], which examined 20-year trends in the pharmacologic treatment of bipolar disorder in the outpatient care setting, prescription of an antidepressant without a mood stabilizer was high among patients with bipolar disorder and increased over time from 17.9% (1997–2000) to 40.9% (2013–2016). Further, prescription of an antidepressant without a mood stabilizer or atypical antipsychotic

remained relatively constant over time—from 14.9% (1997–2000) to 19.5% (2005–2008), then to 16.6% (2013–2016). Similarly, in a systematic review by Greene and colleagues (2018) [10], it was found that 30–60% of patients with bipolar disorder did not receive appropriate treatment, which was defined as the use of guideline-recommended therapy without the use of antidepressants and other psychotropic medications. Also in this study, the most common baseline diagnoses among all patients with bipolar disorder were MDD, anxiety, and substance use disorder, which is consistent with previous studies. Comorbid anxiety disorder has been reported in a third of patients with bipolar disorder [26] and substance use disorders are also highly prevalent (more than 50%) among patients with bipolar disorder [27]. Comorbid conditions, such as anxiety, are often treated with benzodiazepines, which can complicate treatment for bipolar disorder; as such, comorbidities may contribute to the prescription of medications that do not align with bipolar treatment guidelines. Given the high prevalence of antidepressant, mood stabilizer, and atypical antipsychotic use during the baseline period, it is also possible that some of these patients were previously misdiagnosed with MDD, which has been reported to be common in the literature [28]. Since the depressive phase of bipolar disorder is more enduring and debilitating than mania or hypomania [3, 29], patients often seek treatment for depressive symptoms; as a result, these symptoms may be misdiagnosed as unipolar depression. All of these issues can confound and lead to inappropriate treatment of both diagnosed and possibly undiagnosed bipolar disorder.

In general, it has been estimated that between 40% and 50% of patients with bipolar disorder are nonadherent or partially adherent to their treatment [30]. There are many factors associated with nonadherence, including but not limited to adverse effects of medications, the complexity of medication regimens, comorbid substance misuse, and poor therapeutic alliance [31]. Nonadherence to therapy has been associated with increased risk of relapse, recurrence, hospitalization, suicide, and treatment costs [32]. The proportion of patients in this analysis who did not fill medications was high, ranging from 10% to 20% of patients, depending on episode type and number, but this may partly be attributed to the occurrence of short episodes, end of episodes, or effective LOT1 therapy. It is also possible that treatments that are inconsistent with guidelines may be exacerbating nonadherence rates in patients with bipolar disorder. In this study, many patients appeared to be inappropriately prescribed benzodiazepine or antidepressant treatment. While benzodiazepines can be helpful, there is growing concern about misuse, as this medication class can influence decision-making, increase risk of falls, and negatively affect memory [33]. Also, antidepressant therapy use in patients with bipolar disorder may induce rapid cycling [34], which can lead to significant additional challenges. Further research is needed to determine whether prescribing practices that are more consistent with guideline recommendations can improve low adherence rates in patients with bipolar disorder.

The results of this current study should be interpreted within its limitations, most of which are inherent to claims database analyses. The study was limited to individuals with commercial health coverage; therefore, these results may not be generalizable to patients with bipolar disorder who have other insurance, such as Medicaid or Medicare, or no insurance coverage. Selection bias may have occurred because patients with less than defined minimum continuous enrollment were excluded to allow for adequate follow-up time to observe diagnoses and LOT(s). As with all claims data, there is a potential for data coding and/or entry errors, including the potential for missed or misclassification of bipolar episode types, comorbidities, or medication use. In addition, prior diagnoses of bipolar disorder or other conditions might have been missed as a result of limitations of the databases. Also, the exact length of an episode relied on diagnoses in claims; therefore, there is the potential that remission may not have been coded accurately or that patients may not have returned to see their provider when their episodes ended. Further, bipolar treatment status was based on observable treatment and diagnosis data, which may not reflect the true

clinical course of disease and treatment. Medication use was based on filled prescriptions, and prescriptions that were written but not filled, as well as inpatient medications, were not captured. Because some medications have on- and off-label indications, the diagnosis for which medications were prescribed cannot be precisely determined for all cases. Monotherapy antidepressant usage was defined as no use of atypical antipsychotics or typical antipsychotics, mood stabilizers, benzodiazepines, stimulants, or off-label medications (i.e., pimavanserin or tamoxifen); therefore, it is possible that a patient on monotherapy antidepressant could have been taking a sedative/hypnotic at the same time.

CONCLUSION

The results of this retrospective claims study highlight the large heterogeneity in regimens used to treat bipolar disorder and a clear gap between clinical guideline recommendations for the treatment of bipolar disorder and the prescribing patterns observed in clinical practice. The finding that clinical guidelines were not well followed in this study identifies an opportunity to improve adherence to recommended treatment regimens and the potential of newer therapies to address this need.

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Compliance with Ethics Guidelines. This study was exempt from ethics committee approval and institutional review because it is a retrospective analysis which used anonymized and de-identified data certified as fully compliant with US patient confidentiality

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Data Availability. Data that support the findings of this study were used under license from IBM® Watson Health™. Restrictions apply to the availability of these data, which are not publicly available and cannot be shared.

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