REVIEW

Real-World Patterns of Utilization and Costs Associated with Second-Generation Oral Antipsychotic Medication for the Treatment of Bipolar Disorder: A Literature Review

Michael J Doane[1]
Kristine Ogden [ID][2]
Leona Bessonova[1]
Amy K O'Sullivan[1]
Mauricio Tohen[3]

[1]Health Economics and Outcomes Research, Alkermes, Inc., Waltham, MA, USA; [2]Evidence, Worldwide Clinical Trials, Morrisville, NC, USA; [3]Department of Psychiatry and Behavioral Sciences, University of New Mexico, Albuquerque, NM, USA

Correspondence: Leona Bessonova
Health Economics and Outcomes Research, Alkermes, Inc., 852 Winter Street, Waltham, MA, 02451-1420, USA
Tel +1 781 609 6439
Email leona.bessonova@alkermes.com

Objective: Treatment with second-generation antipsychotics (SGAs) for bipolar disorder, including bipolar I disorder (BD-I), is common. This review evaluated real-world utilization patterns with oral SGAs in the United States (US) for bipolar disorder (and BD-I specifically when reported) and economic burden associated with these patterns.

Methods: Structured, systematic searches of MEDLINE®, EMBASE®, and National Health Service Economic Evaluation Database identified primary research studies (published 2008–2018) describing real-world SGA use in adults with bipolar disorder/BD-I.

Results: Among 769 studies screened, 39 met inclusion criteria. Most studies (72%) were analyses of commercial or Medicare/Medicaid claims databases. Patient-related (eg, demographic, comorbidities) and disease-related (eg, mania, psychosis) factors were associated with prescribed SGA. Suboptimal utilization patterns (ie, nonadherence, nonpersistence, treatment gaps, medication switching, and discontinuation) were common for patients treated with SGAs. Also common were SGAs prescribed with another psychotropic medication and SGA combination treatment (use of ≥2 SGAs concurrently). Suboptimal adherence and SGA combination treatment were both associated with increased health care resource use (HCRU); suboptimal adherence was associated with higher total direct medical and indirect costs.

Limitations: Different definitions for populations and concepts limited between-study comparisons. Focusing on SGAs limits contextualizing findings within the broader treatment landscape (eg, lithium, anticonvulsants). Given the nature of claims data, prescribing rationale (eg, acute episodes vs maintenance) and factors influencing observed utilization patterns could not be fully derived.

Conclusion: Despite increased use of SGAs to treat bipolar disorder over the last decade, reports of suboptimal utilization patterns of SGAs (eg, nonadherence, nonpersistence) were common as was combination treatment. Patterns of SGA use associated with additional HCRU and/or costs were suboptimal adherence and SGA combination treatment; economic consequences associated with other utilization patterns (eg, nonpersistence) were unclear. Strategies to improve SGA treatment continuity, particularly adherence, may improve clinical and economic outcomes among people living with bipolar disorder.

Keywords: adherence, antipsychotics, economics, mania, mood disorders, prescribing patterns, review

Introduction

Bipolar disorder is a complex and severe mental health disorder that encompasses a variety of subtypes marked by extreme shifts in mood and energy that can lead to cognitive, functional, and social impairment.[1,2] The bipolar I disorder (BD-I) subtype, defined as having ≥1 lifetime manic episode,[3] accounts for approximately one-quarter of bipolar disorder cases in the United States (US).[4] BD-I has a lifetime prevalence of 2.1% and the average age of onset of BD-I is 22 years in the US.[2] It is debilitating disorder associated with significant medical and psychiatric comorbidities, as well as high rates of premature mortality resulting from both medical comorbidities and suicide.[2,3]

Over 90% of those with BD-I who experience a single manic episode transition to having recurrent mood episodes,[3] necessitating long-term clinical management involving pharmacologic treatment.[1,5,6] A variety of medications are approved to treat or prevent manic episodes, such as "traditional" mood stabilizers (eg, lithium, anticonvulsants including valproate, lamotrigine, and carbamazepine) and antipsychotics. Medication prescribed to resolve an acute episode is generally continued longer-term to prevent new mood episodes and improve patients' overall functioning.[1,7] Guidelines recommend that choice of medication is individualized, informed by response to previous medication(s), patient preferences, the rapidity of response required (combination regimens tend to work more quickly than monotherapy), severity of mania, concerns with adherence, and safety and tolerability profiles.

There are multiple second-generation antipsychotics (SGAs) that are first-line options for initial mood-stabilizing treatment in patients with BD-I, either as monotherapy or in combination with "traditional" mood stabilizers. As of May 2020, seven oral SGAs (aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, and ziprasidone) have been approved by the US Food and Drug Administration (FDA) to treat BD-I acute manic/mixed episodes or as BD-I maintenance therapy.[8] The first regulatory approvals for SGAs to treat BD-I were granted 20 years ago, and over the period since, the volume of outpatient prescriptions for SGAs has outpaced those for "traditional" mood-stabilizing medications.[9–11] From 2013 to 2016, the proportion of outpatient visits that included an SGA prescription was 52.7% compared to 26.4% for those prescribed any mood stabilizer.[9]

BD-I is associated with considerable disease and economic burden, as well as reduced quality of life, relative to other subtypes of bipolar disorder.[2,3,12,13] To better understand real-world use of SGAs to treat patients with mania or predominately manic symptoms in the US, this review was conducted to: 1) characterize real-world utilization patterns with oral SGAs in patients with BD-I [or bipolar disorder in general where BD-I estimates were not available]; and 2) report the relationship between these patterns and HCRU and/or associated medical costs.

Materials and Methods

MEDLINE®, MEDLINE® in-process, EMBASE®, and the National Health Service Economic Evaluation Database (NHS EED) were searched for primary research studies published between 1 January 2008 and 9 July 2018, and abstracts from relevant conferences published between 1 January 2015 and 9 July 2018. Systematic, database-specific search strategies were created using terms related to disease, intervention, and outcomes, and were limited to English-language publications. Structured searches utilized the following Medical Subject Heading terms along with keyword equivalents: bipolar and related disorders, antipsychotic agents, costs and cost analyses, drug prescriptions, drug utilization, and medication adherence. The full search strategy is reported in the Supplementary Material.

The search period for published articles was selected for multiple reasons. First, it captured a decade of published literature on the use of SGAs for the treatment of bipolar disorder at the time the review was conducted. Secondly, since SGAs were first approved in 2001 in the US for the treatment of bipolar disorder, identified papers were likely to describe utilization patterns of SGAs when they were available as an approved treatment for bipolar disorder. Thirdly, most included papers were published after the passage of two federal laws (Mental Health Parity and Addictions Equity Act [MHPAEA] in 2008 and Affordable Care Act [ACA] in 2010, respectively) that changed the insurance landscape and substantially improved mental health pharmacy benefits for patients in the US.[14] Finally, a search of conference abstracts from 2015 and 2018 was included to discover any relevant data that may not have been published as a manuscript.

Studies were included if 1) the population of interest was adults with BD-I, mixed subtypes of bipolar disorder including BD-I, or bipolar disorder generally; and 2) the study evaluated choice and dosing of SGAs,

patterns of SGA use (eg, adherence, persistence), treatment-specific outcomes (eg, side effects), HCRU, and costs. Papers reporting HCRU or costs were included in this review. Scoping searches informed the broader criterion for study population that included general/mixed bipolar disorders in addition to BD-I, as few studies in pilot searches reported data specific to BD-I patients. Additionally, inclusion in this review was limited to studies conducted in real-world settings (ie, not randomized controlled trials or economic evaluations of specific agents) describing cohorts of at least 100 patients in the US over a period of at least six months. Studies were excluded if they focused on narrow or transient bipolar subtypes (eg, bipolar depression, postpartum bipolar disorder). Review articles were not included, but their reference lists were searched for studies that met inclusion criteria but were not captured via the systematic search.

Article titles and abstracts were screened by a single reviewer. In cases of uncertainty, a second reviewer evaluated the title and abstract to confirm inclusion for full-text review. Full-text review was also performed by a single reviewer, with queries resolved through discussion with a second reviewer. Data from included studies were extracted by one researcher into a structured spreadsheet, which was then validated by a second researcher against source publications. Disagreements on the extracted data were flagged and resolved by discussion between the two researchers. Data specific to BD-I were extracted separately where possible.

Costs were converted to 2018 US dollars (USD), using the Consumer Price Index (CPI) for Medical Care, to facilitate descriptive comparisons across studies reporting similar outcomes.[15] If cost-year was not reported, the cost-year was assumed to be the last year of the reported observation period.

Results

A total of 2041 citations were identified across all database searches; all records were combined, and duplicate records and excluded publication types were flagged electronically and removed. The titles and abstracts of the remaining 769 abstracts were screened to determine inclusion. After screening and full-text review, 39 studies met inclusion criteria. Of these, 28 studies (72%) were analyses of commercial or Medicare/Medicaid claims databases and six studies (15%) reported data specific to patients with BD-I. Thirty-seven studies reported the period of data collection (1998–2014); most of these studies (92%) evaluated data collected prior to 2011. Figure 1 presents a PRISMA diagram showing the search and selection process.

Twenty-two studies (56%) reported HCRU or costs of treatment with oral SGAs. Of these, the most frequently studied SGA agent was quetiapine (73%), followed by risperidone (68%), olanzapine (64%), aripiprazole (59%), ziprasidone (50%), and lurasidone (5%). Since most papers were retrospective studies of health care claims, papers did not document whether SGA prescriptions represented treatment for an acute episode or maintenance. Several studies reported aggregated evidence pertaining to SGAs but did not specify the route of administration (ie, oral vs injection), and the route could not be inferred contextually. A list of FDA-approved SGAs for the treatment of BD-I and the chronology of their approvals are included in the Supplementary Material.

Trends in SGA Use and Dosing
Trends in SGA Use

Results of studies suggest that SGA use increased rapidly from 1998 to 2011. In an analysis of Department of Veterans Affairs (VA) health care claims data between 2003 and 2010, SGAs replaced lithium, valproate, and carbamazepine/oxcarbazepine as the most commonly initiated mood-stabilizing treatments for bipolar disorder by 2007.[11] A study of commercial health care claims for outpatient visits for bipolar disorder reported SGA prescribing grew from 18% to 49% between 1998 and 2009. This trend began with off-label use, most commonly with olanzapine and risperidone, prior to the first FDA approvals of SGAs in BD-I.[10]

Another study examined trends in the mix of SGAs prescribed at a bipolar disorder specialty clinic over a 12-year period (2000–2011). During this interval, use of quetiapine and aripiprazole more than doubled, while use of olanzapine and risperidone decreased by more than half. It was suggested that these trends may have been driven by differences in tolerability (eg, fewer side effects associated with aripiprazole, weight gain observed with olanzapine, and extrapyramidal symptoms associated with risperidone), and by improved efficacy observed with quetiapine in bipolar depression.[16]

SGA Dosing

Eight studies described dosing patterns for aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone (Table 1). Seven papers reported daily doses for quetiapine

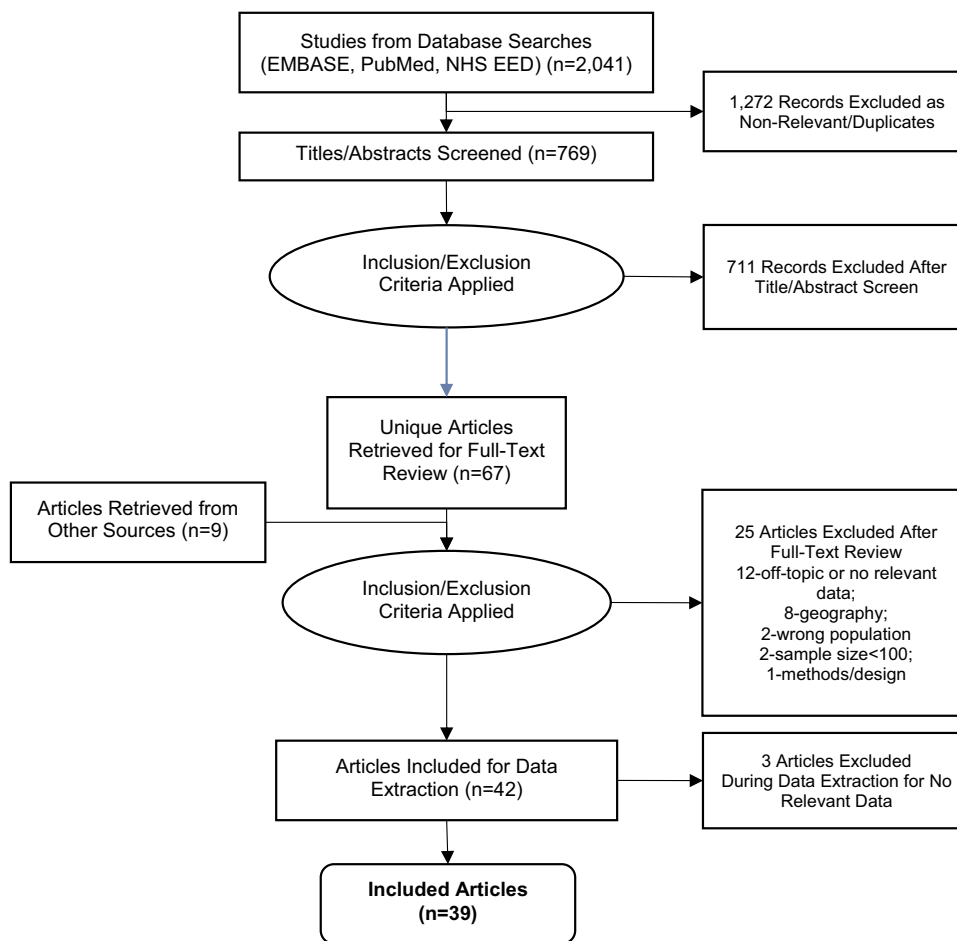**Figure 1** Search Results and Study Selection.
Note: Articles retrieved from other sources refer to papers identified from bibliographic review of relevant published systematic reviews. PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10). Creative Commons.[57]
Abbreviation: NHS EED, National Health Service Economic Evaluation Database.

that fell below the recommended dose range specified in the product label.[17–23] Due to its sedating properties, three studies suggested low dose quetiapine may have been prescribed to treat insomnia and/or anxiety; however, the prescribing rationale for subtherapeutic dose ranges reported could not be confirmed.[18,20,24] Daily doses reported for the other four SGAs generally corresponded to the lower end of the recommended dose range in product labels,[17–23] with two separate analyses suggesting that dosing at the lower end of therapeutic ranges may be associated with attempts to manage side effects and improve tolerability.[20,22] Another study of Medicaid patients with bipolar disorder for whom oral SGAs were prescribed (study period 2000 to 2008) found that fewer than half (45%) received clinically recommended doses after two months of treatment. The proportion of patients receiving doses lower than recommended varied by SGA;

the majority of patients receiving quetiapine (72%) received doses below the clinically recommended range, followed by risperidone (45%), olanzapine and ziprasidone (both 35%), and aripiprazole (20%).[24] A prospective naturalistic study (reporting period 1998–2005) reporting on the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) found that average daily doses of some SGAs were higher in patients treated with more than one SGA compared to those on SGA monotherapy.[18] In a separate analysis from STEP-BD, SGA dosing varied by patient age: younger (vs older) patients were prescribed higher doses for four out of five SGA agents studied.[17]

Choice of SGA

Prescribing patterns described in the literature suggest patient-related (age, gender, race, comorbidities, and

Table 1 SGA Dosing

Study	Data Source [Study Period] Sample	Dose Findings Reported	Dose, mg [Current Recommended Range]				
			Aripiprazole [10–30mg]	Olanzapine [5–20mg]	Quetiapine [400–800mg]	Risperidone [1–6mg]	Ziprasidone [80–160mg]
Al Jurdi et al, 2008[17]	STEP-BD study [1998–2005] n=3615 (67.6% BD-I)	Mean daily dose, overall sample	15.99	9.2	224.79	1.37	90.16
Brooks et al, 2011[18]	STEP-BD study [1998–2005] n=1958 (72% BD-I)	Mean daily dose, SGA monotherapy	16	10	269	2	92
Gianfrancesco et al, 2008[19]	Commercial claims [1999–2004] n=8750 Tx episodes* (70% M/M)	Mean daily dose in any 3-month segment (M/M group), minimum/maximum	13/16.4	9.0/9.7	172.8/239.7	1.7/2.0	76.8/88.7
Jing et al, 2009[21] and Kim et al, 2009[23]	Commercial claims [2003–2006] n=6162 (BD) **	Mean daily dose, starting/maximum	11.2/12.4	9.3/10.2	147/169.8	1.6/1.8	90.3/100.2
Jing et al, 2011[20]	Medicaid claims [2003–2008] n=22,479 (BD)	Mean daily dose, starting/maximum	11.8/13.7	8.2/9.6	149/194	1.4/1.7	80.4/94.4
Kim et al, 2011[22]	Commercial claims [2003–2006] n=7169 (BD)	Mean daily dose, starting/maximum	11.8/13.4	7.8/8.7	140.3/172.2	1.6	83.2/95.5
Rascati et al, 2011[24]	Medicaid claims [2002–2008] n=2446 (BD)	Mean daily dose for patients with clinically recommended doses	16	13	450	3	126

Notes: Current recommended ranges listed are sourced from product package inserts. *A treatment episode was defined as period consisting of ≥2 sequential antipsychotic prescriptions. **This is one dataset that was published in two different analyses.
Abbreviations: BD, bipolar disorder; BD-I, bipolar I disorder; M/M, manic/mixed; SGA, second-generation antipsychotic; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder; Tx, treatment.

treatment history) and disease-related factors (clinical symptoms, eg, presence of mania or psychosis) may influence prescribers' choice of SGA. Younger patients (age 25–34 years) were less likely to receive risperidone (vs olanzapine), while older patients (age 45–64 years) were less likely to receive quetiapine (vs olanzapine). Compared with olanzapine, African-American patients were more likely to receive risperidone and women were more likely to receive quetiapine.[25] Other patient-related factors associated with prescribers' choice of SGA were the presence of comorbid metabolic conditions (eg, diabetes, obesity); for example, selecting a regimen less likely to induce additional weight gain.[11,25,26] Another study found patients who received treatment with lithium were less likely to be prescribed SGA medications.[27]

Disease-related factors associated with initiating SGA treatment included having a complex clinical profile,[26] presence of psychosis,[11,27] mania, or receiving treatment in an inpatient (vs outpatient) setting.[27] Additionally, patients' pre-existing risks for adverse events (AEs) can limit the choice of SGA prescribed. A retrospective analysis estimated the prevalence of pre-existing risk factors for AEs and potential drug–drug interactions for a cohort of bipolar patients newly initiating SGA treatment. After comparing patients' comorbid conditions and concomitant medications against the warnings and precautions from product package inserts, the prevalence of pre-existing AE risk factors was estimated to range from 25% to 88% by individual SGA (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone).[28]

Utilization Patterns with Oral SGA Medication

Twenty-three studies described real-world utilization patterns observed with oral SGAs including adherence, persistence, treatment gaps, medication switching, discontinuation, and combination treatment (use of ≥2 concurrent psychotropic medications). Suboptimal treatment outcomes reported in association with these patterns are described in the sections that follow, noting authors' definitions for these measures.

Adherence

Studies reporting on adherence are shown in Table 2. Some studies reported on adherence to bipolar disorder medication aggregated across several drug classes where SGA-specific adherence data were not available.

Medication possession ratio (MPR) was the most common measure of adherence, and many analyses of health care claims defined adherence as an MPR of ≥0.8.[24,29–31] Utilizing this definition, fewer than 39% of patients with BD-I were adherent with their oral SGA medication at one year in two separate studies.[30] A study of bipolar disorder patients taking SGAs, first-generation antipsychotics (FGAs), or mood stabilizer medications found about one-third (35.3%) were adherent with their regimen over a year of follow-up.[29] There were three analyses that reported relatively high adherence rates for patients prescribed antipsychotics (MPRs ranged from 0.80 to 1.02);[19,32,33] however, these adherence rates may have been due to assessing MPR over treatment episodes (defined as period of ≥2 sequential antipsychotic prescriptions), rather than over a discrete evaluation period (eg, 1 year).

Other studies collected data on medication adherence via self-report from patients, and reported adherence estimates that are similar to those calculated using MPR. During 48,287 follow-up visits among 3640 patients, fewer than half (46.4%) self-reported being adherent with their bipolar disorder medications, which was defined as having missed fewer than 25% of total doses of any one medication.[34] In another patient survey, 33.8% self-reported missing at least one dose of bipolar disorder medications in the prior 10 days.[35]

Less frequently utilized metrics of adherence included cumulative medication acquisition (CMA), cumulative medication gap (CMG), and proportion of days covered (PDC). A cost analysis of Medicaid claims for bipolar disorder patients newly started on SGA monotherapy with olanzapine, risperidone, or quetiapine reported adherence over a 1-year period as measured by CMA and CMG.[25] Across the three treatment cohorts, similar rates were reported for CMA (70% to 76%) and CMG (35% to 38%), respectively. An analysis of multi-state Medicaid claims for bipolar disorder patients newly prescribed SGA therapy reported a PDC of 72% over 1 year of follow-up.[36]

Four analyses evaluated sociodemographic, clinical, and/or treatment-related characteristics associated with suboptimal adherence with oral SGA therapy, which included comorbid substance use disorder,[19,31] a history of suicide attempts,[24] and older age (Table 3).[19,24,33] Two studies examined adherence by prescribed SGA dose. An analysis of commercial health care claims reported those with predominately manic/mixed symptoms who received

Table 2 Adherence with SGAs and BD Medications (Multiple Classes Including SGAs)

Study	Data Source [Study Period]	Sample	Adherence Findings
Bagalman et al, 2010[29]	Commercial claims [2001–2004]	n=1258 (BD) Employed patients receiving psychotropic medication(30.6% index oral SGA)	• At 1 year, mean MPR was 0.58. • Only 35.3% of employees were adherent (MPR ≥0.8) with their BD medication after 1 year.
Baldessarini et al, 2008[35]	Cross-sectional study [2001–2005]	n=429 (79.0% BD-I) Patients recruited by their prescribing physician for a survey(61.3% receiving an antipsychotic)	• Self-report of missing ≥1 dose of BD medication was 33.8% over a 10-day recall period.
Chen et al, 2013[30]	Commercial, Medicare, and Medicaid claims [2005]	n=16,807 (BD-I) Patients newly initiating SGA monotherapy	• At 1 year, mean MPR was 0.19 (overall). • Adherence (MPR ≥0.8) was 8.3% to index SGA after 1 year.
Gianfrancesco et al, 2008[19]	Commercial claims [1999–2004]	n=8750 treatment episodes* (70% M/M) Patients receiving SGA or FGA monotherapy (95% SGA)	• In any 3-month period, mean MPR ranged from 0.8 to 1.02 (M/M cohort) over the 15-month evaluation period.
Gianfrancesco et al, 2008[32]	Commercial claims [1999–2004]	n=8770 treatment episodes* (70% M/M) Patients receiving SGA or FGA monotherapy (95% SGA)	• In any 3-month period, mean MPR ranged from 0.87 to 0.96 (M/M cohort) over the 15-month evaluation period.
Gianfrancesco et al, 2008[33]	Commercial claims [1999–2005]	n=5531 treatment episodes* (69% M/M) Patients initiated on quetiapine or risperidone, alone and in various MS+ADT combinations	• Over a 150-day period, mean MPR was 0.94 (quetiapine) and 0.91 (risperidone) in the monotherapy groups and ranged from 0.86 to 1.00 in the combination treatment groups.
Hassan and Lage, 2009[40]	Commercial claims [2000–2006]	n=1973 (BD) Hospital discharges with an SGA/FGA prescription (98% SGA)	• At 1 year, mean MPR was 0.4565. • The proportion of patients with MPR ≥0.75 was 26.76%.
Lage and Hassan, 2009[39]	Commercial claims [2000–2006]	n=7769 (BD) Patients with ≥1 SGA/FGA claim(95% SGA)	• At 1 year, mean MPR was 0.417. • The proportion of patients with MPR ≥0.75 was 21.3%.
Lang et al, 2011[31]	Medicaid claims [2004–2006]	n=9410 (BD-I) Patients with ≥1 SGA/FGA claim(83.1% oral SGA)	• Among patients receiving oral SGA, mean MPR was 0.63 and only 38.9% were adherent (MPR ≥0.8) at 1 year.
Perlis et al, 2010[34]	Prospective longitudinal cohort study [1998–2005]	n=3640 (BD) Patients receiving ≥1 psychotropic medication	• Across all study visits, 46.4% of patients reported adherence with BD medication.

(Continued)

Table 2 (Continued).

Study	Data Source [Study Period]	Sample	Adherence Findings
Qiu et al, 2009[25]	Medicaid claims [2000–2005]	n=838 (BD) Patients receiving monotherapy with olanzapine, risperidone, or quetiapine	• Adherence with index SGA, as measured by CMA and CMG, was similar across treatment groups at 1 year. CMA ranged from 70% to 76% and CMG ranged from 35% to 38%.
Rascati et al, 2011[24]	Medicaid claims [2002–2008]	n=2446 (BD) Patients initially prescribed SGA therapy	• At 1 year, 58% of patients prescribed a clinically recommended dose of an index SGA were adherent (MPR ≥0.8).
Seabury et al, 2014[36]	Medicaid claims [2001–2008]	n=170,596 (BD) Patients newly initiated on SGA therapy	• At 1 year, the mean proportion of days covered over 12 months for patients with BD was 72%.

Notes: *A treatment episode was defined as period consisting of ≥2 sequential antipsychotic prescriptions. CMA calculated as the sum of days' supply of all SGA prescriptions in the 12-month treatment period after the index date divided by total days between the date of the first fill to the date of the last refill. CMG was calculated as the ratio of total days without treatment divided by total days between the first fill and last refill date.
Abbreviations: ADT, antidepressant therapy; BD, bipolar disorder; BD-I, bipolar I disorder; CMA, cumulative medication acquisition; CMG, cumulative medication gap; FGA, first-generation antipsychotic (also known as typical antipsychotics); M/M, manic/mixed; MPR, medication possession ratio; MS, traditional mood stabilizer medication; SGA, second-generation antipsychotic.

risperidone, olanzapine, and FGAs had reduced adherence (MPR) with higher doses in every 3-month treatment segment over a 15-month period, an effect that was not observed among those receiving aripiprazole, quetiapine, or ziprasidone.[19] In a cohort of Medicaid bipolar patients for whom SGAs were prescribed, only 45% had clinically recommended doses after two months of treatment, and of these, only 58% were adherent (MPR ≥0.8). Level of adherence was not reported for the 55% of patients who received either subtherapeutic or high doses of the index SGA treatment, nor were reasons for prescriptions that fell outside of the clinically recommended dose range described.[24]

One study surveyed patients about factors that contributed to suboptimal adherence with their bipolar disorder medications, such as missing doses or stopping treatment. Patients cited two frustrations that negatively impacted medication adherence: having to take medicine daily (51.1%) and side effects associated with mood-stabilizing psychotropic medications (40.2%). Patients who self-reported suboptimal adherence pointed to adverse effects of bipolar disorder medications such as weight gain (58.5%), excessive sedation (54.2%), and physical awkwardness or tremor (33.1%) to explain their incomplete adherence with prescribed therapies.[35]

Persistence, Treatment Gaps, Switching, and Discontinuation

Studies reporting on treatment persistence and duration of treatment/treatment gaps are summarized in Tables 4 and 5. Although definitions of persistence varied across studies, regardless of the assessment criteria used, persistence with treatment was generally low. An analysis of Medicaid health care claims found that only 18% of patients who were prescribed SGAs at clinically recommended doses were persistent with therapy defined as no gap (>30 days between refills) over a 1-year period. Median time to SGA-nonpersistence (30-day gap in treatment) was approximately three months (96 days), with modest variation depending on the prescribed SGA (low of 72 days with olanzapine; high of 117 with ziprasidone).[24] An analysis of commercial health care claims for employees with bipolar disorder found greater persistence among adherent (MPR ≥0.8) patients; although, over 1 year of follow-up these patients had more treatment gaps (3.62 vs 2.60) for shorter periods (15.57 vs 58.89 days) than those with a MPR <0.8.[29] In evaluating dosing regularity, drug holidays (missing ≥3

Table 3 Factors Associated with Suboptimal Adherence with SGA Regimen in Analyses of Health Care Claims

Patient Characteristic		Factors Associated with Suboptimal Adherence to SGA Regimen			
		Commercial Claims, BD (predominately M/M)		Medicaid Claims, BD-I	Medicaid Claims, BD
		Gianfrancesco et al., 2008[19]	Gianfrancesco et al., 2009[33]	Lang et al., 2011[31]	Rascati et al., 2011[24]
Sociodemographic Characteristics	Age (younger, ≤30 years)			●	
	Age (older, range not specified)	●	●		●
	Race (African American vs. Caucasian)				●
Clinical Characteristics	History of suicide attempt				●
	Current (or history) of comorbid substance use disorder	●		●	
	Baseline psychiatric hospitalization			●	
Treatment-Related Characteristics	Newly initiated SGA			●	
	Higher SGA dose (olanzapine, risperidone)	●			
	Baseline antidepressant use			●	
	Prior or concomitant use of mood stabilizers	●			●
	Concomitant use of SGA with other psychotropic medication		●		
	Hyperprolactinemia as a pre-existing antipsychotic-related side effect	●			

Abbreviations: BD, bipolar disorder; BD-I, bipolar I disorder; M/M, manic/mixed symptoms; SGA, second-generation antipsychotic.

consecutive days of medication, found in 35.8% of analysis periods), single-day omissions (present in 64.7% of periods) and self-directed changes in daily dosing (86.7% of periods) were common.[37]

Of the studies describing utilization patterns for patients newly initiated on SGAs, only one study reported rates of switching treatment and two studies described rates of discontinuation with the index SGA medication. A study of utilization patterns for BD-I patients newly prescribed SGA treatment over a 1-year period reported 8.4% of patients switched treatment (changing from index SGA to another) and most (63.4%) discontinued their index SGA medication. The average time to discontinuation was approximately 2 months, with only one-third of patients who discontinued their index SGA resuming any type of antipsychotic medication within the remaining 1-year evaluation period.[30] A second retrospective study reported that discontinuation rates varied by individual SGA (67% for ziprasidone to 83% for aripiprazole) and fewer than 5% of patients completed a full year of taking their index SGA medication.[22]

Combination Treatment

Fourteen studies reported use of concomitant psychotropic medications in patients prescribed SGAs (Table 6), including SGA combination treatment (use of ≥2 SGAs concurrently) and concomitant use of SGAs with other psychotropic medications (eg, antidepressants, traditional mood stabilizers). The prevalence of SGA combination treatment ranged from 1% in a sample of patients newly initiated on SGAs to 23% of SGA-treated patients insured by a large commercial health plan.[26,30] In the STEP-BD study, SGA combination treatment (vs monotherapy) was associated with no improvement in clinical status and slightly poorer global functioning, although the effect

Table 4 Persistence with Oral SGAs or BD Medication

Study	Data Source [Study Period]	Sample	Persistence Findings
Bagalman et al, 2010[29]	Commercial claims [2001–2004]	n=1258 (BD) Employed patients receiving psychotropic medication (30.6% index oral SGA)	• At 1 year, mean persistence with BD medication was 0.77 (overall, measure for persistence was not defined). • Adherent (vs MPR <0.8) patients had greater persistence at 1 year (0.99 vs 0.64).
Chen et al, 2013[30]	Commercial, Medicare, and Medicaid claims [2005]	n=16,807 (BD-I) Patients newly initiating SGA monotherapy	• At 1 year, 10.5% of patients were persistent to SGA therapy (no gaps >15 days between refills and no continuous concomitant treatment with another SGA ≥30 days).
Lang et al, 2011[31]	Medicaid claims [2004–2006]	n=9410 (BD-I) Patients with ≥1 SGA/FGA claim (83.1% oral SGA)	• At 1 year, mean persistence was 0.84 (±0.26) (defined as the number of days between the first and last day receiving an oral SGA divided by the number of days remaining in the period after the first oral SGA was dispensed).
Rascati et al, 2011[24]	Medicaid claims [2002–2008]	n=2446 (BD) Patients initially prescribed SGA therapy	• At 1 year, 18% of patients prescribed SGA at clinically recommended doses were persistent (no gap >30 days between SGA refills). • The median time-to-SGA-nonpersistence was 96 days with modest variation depending on the index SGA (range: 72 for olanzapine to 117 days for ziprasidone).

Abbreviations: BD, bipolar disorder; BD-I, bipolar I disorder; FGA, first-generation antipsychotic (also known as typical antipsychotics); MPR, medication possession ratio; SGA, second-generation antipsychotic.

size was small. In addition, there was no association between use of combination treatment and illness severity based on number of comorbid diagnoses, duration of illness, number of manic or depressive episodes, or clinical measures collected at baseline.[18]

Combination treatment with SGAs and another class of psychotropic medication was reported more frequently than SGA combination treatment, with rates that ranged from 5% to 78%. Different sample characteristics and inclusion criteria associated with concomitant treatments at baseline contributed to the wide range reported.[22,26] Complex combination treatment (ie, four or more bipolar disorder-related psychotropic medications concomitantly) was reported among 38% of patients receiving a SGA regimen in the STEP-BD study.[38]

HCRU and Costs Associated with Utilization Patterns

Studies reporting the effects of the utilization patterns observed with SGAs on HCRU and costs are summarized in Table 7. Generally, patients with lower antipsychotic adherence were at greater risk of hospitalizations and emergency room visits;[31,39] conversely, those who had higher rates of adherence had lower risks of hospitalization[39,40] and lower outpatient psychiatric care

expenditures.[32] Having an MPR ≥0.75 after a year of treatment was associated with lower risk of all-cause (OR=0.730) and psychiatric-related rehospitalizations (OR= 0.759). Additionally, improvements in MPR above the 75% threshold further decreased odds of both types of rehospitalization.[40] Similarly, bipolar disorder patients with greater adherence to antipsychotic medication also had lower subsequent total and outpatient psychiatric care expenditures driven by decreased risk of requiring acute mental health care (ie, hospitalization, ER visit). Among patients with predominately manic/mixed symptoms followed over 15 months, a single-point increase in MPR was significantly associated with a $192-$686 quarterly reduction in total expenditures and a $112-$583 quarterly reduction in outpatient psychiatric care over every 3-month period of treatment (2018 USD). This inverse relationship between MPR and mental health care expenditures (total and outpatient) was also observed for patients with predominantly depressive symptoms; however, this association was significant in only one of the 3-month treatment periods (months 10 to 12).[32] In addition, in a study of Medicaid patients receiving oral or injectable antipsychotic medications over a 1-year period, those with suboptimal adherence (MPR<0.8) were more likely than adherent

Table 5 Duration of Therapy and Treatment Gaps with SGAs

Study	Data Source [Study Period]	Sample	Treatment Gap and/or Duration of Therapy Findings
Bagalman et al, 2010[29]	Commercial claims [2001–2004]	n=1258 (BD) Employed patients receiving psychotropic medication (30.6% index oral SGA)	• Over 1 year, adherent patients (vs MPR <0.8) had more gaps in therapy (3.62 vs 2.60), but these gaps occurred for shorter durations (15.57 vs 58.89 days).
Chen et al, 2013[30]	Commercial, Medicare, and Medicaid claims [2005]	n=16,807 (BD-I) Patients newly initiating SGA monotherapy	• Average time to first non-compliance was approximately 90 days (defined as gaps between index SGA refills >15 days but <30 days and no evidence of adding or switching to another SGA medication). • Over 1 year, most patients (63.4%) discontinued initial SGA therapy (gap of ≥30 days for index SGA with no evidence of antipsychotic augmentation or switch). The average time to discontinuation was 66 days. • Many (69.7%) did not restart any type of antipsychotic therapy during the remainder of the 1-year follow-up period; one-third resumed antipsychotic therapy after 3 to 6 months.
Kim et al, 2011[22]	Commercial claims [2003–2006]	n=7169 (BD) Patients with ≥1 SGA claim	• Over 1 year, rates of discontinuation (>15 days' gap in coverage) were high (67% [ziprasidone] to 83% [aripiprazole]). • Fewer than 5% of patients completed a full year of follow-up taking their index SGA medication. • The duration of therapy with SGA was comparable across all treatment groups (median of 30 days across all index SGA treatment groups).
Lang et al, 2011[31]	Medicaid claims [2004–2006]	n=9410 (BD-I) Patients with ≥1 SGA/FGA claim (83.1% oral SGA)	• The mean maximum consecutive gap in treatment was 49.3 days for the oral SGA group over a 1-year period.
Gianfrancesco et al, 2008[19]	Commercial claims [1999–2004]	n=8750 treatment episodes* (70% M/M) Patients receiving SGA or FGA monotherapy (95% SGA)	• In the M/M cohort, treatment duration ranged from 7.6 months (aripiprazole) to 9.6 months (risperidone). • For all risperidone- or quetiapine-treated individuals, higher doses were associated with longer duration of treatment among patients with predominantly M/M symptoms.
Gianfrancesco et al, 2009[33]	Commercial claims [1999–2005]	n=5531 treatment episodes* (69% M/M) Patients initiated on quetiapine or risperidone, alone and in various MS/ADT combinations	• Mean treatment duration for both quetiapine and risperidone monotherapy was 12.4 months. • The mean treatment duration for combination therapies (ADT and/or MS) with quetiapine or risperidone ranged from 11.1 to 13.3 months. Comparisons of MPRs for quetiapine/risperidone combinations vs monotherapy showed no clear relationship to treatment duration.
Pilhatsch et al, 2018[37]	Prospective study [NR – 100-day periods]	n=241 Outpatients recruited from a university mood clinic and private practice. (50% SGA)	• Patients took drugs on 84.4% of days. • Irregular daily dosing was frequently reported, mostly due to single-day omissions (64.7% of analysis period) or patients' self-directed dosage changes (86.7% of analysis periods). • Drug holidays (missing ≥3 consecutive days of medication) were found in 35.8% of analysis periods.

Note: *Treatment episode was defined as period consisting of ≥2 sequential antipsychotic prescriptions.
Abbreviations: ADT, antidepressant therapy; BD, bipolar disorder; FGA, first-generation antipsychotic (also known as typical antipsychotics); M/M, manic/mixed; MPR, medication possession ratio; MS, traditional mood stabilizers; NR, not reported; SGA, second-generation antipsychotic.

Table 6 Prevalence of Combination Treatment

Study	Data Source [Study Period] Sample	SGA Combination Treatment (Use of ≥2 SGAs Concurrently)	Combination Treatment (Use of ≥2 Psychotropics Concurrently)	Notes
Aparasu et al, 2009[53]	Cross-sectional study [2003–3004] N=2860 (multiple diagnoses)	10.3%	–	Proportion of treatment visits for BD in which concurrent SGA use was documented
Baldessarini et al, 2008[54]	Commercial claims [2001–2005] N=7406 (55.4% BD-I)	–	48% to 49% (SGA + any psychotropic)	Range for initial and final treatment over 1 year
Baldessarini et al, 2008[35]	Cross-sectional study [2005] N=429 (79.0% BD-I)	–	76.2% (any combination ≥2 psychotropics) 20.0% (>3 psychotropics) 11.2% (antipsychotic + MS)	Combination treatment reported at study baseline
Brooks et al, 2011[18]	STEP-BD study [1998–2005] n=1958 (72% BD-I)	8.3%	–	Calculated (162/1958 [patients prescribed >1 SGA/ patients prescribed ≥1 SGA during the study])
Chen et al, 2013[30]	Commercial, Medicare and Medicaid claims [2002–2008] N=16,807 (BD-I)	1% (baseline) 4.2% (during the study)	–	
Goldberg et al, 2009[38]	STEP-BD study [1998–2005] n=4035 (66% BD-I)	–	38% (SGA + ≥3 any psychotropic)	Study refers to the use of ≥4 psychotropic medications as a "complex regimen"
Guo et al, 2008[55]	Commercial claims [1998–2002] N=67,862 (BD)	–	25.3% (SGA +MS)	
Jing et al, 2011[20]	Medicaid claims [2003–2008] n=22,479 (BD)	4% to 6%	59% to 68% (SGA + ADT) 17% to 31% (SGA +MS)	Rates varied by individual SGA treatment group
Kim et al, 2011[22]	Commercial claims [2003–2006] n=7169 (BD)	–	67.6% to 77.9% (SGA + MS)	Rates varied by individual SGA treatment group
Lang et al, 2011[31]	Medicaid claims [2004–2006] n=9410 (BD-I)	–	78% (SGA + ADT) 68% (SGA + MS) 53.6% (SGA + anxiolytic)	Data reported for the oral SGA treatment group only
Qiu et al, 2009[25]	Medicaid claims [2000–2005] N=838 (BD)	2% to 5%	–	Rates of SGA augmentation over the 1-year evaluation period
Qiu et al, 2010[56]	Medicaid claims [2000–2005] N=3328 (BD)	–	43.4% (SGA + MS)	
Rascati et al, 2011[24]	Medicaid claims [2002–2008] n=2446 (BD)	–	57% (SGA + MS)	
Tohen et al, 2017[26]	Commercial claims [2012–2014] n=3329 (BD)	6.7% to 23%	5% to 7.7% (SGA + MS)	Rates varied by individual SGA treatment group

Abbreviations: ADT, antidepressant therapy (any); BD, bipolar disorder; BD-I, bipolar I disorder; MS, mood stabilizer therapy; SGA, second-generation antipsychotic; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder.

Table 7 Utilization Patterns with SGAs Associated with Increased HCRU or Costs

Study	Data Source [Study Period]	Sample	HCRU/Cost Findings
Bagalman et al, 2010[29]	Commercial claims from the MarketScan research database [2001–2004]	n=1258 Employees with BD who had ≥1 claim for mood stabilizer or SGA therapy (oral SGA was the index BD medication for 30.6% of the sample)	• Employees receiving BD medication who had a MPR <0.8 had incrementally higher adjusted indirect costs over 1 year for increased claims due to absence from work (+$1156), short-term disability (+$427), and workers' compensation (+$541) compared to those with those who were adherent (MPR ≥0.8).
Brooks et al, 2011[18]	STEP-BD study [1998–2005]	n=1958 Longitudinal cohort of BD patients (72% BD-I) who were prescribed ≥1 SGA medication	• Over 21 months, patients receiving ≥2 SGA concurrently reported greater use of medical and mental health related HCRU compared to those receiving SGA monotherapy. • BD-I patients receiving ≥2 SGAs had 80% more general medical HCRU (3.6 v. 2.0) and more than twice the mental health-related HCRU (6.4 vs 2.1) than patients taking SGA monotherapy.
Gianfrancesco et al, 2008[32]	Commercial claims from the PharMetrics database [1999–2004]	n=8770 treatment episodes* (70% predominately manic/mixed symptoms) Patients with BD or manic disorder receiving SGA or FGA monotherapy, evaluated in 3-month segments	• The risk of acute mental health care (hospitalization or ER visit) at the end of treatment was reduced by 2.6% in the M/M cohort for each additional month of antipsychotic treatment. • In M/M individuals, a 1-point increase in MPR (over 3 months) was associated with a $192 to $686 quarterly reduction in total expenditures and a $112 to $583 quarterly reduction in outpatient mental health care over subsequent quarters of treatment.
Hassan and Lage, 2009[40]	Commercial claims from the PharMetrics database [2000–2006]	n=1973 BD patients who received outpatient antipsychotic prescription within 2 weeks of hospital discharge	• Discharged patients prescribed antipsychotics who had higher MPR, had lower risk of rehospitalization over 1 year. • Patients who achieved MPR ≥0.75 had significantly decreased odds of rehospitalization for any cause (OR=0.730), and significantly decreased odds of mental health-related rehospitalization (OR=0.759).
Lage and Hassan, 2009[39]	Commercial claims from the PharMetrics database [2000–2006]	n=7769 BD patients with ≥1 claim for antipsychotic medication	• Over 1 year, higher antipsychotic MPR was associated with lower risk of hospitalization and ER visit. • Patients who achieved MPR ≥0.75 had significantly lower odds of all-cause hospitalization (OR=0.85) and those with MPR ≥0.8 had a significant reduction in the odds of a psychiatric-related hospitalization (OR=0.82).
Lang et al, 2011[31]	Medicaid claims from the MarketScan research database [2004–2006]	n=9410 Patients with BD-I who received ≥1 antipsychotic prescription for oral or injectable SGA or FGA	• Over 1 year of follow-up, patients with suboptimal adherence (vs MPR ≥0.8) had higher rates of acute HCRU (ER visits and hospitalizations). ER visits, all-cause: 72.5% vs 57.4% ER visits, psychiatric: 30.0% vs 23.5% Hospitalization, all-cause: 38.8% vs 33.5% Hospitalization, psychiatric: 35.5% vs 30.9%

Notes: *Treatment episode was defined as period consisting of ≥2 sequential antipsychotic prescriptions.
Abbreviations: BD, bipolar disorder; BD-I, bipolar I disorder; ER, emergency room; FGA, first-generation antipsychotic (also known as typical antipsychotic (also known as typical antipsychotic prescriptions); HCRU, health care resource use; MPR, medication possession ratio; OR, odds ratio; SGA, second-generation antipsychotic; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder.

patients to have an all-cause ER visit (73% vs 57%) or hospitalization (42% vs 37%), respectively.[31]

Increased use of both general medical and psychiatric services was reported for patients receiving SGA combination treatment (use of ≥2 SGAs concurrently) compared to SGA monotherapy in a longitudinal cohort study over a mean follow-up duration of 21 months. BD-I patients with SGA combination treatment had 80% more general medical service visits (3.6 vs 2.0 visits) and more than twice the psychiatric treatment visits (6.4 vs 2.1 visits) than patients receiving SGA monotherapy. Regression analyses that included factors considered proxies for illness severity (eg, age, illness duration, and use of other psychotropic medications) confirmed there was an independent association between SGA combination treatment and medical and psychiatric HCRU.[18]

Discussion

Since 2000, expanded approval of SGAs to treat bipolar disorder has led to their increased use in the clinical management of manic and mixed acute episodes, and as a maintenance treatment, relative to traditional mood stabilizers. Prescribing trends reported in this review[10,11,16] align with a recent US analysis of National Ambulatory Medical Care Survey (NAMCS) data that found SGA prescriptions in the outpatient setting grew from 12.4% to 51.4% over the periods from 1997 to 2000 and 2013 to 2016, respectively. Meanwhile, during these same 4-year periods, use of traditional mood stabilizers, such as lithium, valproate, and carbamazepine/oxcarbazepine, declined substantially from 62.3% to 26.4%.[9]

A greater proportion of outpatient visits may include prescriptions for SGA treatment than traditional mood stabilizers; yet, treatment prevalence rates for bipolar disorder in the US remain low.[41] In a recent epidemiological study for example, the 12-month treatment rate for BD-I was 46%.[2] Among those who do receive any type of oral medication, adherence (MPR ≥80%) is achieved by roughly 60% of patients.[41] This review of real-world studies reported rates of adherence to SGA treatment that were lower still, ranging from 38.9% to as low as 8.3%.[30,31] Other notable suboptimal patterns described included use of SGAs outside of, or at the lower end of, therapeutic recommended ranges;[24] low rates of persistence,[24,30] and long treatment gaps (eg, >30 days).[24,31] The majority of these findings were drawn from retrospective analyses of health care claims (72% of studies in this review), which shed little light on reasons for these trends, or the degree to which factors associated with SGA medication (eg, efficacy or tolerability) or other factors (eg, patient or clinical status) may have influenced these findings. This review also highlights a large gap in the knowledge base, underscoring the need for more prospective, real-world research that incorporates input from patients and clinicians to help illuminate what factors may be influencing utilization patterns observed with SGA treatment, as well as their economic impact on patients and health systems.

A common reason for nonadherence to bipolar medication cited in the extant literature is patients' experience of side effects. Studies exploring factors associated with nonadherence to mood-stabilizing treatment (including antipsychotics) have found that patients' negative attitudes toward medications,[42–44] worry about medication,[45] and adverse effects of medication (eg, weight gain, cognitive effects, sedation) contribute to nonadherence.[44,46] In a recent study of BD-I patients taking oral antipsychotics, experience of medication side effects was cited as a reason for stopping medication nearly half of the time. When participants were asked to describe the adverse effects of antipsychotics they wanted to avoid most in a new medication, the most common answers were medication-induced anxiety (50%), weight gain (48%), and "feeling like a zombie" (47%).[47] Similar findings were reported in this review, with 40% of patients (in a survey) attributing their nonadherence with mood-stabilizing psychotropic medications to side effects, suggesting a need for treatments with better benefit/risk profiles to improve patients' adherence with medication.

The association between treatment nonadherence and poor clinical/economic outcomes, coupled with evidence that modest improvements in adherence can significantly reduce HCRU and/or costs associated with inadequate symptom control,[32,39,] call for increased efforts to support patients in maintaining continuous pharmacotherapy. In a 2018 retrospective study, published outside the date range for this review, analyses showed patients newly initiated on antipsychotic medication who were fully adherent (PDC ≥80%) for ≥6 months had significantly lower adjusted rates of psychiatric hospitalization (6.0%) compared to those who were partially adherent (8.3%, PDC ≥40% and <80%) or nonadherent (8.8%, PDC <40%).[48] To this end, building upon interventions targeted to other factors associated with nonadherence, such as simplifying medication regimens,[38,49,50] programming medication reminders,[44,51] and programs to strengthen the patient-clinician therapeutic alliance[5,6,44] need to be a research priority as well as part of ongoing clinical management of patients.

This review has several limitations. It considered only studies published between 2008 and 2018, in English,

describing US data. Most studies (92%) evaluated data collected prior to 2011; these older data may not reflect contemporary practice patterns. Most studies used pre-DSM-5 definitions of bipolar disorder subtypes. Because DSM-5 criteria broaden the definition of bipolar disorder,[52] outcomes reported from studies using earlier DSM criteria may not be representative of current clinical experience. In addition, publications were excluded if they considered fewer than 6 months of treatment, which may have excluded relevant publications. Wherever possible, the primary focus of investigation was BD-I. However, in the absence of relevant research for BD-I populations, evidence related to general bipolar disorder populations was described. Including findings based on individuals across bipolar disorder subtypes could conceivably mischaracterize results as applied to BD-I patients.

There are many treatment options for bipolar disorder; focusing on SGA therapy may limit the degree to which these findings may be applied within the broader treatment landscape. Some of the real-world studies did not break results out by drug class or by SGA agent. This led to some additional limitations. For example, it was not always possible to separate out the effects of individual drug classes on adherence or persistence. Most real-world papers were retrospective analyses of health care claims data; it is well established that data collected for reimbursement are subject to coding errors and sampling issues that can limit the generalizability of the patterns observed. Further, claims provide no direct information from clinicians or patients describing the reasons for initiating/ stopping treatment with SGAs (eg, treatment for acute episodes vs maintenance), the planned duration of treatment, choice of dose, or choice to prescribe combination regimens in the real-world setting. Few analyses considered disease severity or complexity; thus, the degree to which severity of bipolar symptoms or medical comorbidities may have influenced the associated data reported are unknown. Finally, although the terminology used to describe adherence and persistence was similar across studies, operational definitions varied, potentially influencing the comparability of findings, as well as the interpretability of reported results. However, the overall focus on real-world evidence was a strength of this review in terms of understanding current clinical practice, its effects on outcomes, and barriers to improved SGA treatment.

Conclusion

SGA treatment is routinely prescribed to treat bipolar disorder, yet reports of suboptimal utilization patterns (ie, nonadherence, nonpersistence, treatment gaps, medication switching, and discontinuation) with SGAs are common. Also common were SGAs prescribed with another psychotropic medication and SGA combination treatment. Of the utilization patterns described in this review, two (suboptimal adherence, SGA combination treatment) were found to have a likely economic impact for patients and the health care system. Both suboptimal adherence and SGA combination treatment were associated with increased HCRU. Additionally, increased direct and indirect medical costs were observed in SGA-treated cohorts with suboptimal adherence. Other utilization patterns with the potential to affect HCRU or costs included nonpersistence, treatment gaps (ie, treatment episodes with one or more periods of no SGA treatment), switching, and early discontinuation of SGA medication; however, cost estimates associated with these patterns were not reported in the identified literature. Strategies to improve treatment continuity, particularly adherence with SGA medications, as well as to reduce the need for combination treatments may improve clinical and economic outcomes among people living with bipolar disorder.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Leona Bessonova, Michael J. Doane, and Amy K. O'Sullivan are employees of Alkermes, Inc.; Leona

Bessonova and Amy K. O'Sullivan may own stock/options in the company and Michael J. Doane owns Alkermes, Inc stock. Kristine Ogden is an employee of Worldwide Clinical Trials, Inc., which has received consulting fees from Alkermes, Inc. for conducting this study. Leona Bessonova reports personal fees from Alkermes Inc., outside the submitted work. Mauricio Tohen was an employee of Lilly (1997 to 2008) and has received honoraria from or consulted for Abbott, AstraZeneca, Alkermes, Allergan, Bristol-Myers Squibb, GlaxoSmithKline, Intracellular Therapies, Lilly, Johnson & Johnson, Otsuka, Merck, Gedeon Richter Plc, Sunovion, Forest, Roche, Elan, Lundbeck, Teva, Pamlab, Minerva, Neurocrine, Pfizer, Wyeth and Wiley Publishing; his spouse was a full time employee at Lilly (1998–2013).

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