20-Year Trends in the Pharmacologic Treatment of Bipolar Disorder by Psychiatrists in Outpatient Care Settings

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Objective: Pharmacological options for treating bipolar disorder have increased over the past 20 years, with several second-generation antipsychotics receiving regulatory approval in the 1990s. The authors describe trends in use of pharmacological agents in the outpatient management of bipolar disorder.

Methods: Using nationally representative data from the 1997–2016 National Ambulatory Medical Care Surveys, the authors examined trends in the use of mood stabilizers, first- and second-generation antipsychotics, and antidepressants among psychiatrist visits for which bipolar disorder was listed among the primary diagnoses. A logistic regression model was used to identify statistically significant trends, with covariates including age, gender, race/ethnicity, and primary insurance.

Results: Antipsychotics were increasingly more commonly prescribed, increasing from 12.4% of outpatient visits for bipolar disorder in the 1997–2000 period to 51.4% in the 2013–2016 period (adjusted odds ratio=5.05, 95% CI=3.65–7.01). Use of mood stabilizers decreased from 62.3% of visits for bipolar disorder in the 1997–2000 period to 26.4% in the 2013–2016 period (adjusted odds ratio=0.18, 95% CI=0.13–0.27). Prescription of antidepressants occurred in 47.0% of visits for bipolar disorder in the 1997–2000 period and 57.5% in the 2013–2016 period. Prescription of an antidepressant without a mood stabilizer increased substantially, from 17.9% in the 1997–2000 period to 40.9% in the 2013–2016 period (adjusted odds ratio=2.88, 95% CI=2.06–4.03).

Conclusions: Substantial changes have occurred in the treatment of bipolar disorder over the past 20 years, with second-generation antipsychotics in large measure supplanting traditional mood stabilizers. Antidepressant prescriptions persisted despite a lack of evidence for their efficacy in bipolar disorder and concerns about increasing the risk of mania. Research is needed to compare the real-world effectiveness and tolerability of newer antipsychotics with those of traditional mood stabilizers.

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Bipolar disorder affects up to 4.5% of the adult population in the United States (1) and can lead to significant adverse mental and physical health outcomes as well as a substantial economic burden (2). Traditionally, lithium was considered the treatment of choice for bipolar disorder, with evidence suggesting that lithium has a specific protective effect against suicide (3, 4), even compared with other mood stabilizers (5).

Over the past 20 years, the pharmacological options for treating bipolar disorder have increased. Most notably, several second-generation antipsychotics received regulatory approval in the 1990s and 2000s for the treatment of bipolar disorder (6). A study of prescribing patterns in Scotland showed large increases in the use of second-generation antipsychotics for the treatment of bipolar disorder after their regulatory approval (7), and similar trends were seen in Denmark (8). Few studies have examined how the availability of these new medications has affected prescribing patterns for patients with bipolar disorder in the United States. One study provided evidence that U.S. Food and Drug Administration (FDA) approval of olanzapine led to a substantial increase in olanzapine use for bipolar disorder between 1998 and 2009 and a smaller overall increase in use of second-generation antipsychotics (9).

Psychiatrists represent a major source of care for patients with bipolar disorder (10). It is therefore important to understand how trends in outpatient psychiatric prescribing practices may have shifted after regulatory approval of second-generation antipsychotics and how these practices compare with evidence-based guidelines. The purpose of this study was to document these trends and to compare recent national prescribing patterns with evidence-based guidelines for the management of bipolar disorder.

See related feature: **Editorial** *by Dr. Thase (p. 651)*

METHODS

Data Source

Data from 1997 to 2016 (the most recent data available) from the National Ambulatory Medical Care Survey (NAMCS) were used to examine trends in prescribing by psychiatrists for patients with bipolar disorder. The National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention conducted the survey annually by sampling a nationally representative group of office-based visits to physicians. To evaluate changes over time with improved stability of estimates (11), we made an a priori decision to combine annual visit observations into 4-year blocks: 1997–2000, 2001–2004, 2005–2008, 2009–2012, and 2013–2016. Physicians or their staff were queried about demographic and clinical information on each patient visit (11). This study was exempted from the Institutional Review Board at Yale School of Medicine. Further details of the survey, including descriptions, questionnaires, sampling methodology, and data sets are available on the NCHS web site (11). This study adhered to the reporting guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (12).

Survey Methods

The NAMCS survey is conducted using a three-stage sampling design. First, a sample of 112 primary sampling units is drawn, then a sample of practicing physicians within these sampling units is drawn, and, finally, a systematic random sampling of patient visits to these physicians is performed. The analysis was limited to visits to psychiatric providers by patients of all ages for whom bipolar disorder was a listed diagnosis. The NAMCS collects up to three diagnoses for each visit, using ICD-9-CM codes from 1997 to 2015 and ICD-10 codes in 2016. Bipolar disorder was defined using these diagnosis codes (see Table S1 in the online supplement). Comorbidity was assessed at each visit by the additional diagnoses of psychotic disorders, anxiety disorders, substance use disorders, and other disorders (see Table S2 in the online supplement).

Medication Classification

The NAMCS collected up to six medications prescribed in the 1997–2003 surveys; up to eight medications prescribed in the 2004–2011 surveys; up to 10 medications prescribed in the 2012–2013 surveys; and up to 30 medications prescribed in the 2014–2016 surveys. We used generic names to identify prescription medications and included generic names that are virtually synonymous according to several drug databases (e.g., *UpToDate* and *American Hospital Formulary Service*). For example, valproic acid includes valproate sodium, divalproex sodium, and other similar terms. Mood stabilizers were defined to included lithium, carbamazepine, lamotrigine, and valproic acid. Based on a lack of evidence for efficacy in bipolar disorder in treatment guidelines and systematic reviews (13–16), gabapentin, oxcarbazepine, and topiramate were not included as mood stabilizers but were analyzed separately, as these medications are commonly prescribed for patients with bipolar disorder. We used definitions from the *2019 American Hospital Formulary Service* (AHFS) *Compendium* (17) to classify second-generation antipsychotics: aripiprazole, asenapine, cariprazine, iloperidone, lurasidone, paliperidone, risperidone, quetiapine, olanzapine, clozapine, and ziprasidone. First-generation antipsychotics were classified according to AHFS definitions and included haloperidol, chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, thiothixene, loxapine, molindone, and pimozide. Antidepressants included monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine inhibitors, and "other" antidepressants (bupropion, mirtazapine, vilazodone, nefazodone, vortioxetine, and trazodone). We also analyzed trends in the use of benzodiazepines and stimulants (18–20) in visits for which bipolar disorder was listed among the primary diagnoses.

Demographic and Clinical Data

Demographic data collected by the NAMCS included age, gender, race/ethnicity, payment source (Medicare, Medicaid, private insurance, and other), whether the reason for the visit was acute or chronic, whether the patient received any psychotherapy, and how much time the patient spent with the physician.

Analysis

We compared demographic variables, diagnostic subtype, and the psychopharmacological management composition of psychiatric visits of patients diagnosed with bipolar disorder over time. We then analyzed trends of medication classes (mood stabilizers, antipsychotics, and antidepressants). We separately examined trends in use of antidepressants without a mood stabilizer and in use of antidepressants without a mood stabilizer or an antipsychotic. In the main analysis, we included all medications. Given the change in number of medications recorded by the NAMCS over the period studied, we conducted a sensitivity analysis, limiting the analysis to the first six medications prescribed only (see Table S3 in the online supplement). As a control against which to compare the trends discovered in visits for bipolar disorder, we examined trends of visits for schizophrenia in a post hoc analysis.

A series of logistic regression models were fitted to assess the strength of associations between survey year as the independent variable of interest and age, gender, and race/ethnicity as dependent variables. For the survey year variable, the first time period (1997–2000) was assigned a value of 0, the second (2001–2004) a value of 0.25, the third (2005–2008) a value of 0.5, the fourth (2009–2012) a value of 0.75, and the fifth (2013–2016) a value of 1. We calculated unadjusted and adjusted odds ratios for the study period effect; covariates included age, gender, race/ethnicity, and the primary source of payment. We used Stata 15.1 MP/6-Core (Stata Corp., College

Station, Tex.) for all analyses, and we employed the *svy* commands to account for the complex survey sampling design of the NAMCS (i.e., unequal probability of selection, clustering, and stratification).

RESULTS

Sample Characteristics

A total of 4,419 visits to a psychiatric provider by a patient diagnosed with bipolar disorder were sampled by NAMCS during the period 1997–2016, which represents approximately 4.2 million visits nationally. Throughout the 20-year period examined, more women than men had outpatient visits for bipolar disorder (Table 1). The proportion of outpatient visits for black and Hispanic patients increased over time (p=0.007). There were no statistically significant trends in the proportion of visits covered by private as compared with public insurance or in the regional distribution of outpatient visits. Over time, a smaller percentage of patients received psychotherapy (p=0.009) and a smaller percentage had visits exceeding 30 minutes in duration as compared with visits of 16–30 minutes (p=0.014). The total number of visits for bipolar disorder increased from approximately 467,000 in the 1997–2000 period to 1.06 million in the 2013–2016 period. The total number of visits for schizophrenia did not increase during this interval (approximately 380,000 in the 1997–2000 period and approximately 370,000 in the 2013–2016 period) (see Table S4 in the online supplement).

Prescriptions for Psychotropic Medications

Antipsychotics. The percentage of visits for bipolar disorder that included antipsychotic prescriptions increased markedly, from 19.1% in the 1997–2000 period to 52.7% in the 2013–2016 period (Table 2). This was driven by a large increase in use of second-generation antipsychotics during this interval, from 12.4% to 51.4%, while use of first-generation antipsychotics decreased, from 7.0% to 1.7% (Figure 1). Sensitivity analyses revealed a similar pattern of use (see Table S3 in the online supplement).

Mood stabilizers. Visits for bipolar disorder that included prescriptions for any mood stabilizer decreased from 62.3% in the 1997–2000 period to 26.4% in the 2013–2016 period. This was driven primarily by a decrease in use of non-lithium mood stabilizers (carbamazepine and valproic acid) from 35.4% to 4.9% (adjusted odds ratio=0.07, 95% CI=0.04–0.11) and by a decrease in use of lithium from 30.4% to 17.6% (adjusted odds ratio=0.46, 95% CI=0.29–0.71). Sensitivity analyses revealed a similar pattern of use (see Table S3 in the online supplement).

Antidepressants. Antidepressant prescriptions for the study period, with and without antipsychotics and mood stabilizers, are summarized in Figure 2. The prescription rate for any antidepressant was 47.0% of visits for bipolar disorder in the 1997–2000 period and 57.5% of visits in the 2013–2016 period (odds ratio=1.37, 95% CI=1.02–1.84; adjusted odds ratio=1.27, 95% CI=0.93–1.75). There was a decrease in the percentage of visits for bipolar disorder that included use of MAO inhibitors (adjusted odds ratio=0.36, 95% CI=0.17–0.77) and an increase in the percentage of those that included use of serotonin-norepinephrine reuptake inhibitors (adjusted odds ratio=1.98, 95% CI=1.33–2.96) or "other" antidepressants (adjusted odds ratio=1.86, 95% CI=1.22–2.84), which included bupropion, mirtazapine, vilazodone, nefazodone, and vortioxetine.

Other psychotropic medication use. There was no significant change in the prescription rate of benzodiazepines. There was an overall increase in the use of stimulants, from 5.3% in the 1997–2000 period to 9.8% in the 2013–2016 period (adjusted odds ratio=2.75, 95% CI=1.44–5.27).

Unopposed antidepressant use. The proportion of visits to psychiatrists for bipolar disorder in which any antidepressant was prescribed without a mood stabilizer increased from 17.9% in the 1997–2000 period to 40.9% in the 2013–2016 period (adjusted odds ratio=2.88, 95% CI=2.06–4.03). There was no change in use of any antidepressant without either a mood stabilizer or an antipsychotic (adjusted odds ratio= 1.05, 95% CI=0.73–1.51).

Psychotherapy

Among visits for which bipolar disorder was listed among the primary diagnoses, the use of psychotherapy decreased from 50.9% in the 1997–2000 period to 35.7% in the 2013–2016 period (adjusted odds ratio=0.44, 95% CI=0.26–0.73).

DISCUSSION

Substantial changes have occurred over the past two decades in the pharmacological management of bipolar disorder by outpatient psychiatrists. Second-generation antipsychotics have in large measure supplanted lithium and other mood stabilizers in the absence of any comparative effectiveness data indicating improvement in outcomes. There has also been a persistence of the prescribing of antidepressants despite a consistent lack of evidence for their efficacy in bipolar disorder in clinical trials and concerns about inducing manic switch (21–23). Finally, the use of psychotherapy by psychiatrists in the outpatient management of bipolar disorder has decreased substantially.

Second-Generation Antipsychotics and Mood Stabilizers

Several factors may have contributed to the switch from traditional mood stabilizers to second-generation antipsychotics in the outpatient psychiatric management of bipolar disorder. During the study period, the following second-generation antipsychotics received regulatory approval for the treatment of bipolar disorder: olanzapine (2000; manic and mixed phases), olanzapine/fluoxetine combination (2003; depressed phase), risperidone (2003; manic and mixed

TABLE 1. Demographic and clinical characteristics of outpatient visits to psychiatrists among patients with bipolar disorder by period, 1997–2016[a]

Measure or Variable	1997–2000	2001–2004	2005–2008	2009–2012	2013–2016	Secular Trends: Unadjusted Odds Ratio	95% CI	p	Adjusted Odds Ratio[b]	95% CI	p
	N	N	N	N	N						
Unweighted visits	504	889	864	1,313	849						
Weighted visits (row %)	467,057 (11.1%)	753,228 (17.8%)	867,632 (20.6%)	1,074,923 (25.5%)	1,059,311 (25.1%)						
	Mean	Mean	Mean	Mean	Mean						
Age											
≤18	12.3	16.2	9.9	7.0	8.4	0.45	0.20, 0.99	0.047	0.41	0.20, 0.83	0.013
19–44	44.8	42.7	43.3	44.2	43.3	0.99	0.75, 1.31	0.947	1.02	0.77, 1.36	0.869
45–64	35.6	34.5	39.6	41.5	35.5	1.09	0.79, 1.49	0.597	1.07	0.78, 1.47	0.657
≥65	7.3	6.5	7.2	7.3	12.9	2.14	1.26, 3.64	0.005	2.21	1.28, 3.80	0.004
Gender											
Male	40.6	39.1	32.2	39.6	36.2	0.91	0.67, 1.23	0.530	1.09	0.82, 1.46	0.562
Female	59.4	60.9	67.8	60.4	63.8	1.12	0.81, 1.50	0.530	0.92	0.69, 1.23	0.562
Race/ethnicity											
Non-Hispanic white	91.4	87.2	85.5	51.5	81.3	0.46	0.29, 0.72	0.001	0.44	0.27, 0.71	0.001
Non-Hispanic black	3.6	5.3	6.0	7.8	6.1	1.60	0.95, 2.67	0.076	1.62	0.97, 2.73	0.068
Hispanic	2.6	4.2	5.9	7.7	6.2	2.10	1.18, 3.75	0.012	2.19	1.17, 4.09	0.014
Non-Hispanic other	2.5	3.4	2.5	3.0	6.4	2.74	0.99, 7.56	0.052	2.86	0.98, 8.29	0.054
Insurance coverage											
Private	45.2	48.4	48.1	43.8	46.0	0.96	0.64, 1.43	0.833	1.02	0.68, 1.54	0.913
Medicare	16.1	12.3	20.0	17.7	18.6	1.40	0.96, 2.04	0.082	1.10	0.74, 1.62	0.635
Medicaid	9.1	17.9	15.5	17.5	16.4	1.37	0.75, 2.53	0.308	1.58	0.86, 2.90	0.142
Other	29.7	21.4	16.5	21.0	19.1	0.71	0.42, 1.18	0.180	0.73	0.44, 1.22	0.232
Major reason for visit											
Acute problem	12.8	3.6	4.2	4.3	4.1	0.37	0.16, 0.88	0.024	0.44	0.19, 1.00	0.049
Chronic problem	85.7	96.2	94.0	93.7	94.2	1.38	0.67, 2.85	0.381	1.82	0.68, 2.55	0.411
Other	1.6	0.2	1.8	2.0	1.8	2.07	0.30, 14.45	0.464	1.70	0.25, 11.39	0.584
Region											
Northeast	27.5	19.0	25.9	21.6	30.0	1.31	0.64, 2.69	0.455	1.33	0.67, 2.63	0.416
Midwest	22.5	21.6	15.4	21.4	19.3	0.9	0.46, 17.76	0.752	0.98	0.49, 1.96	0.959
South	27.6	36.0	38.6	35.0	30.6	0.96	0.53, 1.76	0.903	0.95	0.51, 1.76	0.862
West	22.4	23.4	20.2	22.0	20.1	0.86	0.45, 1.65	0.656	0.8	0.42, 1.51	0.487
Time spent with doctor											
≤15 minutes	22.6	21.0	37.6	24.8	25.1	1.09	0.63, 1.87	0.766	1.09	0.62, 1.93	0.756
16–30 minutes	33.0	45.1	35.5	44.2	45.6	1.45	0.93, 2.26	0.101	1.47	0.94, 2.30	0.094
>30 minutes	44.5	33.9	26.9	31.0	29.3	0.62	0.40, 0.96	0.033	0.59	0.36, 0.98	0.039
Comorbid disorders											
Anxiety disorder	11.5	17.3	18.9	16.0	24.3	1.88	1.13, 3.14	0.015	1.85	1.10, 3.11	0.020
Psychotic disorder	0.9	1.5	1.6	2.4	2.2	2.14	0.56, 8.15	0.265	1.91	0.52, 7.08	0.331
Substance use disorder	7.3	7.1	7.8	10.7	9.8	1.57	1.01, 2.46	0.047	1.53	0.95, 2.46	0.078
Other	4.3	5.0	4.1	4.2	4.5	0.95	0.48, 1.88	0.885	0.91	0.45, 1.83	0.783
	%	%	%	%	%						
Metropolitan Statistical Area	83.8	89.5	90.7	93.3	95.4	3.61	1.38, 9.45	0.009	3.96	1.42, 11.07	0.009
Psychotherapy	50.9	57.3	46.8	50.8	35.7	0.50	0.30, 0.82	0.007	0.44	0.26, 0.73	0.001

[a] Data are from the National Ambulatory Medical Care Survey, 1997–2016.
[b] Accounted for age, gender, race/ethnicity, and source of payment.

phases), ziprasidone (2004; manic and mixed phases), quetiapine (2004; manic and depressed phases), aripiprazole (2004; manic and mixed phases), lurasidone (2013; depressed phase), asenapine (2015; manic and mixed phases), and cariprazine (2015; depressed phase) (24). After each regulatory approval, intensive marketing campaigns were initiated to promote products to physicians and patients. Such marketing efforts can have a substantial impact on the utilization of psychotropic medications, including antipsychotics (25).

Direct-to-consumer advertising of pharmaceutical products is associated with much more rapid adoption of second-generation antipsychotics in the United States compared with countries with more restrictive policies on this type of

TABLE 2. Trends for medications prescribed during office-based visits to psychiatrists for patients with bipolar disorder by secular period, 1997–2016[a]

Measure or Variable	1997–2000	2001–2004	2005–2008	2009–2012	2013–2016	Secular Trends					
						Unadjusted Odds Ratio	95% CI	p	Adjusted Odds Ratio[b]	95% CI	p
	N	N	N	N	N						
Unweighted visits	504	889	864	1,313	849						
Weighted visits (row %)	467,057 (11.1%)	753,228 (17.8%)	867,632 (20.6%)	1,074,923 (25.5%)	1,059,311 (25.1%)						
	Mean	Mean	Mean	Mean	Mean						
Any antipsychotic	19.1	31.8	51.5	53.0	52.7	3.80	2.77, 5.21	<0.001	4.00	2.94, 5.45	<0.001
First-generation antipsychotics	7.0	3.1	2.8	3.1	1.7	0.32	0.17, 0.60	<0.001	0.23	0.12, 0.45	<0.001
SGAs	12.4	29.4	49.6	51.4	51.4	4.64	3.34, 6.46	<0.001	5.05	3.65, 7.01	<0.001
FDA-approved SGAs	12.1	28.2	49.1	48.6	50.1	4.43	3.18, 6.19	<0.001	4.80	3.45, 6.69	<0.001
Any mood stabilizer	62.3	50.3	28.5	23.7	26.4	0.20	0.14, 0.29	<0.001	0.18	0.13, 0.27	<0.001
Lithium	30.4	20.7	17.3	13.9	17.6	0.50	0.33, 0.76	0.001	0.46	0.29, 0.71	<0.001
Carbamazepine or valproic acid	35.4	24.8	7.6	7.4	4.9	0.07	0.05, 0.11	<0.001	0.07	0.04, 0.11	<0.001
Lamotrigine	2.1	9.7	5.8	4.1	4.7	0.73	0.46, 1.15	0.173	0.70	0.44, 1.12	0.137
Other anticonvulsants	6.3	19.9	12.3	12.3	12.5	0.96	0.62, 1.48	0.859	0.91	0.59, 1.41	0.684
Gabapentin	6.0	9.1	3.9	4.1	4.7	0.53	0.34, 0.85	0.008	0.45	0.28, 0.73	0.001
Oxcarbazepine	0.0	5.7	4.5	3.3	5.3	1.85	0.83, 4.13	0.134	1.82	0.82, 4.03	0.143
Topiramate	0.3	5.7	4.5	5.0	3.1	1.20	0.75, 1.93	0.449	1.28	0.76, 2.15	0.345
Any antidepressant	47.0	50.2	55.1	49.9	57.5	1.37	1.02, 1.84	0.036	1.27	0.93, 1.75	0.133
TCAs or MAOIs	6.2	3.5	3.1	2.2	2.9	0.44	0.20, 0.98	0.044	0.36	0.17, 0.77	0.009
SSRIs	24.0	31.4	30.7	26.0	25.7	0.87	0.65, 1.16	0.349	0.85	0.63, 1.14	0.272
SNRIs	4.5	6.6	13.7	13.0	11.4	2.16	1.41, 3.31	<0.001	1.98	1.33, 2.96	0.001
Other	19.0	17.5	19.8	19.2	29.8	1.94	1.33, 2.84	0.001	1.86	1.22, 2.84	0.004
Bupropion	9.8	11.8	10.9	10.4	12.4	1.15	0.78, 1.69	0.488	1.13	0.75, 1.72	0.560
Mirtazapine	2.4	2.1	1.9	1.7	4.1	1.96	0.90, 4.28	0.092	1.69	0.76, 3.78	0.201
Other	8.4	5.0	7.8	8.4	15.8	3.06	1.76, 5.32	<0.001	2.93	1.62, 5.30	<0.001
Antidepressant without mood stabilizer	17.9	20.7	38.9	35.6	40.9	2.98	2.16, 4.11	<0.001	2.88	2.06, 4.03	<0.001
Antidepressant without antipsychotic	38.0	34.8	28.7	21.9	25.5	0.49	0.36, 0.67	<0.001	0.45	0.33, 0.61	<0.001
Antidepressant without mood stabilizer or antipsychotic	14.9	13.0	19.5	14.2	16.6	1.13	0.78, 1.63	0.512	1.05	0.73, 1.51	0.793
Benzodiazepines	24.2	27.6	30.3	33.4	31.2	1.41	1.00, 1.97	0.047	1.30	0.95, 1.78	0.097
Stimulants	5.3	3.5	6.3	7.8	9.8	2.67	1.38, 5.16	0.004	2.75	1.44, 5.27	0.002

[a] Data are from the National Ambulatory Medical Care Survey, 1997–2016. FDA=U.S. Food and Drug Administration; MAOI=monoamine oxidase inhibitor; SGA=second-generation antipsychotic; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.
[b] Accounted for age, gender, race/ethnicity, and source of payment.

marketing (13). After regulatory approval, marketing campaigns were initiated to promote the new medications to physicians. Such marketing efforts could have had a substantial impact on the use of psychotropic medications, including antipsychotics (25). In 2005, for example, about $513 million was estimated to have been devoted to U.S. promotional spending on antipsychotic medications, some 10% of which was for direct-to-consumer advertising (26), although an unknown percentage was specifically for bipolar disorder. Policies that limit marketing (i.e., gift restriction policies) have in turn been associated with lower rates of prescribing newly marketed medications (27). Taken together, this literature suggests that pharmaceutical marketing may have contributed to the substantial increase in second-generation antipsychotic prescriptions by U.S. psychiatrists in outpatient visits for bipolar disorder over the past 20 years.

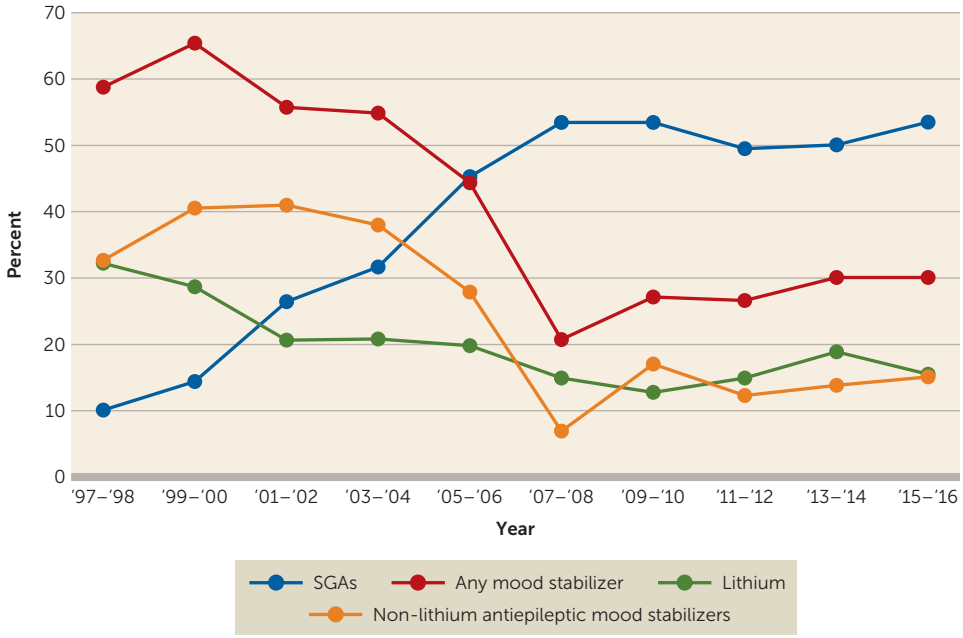
Many of the traditional mood stabilizers were off patent during this period and therefore were not the focus of major marketing efforts, which may have accounted for their decline in use. Within these broader trends, and supporting the hypothesis that marketing was a large driver of changes in prescribing patterns, increases in the use of valproic acid (approved in 1995) (28) and lamotrigine (approved in 2003) were seen after their regulatory approval. Alternatively, it is

possible that the increase in second-generation antipsychotic prescribing was a result of other factors. For instance, clinicians may find that second-generation antipsychotics are more tolerable in the short term than traditional mood stabilizers or that they are effective therapeutic options when treating patients with comorbid disorders that are typically excluded in randomized controlled trials (29).

During the study period, the total number of visits for bipolar disorder nationwide increased from approximately 467,000 in the 1997–2000 period to 1.06 million in the 2013–2016 period. Given that the frequency of visits per patient for other mood disorders tended to decline during this period (30), it is likely that there was a substantial increase in the total number of individuals diagnosed with bipolar disorder by U.S. psychiatrists. Our post hoc analysis revealed that the total number of visits for schizophrenia did not increase during the same period, suggesting that changes to the NAMCS methodology are not related to the increase seen in visits for bipolar disorder. Some factors that may have contributed to this increase include expansion in insurance coverage for mental health conditions (31) and marketing campaigns by manufacturers of second-generation antipsychotics to broaden the concept of bipolar disorder in order to increase sales (32, 33). It is noteworthy that the clinical criteria for bipolar disorder have not changed significantly between editions of DSM during the period examined (34, 35).

Physician factors may also contribute to these trends in pharmacological management. Psychiatrists may have become increasingly uncomfortable prescribing medications with the potential for serious and acute medical side effects (such as lithium), as evidenced by the declining use of MAO inhibitors. The need for blood level monitoring with some of the mood stabilizers could also be a factor driving physician preference and the decreased use of mood stabilizers over the past 20 years. This may also be influenced by the fact that a large proportion of psychiatrists are solo practitioners and may not have a readily available mechanism for drawing and following blood levels (36). Finally, the increase in use of second-generation antipsychotics for adults with bipolar disorder may also be part of a broader trend in increasing use of these agents for a variety of indications and patient groups (37), including schizophrenia, the treatment of children, elderly individuals, adults with nonpsychotic depression, and individuals with anxiety disorders and insomnia (38–42).

FIGURE 1. Prescribing trends for second-generation antipsychotics (SGAs) and mood stabilizers in the treatment of bipolar disorder in office-based visits to psychiatrists, 1997–2016[a]

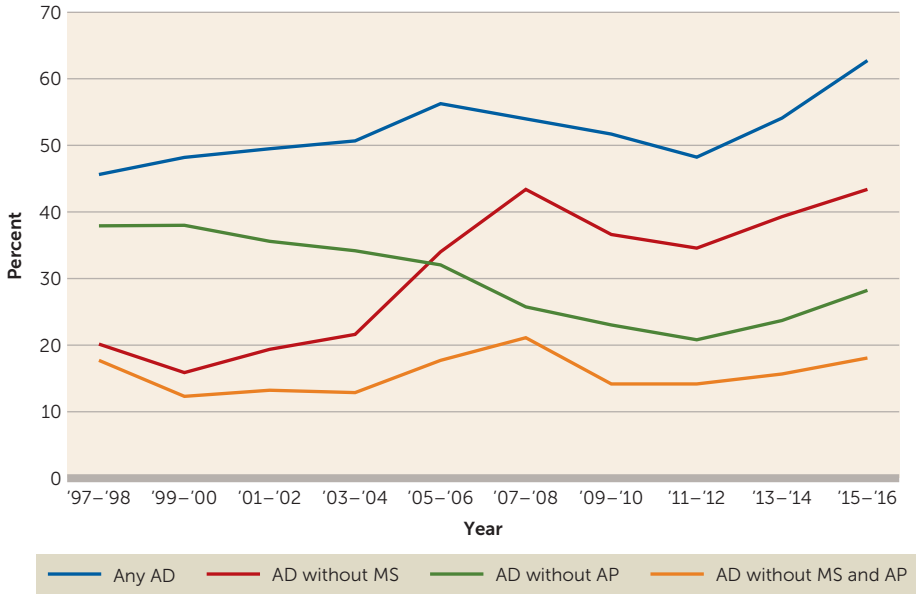


[a] Data are from the National Ambulatory Medical Care Survey, 1997–2016.

Implications for Public Health

An increase in second-generation antipsychotic use coincident with declining use of traditional mood stabilizers may have important implications for public health. Relatively little research has been conducted evaluating the comparative effectiveness of second-generation antipsychotics and traditional mood stabilizers. In a small randomized controlled trial, Berk et al. found more favorable outcomes with lithium compared with quetiapine among individuals with bipolar disorder after a first-time manic episode (43). The Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness) study also compared these drugs in a study of 482 patients with bipolar disorder and found no significant difference in improvements in symptom severity on standardized rating scales (44). These prospective studies are too small to detect changes in relatively rare but significant health outcomes, such as emergency department visits, hospital admissions, suicide attempts, and suicide. Several studies have shown that lithium has protective effects against suicide and suicidal behavior (3, 4, 45), with evidence that nonlithium mood stabilizers can also have some protective effects against suicidal behavior (46). We are aware of only one large observational study (N=6,671 patients with bipolar disorder) that has compared quetiapine and lithium (along with other mood stabilizers) for their effects on self-harm and suicide (5); the study found lower rates of self-harm among individuals treated with lithium compared with those treated with quetiapine or other mood stabilizers (205 compared with 417 per 10,000 person-years of exposure, $p<0.01$). Individuals treated with lithium also had lower rates of suicide (7 compared with 19 per 10,000 person-years of

FIGURE 2. Prescribing trends for antidepressants in the treatment of bipolar disorder in office-based visits to psychiatrists, 1997–2016[a]



[a] Data are from the National Ambulatory Medical Care Survey, 1997–2016. AD=antidepressant; AP=antipsychotic; MS=lithium and antiepileptic mood stabilizers.

exposure), although the difference was not statistically significant. In light of the transformation in the pharmacological management of bipolar disorder, further studies are warranted to better understand the comparative safety and effectiveness of second-generation antipsychotics and traditional mood stabilizers.

Antidepressant Use in Bipolar Disorder

Several reasons may underlie the finding that antidepressant prescribing has persisted over the past 20 years. Individuals with bipolar disorder generally spend the majority of time in depressive phases as opposed to manic phases (47), which may prompt providers to treat these symptoms with antidepressants. In addition, treatment refractoriness is a common and serious problem in the management of bipolar disorder. Relatedly, many mood stabilizers and second-generation antipsychotics can have side effects that prove difficult to tolerate. Providers may prescribe antidepressants for bipolar disorder if traditional "on-label" medications have failed to achieve remission or proven intolerable. Nonetheless, the practice of using antidepressants in the management of bipolar disorder is generally given a lower priority in treatment algorithms, given the lack of evidence for efficacy (16, 48).

The use of antidepressants without a concomitant mood stabilizer increased substantially during the study period, which was likely related to an overall decline in mood stabilizer use. The use of antidepressants without either a mood stabilizer or an antipsychotic did not significantly change. Notably, evidence suggests that antidepressants, when combined with mood stabilizers or antipsychotics, are not associated with an increased risk of hospital readmissions (49, 50). However, unopposed antidepressant use has been shown in large samples to heighten the risk of mania (50). Although the NAMCS survey data do not permit evaluation of the quality of care of patients and individual patient characteristics that likely influence treatment practices, the prescribing patterns in community practice nevertheless suggest a possible need for quality improvement initiatives to educate and provide feedback for practicing psychiatrists.

In addition, it is possible that the increases seen in the use of antidepressants and antipsychotics are related to the FDA approval of the olanzapine/fluoxetine combination in 2003 for the treatment of bipolar disorder. However, we conducted a sensitivity analysis of second-generation antipsychotic prescribing trends without olanzapine/fluoxetine (see Figure S1 in the online supplement), which showed similar trends over time. Hence, we believe that the regulatory approval of olanzapine/fluoxetine for treating bipolar disorder is unlikely to have driven the increase use in antidepressant use.

Use of Psychotherapy

Our study showed a substantial decrease in the use of psychotherapy in psychiatric outpatient visits for bipolar disorder over the past 20 years, from 50.9% to 35.7%, which is part of a larger trend of decreasing psychotherapy provided by psychiatrists (51). Psychosocial interventions, including psychotherapy and psychoeducation, are a critical component of comprehensive management, to enhance treatment adherence, address psychosocial consequences from previous episodes, and manage residual symptoms or mood instability between major episodes (52). Individuals who received intensive psychotherapy have been found to have improved outcomes compared with those who did not receive intensive psychotherapy (53).

Limitations

Several limitations of this study deserve comment. First, the diagnoses of bipolar disorder were based on clinical judgment rather than independent research diagnostic assessments. In addition, the NAMCS samples are not sufficiently large to generate stable estimates of treatments by bipolar subtype (i.e., bipolar I disorder versus bipolar II disorder) or by single antipsychotic. In our preliminary analyses, we found that the proportion of visits to psychiatrists in which bipolar II disorder was

listed among the primary diagnoses was stable over time, from 2.1% in the 1997–2000 period to 2.2% in the 2013–2016 period (adjusted odds ratio=0.94, 95% CI=0.80–1.11). We further conducted a sensitivity analysis excluding bipolar II disorder (see Table S5 in the online supplement) and found that the prescribing trends were similar to those in the main findings. Further research is needed, however, to examine the pharmacoepidemiology of bipolar II disorder and ascertain whether patients with this disorder receive different treatments. Second, the results concern visits in which bipolar disorder was listed among the primary diagnoses rather than individual patients. NAMCS captures an unknown number of patients who made repeat visits during the survey period. Third, although we controlled for relevant covariates, there may be unmeasured clinical factors that contributed to or explain the observed changes in prescribing patterns. Fourth, the NAMCS samples patient visits and does not permit assessment of long-term use of pharmacological treatment. Fifth, the data are derived from physician reports of patient visits and do not provide measures of symptom severity or treatment history that might account for the observed trends. Finally, the survey does not cover all outpatient settings in which patients with bipolar disorder receive care, such as clinics based in hospitals, and no effort was made to evaluate the treatment of bipolar disorder in primary care.

CONCLUSIONS

There has been a substantial increase in the use of second-generation antipsychotics in the outpatient psychiatric management of adults diagnosed with bipolar disorder, accompanied by a decrease in the use of lithium and other mood stabilizers. These findings could have important implications for public health and demonstrate a need for comparative analyses between second-generation antipsychotics and older mood stabilizers such as lithium and valproic acid with respect to efficacy, tolerability, and side effects. The data also revealed an enduring use of antidepressants in adults with bipolar disorder, suggesting that quality improvement initiatives may be useful in an effort to bring practice into better harmony with evidence-based guidelines for the outpatient management of bipolar disorder.

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