Psychotropic Medications for Patients With Bipolar Disorder in the United States: Polytherapy and Adherence

Ross Baldessarini, M.D.
Henry Henk, Ph.D.
Ami Sklar, M.P.H.
Jane Chang, M.P.H.
Leslie Leahy, Ph.D.

Objective: **Because treatments for bipolar disorder include a growing number of psychotropic agents, the authors evaluated psychotropic polytherapy and adherence to treatment among U.S. patients with bipolar disorder.** ***Methods:*** **National health plan claims data (2000–2004) were used to identify patients diagnosed as having bipolar disorder who had continuous benefits and had not been prescribed medication for bipolar disorder for six months or more. The study compared drugs dispensed to these patients initially and at one year and characterized patients who were adherent to mood-stabilizers.** ***Results:*** **A total of 7,406 patients had a bipolar disorder: bipolar I (55%), bipolar II (15%), or bipolar disorder not otherwise specified (30%). Women represented 57% of the sample; mean±SD age was 35.4±12.4 years. Initial prescription fills involved one psychotropic agent in 67% of patients, and two or more psychotropics (polytherapy) in 33%. Initial prescription drug selections involved: antidepressants > anticonvulsants ≥ antipsychotics > sedatives > lithium; initial mood stabilizer use ranked: valproate > lithium > carbamazepine or oxcarbazepine > lamotrigine; antipsychotics ranked: olanzapine > quetiapine ≥ risperidone > ziprasidone > aripiprazole > clozapine. Rankings were similar at one year, when only 31% of patients received monotherapy (a 2.2-fold decline), 32% received polytherapy, and 37% received no psychotropics. Initially patients received 1.42 psychotropic drugs per person; at one year, patients received 175, and at both times polytherapy was less likely with lithium than with anticonvulsants. In multivariate modeling, one-year mood stabilizer use was greater with the following: older age, type of mood stabilizer (lamotrigine > valproate > carbamazepine or oxcarbazepine > lithium) and was associated with more psychiatric office and emergency visits, clinician type (more common with psychiatrists than with primary care physicians), and nonuse of off-label anticonvulsants.** ***Conclusions:*** **Polytherapy was used by one-third of patients initially and at one year, antidepressant use was highly prevalent initially and later, but lack of treatment was prevalent at one year. Plausible clinical and treatment factors were associated with sustained mood stabilizer adherence. (*Psychiatric Services* 59:1175–1183, 2008)**

Dr. Baldessarini is affiliated with the Department of Psychiatry, Harvard Medical School, Boston. Dr. Henk and Ms. Sklar are with the Department of Health Economics and Outcomes Research, i3 Innovus, Eden Prairie, Minnesota. At the time this study was conducted, Ms. Chang and Dr. Leahy were with the Department of Research, Novartis Corporation, East Hanover, New Jersey. Send correspondence to Dr. Baldessarini at the McLean Division of Massachusetts General Hospital, 115 Mill St., Belmont, MA 02478-9106 (e-mail: rjb@mclean.org). *Preliminary findings were presented at the annual meeting of the American Psychiatric Association, May 19–24, 2007, San Diego, California.*

Treatment of patients diagnosed as having bipolar disorders has evolved rapidly in recent years. A growing number of medicines have received U.S. Food and Drug Administration (FDA) and international regulatory approval for use in treating acute mania or bipolar depression or for long-term maintenance treatment aimed at limiting recurrence risks (1). Despite a growing array of effective and reasonably safe treatments, residual morbidity among patients treated by contemporary community standards remains high. Previous follow-up studies of treated patients with bipolar I disorder who had been ill for several years (2–4) or following first episodes (5) have found residual morbidity in 40% of the follow-up period. Approximately three-quarters of the residual morbidity was depressive or dysthymic (2–5). Unresolved depressive morbidity is probably an important contributor to substance abuse, functional disability, and excess mortality because of high suicide rates in early years and because of medical disorders in later years (6–12).

Prominent residual depressive morbidity among treated patients with bipolar disorder encourages empirical use of antidepressants in both short- and long-term treatment, despite limited evidence of their efficacy and safety in the treatment of bipolar depression (13–16). In addition, residual morbidity and the growing number of options for treating such patients encourage use of multiple

mood-altering and other psychotropic agents (polytherapy), despite very limited evidence of additional effectiveness or of the relative safety of such empirical interventions (1,17, 18). Moreover, polytherapy may have the paradoxical effect of limiting adherence to critically required long-term mood-stabilizing treatment for patients with bipolar disorder (19). A recent analysis of pharmacy benefits records of a national sample of U.S. patients diagnosed as having bipolar disorder considered new treatments with single psychotropic agents (20). Antidepressants were, by far, the most commonly prescribed psychotropics in initial monotherapies, and both lithium and antidepressants were retained longer than other psychotropics, including anticonvulsants, antipsychotics, and sedatives (20).

We report new findings from independent national health care claims data, focusing on initial polytherapy, changes in treatment over one year, and factors associated with long-term treatment adherence.

Methods

Data source

Study data were obtained from a proprietary research database containing eligibility information and pharmacy and medical claims data from a large commercial U.S. health plan providing coverage for physician, hospital, and prescription drug services, including services for psychiatric disorders. The health plan provides data from both self-insured employers (including retirees with employer-provided Medicare Supplemental Plans) and employer-sponsored commercially insured subscribers representing a geographically diverse sampling of approximately 14 million persons across the United States, with a concentration in the South and Midwest. We derived data from claims submitted by care providers to obtain payment for services rendered. Computerized files used were deidentified and accessed by protocols in compliance with the United States Health Insurance Portability and Accountability Act of 1996 to ensure confidentiality. Data derived from the same source have been used previously for various utilization, safety, and economic analyses (20–23), but they have not been used for analyses of treatments provided to patients diagnosed as having bipolar disorders.

Medical and pharmacy claims

Medical claims or encounter data were collected from all available sites for all types of services provided and were coded in conformance with insurance industry standards. Claims for ambulatory services submitted by individual providers (usually physicians) use Health Care Financing Agency (HCFA)–1500 forms and claims for hospital-based services use UB-92 forms (www.cms.hhs.gov).

Facility service records contain information on up to nine diagnoses and six procedures, categorized by *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis codes (24), and they contain information on procedure codes based on *ICD-9-CM,* Current Procedural Terminology (CPT), or HCFA Common Procedure Coding System (HCPCS) protocols (www.cms.hhs.gov/home/medicare.asp). Facility claims contain categories of most services but may not account for all drugs administered in the hospital. Provider service records contain information on up to four diagnoses recorded with *ICD-9-CM* codes and one procedure recorded using *ICD-9-CM*, CPT, or HCPCS codes. Claims for pharmacy services include drug names, dosage forms, drug strengths, fill dates, and number of days' supply.

Study population and characteristics

Health plan members initiating treatment for bipolar disorders were identified using eligibility criteria and medical and pharmacy claims data acquired between January 1, 2001, and December 31, 2005. To be included in the study, persons were required to be continuously enrolled in the health plan for six months before and for 12 months after a first prescription fill for a psychotropic medication. Persons were considered for the study if they were diagnosed as having bipolar disorder, were aged 17 years or older, were newly initiating pharmacological treatment for bipolar disorder (no psychotropic prescription fills in the preceding six months). Patients were entered in the study between January 1, 2001, and December 31, 2004, and were followed for 12 months after initiating treatment. Persons diagnosed as having schizophrenia, epilepsy, or migraines were excluded.

Demographic characteristics were assigned according to information reported in index claims for the first psychotropic prescription fill, including sex, current age, and geographic region. If more than one prescription by more than one prescriber was filled on the index date, the provider type was assigned hierarchically in the following order: psychiatrist, general practitioner, other specialist, and unknown.

Diagnosis of bipolar disorder and its subtypes was based on the presence of *ICD-9-CM* diagnosis codes indicating such illnesses that were then converted to corresponding *DSM-IV* codes according to guidelines provided by the American Health Information Management Association (AHIMA) (25). For this study, patients who ever had an *ICD-9-CM* diagnosis of bipolar affective disorder (*ICD-9-CM* codes 296.4–296.66), corresponding with *DSM-IV* bipolar I disorder (*DSM-IV* codes 296.4–296.66), were considered to have type I bipolar disorder; those who did not have bipolar disorder type I but had ever been diagnosed as having *ICD-9-CM* manic-depressive psychosis, other or unspecified type (296.89), corresponding to *DSM-IV* bipolar II disorder (296.89), were considered to have type II bipolar disorder; those who did not have type I or II bipolar disorder but had ever been diagnosed with *ICD-9-CM* affective psychosis, other or unspecified (296.7, 296.80), or with *ICD-9-CM* atypical manic or depressive disorder (296.81–296.82) were considered to have bipolar disorder not otherwise specified.

Patients also were categorized according to their apparent illness complexity, on the basis of selected clinical factors and presence of higher-severity bipolar disorder indicators or comorbid conditions that may complicate treatment, all as detailed by

Solz and Gilbert (26) and applied to other illnesses (26,27). We consulted with clinical and coding experts to identify *ICD-9-CM* codes associated with relatively high-severity bipolar disorders and complex illness management. Indicators of higher illness complexity included diagnostic indicators for moderate or severe bipolar disorder (296.xx with fifth digit classification as "moderate" or "severe" or with psychotic features), an indication of self-harm (E950.x–E959) or overdose (969.xx), or presence of certain comorbid disorders (including bulimia nervosa [307.51], impulse-control disorder [312.30], or chronic fatigue syndrome [780.71]). Remaining patients with bipolar disorder were considered to represent relatively lower levels of illness complexity, and substance use comorbidity was considered separately.

We also calculated comorbidity scores at baseline and during follow-up by using an algorithm developed by Charlson and collaborators (28) and adapted by Deyo and colleagues (29) for use with administrative claims databases. To better identify patients with specific clinical conditions used to score comorbidity, required diagnosis codes were updated in consultation with clinical and coding experts to reflect recent changes or additions to the codes, without change in the number or identity of clinical conditions used to calculate comorbidity scores. These included diagnosis of the clinical state (depressed, manic or hypomanic, mixed, or unspecified) closest in time to the initial prescription fill was determined.

Treatment regimens

Psychotropic medicines provided were categorized as mood stabilizers, including lithium and anticonvulsants (carbamazepine or oxcarbazepine, valproate [any salt of valproic acid, including divalproex], and lamotrigine); antipsychotics, including modern antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) and older neuroleptics (chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, pimozide, promazine, thioridazine, thiothixene, trifluoperazine, and trifluprom azine); antidepressants, including serotonin reuptake inhibitors (SRIs) (citalopram as its racemate or R-isomer, fluoxetine, fluvoxamine, paroxetine, and sertraline) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (duloxetine and venlafaxine), tricyclic antidepressants (including amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, protriptyline, nortriptyline, and trimipramine), monoamine oxidase (MAO) inhibitors (isocarboxazid, phenelzine, and tranylcypromine), and modern antidepressants (including bupropion, mirtazapine, nefazodone, and trazodone). We also identified concomitant use of anxiolytic-sedatives, or hypnotics, including benzodiazepines, as well as miscellaneous anticonvulsants of unproved efficacy in bipolar disorders (gabapentin, levetiracetam, tiagabine, topiramate, and zonisamide). Initial treatments and combinations were assigned as psychotropic prescriptions dispensed during the first 30 days of treatment. Final regimens were assigned by psychotropic prescriptions dispensed within the final 90 days of follow-up.

We also examined overall health care utilization during follow-up and recorded office or emergency service visits, hospitalizations, and hospital days per patient, based on services rendered, as identified in the claims database.

To evaluate mood stabilizer adherence, specifically, we identified a subgroup of patients who took a single mood stabilizer and initiated treatment with lithium or a mood-stabilizing anticonvulsant (carbamazepine, lamotrigine, oxcarbazepine, or valproate) and neither switched nor augmented therapy with any other mood stabilizer during follow-up. We measured mood stabilizer adherence by using a medication possession ratio (MPR). MPR is the percentage of the past 365 days with apparent access to an initial mood stabilizer. Also, a lower MPR would capture both treatment nonadherence and interruptions in treatment.

Analytic approach

We analyzed patient demographic and clinical characteristics, treatment regimens, and health care utilization in the study sample. We considered initial treatment patterns and examined changes in treatment during a year of follow-up, comparing all single and multiple psychotropic prescriptions dispensed during the first 30 days (initial treatment) to those during the final 90 days of follow-up (final treatment).

To identify characteristics associated with treatment adherence in the subsample of patients treated with a single mood stabilizer for up to a year, we compared factors of potential interest (including sex, age, diagnostic type, comorbidities, health care service use, prescriber type, geographic regions, mood-stabilizer treatment, and psychotropic cotreatments), contrasting adherent patients (MPR $\geq$80%) and nonadherent patients (MPR <80%) in preliminary bivariate comparisons. Factors differing between these adherence subgroups were further evaluated by multivariate least-squares regression modeling. Modeling included days hospitalized per patient to control for potential effects of prolonged hospitalizations with incompletely recorded inpatient pharmacy claims. Index year of starting treatment was also included to adjust for possible changes in prescribing patterns over time. When multiple items were considered in some comparisons, one was selected as a comparator against which effects of other factors on treatment adherence were related.

Data are reported as means and standard deviations (SDs) unless stated otherwise, and statistical tests required two-tailed $p<.05$ for significance. Analyses used commercial statistical software (SAS 9.1.3).

Results

Sample

A total of 7,406 treated patients met study inclusion criteria; 55% were identified as having bipolar I disorder, 15% as having bipolar II disorder, and 30% as having bipolar disorder not otherwise specified (Table 1). Mean age was 35.4±12.4 years, and a slight majority (57%) were women. More cases were located in the South (42%) and Midwest (40%) than in the West

Table 1

Characteristics of 7,406 patients diagnosed as having bipolar disorder with initial prescription fills for psychotropic medication in 2000–2004

Characteristic	N	%
Age (M±SD)[a]	35.4±12.4	
Sex		
Female	4,192	56.6
Male	3,214	43.4
Bipolar diagnostic type		
Type I	4,104	55.4
Type II	1,077	14.5
Not otherwise specified	2,225	30.0
U.S. geographic region		
South	3,094	41.8
Midwest	2,953	39.9
West	766	10.3
Northeast	593	8.0
Prescriber type		
Psychiatrist	2,738	37.0
Primary care physician	2,192	29.6
Other specialist	585	7.9
Unknown	1,891	25.5
Illness complexity[b]		
Low	3,128	42.2
High	4,278	57.8
Baseline comorbidity		
Comorbidity index (M±SD score)[c]	.22±.68	
Anxiety disorder	61	.8
Alcohol or other substance abuse	430	5.8
Baseline clinical state		
Mixed	3,446	46.5
Depressive	2,332	31.5
None stated	861	11.6
Manic	568	7.7
Bipolar disorder not otherwise specified	153	2.1
Hypomanic	46	.6
Service utilization per person in the past 12 months (M±SD)		
All outpatient visits	19.6±17.1	
Bipolar disorder–related outpatient visits	4.45±7.08	
Emergency visits[d]	1.30±3.82	
Bipolar disorder–related emergency visits[d]	.42±2.38	
Hospitalizations	.47±.91	
Psychiatric hospitalizations	.22±.54	
Days hospitalized	3.11±10.6	
Year sampled		
2001	2,188	29.5
2002	1,817	24.5
2003	1,856	25.1
2004	1,545	20.9

[a] Median age, 35 years; range, 17–86 years

[b] Indicators of higher illness complexity included diagnostic indicators for moderate or severe bipolar disorder (*ICD-9-CM* code 296.xx with fifth digit classification as "moderate" or "severe" or with psychotic features), an indication of self-harm (*ICD-9-CM* code E950.x–E959) or overdose (*ICD-9-CM* code 969.xx), or presence of certain comorbid disorders (including bulimia nervosa [307.51], impulse-control disorder [*ICD-9-CM* code 312.30], or chronic fatigue syndrome [*ICD-9-CM* code 780.71]). Remaining patients with bipolar disorder were considered to represent relatively low complexity of illness.

[c] As measured by the Charlson Comorbidity Index. Possible scores range from 0 to 37, with higher scores indicating greater levels of comorbidity and of illness complexity.

[d] Emergency visits pertain to services in hospital emergency rooms.

(10%) or Northeast (8%) of the United States, closely paralleling the overall population distribution of the health plan. Most patients (67%) were treated initially by psychiatrists (37%) or primary care physicians (30%).

Initial treatments

Among all 7,406 patients, 67% had an initial prescription fill for a single primary mood-altering drug (monotherapy), and 33% (2,444) had initial prescription fills for two or more major psychotropic drugs (polytherapy; major psychotropic drugs include anticonvulsants with mood-stabilizing or antimanic effects, lithium salts, antipsychotics, or antidepressants) (Figure 1). If sedatives and miscellaneous anticonvulsants are included, 43% (N=3,191) would have had polytherapy (Table 2). Initial prescription fills for primary monotherapies ranked as follows: antidepressants > anticonvulsants > antipsychotics > lithium. With initial prescription fills for polytherapy, antidepressants (79% of patients) were often used in combination with other agents more than were anticonvulsants (49%), antipsychotics (50%), or lithium (16% of patients). Overall, initial utilization rates ranked as follows: antidepressants > anticonvulsants ≥ antipsychotics > sedatives (anxiolytics or hypnotics) > lithium > miscellaneous anticonvulsants (Figure 1). Almost all antidepressants and antipsychotics given were modern agents.

Treatments at follow-up

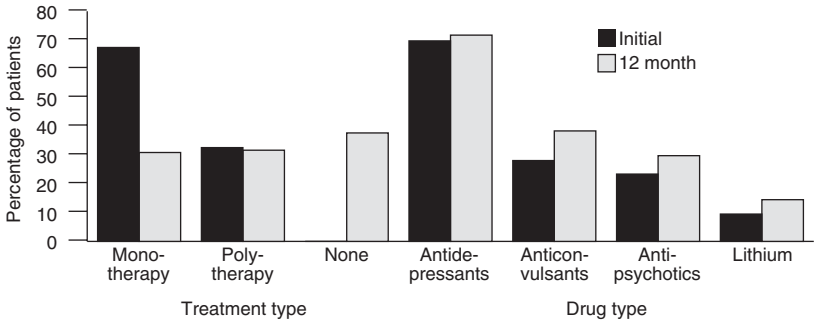
At one year, 2.2-fold fewer (31%) patients received monotherapy, 32% received two or more primary psychotropics (mood stabilizers, antipsychotics, or antidepressants), 50% of those still being treated received two or more major psychotropic drugs that act on the central nervous system and are used with the intention of mood stabilization (not including sedatives and miscellaneous anticonvulsants), and 37% had no evidence of receiving a primary mood-altering agent in the preceding 90 days (Table 2 and Figure 1). Although adequate clarification of the basis of being untreated at one year was not feasible, this untreated subgroup was not less likely to be in the care of a psychiatrist than other types of providers (data not shown).

Major changes from baseline to one year were for patients moving from monotherapy (67%) to no treatment (37%). Among monotherapies

at one-year, antidepressants again dominated, followed by anticonvulsants, lithium, and antipsychotics. For polytherapy during follow-up, most regimens also included antidepressants, as well as prevalent use of anticonvulsants and antipsychotics and a slightly greater use of lithium. Overall utilization rates among those being treated at follow-up ranked as follows: antidepressants (72%) > other mood-altering anticonvulsants (38%) > antipsychotics (30%) > sedatives (24%) > lithium (15%) > miscellaneous anticonvulsants (12%) (Table 2 and Figure 1).

Figure 1

Initial and final (12-month) psychotropic treatments for 7,406 patients with bipolar disorder who had not been prescribed medication for bipolar disorder for six months or more before study entry[a]



[a] Note that antidepressants were very prominent at both times and that more than 30% of patients used polytherapy (two or more major psychotropic drugs) at both times. Also, monotherapy fell from nearly 70% of patients at entry to about 30% at one year, and nontreatment became prevalent at one year.

Adherence to mood stabilizer treatment

Among the 7,406 study patients, 2,197 (30%) were given a prescription for a single mood stabilizer at baseline and had no evidence of switching or augmenting this basic treatment with an additional mood stabilizer (anticonvulsant or lithium) during follow-up. In this subsample of patients given a single mood stabilizer, valproate (N=1,125, or 51%) was the most commonly used agent, followed by lithium (N=517, or 24%), carbamazepine or oxcarbazepine (N=308, or 14%), and lamotrigine (N=247, or 11%). However, many of the patients in this subsample were also given an antidepressant (N=1,213, or 55%), sedative (N=791, or 36%), or antipsychotic drug (N=763, or 35%), and a minority (N=306, or 14%) received a miscellaneous anticonvulsant at some time, with an average of 2.85±1.72 psychotropics per person (median=2, range=1–12), even with nominally simplified treatment. Only 28% (N=620) of the subsample were considered adherent (MPR ≥80%) to their single mood stabilizer therapy, and 72% (N=1,577) were considered nonadherent (MPR <80%).

Of note, patients given lithium as the single mood stabilizer were much less likely to receive adjunctive psychotropic agents during the following year than were those whose single mood stabilizer was an anticonvulsant. This difference was significant for all types of psychotropic drugs except anxiolytics, and it was particularly striking with antidepressants (Table 3).

Factors associated with mood stabilizer adherence

Preliminary, unadjusted, bivariate comparisons of the treatment-adherent subgroup (N=620) and the nonadherent subgroup (N=1,577) indicated minor differences between each other or versus the overall cohort of 7,406 patients with respect to geographic distribution, year of study entry, sex, entry age, diagnosis, illness complexity, comorbidity index score, and prescriber type (data not shown). Moreover, the subgroups were very similar in utilization rates for adjunctive psychotropics other than the identified primary mood stabilizer. A larger proportion of adherent patients received lithium or lamotrigine, whereas nonadherent patients were more often given valproate, carbamazepine, or oxcarbazepine. Adherent patients also were less likely to abuse alcohol or drugs, compared with nonadherent patients (N=24, or 3.9%, versus N=120, or 7.6%), but they were somewhat more likely to have a comorbid anxiety disorder (N=6, or 1.0%, versus N=7, or .4%). Also of interest, patients adherent to mood stabilizers had 20% more total outpatient visits per person per year (19.0 versus 15.8) and 55% more ambulatory visits related to bipolar disorder (6.8 versus 4.4); they also had 44% more emergency service visits related to bipolar disorder (.52 versus .36 per person per year), but they had 27% fewer hospitalizations for all reasons (.30 versus .41 per person per year, mainly for nonpsychiatric indications) and 37% fewer hospitalization days (1.7 versus 2.7 per person per year) (data not shown).

Multivariate analyses based on the preceding observations and inclusion of factors considered clinically plausible indicated several measures that were independently and significantly associated with mood stabilizer adherence, based on MPR as the outcome measure. MPR was higher with older age ($p<.001$), lack of substance abuse ($p=.001$), treatment by a psychiatrist versus a primary care physician ($p=.008$), and lower illness complexity ($p=.013$) (Table 4). Adherence to specific mood stabilizers was ranked as follows: lamotrigine ≥ lithium ≥ valproate or carbamazepine or oxcarbazepine ($p<.001$). Treatment adherence was lower if co-treatment with miscellaneous anticonvulsants was used ($p=.004$). However, no significant associations were found between MPR and co-treatment with antidepressants or antipsychotics, nor with sex, diagnostic subtype, comorbidity index, or geographical region.

Finally, in multivariate modeling, greater mood stabilizer adherence was associated significantly with more bipolar disorder–related outpatient and emergency service visits (both $p<.001$) but much lower utilization of emergency services for indications not related to bipolar disorder

Table 2

Initial and final (12-month) psychotropic treatments for 7,406 patients with bipolar disorder who had not been prescribed medication for bipolar disorder for six months or more before study entry[a]

	Initial treatment						Final treatment							
	Mono-therapy		Poly-therapy		All participants		Mono-therapy		Poly-therapy		All treated		All participants	
Treatment	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any psychotropic treatment	4,992	67.4	2,414	32.6	7,406	100.0	2,292	30.9	2,349	31.7	4,641	62.7	7,406	100.0
Mood stabilizer														
Any mood stabilizer	1,209	24.2	1,488	61.6	2,697	36.4	724	31.6	1,592	67.8	2,316	49.9	2,316	31.3
Lithium salts	318	6.4	382	15.8	700	9.5	217	9.5	458	19.5	675	14.5	675	9.1
Anticonvulsant	891	17.8	1,189	49.3	2,080	28.1	507	22.1	1,276	54.3	1,783	38.4	1,783	24.1
Valproate	563	11.3	253	10.5	410	5.5	90	3.9	311	13.2	401	8.6	401	5.4
Carbamazepine or oxcarbazepine	157	3.1	827	34.3	1,390	18.8	288	12.6	712	30.3	1,000	21.5	1,000	13.0
Lamotrigine	171	3.4	155	6.4	326	4.4	129	5.6	342	14.6	471	10.1	471	6.4
Antipsychotic														
Any antipsychotic	530	10.6	1,206	50.0	1,736	23.4	212	9.2	1,169	49.8	1,381	29.8	1,381	18.6
First-generation antipsychotic	14	.3	58	2.4	72	1.0	6	.3	41	1.7	47	1.0	47	.6
Second-generation antipsychotic	516	10.3	1,166	48.3	1,682	22.7	206	9.0	1,146	48.8	1,352	29.1	1,352	18.3
Aripiprazole	16	.3	45	1.9	61	.8	11	.5	94	4.0	105	2.3	105	1.4
Clozapine	1	.0	1	.0	2	.0	0	—	2	.1	2	.0	2	.0
Olanzapine	305	6.1	511	21.2	816	11.0	69	3.0	413	17.6	482	10.4	482	6.5
Quetiapine	86	1.7	345	14.3	431	5.8	69	3.0	424	18.1	493	10.6	493	6.7
Risperidone	91	1.8	312	12.9	403	5.4	50	2.2	261	11.1	311	6.7	311	4.2
Ziprasidone	17	.3	54	2.2	71	1.0	7	.3	88	3.7	95	2.0	95	1.3
Antidepressant														
Any antidepressant	3,253	65.2	1,910	79.1	5,163	69.7	1,356	59.2	1,973	84.0	3,329	71.7	3,329	45.0
Older antidepressant (tricyclics or monoamine oxidase inhibitors)	146	2.9	131	5.4	277	3.7	36	1.6	110	4.7	146	3.1	146	2.0
Modern antidepressant[b]	3,107	62.2	1,867	77.3	4,974	67.2	1,320	57.6	1,941	82.6	3,261	70.3	3,261	44.0
SRI	2,087	41.8	1,289	53.4	3,376	45.6	790	34.5	1,242	52.9	2,032	43.8	2,032	27.4
SNRI	348	7.0	262	10.9	610	8.2	184	8.0	391	16.6	575	12.4	575	7.8
Miscellaneous[c]	672	13.5	886	36.7	1,558	21.0	346	15.1	927	39.5	1,273	27.4	1,273	17.2
None of the preceding agents[d]	0	—	0	—	0	—	0	—	0	—	0	—	2,765	37.3
Other agent														
Any sedative	792	15.9	545	2.6	1,337	18.1	494	21.6	637	27.1	1,131	24.4	1,429	19.3
Anxiolytic[e]	592	11.9	380	15.7	972	13.1	360	15.7	461	19.6	821	17.7	1,052	14.2
Hypnotic[f]	273	5.5	232	9.6	505	6.8	186	8.1	254	10.8	440	9.5	536	7.2
Miscellaneous anticonvulsant[g]	328	6.6	219	9.1	547	7.4	245	10.7	329	14.0	574	12.4	694	9.4

[a] Totals do not add to 100% because of overlapping combinations. Note that use of any combination of major psychotropic drugs that act on the central nervous system and are used with the intention of mood stabilization (all polytherapy) is even higher if sedatives and miscellaneous anticonvulsants are included: baseline: 43.1% (3,191 of 7,406 treated patients) and even higher at one year: 61.5% (2,855 of 4,641 treated patients). Agents per patient averaged 1.42±.68 initially and 1.75±.91 at one year.

[b] SRI, serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor (for example, duloxetine and venlafaxine)

[c] Miscellaneous antidepressant (for example, bupropion, mirtazapine, nefazodone, and trazodone)

[d] Not prescribed a mood stabilizer, antipsychotic, or antidepressant

[e] For example, benzodiazepines (for anxiety) and buspirone

[f] For example, benzodiazepines (for sleep), eszopiclone, ramelton, zaleplon, and zolpidem

[g] Miscellaneous anticonvulsant (not proved effective in bipolar disorders)—for example, gabapentin, tiagabine, topiramate, and zonisamide

(p<.001). These variations in service utilization rates (Table 4) suggest that greater adherence may have been associated with closer outpatient follow-up, with complex implications for the economics of treatment.

Discussion

This study examined all initial psychotropic treatments for U.S. patients who were diagnosed as having bipolar disorder who had not received medication for bipolar disorder for at least six months at baseline. The study also reassessed treatments a year later and examined treatment adherence in some detail by using a national claims database not previously employed for the study of treatment of such pa-

Table 3

Relative rates (RR) of use of adjunctive psychotropics during one year of sustained primary mood-stabilizing treatment with lithium versus anticonvulsants[a]

	Lithium (N=517)		Anticonvulsants (N=1,680)					
Adjunctive treatment	N	%	N	%	RR	95% CI	χ^2	p
Antidepressant	248	48.0	965	57.4	.835	.757–.922	14.34	<.001
Antipsychotic	156	30.2	607	36.1	.835	.722–.966	6.19	.013
Hypnotic	56	10.8	254	15.1	.716	.546–.940	6.00	.014
Anticonvulsant	58	11.2	248	14.8	.760	.581–.994	4.14	.042
Anxiolytic	106	20.5	380	22.6	.906	.749–1.098	1.03	.311

[a] Adjunctive psychotropic agents received during follow-up with use of lithium or a mood-stabilizing anticonvulsant as the primary mood stabilizer among 2,197 patients with bipolar disorder. Among lithium-treated patients there was relatively less use of all types of adjunctive agents except anxiolytics (owing to greater statistical power [N], the effect on antidepressants is particularly significant). Numbers do not add up to total subject numbers because of use of multiple agents per patient.

tients. New findings included the following: one-third of newly treated patients were started on polytherapy (two or more major psychotropic drugs), and even more treated patients received multiple psychotropic drugs a year later. However, at the one-year follow-up, 37% were not receiving any psychotropic medicine (a mood stabilizer, antipsychotic, or antidepressant). As noted previously (20), antidepressants were by far the most commonly prescribed psychotropic drugs for American patients diagnosed as having bipolar disorders (Table 2).

Study limitations

Health care insurance claims data are valuable for efficient and effective examination of clinical outcomes, treatment patterns, resource utilization, and costs. However, such data are collected to guide reimbursements and are limited when used for research purposes. Notably, a claim for a filled prescription does not prove medication was taken as prescribed. Also, medications may be provided without a prescription (for example, samples from a clinician or medications administered in a hospital), which typically are not captured in claims data. Similarly, the presence or absence of a diagnosis code in a claim does not guarantee presence or absence of a specific disorder, nor does it guarantee the accuracy of clinical assessment and documentation. Important clinical information—including specific, current, symptomatic indications for a treatment; details of illness history; test results; and physical findings—often is not available in claims files. Finally, the population studied may not be representative of all patients with bipolar disorder, and there may be a risk of underdiagnosis of bipolar disorder among insured patients, for example, to avoid poten-

Table 4

Multivariate regression modeling showing factors associated with one-year treatment adherence to a mood stabilizer (medication possession ratio)

Covariate	Coefficient (β)	95% CI	p
Mood stabilizer			<.001
Lithium (reference)			
Lamotrigine	5.21	.01 to 10.4	
Valproate	–5.23	–8.67 to –1.79	
Carbamazepine or oxcarbazepine	–4.78	–9.53 to –.04	
Age	.56	.45 to 0.67	<.001
Baseline comorbidity:			
alcohol or drug abuse	–9.18	–14.8 to –3.60	.001
Service utilization			
Bipolar disorder–related office visits	.75	.56 to .94	<.001
Bipolar disorder–related emergency visits	9.46	4.30 to 14.6	<.001
Any emergency room visit	–5.98	–9.41 to –2.55	<.001
Hospital days	–.23	–.40 to –.05	.011
Psychotropic co-treatment			
No use of miscellaneous anticonvulsant (reference)			
Miscellaneous anticonvulsant	–5.98	–10.1 to –1.91	.004
Illness complexity			.013
Lower (reference)			
Higher	–3.85	–6.90 to –.81	
Prescriber type			.008
Psychiatrist (reference)			
Primary care physician	–5.70	–9.88 to –1.52	

[a] Data (coefficients [β] and their confidence intervals [CI]) pertain to 2,197 patients diagnosed as having bipolar disorder and receiving a single mood stabilizer for 12 months. Coefficient values reflect change in medication possession ratio (MPR) resulting from a one-unit change in a covariate (positive values=positive association with MPR), sometimes versus a comparator, as noted, when multiple comparisons are involved. For example, MPR is 9.18 percentage points lower among patients with evidence of alcohol or drug abuse and 5.21 points greater among patients treated with lamotrigine versus lithium. Other factors not related to MPR included sex, diagnostic type, geographic region, comorbidity index score, and co-treatment with antidepressants or antipsychotics. The model was adjusted for year of treatment initiation, to control for changes in treatment options and prescribing patterns over time, and for number of days hospitalized, because medications administered in a hospital are not always captured in claims data.

tial stigmatization. The study patients represent a largely working population with geographic distribution similar to the enrollment patterns of the health plan. Despite their limitations, claims data, including data from the source used in this study, have been widely employed in research and can provide indications of clinical practice patterns and their changes over time (20–23).

Polytherapy

Prevalent use of polytherapy initially as well as later in treatment of U.S. patients with bipolar disorder probably reflects the growing availability of both FDA-approved and off-label treatment options, as well as incomplete therapeutic responses among most patients with bipolar disorders (2–5). Available data were not adequate to specify the basis of the striking rate of treatment discontinuation (37%) found by one year (Table 2). Nontreatment is likely to reflect dissatisfaction with treatment, intolerance of it, or a perceived lack of active symptoms requiring treatment, arising from misunderstanding among patients or clinicians of the crucial role of long-term prophylaxis in the treatment of bipolar disorder even through periods of euthymia (1,30). A particularly striking finding was that polytherapy, particularly involving cotreatment with antidepressants, was much less prevalent among patients using lithium than among those using an anticonvulsant as a primary mood stabilizer. This finding is consistent with previous reports of relatively high proportions of patients maintained on mood-stabilizing monotherapy among those treated with lithium versus an anticonvulsant (3,31). These trends may suggest superior efficacy of lithium as a primary mood-stabilizing agent, including its effect on suicidal risk (32,33).

Antidepressant use

In accord with a previous analysis (20), we found again that antidepressants were by far the most commonly prescribed psychotropic medications for patients with bipolar disorder in the United States, both initially and during long-term follow-up (70%–72% of treated patients). Their popularity probably reflects both the clinical perception that such treatments are relatively well tolerated despite indications that treatment response in depressive phases of the disorder is limited (2–5,14–20). In addition, adverse behavioral effects of antidepressants—such as mixed states, mild hypomania, and moderately increased cycling—may be overlooked or misdiagnosed (1). Intensive reliance on antidepressants is all the more remarkable given limited evidence of their short- and especially long-term efficacy and psychiatric safety in bipolar disorder (16,18,34). Far less commonly employed treatments were FDA-approved and research-supported mood stabilizers (1), which were prescribed for only a minority of the patients initially (36%) and at follow-up (50% of those treated and only 31% of all patients) (Table 2). Anticonvulsants (28% of patients initially and 24% of those treated at follow-up, most often valproate) were prescribed much less frequently than antidepressants (≥70% of patients) but more often than lithium (9% of patients on average) (Table 2).

Treatment adherence

Additional new findings included identification of factors independently and significantly associated with long-term adherence to an initial mood-stabilizing treatment (Table 3). Perhaps not surprisingly (1,19,20), only a minority (30%) of U.S. patients diagnosed as having bipolar disorder were nominally continued for a year on an initial mood stabilizer, and only 28% of this subsample were considered to be treatment adherent, on the basis of an MPR ≥80% averaged over 12 months. Factors associated with greater treatment adherence included being older, use of lamotrigine or lithium, lack of substance abuse, and treatment by a psychiatrist rather than a primary care physician. Inferior adherence was associated with use of valproate (the most commonly prescribed anticonvulsant mood stabilizer), use of carbamazepine or oxcarbazepine, use of supplemental anticonvulsants that lack FDA-approval for use in bipolar disorder, alcohol or drug abuse, and greater illness complexity.

Finally, we found complex associations between treatment adherence and utilization of health services. Office, and especially emergency service, visits for bipolar disorder–related care were more frequent in association with greater treatment adherence, whereas emergency service utilization for other indications and days per year of hospitalization for any reason were lower with greater adherence to mood stabilizer treatment (Table 3). The lesser utilization of emergency and inpatient services suggests potential cost savings with greater adherence to mood-stabilizing treatments. On the other hand, greater use of ambulatory and emergency services for bipolar disorder–related indications suggests that greater treatment adherence may reflect relatively close monitoring, with more frequent clinician contacts. However, the available data do not permit clarification of cause-effect relationships between treatment adherence and utilization of clinical services.

Conclusions

Whatever their interpretation, the findings presented here underscore the clinical impression that polytherapy, discontinuous long-term treatment, and heavy reliance on largely unproved antidepressant treatment all are prominent characteristics of contemporary treatment of patients diagnosed as having bipolar disorders in the United States. Use of antidepressants was highly prevalent and sustained, despite limited evidence of their efficacy or safety in bipolar depression. Mood-altering polytherapy was used by about one-third of patients at the start of new treatment and at follow-up a year later, but was less prevalent when lithium was the primary mood stabilizer, rather than an anticonvulsant or antipsychotic agent. At one year of follow-up, 62% of patients still being treated were taking two or more major centrally active drugs of all types (polytherapy). A remarkable new finding was that at one year the proportion of patients not receiving psychotropic treatment was about as prevalent as the proportions receiving mood-stabilizing monotherapy or polytherapy, but the

reason for this finding requires further clarification. Adherence to long-term mood stabilizer treatment, although uncommon, was associated with several plausible clinical factors. Our findings of heavy reliance on antidepressants and polytherapy, low mood stabilizer utilization and adherence rates, and high rates of dropout from long-term mood-stabilizing treatment strongly suggest that more effective and better-tolerated mood-stabilizing treatments are required for patients with bipolar disorders, along with redoubled educational efforts to underscore the importance of sustained, long-term prophylactic treatment of such patients, even through periods of relative euthymia.

Acknowledgments and disclosures

This study was supported by Novartis Corporation, the Bruce J. Anderson Foundation, and the McLean Private Donors Psychopharmacology Research Fund (to RJB). The authors thank Jessica Goren, Pharm.D., for providing helpful suggestions, including the need to compare polytherapy with types of primary mood stabilizer.

Dr. Baldessarini has recently served as a consultant for, or carried out investigator-initiated research supported with funds from, Auritec Pharmaceuticals, Biotrofix, Luitpold Pharmaceuticals, Eli Lilly and Company, IFI SpA, Janssen Pharmaceuticals, JDS-Noven Pharmaceuticals, NeuroHealing Pharmaceuticals, Novartis Pharmaceuticals, and Solvay Pharmaceuticals. The other authors report no competing interests.

References

1. Baldessarini RJ, Tarazi FI: Pharmacotherapy of psychosis and mania, in Goodman and Gilman's the Pharmacological Basis of Therapeutics, 11th ed. Edited by Brunton LL, Lazo JS, Parker KL. New York, McGraw-Hill, 2005
2. Judd LL, Akiskal HS, Schettler PJ, et al: The long-term natural history of the weekly symptomatic status of bipolar I disorder. Archives of General Psychiatry 59:530–537, 2002
3. Post RM, Denicoff KD, Leverich GS, et al: Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. Journal of Clinical Psychiatry 64:680–690, 2003
4. Joffe RT, MacQueen GM, Marriott M, et al: A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. Bipolar Disorders 6:62–66, 2004
5. Baldessarini RJ, Salvatore P, Tohen M, et al: Morbidity from onset in first-episode bipolar I disorder patients: the International-300 study. Neuropsychopharmacology 29(suppl 1):S88, 2004
6. Angst F, Stassen HH, Clayton PJ, et al: Mortality of patients with mood disorders: follow-up over 34–38 years. Journal of Affective Disorders 68:167–181, 2002
7. Tondo L, Isacsson G, Baldessarini RJ: Suicide in bipolar disorder: risk and prevention. CNS Drugs 17:491–511, 2003
8. Frye MA, Calabrese JR, Reed ML, et al: Healthcare resource utilization in bipolar depression compared with unipolar depression: results of a United States population-based study. CNS Spectrums 11:704–710, 2006
9. Thase ME: Pharmacotherapy of bipolar depression: an update. Current Psychiatry Reports 8:478–488, 2006
10. Dutta R, Boydell J, Kennedy N, et al: Suicide and other causes of mortality in bipolar disorder: longitudinal study. Psychological Medicine 37:839–847, 2007
11. Huxley N, Baldessarini RJ: Disability and its treatment in bipolar disorder patients. Bipolar Disorders 9:183–196, 2007
12. Tondo L, Baldessarini RJ: Risks of suicidal ideation, attempts and suicides among 2,826 men and women with types I and II bipolar, and recurrent major depressive disorders. Acta Psychiatrica Scandinavica 116:419–428, 2007
13. Ghaemi SN, Rosenquist KJ, Ko JY, et al: Antidepressant treatment in bipolar vs unipolar depression. American Journal of Psychiatry 161:163–165, 2004
14. Baldessarini RJ: Drug therapy of depression and anxiety disorders, in Goodman and Gilman's the Pharmacological Basis of Therapeutics, 11th ed. Edited by Brunton LL, Lazo JS, Parker KL. New York, McGraw-Hill, 2005
15. Ghaemi SN, Goodwin FK: Antidepressants for bipolar depression. American Journal of Psychiatry 162:1545–1246, 2005
16. Ghaemi SN, Wingo AP, Filkowski MA, et al: Effectiveness of long-term antidepressant treatment in bipolar disorder: a meta-analysis. Acta Psychiatrica Scandinavica, in press
17. Baethge C, Baldessarini RJ, Mathiske-Schmidt K, et al: Long-term combination therapy vs monotherapy with lithium and carbamazepine in 46 bipolar I patients. Journal of Clinical Psychiatry 66:174–182, 2005
18. Lin D, Mok H, Yatham LN: Polytherapy in bipolar disorder. CNS Drugs 20:29–42, 2006
19. Baldessarini RJ, Perry R, Pike J: Factors associated with treatment nonadherence among US bipolar disorder patients. Human Psychopharmacology 116:419–428, 2007
20. Baldessarini RJ, Leahy L, Arcona S, et al: Prescribing patterns of psychotropic medicines in the United States for patients diagnosed with bipolar disorders. Psychiatric Services 58:85–91, 2007
21. Harley CR, Riedel AA, Hauch O, et al: Anticoagulation therapy in patients with chronic atrial fibrillation: a retrospective claims data analysis. Current Medical Research Opinion 21:215–222, 2005
22. Shetty S, Secnik K, Oglesby AK: Relationship of glycemic control to total diabetes-related costs for managed care health plan members with type-2 diabetes. Journal of Managed Care Pharmacy 11:559–564, 2005
23. Darkow T, Henk HJ, Thomas SK, et al: Treatment interruptions and non-adherence with imatinib and associated healthcare costs: retrospective analysis among managed care patients with chronic myelogenous leukemia. Pharmacoeconomics 25:481–496, 2007
24. International Classification of Diseases, Ninth Revision, Clinical Modification. Geneva, World Health Organization, 1975
25. Albaum-Feinstein A: DSM-IV Crosswalk: Guidelines for Coding Mental Health Information. Chicago, American Health Information Management Association, 1999. Available at www.ahima.org
26. Solz H, Gilbert K: Health claims data as a strategy and tool in disease management. Journal of Ambulatory Care Management 24:69–85, 2001
27. Arocho R, Solis A, Wade S, et al: Exploring methodological challenges of investigating comparison groups with different underlying characteristics: case study. Journal of Managed Care Pharmacy 8:353–359, 2002
28. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases 40:373–383, 1987
29. Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Journal of Clinical Epidemiology 45:613–619, 1992
30. Smith LA, Cornelius V, Warnock A, et al: Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. Bipolar Disorders 9:394–412, 2007
31. Tohen M, Zarate CA Jr, Hennen J, et al: The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. American Journal of Psychiatry 160:2099–2107, 2003
32. Baldessarini RJ, Tondo L, Davis P, et al: Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disorders 8:625–639, 2006
33. Baldessarini RJ, Tondo L: Lithium and suicidal risk. Bipolar Disorders 10:114–115, 2008
34. Truman CJ, Goldberg JF, Ghaemi SN, et al: Self-reported history of manic/hypomanic switch associated with antidepressant use: data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Journal of Clinical Psychiatry 68:1472–1479, 2007