Article

# Trends in the Treatment of Bipolar Disorder by Outpatient Psychiatrists

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**Objective:** This study examined recent changes in the prescribing patterns for medications to treat bipolar disorder in office-based psychiatric practice.

**Method:** The authors analyzed physician-reported data from the National Ambulatory Medical Care Survey for 1992–1995 and 1996–1999, focusing on physicians specializing in psychiatry. Demographic, clinical, and medication prescription characteristics of patients' visits were compared to identify changes between the periods. Logistic regression models were used to identify predictors of medication prescription, with adjustment for the presence of other covariates.

**Results:** In both survey periods, over one-third of the total psychiatrist visits by patients with bipolar disorder did not include prescription of a mood stabilizer. There was a decrease in the use of lithium over time, accompanied by an increase in the use of valproic acid. Antipsychotic medication was prescribed more frequently for the bipolar manic and mixed subtypes, and there was a secular increase in the use of the newer antipsychotics. During each time period, prescription of antidepressants was common, often in the absence of a mood stabilizer.

**Conclusions:** Despite important advances in the range of mood stabilizers available, the pharmacological treatment of bipolar disorder continues to be an area with substantial opportunity for quality improvement.

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In the last decade, a number of pharmacological agents have shown efficacy in the treatment of bipolar disorder, and several guidelines have been published to suggest appropriate clinical management (1–3). Without treatment, patients with bipolar disorder face substantial distress and impairment and have a significant risk of morbidity and mortality (4, 5). Traditionally, lithium has been considered the treatment of choice for bipolar disorder. However, more recently, valproic acid has become an increasingly popular alternative to lithium as a first-line treatment and has even been suggested to be superior to lithium for certain subgroups of patients with bipolar disorder (6–8).

Previous studies have shown that substantial variation occurs in the pharmacological treatment of bipolar disorder. A naturalistic study by Goldberg and coworkers (9) revealed that about one-third of their patients were taking lithium alone, an additional one-third were taking lithium plus an antipsychotic, and almost another one-third were not taking any medication at the long-term follow-up. In another study, 68% of bipolar outpatients were taking lithium, 13% were taking a mood stabilizer other than lithium, with or without antidepressants or antipsychotics, 10% were taking only antidepressants or antipsychotics, and 7% were not taking any psychotropic medication (10). In addition, there are data suggesting that prescription patterns of mood stabilizers have changed over the last few years, with an increase in the prescription of anticonvulsants and a decrease in the use of lithium (11–13).

Because office-based psychiatrists are a major source of care for patients with bipolar disorder (14, 15), it is important to document the extent to which their prescribing practices conform to evidence-based standards. Compliance with these critically important recommendations has never been examined in a nationally representative sample of bipolar outpatients, to our knowledge.

The purpose of this analysis was to examine the rates of guideline adherence, to identify factors that are associated with practice variation, and to study temporal trends in the treatment of a nationally representative sample of visits to office-based psychiatrists by patients with a diagnosis of bipolar disorder.

## Method

### *Source of Data*

Data were drawn from the National Ambulatory Medical Care Survey. The National Ambulatory Medical Care Survey, which is conducted annually by the National Center for Health Statistics, samples a nationally representative group of visits to physicians in office-based practice. We followed the recommendations of the National Center for Health Statistics in combining data from contiguous survey years to establish a larger base upon which to derive estimates. In order to detect changes in practice patterns in delivery of care through time, we grouped the visits from 1992 to 1995 and those from 1996 to 1999. Attending physicians or their office staff completed a one-page form about each patient visit. The form included basic demographic characteristics of the patients, their source of payment for the visit, their diagnoses, and their medications, including new prescriptions ordered, sup-

plied, or administered and medications continued, with or without new orders. Only minor modifications were made to the survey between 1992 and 1999. The rate of response through the years varied from 70% to 73%.

### Survey Design

The surveys were conducted by means of a three-stage sampling design. First, a probability sample of 112 primary sampling units (a county, a group of adjacent counties, or a standard metropolitan statistical area) was drawn, then a probability sample was drawn of practicing physicians within these primary sampling units, and, finally, a systematic random sample was drawn of the visits to these physicians over a 1-week period. Physicians who expected to see more than 10 patients per day recorded visits on the basis of a predetermined sampling interval. Some patient duplication may have occurred with this sampling strategy. The current analysis was confined to visits to psychiatrists.

### Variables

"Mood stabilizers" included lithium, carbamazepine, valproic acid, gabapentin, lamotrigine, and topiramate. "Antidepressant drugs" included tricyclic (and tetracyclic) antidepressants; the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, fluvoxamine, paroxetine, and citalopram; and "other antidepressants," including trazodone, venlafaxine, nefazodone, and monoamine oxidase inhibitors. Because bupropion has been reported to have a lower incidence of medication-induced mania, it was considered as part of a special class of antidepressants for the purposes of our analyses.

Data were collected regarding patient age, sex, and race, as determined by physician judgment. In addition, the surveys included a status code that classified visits according to whether the physician (or another physician in the same office) had ever seen the patient before.

Data collected on sources of payment for the visit were collapsed into three nonmutually exclusive categories: Medicare, Medicaid, and other government insurance were grouped together as "public insurance"; commercial insurance, including Blue Cross/Blue Shield, was considered to be "private insurance"; and a residual category was created that combined self-pay, uncompensated care, workers compensation, and unknown sources of payment. An additional variable was created to identify patient visits covered by prepaid plans, such as health maintenance organizations, independent practice associations, preferred provider organizations, and other prepaid arrangements.

Up to five ICD-9 codes were specified for each patient visit. Visits with codes 296.0, 296.1, or 296.4 were classified as regarding patients with bipolar mania. Visits assigned code 296.5 were classified as those by bipolar depressed patients. Visits that used code 296.6 were considered as regarding bipolar mixed patients, and visits assigned codes 296.7 or 296.8 were classified as for patients with bipolar disorder, unspecified. "Comorbidity" was defined as for visits assigned an additional code: 290–319, 327–328, 780.1, or 995.5.

### Analysis

We examined rates per 100 psychiatrist visits by demographic and insurance characteristics of the sample, the patient diagnostic subtype, and the pharmacological management of the patient. We then examined the association of diagnostic and medication management characteristics of the visits with the patient demographic group, payment source for the visit, whether the patient was previously seen by the psychiatrist, patient diagnostic group, and number of diagnoses made during those visits.

In order to detect changes in practice patterns over time, we grouped the demographic and clinical characteristics of the patients visiting a psychiatrist from 1992 to 1995 and from 1996 to 1999 and compared the patterns of diagnosis and pharmacological treatment during both periods. Because sample sizes of the surveys were larger in the earlier years of the National Ambulatory Medical Care Survey, a larger proportion of the visits in which a diagnosis of bipolar disorder was made occurred from 1992 to 1995.

### Statistical Methods

Because of the complex survey design, the National Center for Health Statistics weights each visit using data from the Bureau of the Census to mirror the U.S. population. The construction of the weighting has three components: inflation by reciprocals of sampling probabilities, adjustment for nonresponse, and a ratio adjustment to fixed totals. The adjustment for nonresponse replaces patient visits to nonrespondents with visits to respondents in the same specialty area and the same primary sampling unit on the basis of data for a given specialty over the number of sampled physicians in that specialty from the master files of the American Medical Association and the American Osteopathic Association. It is important to note that these master files include listings of all physicians in the United States—not only those who are members of these professional organizations. A statistical adjustment developed by Pothoff and co-workers that tends to overcompensate for stratification artifacts (16) was used to calculate standard errors of the survey estimates.

Chi-square statistics were used to test for differences in the distribution of categorical variables across the two time periods. T tests were used to examine the differences among continuous variables. Stepwise logistic regressions were conducted to examine patient demographic and clinical factors associated with medication regimens.

## Results

### Characteristics of the Sample

A total of 865 visits to a psychiatrist by patients with a diagnosis of bipolar disorder were sampled from the National Ambulatory Medical Care Survey between 1992 and 1999, representing a total of 5,025,601 visits nationwide. There were no significant differences in the demographic characteristics of the 1992–1995 and the 1996–1999 samples. In both periods, the majority of visits were made by patients with bipolar disorder who were in the fourth or fifth decades of life. Visits by women were almost twice as frequent as visits by men. More than 92% of the visits were made by patients who had been seen previously by the same psychiatrist. Although there were no significant secular changes in payment source for the visits, the proportion of visits that were covered by a prepaid insurance plan more than doubled between the two time periods (Table 1).

There were significant changes in the diagnostic patterns of the bipolar patients: the proportion of visits by patients with a diagnosis of the manic or mixed subtype of bipolar disorder almost doubled, while the proportion of visits by patients who were diagnosed as having an unspecified subtype of bipolar disorder decreased proportionately. There was little change in the proportion of visits by patients with a diagnosis of depressed subtype (Table 1). A comorbid psychiatric diagnosis was noted in a relatively small number of visits.

**TABLE 1. Demographic and Clinical Characteristics of Outpatient Visits to Psychiatrists by Patients With Bipolar Disorder in the National Ambulatory Medical Care Survey[a]**

| | Visits During 1992–1995 (N=593) | | Visits During 1996–1999 (N=272) | |
|---|---|---|---|---|
| Characteristic | Percent | 95% CI | Percent | 95% CI |
| Patient's age (years) | | | | |
| 0–35 | 29.7 | 26.1–33.3 | 30.9 | 27.3–34.5 |
| 36–50 | 42.4 | 38.6–46.24 | 40.4 | 36.6–44.2 |
| 51–64 | 16.4 | 13.6–19.3 | 22.3 | 19.1–25.5 |
| 65 or more | 11.5 | 9.0–14.0 | 6.4 | 4.5–8.3 |
| Patient's sex | | | | |
| Female | 64.2 | 60.5–68.0 | 59.6 | 54.2–65.0 |
| Male | 35.8 | 32.1–40.0 | 40.4 | 35.0–45.8 |
| Patient's race | | | | |
| White | 90.9 | 88.7–93.1 | 90.3 | 87.1–93.6 |
| Nonwhite | 9.1 | 6.9–11.3 | 9.7 | 6.5–12.9 |
| Payment source | | | | |
| Private insurance | 44.6 | 40.7–48.5 | 44.1 | 38.7–49.5 |
| Public insurance | 32.1 | 28.5–35.7 | 25.8 | 21.0–30.6 |
| Other | 30.9 | 27.3–34.5 | 29.0 | 24.0–34.0 |
| Prepaid visit | | | | |
| Yes | 14.5 | 11.8–17.2 | 34.0 | 28.8–39.1 |
| No | 85.5 | 82.8–88.2 | 66.0 | 60.8–71.1 |
| Patient's history with provider | | | | |
| Previously seen | 92.2 | 90.11–94.3 | 90.4 | 87.2–93.6 |
| Not previously seen | 7.8 | 5.7–9.9 | 9.6 | 6.4–12.8 |
| Subtype of bipolar disorder | | | | |
| Manic | 8.4 | 6.2–10.6 | 17.0 | 12.9–21.1 |
| Depressed | 13.5 | 10.8–16.2 | 14.8 | 10.9–18.7 |
| Mixed | 20.0 | 16.9–23.1 | 36.2 | 31.0–41.4 |
| Other or unspecified | 58.1 | 54.3–62.0 | 32.0 | 26.9–37.1 |
| Any comorbid disorder | 18.7 | 15.7–21.7 | 26.6 | 21.8–31.4 |
| Substance abuse[b] | 4.8 | 3.1–6.5 | 9.7 | 6.5–12.9 |
| Anxiety disorder[c] | 3.6 | 2.1–5.1 | 9.7 | 6.5–12.9 |
| Other mental disorder[d] | 11.5 | 9.0–14.0 | 9.7 | 6.5–12.9 |

[a] Rates are based on weighted sampling. See text for definition of the diagnostic groupings. Groups were not mutually exclusive.
[b] Includes ICD codes 291, 292, 303–305, 327, and 328.
[c] Includes ICD codes 300.0–300.3, 300.5–300.9, and 309.8.
[d] Includes ICD codes 290–319 (except 291, 292, 296.0, 296.1, 296.4–296.9, 300.0–300.3, 300.5–300.9, 303–305, 309.8), 327, 328, 780.1, and 995.5. Because of codiagnosis, these groups were not mutually exclusive (i.e., patients could have more than one comorbid condition).

**TABLE 2. Medications Prescribed During Outpatient Visits to Psychiatrists by Patients With Bipolar Disorder in the National Ambulatory Medical Care Survey[a]**

| | Visits During 1992–1995 (N=593) | | Visits During 1996–1999 (N=272) | |
|---|---|---|---|---|
| Medication | Percent | 95% CI | Percent | 95% CI |
| Any psychotropic | 83.6 | 80.7–86.4 | 77.9 | 74.7–81.1 |
| Any mood stabilizer | 64.2 | 60.5–67.9 | 59.1 | 5.3–62.9 |
| Lithium | 50.9 | 47.0–54.8 | 30.1 | 26.5–33.7 |
| Any anticonvulsant | 19.4 | 16.3–22.5 | 34.4 | 30.7–38.1 |
| Valproic acid | 10.9 | 8.5–13.3 | 26.6 | 21.8–31.4 |
| Carbamazepine | 9.0 | 6.8–11.2 | 6.4 | 3.7–9.1 |
| Newer anticonvulsants | 0.0 | 0.0–0.0 | 5.4 | 2.9–7.9 |
| Any antidepressant | 45.8 | 41.9–49.7 | 45.7 | 40.3–51.1 |
| Selective serotonin reuptake inhibitors | 22.4 | 19.1–25.6 | 25.8 | 21.0–30.6 |
| Tricyclics | 12.1 | 9.6–14.6 | 4.3 | 2.1–6.5 |
| Bupropion | 8.4 | 6.2–10.6 | 7.5 | 4.6–10.4 |
| Other antidepressants | 15.2 | 12.4–18.0 | 20.4 | 16.0–24.8 |
| Antidepressant without mood stabilizer | 21.2 | 18.0–24.4 | 23.4 | 18.8–28.0 |
| Any antipsychotic | 22.3 | 19.1–25.5 | 29.0 | 24.0–34.0 |
| Conventional | 21.2 | 18.0–24.4 | 12.8 | 9.1–16.4 |
| Newer | 1.2 | 0.4–2.0 | 17.0 | 12.9–21.1 |
| Benzodiazepines | 29.1 | 25.6–32.6 | 22.6 | 18.0–27.2 |
| Any combination therapy | 44.2 | 40.3–48.1 | 46.2 | 40.8–51.6 |
| More than one mood stabilizer | 6.1 | 4.2–8.0 | 5.4 | 2.9–7.9 |
| Mood stabilizer plus antidepressant | 24.8 | 21.4–28.2 | 22.6 | 18.0–27.2 |
| Mood stabilizer plus antipsychotic | 13.3 | 10.7–15.9 | 17.2 | 13.1–21.3 |
| Mood stabilizer plus benzodiazepine | 14.5 | 11.8–17.2 | 14.0 | 10.2–17.8 |
| Antipsychotic plus antidepressant | 7.9 | 5.8–10.0 | 11.8 | 8.3–15.3 |

[a] Rates are based on weighted sampling. See text for definition of the medication groupings.

### *Prescriptions for Psychotropic Drugs*

During most visits in which a bipolar disorder was diagnosed, at least one psychotropic medication was prescribed or continued in both periods (83.6% in 1992–1995 and 77.9% in 1996–1999) (Table 2). During the 1992–1995 period, 26.8% of patient visits included prescription or continuation of one psychotropic medication, 37.3% of the visits included prescription of two medications, and 19.5% included three or more prescriptions. During the 1996–1999 period, 26% of the patient visits included prescription of or continuation of one psychotropic medication, 32.3% of the visits included prescription of two medications, and 19.6% included three or more prescriptions. While the number of psychotropic medications prescribed per visit was similar in 1992–1995 and in 1996–1999, the prescription patterns were substantially different during those periods. Slightly more than one-half of the visits included a prescription for lithium in the 1992–1995 survey, compared to only about 30% in the 1996–1999 period ($\chi^2$=10.5, df=1, p=0.001) (Table 2). In contrast, the proportion of visits during which valproic acid was prescribed increased from 10.9% in the 1992–1995 period to 26.6% in the 1996–1999 period ($\chi^2$=10.6, df=1, p=0.001) (Table 2). A small proportion of the visits included prescription of carbamazepine or, in the 1996–1999 period, one of the newer anticonvulsants, such as lamotrigine, gabapentin, or topiramate.

Over one-third of the samples from both time periods received no mood stabilizer. In contrast, during over 45% of the visits in both periods, patients were prescribed an antidepressant, generally an SSRI. Approximately 8% were prescribed bupropion. About one-half of the visits during both periods that included an antidepressant prescription did not include prescription of a mood stabilizer. There were no significant changes in the prescription patterns of those agents over time ($\chi^2$=0.2, df=1, p=0.70). However, there was a significant increase in the proportion of visits during which a newer antipsychotic was prescribed ($\chi^2$=23.1, df=1, p<0.001) (Table 2). Almost one-half of the visits

during both time periods included prescription of a combination medication regimen, but there were no secular changes in the proportion of the visits in which more than one medication was used ($\chi^2$=0.1, df=1, p=0.80) or in how the medications were combined.

When we used age, race, sex, type of insurance, presence of comorbidity, and bipolar disorder subtype as covariates, stepwise logistic regression identified the mixed subtype as a predictor of prescription of valproic acid (odds ratio=2.4, 95% confidence interval [CI]=1.1–5.4). When we used the same model, prescription of "any antipsychotic" was associated with the manic (odds ratio=2.9, 95% CI=1.2–7.2) and mixed (odds ratio=2.3, 95% CI=1.2–4.7) subtypes of bipolar disorder. The prescription of newer antipsychotics was associated with a diagnosis of manic (odds ratio=10.3, 95% CI=2.0–52.0) or mixed (odds ratio=6.9, 95% CI=1.6–30.1) subtypes. Prescription of "any antidepressant" was inversely associated with manic subtype (odds ratio=0.4, 95% CI=0.1–0.9) but not with a diagnosis of depressive subtype (odds ratio=1.6, 95% CI=0.7–3.3). No predictors could be identified for prescription of lithium, benzodiazepines, or a combination regimen. After we additionally adjusted for period effects, all of the associations remained significant, except the association between the prescription of valproic acid and the mixed subtype (odds ratio=1.7, 95% CI=0.6–4.9). In contrast, the survey period became associated with the prescription of valproic acid. Visits during the 1996–1999 period were more than twice as likely as visits from the 1992–1995 period to include a prescription for valproic acid after adjustment for the other covariates in the model (odds ratio=2.3, 95% CI=1.2–4.8).

## Discussion

The data from our study suggest that over the last decade there have been substantial changes in the diagnosis and management of patients with bipolar disorder.

### *Mood Stabilizers*

Although lithium was the most frequently prescribed mood stabilizer in the 1992–1995 period, the proportion of visits in which it was prescribed decreased by 40% over the next 4 years. In contrast, the use of anticonvulsants almost doubled during the same time period, and the proportion of visits during which valproic acid was prescribed increased by 250%. These trends may be related to the ease of prescription of valproic acid, its tolerability, and the increased awareness among psychiatrists and patients regarding the efficacy of valproic acid. The greater use of valproic acid was accompanied by an increase in the diagnosis of mixed episodes and a more frequent diagnosis of comorbid substance abuse—two situations in which preliminary data have suggested that valproic acid might be superior to treatment with lithium (6–8, 17, 18). However, our analysis suggests that the selection of a mood stabilizer by office-based psychiatrists for this sample of patient visits was not associated with the clinical characteristics of the patients. Our findings underscore the need for controlled trials of lithium and valproic acid that may provide an empirical basis for these changes in the treatment patterns for patients with bipolar disorder.

Despite the availability of treatments with broadly documented efficacy for bipolar disorder, we found that over one-third of the patient visits to office-based psychiatric practices during both periods did not include the prescription of a mood stabilizer. Some of these patients may have achieved no improvement while taking those medications, been intolerant to their side effects, or been unwilling to take them. Although it is possible that some patients with bipolar disorder may remain euthymic without a mood stabilizer, our findings suggest that a substantial number of these patients may be at unnecessary risk of relapse (5, 9, 19, 20).

### *Antidepressants*

The use of antidepressants was also at significant variance with the recommendations of published guidelines (1–3). Antidepressants were prescribed during almost one-half of the patient visits. During a substantial number of these visits (about 47% in 1992–1995 and 50% in 1996–1999), antidepressants were prescribed without a mood stabilizer. This is surprising, because all antidepressants have been related to the emergence of mania (21–23). In addition, bupropion, which is generally preferred over other antidepressants in this population because of its lower manicogenic properties (24–27), accounted for only about 8% of the prescriptions made during these visits and showed no increase in use over the years. All these findings raise questions about the appropriateness of antidepressant use in outpatient psychiatric practice and suggest that this may be an area to target for quality-improvement initiatives. Reasons for deviation from guideline-recommended treatment may include insufficient familiarity with the published literature or the unintended effects of medication marketing. It is also possible that the clinical characteristics of patients with bipolar disorder, as seen in office-based practice, substantially differ from those noted in the clinical trials that inform the practice guidelines; hence, the patients may respond differently to these medications. However, because the National Ambulatory Medical Care Survey does not collect longitudinal data, it is not possible to evaluate the effect of guideline nonconformance on treatment outcomes.

### *Antipsychotics and Benzodiazepines*

There was no significant change in the overall proportion of patients who were prescribed antipsychotics. However, over the years, there was a decrease in the use of conventional antipsychotics and a corresponding increase in the use of the newer antipsychotics, probably related to

their more benign side effect profile and the mood-stabilizing properties of some of these medications (28, 29).

Benzodiazepines were prescribed in 27% of the visits over both time periods. Because over 90% of the benzodiazepines were often prescribed in combination with a mood stabilizer and for patients who had been seen previously, it is likely that benzodiazepines were commonly used to treat acute anxiety or insomnia, as recommended by APA guidelines (1). The estimated proportion of visits in which benzodiazepines were prescribed is in line with previously published findings (9).

### *Combined Regimens*

Consistent with prior studies (9, 10), use of combined regimens was common. This may reflect the complexity of managing bipolar disorder. There are data that suggest that combinations of mood stabilizers (30), or a mood stabilizer in conjunction with an antipsychotic (31–33), may have higher efficacy than either medication alone. However, the extent and variety of combinations documented in this study suggest that there is a substantial discrepancy between evidence-based treatments and routine clinical practice in the treatment of bipolar disorder. Identification of patient subgroups that may benefit from these combined regimens is an important area for future research.

This study has several limitations. First, diagnoses in the National Ambulatory Medical Care Survey are based on the independent judgment of the clinician and are not subject to expert validation. Second, doses of prescribed medications are not collected, thus limiting the dimensions of the prescribing practices that can be examined. A study by Marcus and coworkers (34) documented that therapeutic monitoring of serum lithium levels in Medicaid patients were not conducted in 36.5% of the sample, suggesting that even when they are prescribed, mood stabilizers may not be used at optimal doses. Third, data from the National Ambulatory Medical Care Survey are cross-sectional, precluding an examination of the duration and sequence of medication trials. Fourth, it is possible that patients may be taking psychotropic medications prescribed elsewhere and not reporting that fact to their psychiatrists, although we think this as an uncommon practice. Fifth, there is limited information about the characteristics of the prescribing physicians, which may be associated with prescribing practice. Finally, the sample was restricted to office-based visits and does not contain information on practice patterns in other settings, such as in clinics operated by general hospitals.

In summary, there has been a recent tendency among office-based psychiatrists to more clearly define the diagnostic subtypes of bipolar disorder they see in practice and a parallel switch from the use of lithium to use of valproic acid as a preferred pharmacological option. The reasons for this change in pharmacological management remain unclear. In general, the pharmacological treatment of bipolar disorder still departs substantially from the management principles outlined by published guidelines, suggesting that this may be an important area for quality improvement.

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