Diagnosing Bipolar Disorder and the Effect of Antidepressants: A Naturalistic Study

S. Nassir Ghaemi, M.D.; Erica E. Boiman, B.A.; and Frederick K. Goodwin, M.D.

Objectives: To determine if bipolar disorder is accurately diagnosed in clinical practice and to assess the effects of antidepressants on the course of bipolar illness.

Method: Charts of outpatients with affective disorder diagnoses seen in an outpatient clinic during 1 year (N = 85 with bipolar or unipolar disorders) were reviewed. Past diagnostic and treatment information was obtained by patient report and systematic psychiatric history. Bipolar diagnosis was based on DSM-IV criteria using a SCID-based interview.

Results: Bipolar disorder was found to be misdiagnosed as unipolar depression in 37% of patients who first see a mental health professional after their first manic/hypomanic episode. Antidepressants were used earlier and more frequently than mood stabilizers, and 23% of this unselected sample experienced a new or worsening rapid-cycling course attributable to antidepressant use.

Conclusion: These results suggest that bipolar disorder tends be misdiagnosed as unipolar major depressive disorder and that antidepressants seem to be associated with a worsened course of bipolar illness. However, this naturalistic trial was uncontrolled, and more controlled research is required to confirm or refute these findings.

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Received April 11, 1999; accepted March 23, 2000. From the Psychopharmacology Program, Cambridge Hospital, Consolidated Department of Psychiatry, Harvard Medical School, Cambridge, Mass. (Dr. Ghaemi); and the Department of Psychiatry, The George Washington University, Washington, D.C. (Ms. Boiman and Dr. Goodwin).

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Reprint requests to: S. Nassir Ghaemi, M.D., Harvard Bipolar Research Program, Massachusetts General Hospital, 15 Parkman St., WAC-812, Boston, MA 02114.

The relative safety of antidepressants in the treatment of bipolar disorder continues to be a matter of controversy. Some have suggested that antidepressants can produce a long-term worsening of the course of bipolar illness through the induction of treatment resistance and rapid-cycling episodes.[1–5] Others have reported no long-term risks, particularly in bipolar II disorder.[6–9] Current standard recommendations in texts and journals limit antidepressant use in bipolar disorder.[10,11] However, clinicians have come down strongly on the side of frequent antidepressant use. Current practice data based on the National Disease and Therapeutic Index[12] indicate that antidepressant agents, as a class and individually, are more frequently prescribed than mood stabilizers for patients with bipolar disorder. Therefore, while it is not new to recommend the use of mood stabilizers rather than antidepressants, clinical practice patterns do not indicate that clinicians are heeding such recommendations.

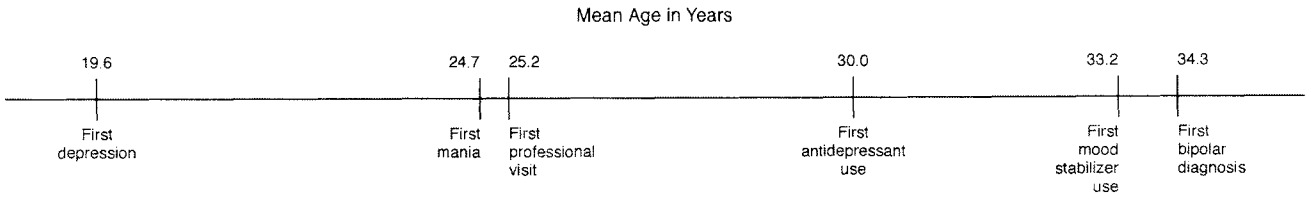
Why is this the case? Do antidepressants pose risks in bipolar disorder?

The purpose of this study was to systematically assess diagnostic rates of bipolar illness in an unselected outpatient psychiatric sample and to examine the outcome of antidepressant treatments.

METHOD

Charts of all consecutive patients diagnosed with affective disorders seen by 1 treating clinician (S.N.G.) during 12 months in an urban academic hospital were reviewed. Formal Structured Clinical Interview for DSM-IV (SCID)[13] diagnoses were made using the mood modules of the SCID. These diagnoses were made prospectively by a psychiatrist with expertise in affective disorders (S.N.G.). Data included in this assessment came from clinical interview with the patient and outside report from family or other sources. It should be emphasized that the diagnosis of affective disorder in these patients was not made retrospectively at the time of chart review, but prospectively during the clinical interview and was then compared with referral diagnoses from past mental health treatment.

Figure 1. Subsample of Bipolar Patients Previously Diagnosed With Unipolar Major Depressive Disorder (N = 29)



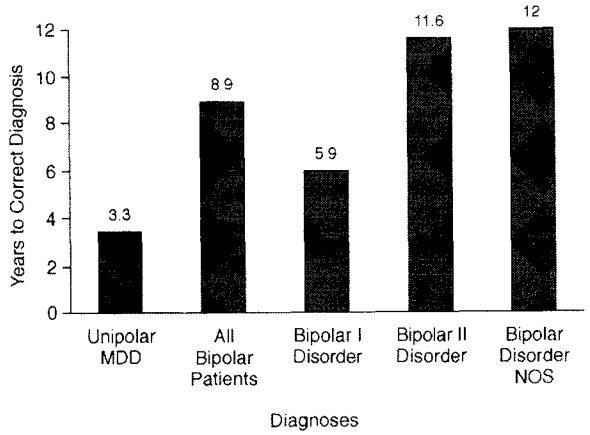
Other clinical and demographic data gathered at clinical interview were the following: age; sex; family history of psychiatric illness; age at onset of depression, mania, and hypomania; numbers of episodes of each type; percentage of time spent in each phase of illness; age at first consultation with a mental health professional and with a psychiatrist; number of psychiatrists and mental health professionals seen prior to correct diagnosis; previous diagnoses; and age at first correct diagnosis. Information was also gathered regarding past antidepressant and mood stabilizer use and effects, including whether mania, hypomania, or rapid cycling occurred subsequent to antidepressant use. Where possible, attempts were made to verify these historical data with outside reports from family or other sources, including hospital charts and previous physician records.

Statistical analyses consisted of nonparametric tests where frequency distributions indicated non-normal distributions of raw data, and parametric tests otherwise. The tests used were the unpaired t test, the Wilcoxon signed rank test, the Mann-Whitney U test, the Kruskal-Wallis test, and the chi-square test. Means and standard deviations were computed for parametric data. All statistical analyses were performed using the Statview statistical program (Abacus Concepts, Inc., Berkeley, Calif.) for the personal computer.

RESULTS

The diagnostic breakdown of the sample (N = 90, 49 men, 41 women) was 34% unipolar major depressive disorder (N = 31), 30% bipolar I (N = 27), 12% bipolar II (N = 11), 18% bipolar not otherwise specified (NOS) (N = 16), and 6% (N = 5) with other mood disorders (secondary depression and dysthymia). Figure 1 shows a time line for diagnosis and treatment of the subgroup of bipolar patients who had previously been diagnosed with unipolar major depressive disorder (N = 29; 56%). Of this subgroup, 38% (11/29) had a family history of bipolar disorder, compared with 17% (5/31) of the sample in the study diagnosed as unipolar major depressive disorder based on DSM-IV criteria applied to a SCID-based interview ($\chi^2 = 6.087$, p = .014, N = 74). Bipolar patients previously diagnosed with unipolar depression had a somewhat later onset of mania than those previously diagnosed bipolar (6.6 years), but this difference was not statistically significant (U = 65.5, p = .22, N = 27, Mann-Whitney U test). Notably, of the 19 bipolar patients whose first manic or hypomanic episode occurred prior to their first visit to a mental health professional, 7 (37%) were nonetheless diagnosed with unipolar major depressive disorder.

Figure 2. Years to Correct Diagnosis From First Seeking Professional Help[a]



[a]Abbreviations: MDD = major depressive disorder, NOS = not otherwise specified. Differences between diagnoses were statistically significant (H = 6.34, p = .04, N = 82, Kruskal-Wallis test).

Figure 2 depicts the time to correct diagnosis from the time of first mental health professional help. The differences observed between diagnoses are statistically significant (H = 6.34, p = .04, N = 82, Kruskal-Wallis test). Post hoc analyses indicated that these differences were statistically significant between all patients with bipolar disorder

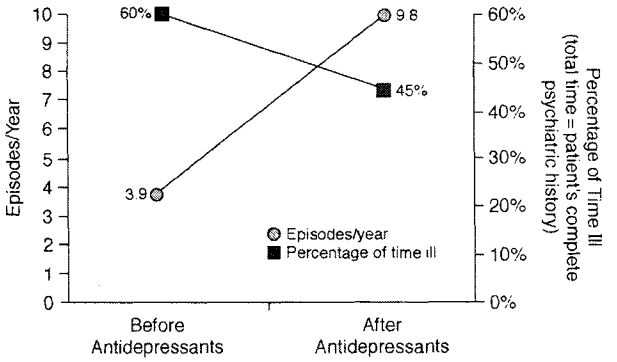
(type I, type II, and NOS) and unipolar major depressive disorder (mean ± SD years to diagnosis = 8.9 ± 9.8 years for bipolar disorder vs. 3.3 ± 7.2 years for unipolar major depressive disorder; U = 463.5, p = .003, N = 81, Mann-Whitney U test). The type of mental health professional seen was somewhat relevant to rapidity of diagnosis. The diagnosis of bipolar disorder occurred about 6.5 ± 10.7 years after the first visit to a psychiatrist, compared with about 8.9 ± 9.8 years after the first visit to any mental health professional (z = –4.2, p < .0001, N = 86, Wilcoxon signed rank test). The professionals previously seeing our patients included twice as many allied mental health professionals as psychiatrists (mean ± SD = 3.2 ± 3.4 vs. 1.5 ± 2.1; z = –5.133, p < .0001, N = 86, Wilcoxon signed rank test) before the diagnosis of bipolar disorder was made.

Among all the patients diagnosed (or rediagnosed) in our clinic as bipolar (N = 54), 78% (N = 42) had received antidepressants at some time, while only 56% (N = 30) had ever received mood stabilizers (χ^2 = 6.087, df = 1, p = .014, N = 54), and only 33% (18/54) had received mood stabilizers alone. Fifty-five percent (21/38) of the bipolar patients who received antidepressants for whom data were available developed hypomania or mania while taking them, and 23% (8/35) developed new or accelerated rapid cycling. Of the 8 patients who had sufficient historical information to establish rapid cycling prior to antidepressant use, 3 experienced worsening of rapid cycling with antidepressant treatments. Of 27 patients who did not have rapid cycling prior to antidepressant use, 5 developed rapid cycling on treatment with these drugs.

Figure 3 depicts the effect of antidepressants on the annual number of mood episodes and the proportion of time spent ill with mania, hypomania, or depression, again, in patients for whom sufficient data were available (N = 16). There was an absolute increase in number of mood episodes per year while antidepressants were being used, but this difference was not statistically significant (z = –1.29, p = .20, N = 16, Wilcoxon signed rank test). There was also a decline in proportion of time ill in the same group, which approached statistical significance (z = –1.80, p = .07, N = 16, Wilcoxon signed rank test).

Patients in the bipolar group who had ever received antidepressants (78%, 42/54) experienced significantly more time depressed (53.2% ± 31.0% of their lives) than the 12 bipolar patients never treated with antidepressants (29.8% ± 26.9% of their lives, t = 2.09, p = .04, 2-tailed unpaired t test). There was also a statistical trend that the antidepressant-treated group experienced less time euthymic (35.2% ± 32.2% of their lives) than those never treated with antidepressants (56.0% ± 30.8% of their lives, t = –1.75, p = .09, 2-tailed unpaired t test). Further, while there were absolute increases in manic (4.5 ± 9.7 vs. 1.1 ± 1.9 episodes) and depressive episodes (13.9 ± 23.6 vs. 4.1 ± 3.8 episodes) in the antidepressant-treated bipolar group versus the non–antidepressant-treated bipolar group, these differences were not statistically significant due to the small sample size.

Figure 3. Effect of Antidepressants on Rapid Cycling and Duration of Illness[a]



[a]Mood episodes per year increased more than 2-fold with antidepressant use, but this was not statistically significant (z = –1.29, p = .20, N = 16, Wilcoxon signed rank test). There was a statistical trend toward a decrease in percent of time ill (z = –1.80, p = .07, N = 16, Wilcoxon signed rank test).

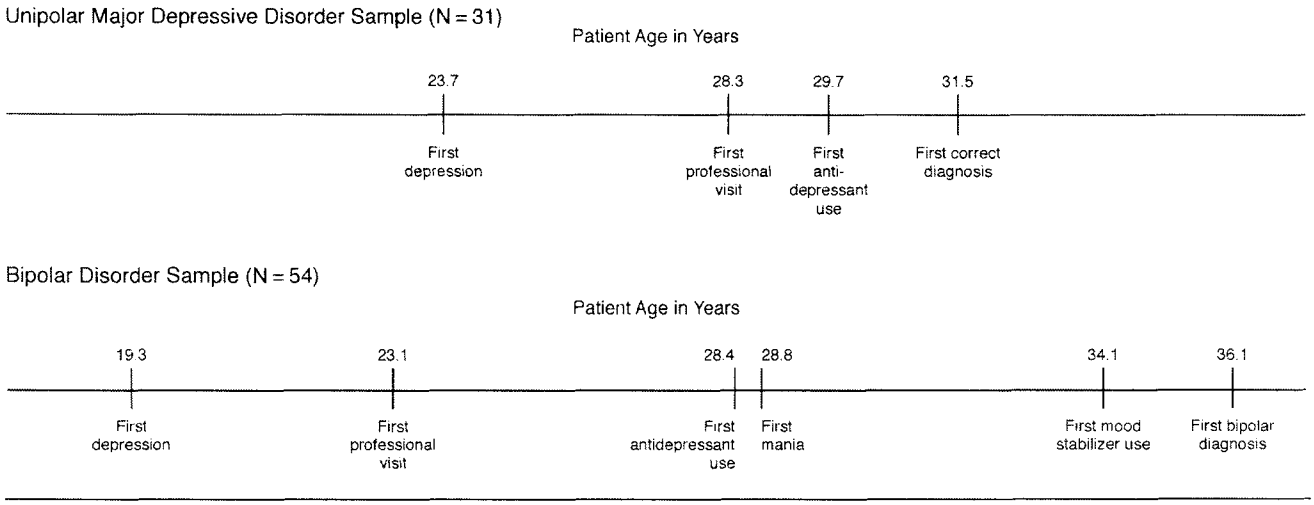
As seen in Figure 4, there was a statistical trend toward an earlier onset of illness among bipolar patients than among unipolar patients (U = 632.5, p = .10, N = 83, Mann-Whitney U test). In bipolar patients, major depression occurred significantly earlier than mania or hypomania (mean difference for mania = 5.7 years, z = –2.8, p = .006, N = 27, Wilcoxon signed rank test; mean difference for hypomania = 6.2 years, z = –2.3, p = .02, N = 31, Wilcoxon signed rank test). In the bipolar sample, periods of depression lasted longer than periods of mania or hypomania, with patients spending nearly half their adult lives depressed (mean = 49% ± 31%), versus 12% ± 9% of their lives manic or hypomanic (z = –5.6, p < .0001, N = 46, Wilcoxon signed rank test).

Patients with unipolar depression were also more readily diagnosed and treated appropriately than patients with bipolar disorder (see Figure 4).

DISCUSSION

Conclusions based on these findings are limited by the uncontrolled nature and the limited sample size of this

Figure 4. Time Lines for Disorder, Diagnosis, and Treatment



study. The main specific results were that 37% of the sample was misdiagnosed as having unipolar major depressive disorder by a mental health professional after the onset of the first manic or hypomanic episode and that 23% developed a new or worsening rapid-cycling course associated with antidepressant use.

It might be argued that this sample is unrepresentative due to the high ratio of bipolar to unipolar illness. Yet this study included patients with type II and NOS diagnoses, who are sometimes excluded in other reports.[14] Often, much is made of the academic tertiary-care setting and the lack of generalizability of the more refractory patients seen there. That was not the case with this sample. Almost all of the patients belonged to a university-run health maintenance organization (HMO), and their psychiatric care occurred in what was essentially a primary care setting. Few patients had refractory illness, and most did not come to the university seeking specialized care, but rather because it represented their only source of care as part of the HMO. This is, lamentably perhaps, quite generalizable to the typical patient today. This sample is thus unselected and minimally affected by sampling bias of the kind mentioned.

In fact, these findings are consistent with previous studies in other settings. Egeland and colleagues[15] reported that about 10 years elapsed from onset of illness before Amish individuals with bipolar disorder received treatment; however, some of that delay may have been due to a reluctance to seek treatment on the part of the patients rather than misdiagnosis or undertreatment by clinicians. Others have reported confusion of bipolar disorder with other conditions in special populations, such as attention-deficit disorder in adolescents[16] or schizophrenia in psychotic patients,[17] but the generalizability of these results to adult patients, most of whom have nonpsychotic bipolar illness, is uncertain. The Epidemiologic Catchment Area study[14] reported that only 32% of patients with bipolar disorder receive mental health treatment, but, again, how much of this undertreatment is due to patients' lack of insight or compliance is not known. A self-report survey of members of the National Depressive and Manic-Depressive Association[18] found that bipolar disorder was diagnosed after an average of 8 years had elapsed from patients' first mental health professional visit. Also, 48% of patients received a bipolar diagnosis only after seeing 3 or more mental health professionals, and 57% received another major psychiatric diagnosis; the most common diagnosis was unipolar major depressive disorder (44%), followed by schizophrenia (34%). We previously reported a 40% misdiagnosis rate of bipolar disorder as unipolar depression in hospitalized patients.[19]

The finding that long-term rapid cycling is associated with antidepressant use also agrees with a number of studies. Kukopulos et al.[20] first described an association between antidepressant use and a new or worsening rapid-cycling course of illness in bipolar patients. Altshuler and associates[3] retrospectively found that 35% of patients with treatment-resistant bipolar disorder referred to the National Institute of Mental Health appeared to have devel-

oped a treatment-resistant course in relation to chronic antidepressant use. They also reported a possibly greater risk for antidepressant-induced rapid cycling in bipolar disorder type II than in bipolar disorder type I. In another retrospective study of patients with rapid-cycling bipolar disorder, Wehr and Goodwin[2] identified about 50% of patients as having a history consistent with antidepressant-related rapid cycling. Although these studies are retrospective and are limited to rapid-cycling or treatment-resistant samples, with possibly limited generalizability to most patients with bipolar disorder, our sample was unselected and nonrefractory.

Naturalistic, retrospective studies, such as this one, are subject to recall bias and type II error owing to limited sample size. Yet they are still useful in providing evidence with real-world samples that are often excluded from controlled research studies. Nonetheless, more controlled research on this topic is needed.

CONCLUSION

This naturalistic study, uncontrolled and limited in sample size, found that bipolar disorder was misdiagnosed in 37% of the sample and that antidepressants were associated with a rapid-cycling course of illness in about 23% of patients. Given the importance of the differential diagnosis of bipolar versus unipolar disorder, these results suggest that further controlled research is imperative and that great clinical diligence needs to be exercised in diagnosing and treating these populations.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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