Why Do Clinicians Maintain Antidepressants in Some Patients With Acute Mania? Hints From the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM), a Large Naturalistic Study

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Objective: Antidepressants are supposed to be withdrawn during a manic episode. The aim of this study was to analyze the characteristics of manic patients who received antidepressants during a manic phase in a large, naturalistic study.

Method: The European Mania in Bipolar Longitudinal Evaluation of Medication was a 2-year prospective observational study of inpatients and outpatients with acute mania/mixed mania (*DSM-IV* or *ICD-10* criteria) conducted in 14 European countries. Of 2,416 manic patients who continued into the maintenance phase of the study, 345 (14%) were taking an antidepressant and 2,071 (86%) were not taking an antidepressant at baseline, week 1, and/or week 2 postbaseline. Demographic and clinical variables were collected at baseline and each study visit up to 24 months. Outcome measures included the Clinical Global Impressions-Bipolar Disorder scale (CGI-BP overall, mania, and depression scores) at 12 weeks and 24 months, the 5-item Hamilton Depression Rating Scale (HDRS-5), and the Young Mania Rating Scale (YMRS) at 12 weeks only. The present study was conducted from December 2002 to June 2004.

Results: More antidepressant maintenance use was seen in patients with mixed episodes ($P < .001$), rapid cyclers ($P < .02$), patients with more previous depressive episodes ($P < .001$), and patients with higher mean HDRS-5 score at baseline ($P < .001$)—specifically patients with anxiety ($P = .013$). Patients in the antidepressant group had significantly higher CGI-BP depression scores ($P < .001$) and a significantly higher rate of depression relapse ($P < .001$) at both 12 weeks and 24 months.

Conclusions: Patients with mania receiving antidepressants are more likely to be outpatients with mixed episodes, anxiety, or rapid cycling and have a higher risk of depression relapse during follow-up.

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Irritability, agitation, impulsivity, aggression, and psychosis are symptoms that characterize the hyperaroused state in manic and mixed patients.[1] Acute manic episodes can have devastating consequences. Manic patients often require inpatient hospital care, with hospital admissions frequently occurring involuntarily.[2] Bipolar disorder patients may experience cognitive impairment, and the number of manic episodes correlates with poor cognitive functioning.[3] Moreover, several studies showed that there is a strong relationship between manic episodes and functional impairment.[4–6]

The primary goal of treatment of mania is to restore behavioral control as quickly as possible in order to minimize danger to self and others and to limit the high economic, social, and personal costs of manic episodes.[1,7] Despite inconsistent recommendations in the current treatment guidelines with regard to the treatment of mania, most recommend the use of lithium plus an antipsychotic or valproate plus an antipsychotic as the first line of treatment, atypical antipsychotics are preferred over typical ones, and mood stabilizer monotherapy is advised for mild to moderate cases.[8–10] Consensus is, however, provided in the recommendation that antidepressant medication should be discontinued if an individual is in a manic, hypomanic, or mixed-state episode.[11–13]

Although it has been argued that antidepressants may exacerbate manic and mixed episodes and worsen the long-term course of bipolar disorder,[14,15] some studies found no significant differences between the rate of switches to mania or rapid cycling between those taking and not taking antidepressants.[16,17] Nevertheless, there are sporadic case reports of the development of manic symptoms after discontinuation of antidepressants in bipolar depressed patients.[7,18] In clinical practice, regardless of the recommendations of treatment guidelines and the lack of evidence that antidepressants might help to treat certain symptoms of mania, comorbid conditions, or prevent subsequent episodes, the indication is that clinicians, wrongly or not, use antidepressants quite frequently, especially when treatment is ongoing when seen by the psychiatrist.[19,20] There is very little information on why clinicians do not follow guidelines and discontinue antidepressants in acutely manic patients.

The European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study is a large, multicenter, European, observational study of the treatment of mania in bipolar disorder, which represents an excellent opportunity to understand the treatment provided to patients with mania across Europe. The aims of the current article were to describe the frequency of antidepressant use and the factors associated with taking an antidepressant during the acute phase of illness, as well to analyze the longer term outcomes of such patients.

METHOD

Study Design and Patients

EMBLEM is a 2-year prospective, observational study of health outcomes associated with the treatment of mania in bipolar disorder. The study was conducted in 14 European countries on outcomes of patients with a manic/mixed episode. A total of 3,684 inpatients and outpatients were enrolled at the discretion of the treating psychiatrist if they initiated or changed oral medication for the treatment of acute mania in bipolar disorder (antipsychotics, anticonvulsants, and/or lithium) within the standard course of care. Patients met the standard diagnostic criteria (generally, *DSM-IV* or *ICD-10*) for a manic/mixed episode. The present study was conducted from December 2002 to June 2004.

EMBLEM was divided into 2 phases: (1) an acute phase, with assessments at 1, 2, 3, 6, and 12 weeks postbaseline; and (2) a maintenance phase, with assessments at 6, 12, 18, and 24 months postbaseline. This article focuses on results at 24 months and includes all patients who entered the maintenance phase of the study. In the analysis, those patients who received antidepressants during the acute manic phase at baseline and for the duration of at least the first 2 weeks of treatment were included in the antidepressant group. This timescale was used to avoid including patients who were being tapered off antidepressants at baseline. Patients not taking an antidepressant at any or all of the first 3 visits (baseline and weeks 1 and 2 postbaseline) were included in the group not taking antidepressants.

The study was approved in all countries according to local requirements for ethics and/or regulatory approvals for observational studies. Patients provided informed consent for the collection of data during the observation period and analyses of data. Further details of the study design and methods are available elsewhere.[6,21]

Medication

The decision to initiate or change medication and the type of medication selected were independent from the study design and entirely at the discretion of the treating psychiatrist; once the decision to start a new oral treatment of mania was made, investigators could include the patient in the study. As 1 of the study objectives was to analyze treatment effectiveness including the use of olanzapine monotherapy versus combination treatment, as reported elsewhere,[22] investigators were asked, but not required, to enroll approximately the same number of patients initiating olanzapine as the number of patients initiating any other antipsychotic, anticonvulsant, or lithium. Patients were not required to remain on the medication started at baseline and could change medication at any time according to clinical need as determined by the treating physician. Information on medication for treating bipolar disorder (antipsychotics, anticonvulsants, lithium, and antidepressants, with respective doses and mode of intake) and concomitant medications (specifically anticholinergics, benzodiazepines, other hypnotics) was recorded at each visit.

Assessments

The characteristics of the patient sample were assessed at baseline by collecting sociodemographic data, psychiatric history and comorbidities, history of suicide attempts, compliance with treatment, and functional status.

Symptom severity of mania and depression were captured using the following clinical assessment scales: (1) Clinical Global Impressions-Bipolar Disorder (CGI-BP)[23] overall score in the 12 months prior to enrollment, and CGI-BP overall, mania, depression, and CGI psychosis scores respectively assessing current status at each visit (all rated for severity, 1–7); (2) the Young Mania Rating Scale (YMRS)[24]; and (3) the 5-item version of the Hamilton Depression Rating Scale (HDRS-5).[25,26] The YMRS and HDRS-5 were collected up to 12 weeks only.

Statistical Analyses

The distribution of the baseline characteristics of the sample, including sociodemographic and clinical measures, was analyzed with descriptive statistics.

For continuous data with a normal distribution, a 2-sample *t* test was used to test the difference between the antidepressant group and the group not taking antidepressants. A paired *t* test was used to compare changes in outcomes (from baseline to the 24-month endpoint) for patients within each treatment group. Where assumptions of normality were not adequately met, differences between groups were tested using the Wilcoxon test. Differences in categorical parameters between groups, as well as within-group changes from baseline to endpoint, were tested using a χ^2 test. For all comparisons, a level of significance of .05 was applied. Longitudinal evaluation of change in outcome was performed using last observation carried forward (LOCF). A sensitivity analysis with LOCF, observed case analysis and mixed-effects model repeated measures was also performed. Kaplan-Meier estimations of the survival distribution were used to study the time to discontinuing antidepressant and the time to relapse of bipolar disorder. Bipolar disorder relapse was defined from 12 weeks postbaseline as (1) a CGI-BP overall score increase from the previous visit and a rating of 4 or more at the last visit or (2) inpatient admission for an acute episode of bipolar disorder or (3) the psychiatrist's opinion that the patient has had a relapse since their previous assessment. Depression relapse was defined as an increase in CGI-BP depression score from the previous visit and a rating of 4 or more at the last visit.

A logistic regression model was used to identify factors associated with maintenance of antidepressants in patients presenting with acute mania. The baseline variables introduced in the multivariate model were based on theoretical relevance and statistical significance in the univariate analysis: sex, age (18–34, 35–64, ≥65 years), country, patient status (inpatient, outpatient), education level (low, high), atypical antipsychotics, valproate, and lithium prescribed at baseline (yes, no for each), type of episode (mixed or manic), number of episodes in previous 12 months (0, ≥1), number of depressions in previous 12 months (0, ≥1), rapid cycler

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(yes or no), CGI-BP overall, YMRS, HDRS-5, suicide attempt in previous 12 months (0, ≥1), and alcohol use problem or cannabis use problem in previous 3 months (yes, no for each). Data from the logistic regression model are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The logistic model was repeated using the 5 items of the HDRS-5 individually in place of the total score. All data were analyzed using SAS version 9.1 (SAS Institute, Inc.; Cary, North Carolina).

RESULTS

Baseline Patient Characteristics

A total of 2,416 manic patients continued in the maintenance phase of the study and were eligible for analysis. Of these patients, 345 (14.3%) fulfilled criteria to be included in the antidepressant group and 2,071 (85.9%) were included in the group not taking antidepressants. Five hundred thirty psychiatrists participated in EMBLEM. France, Greece, Italy, and the Netherlands were the countries that included the most patients (771, 624, 437, and 167, respectively). Globally, antidepressant use varied across countries ($P<.001$).

Of the total sample, 1,496 (62.0%) were outpatients and 918 (38.0%) were inpatients. Inpatients were significantly less likely to be taking antidepressants ($P<.001$), and the mean number of outpatient consultations was significantly higher for patients in the antidepressant group compared with those in the group not taking antidepressants ($P<.001$). Baseline demographic and clinical characteristics of patients taking and not taking antidepressants are summarized in Table 1.

Table 1. Demographic and Clinical Characteristics at Baseline of 2,416 Manic/Mixed Patients by Antidepressant-Use Group in the EMBLEM Study

Variable	No Antidepressant (n = 2,071)[a,b]	Antidepressant (n = 345)[a,b]	*P*
Female gender, n (%)	1,113 (55.2)	223 (67.2)	<.001
Age, mean (SD), y	44.3 (13.5)	46.9 (13.2)	<.005
Age at first symptoms, mean (SD), y	29.7 (10.9)	30.9 (11.9)	.16
Age at first hospitalization, mean (SD), y	31.6 (11.8)	33.9 (12.0)	.006
Type of episode, n (%)			<.001
Manic	1,643 (81.5)	141 (41.2)	
Mixed	372 (18.5)	201 (58.8)	
Rapid cycler, n (%)	249 (13.6)	104 (32.2)	<.001
Delusions/hallucinations during current episode, n (%)	973 (51.2)	116 (37.3)	<.001
Alcohol problem ever, %	25.1	25.6	.86
Cannabis problem ever, %	12.8	11.6	.54
Substance problem ever, %	6.7	7.3	.71
Independent residence in previous 4 weeks, %	56.7	66.7	.0017
Activities participated in the previous 4 weeks (≥5), %	38.7	26.1	<.001
Severe work impairment in previous year, %	16.3	15.9	.07
No. of outpatient consultations, mean (SD)	7.9 (11.8)	9.3 (10.0)	<.001
Country, n (%)			<.001
Belgium	61 (2.9)	15 (4.3)	
Finland	26 (1.3)	2 (0.6)	
France	595 (28.7)	176 (51.0)	
Great Britain	184 (8.9)	18 (5.2)	
Greece	552 (26.7)	72 (20.9)	
Italy	393 (19.0)	44 (12.8)	
Netherlands	156 (7.5)	11 (3.2)	
Norway	28 (1.4)	2 (0.6)	
Portugal	76 (3.7)	5 (1.4)	
Education, n (%)			.0133
None	22 (1.1)	7 (2.0)	
Primary school	332 (16.3)	70 (20.4)	
Secondary school	486 (23.8)	68 (19.8)	
Secondary school (upper)	557 (27.3)	103 (30.0)	
Postsecondary vocational training	278 (13.6)	29 (8.5)	
University	366 (17.9)	66 (19.2)	
Status (inpatient), n (%)	858 (41.5)	60 (17.4)	<.001

[a]At baseline, week 1, and/or week 2 postbaseline.
[b]The denominator may change across variables due to missing data.
Abbreviation: EMBLEM = European Mania in Bipolar Longitudinal Evaluation of Medication.

Medication Use

At baseline, patients belonging to the antidepressant group received less lithium (18.8% versus 24.5%; $P=.022$) and more valproate (38.3% versus 32.2%; $P=.027$) and also had fewer atypical antipsychotic prescriptions compared with patients not taking antidepressants (64.9% versus 77.3%; $P<.001$). Most prescriptions of antidepressants were selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (74.1%), especially citalopram and venlafaxine (16.8% and 18.8%, respectively).

Factors Associated With Antidepressant Maintenance

The logistic regression model identified several baseline factors significantly associated with maintenance of antidepressant use during the manic episode. Antidepressant maintenance varied across some countries ($P<.05$). In addition, more antidepressant maintenance use was seen in patients with mixed episodes versus manic episodes (OR, 3.28; 95% CI, 2.16–4.97; $P<.001$), rapid cyclers versus nonrapid cyclers (OR, 1.67; 95% CI, 1.08–2.56; $P=.020$), patients with more previous depressive episodes (OR, 2.53; 95% CI, 1.77–3.63; $P<.001$), and patients with higher mean HDRS-5 scores at baseline (OR, 1.13; 95% CI, 1.06–1.21; $P<.001$). Alternatively, antidepressant maintenance was less likely in patients with a higher level of education (OR, 0.70; 95% CI, 0.51–0.96; $P=.029$), higher baseline YMRS scores (OR, 0.98; 95% CI, 0.96–1.00; $P=.022$), and inpatient status (OR, 0.31; 95% CI, 0.21–0.47; $P<.001$). Interestingly, history of suicide attempts ($P=.323$), alcohol abuse ($P=.854$), and other comorbidities in Axis I were not associated with antidepressant use. However, when individual HDRS-5 items were included in the logistic regression analysis, the anxiety item was the only one that was statistically significantly associated to antidepressant prescription (OR, 1.24; 95% CI, 1.04–1.46; $P=.013$). The use of antimanic medication

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Table 2. CGI-BP Ratings at Baseline and at 12 Weeks and 24 Months Postbaseline in Patients Taking an Antidepressant and Patients Not Taking an Antidepressant During the Acute Phase

Variable	No Antidepressant (n = 2,071)[a,b]	Antidepressant (n = 345)[a,b]	*P*
Baseline, mean (SD)			
CGI-BP mania	4.86 (0.98)	4.29 (0.87)	< .001
CGI-BP depression	1.69 (1.05)	3.02 (1.38)	< .001
CGI-BP overall	4.73 (1.08)	4.39 (0.92)	< .001
12 weeks			
CGI-BP mania, mean (SD)	2.22 (1.27)	2.07 (1.13)	.085
CGI-BP depression, mean (SD)	1.65 (1.06)	2.11 (1.25)	< .001
CGI-BP overall, mean (SD)	2.64 (1.33)	2.63 (1.25)	.88
Relapse, n (%)	871 (44.1)	165 (49.3)	.078
Depression relapse, n (%)	308 (15.6)	89 (26.6)	< .001
24 months			
CGI-BP mania, mean (SD)	1.84 (1.26)	1.84 (1.25)	.76
CGI-BP depression, mean (SD)	1.60 (1.00)	2.02 (1.21)	< .001
CGI-BP overall, mean (SD)	2.21 (1.40)	2.35 (1.38)	.057
Relapse, n (%)	908 (54.2)	164 (60.3)	.060
Depression relapse, n (%)	324 (19.3)	85 (31.3)	< .001

[a]At baseline, week 1, and/or week 2 postbaseline.
[b]The denominator may change across variables due to missing data.
Abbreviation: CGI-BP = Clinical Global Impressions-Bipolar Disorder.

(atypical antipsychotics, lithium, or valproate) was not associated with antidepressant maintenance.

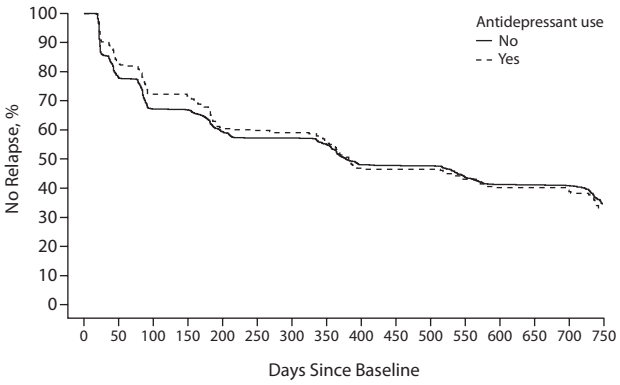
The sensitivity analysis with observed case analysis and mixed-effects model repeated measures revealed no significant differences from the LOCF analysis.

Outcome

Table 2 summarizes the CGI-BP, mania and depression scores at baseline, 12 weeks, and 24 months for the patients taking antidepressants and not taking antidepressants during the acute phase. In the antidepressant group, the mean severity of depression, as measured by the CGI-BP depression, decreased from 3.02 at baseline to 2.11 and 2.02 at 12 weeks and 24 months, respectively (reflecting a move from mildly to minimally ill). The corresponding values in the group not taking antidepressants were 1.69, 1.65, and 1.60. The CGI-BP depression subscale scores were significantly different between the antidepressant group and the group not taking antidepressants ($P < .001$) at all 3 time points. Although the CGI-BP mania and overall scores were significantly different between the antidepressant group and the group not taking antidepressants at baseline ($P < .001$), there were no significant between-group differences at 12 weeks or 24 months.

Total relapse rates increased in both groups during the 24-month follow-up as shown in Table 2. In the antidepressant group, the relapse rate increased from 49.3% at 12 weeks to 60.3% at 24 months. In the group not taking antidepressants, the relapse rates were 44.1% and 54.2% at 12 weeks and 24 months, respectively. The differences between the groups were not significant. The time to relapse of bipolar disorder by antidepressant use is shown in Figure 1. There was a significantly higher rate of depression relapse in the antidepressant group compared with the group not taking antidepressants at both 12 weeks (26.6% versus 15.6%; $P < .001$) and 24 months (31.3% versus 19.3%; $P < .001$) as shown in Table 2. Finally, at the 24-month endpoint, 59.1% of manic patients taking antidepressants had discontinued the treatment. The survival analysis of time to discontinuing antidepressant treatment is shown in Figure 2.

Figure 1. Survival Analysis of Time to Bipolar Disorder Relapse[a] by Antidepressant Use During the 24-Month Period[b]



[a]The first occurrence of the event is analyzed.
[b]Antidepressant, n = 342; not taking an antidepressant, n = 2,008.

DISCUSSION

Bipolar disorder diagnosis and treatment are a challenge in everyday clinical practice.[27] Expert consensus guidelines provide some direction for clinical practitioners about how to treat the illness. However, questions remain as to what extent treatment guidelines influence clinicians' actual practice. Antidepressant use in bipolar disorder is a highly controversial issue and there are no clear guides for their use, but there is some consensus in advising their discontinuation during a manic episode. This article describes the antidepressant prescription patterns of European clinicians during an acute manic episode. It aims to understand possible reasons for the maintenance use of antidepressants against the advice of clinical guidelines.

The factors that have been identified in this study as associated with maintained antidepressant therapy during a manic episode include country of origin, mixed episode, rapid cycling, history of high number of depressive episodes, low educational level, low YMRS score, and outpatient condition, but not suicide risk or comorbidity, although anxiety as a symptom was retained in the model. Taken together, these factors provide an interesting picture of the patients likely to be maintained on antidepressants during mania and, thus, on the potential reasons why clinicians carry out this practice which is at odds with treatment guidelines.

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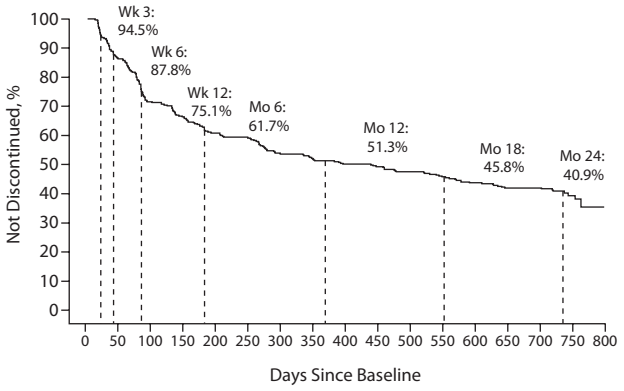
Figure 2. Survival Analysis of Time to Discontinuing Antidepressant Treatment[a,b]



[a]The first occurrence of the event is analyzed.
[b]n = 345.

In our sample, only 24% of all manic patients had a mixed episode, but 58% of the 345 patients who were on antidepressants had a mixed episode. This indicates, as confirmed in the multivariate analysis, that mixed features were associated with antidepressant treatment during an acute episode, and is against current recommendations.[11,12] Possible explanations for the relatively high prescription rates of antidepressant in mixed manic patients could be (1) an attempt to treat concurrent depressive symptoms; (2) that clinicians are afraid of a possible switch to depression after the improvement of manic symptoms, as mixed patients are more prone to switch to depression[28]; or (3) clinicians are trying to avoid an exacerbation of mania after discontinuation of the treatment,[7,18] given that mood stabilizers do not necessarily protect against drug-induced phase switch,[7] or withdrawal effects of antidepressants. Another issue is to what extent the patients taking antidepressants have an antidepressant-induced mania. However, it would be counterintuitive for clinicians to maintain the antidepressant, as drug-induced episodes are mainly treated by withdrawal of the drug that is responsible for the syndrome, and antidepressants are considered to induce and worsen mixed states.[29–31]

The patients on antidepressant therapy showed more severe depressive features, characterized by greater number of previous depressive episodes, higher scores of HDRS-5 or mixed-state at baseline, and higher rates of depression relapse in the 2-year follow-up period, but with less severe manic features. It is widely known that patients with bipolar disorder spend about 3 times as much time depressed as manic[32–34] and that the episodes of depression are the most frequent cause of disability among these patients with bipolar disorder.[32,35,36] In addition, it has been suggested that depression onset has both therapeutic and prognostic implications and may be associated with poor outcome.[33,37] With rapid cycling patients, in particular, there is a similar pattern, and such patients would theoretically be the poorest candidates to receive antidepressants because these drugs have been reported to accelerate cycling.[14] However, rapid cycling has been associated with antidepressant therapy.[29]

Several sociodemographic characteristics, including sex and age, have been reported to affect the pharmacologic treatment of bipolar disorder. The findings of this study, however, does not confirm previous reports of women as well as older patients receiving more antidepressant therapy than younger and male patients.[38,39] There were significant differences on antidepressant prescriptions between countries, which can be explained by local variations in access to mental health care. The patients receiving antidepressants during mania were more likely to have a low educational level, suggesting that higher education might allow better understanding of the caveats of staying on antidepressant treatment or the ability to detect depression relapse more effectively than less well-educated patients. However, having lower education level does not adequately explain higher antidepressant use. Regarding treatment, a growing number of psychotropic drugs are used to treat bipolar disorder, often off-label and in complex combinations.[40,41] Current guidelines include polypharmacy due to the complexity of bipolar disorder and resistance to treatment (in some cases).[8,42] This study shows that polypharmacy is the common international trend. However, medication was not a significant factor in the multivariate analysis, suggesting that there are no medications with a particular likelihood of being combined with antidepressants in manic patients.

The type of antidepressant prescription is also worth discussing. Assuming that antidepressants were not prescribed for the treatment of mania but rather maintained in patients who presumably had a previous depressive episode, the choice of antidepressant should theoretically be guided by safety and efficacy in bipolar depression. Experts and guidelines recommend that if an antidepressant is used, SSRIs or bupropion would be the first choice, with venlafaxine and monoamine oxidase inhibitors preferred for more resistant cases.[43] However, venlafaxine and bupropion are associated with a similar range of acute response and remission in bipolar depression,[44] and a recent placebo-controlled trial could not find any advantage of either paroxetine or bupropion over placebo in bipolar depression.[17] Moreover, previous studies reported a significantly increased risk of switches into hypomania or mania associated with venlafaxine,[44,45] while bupropion appears to be less likely to induce cycling.[31,41] Surprisingly, in this study venlafaxine was the antidepressant most commonly prescribed, while bupropion was prescribed for only 1 patient.

Prescription of antidepressant might aggravate or maintain mixed states (agitate syndrome) considered as lack of response, so clinicians might switch to another antidepressant or increase the dose, thereby worsening the outcomes of the disease.[46] This might explain the high percentage of antidepressant maintenance after 2 years of follow-up (40.9%) in the present study. A further important reason for the low use of bupropion may be that in some countries this drug has been licensed only for the treatment of nicotine withdrawal.

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Some studies suggest that bipolar patients who discontinue antidepressant treatment are 3 times more likely to suffer a depressive recurrence than those who stay on their antidepressant.[32,47,48] Interestingly, we found that patients on antidepressant therapy experienced a higher depression relapse rate than the group not on antidepressants. On the other hand, the number of total bipolar relapses was similar in both groups. Paradoxically, antidepressant therapy not only appeared to protect against depressive relapses but also did not induce manic relapses. Moreover, it is important to consider that more than half of the sample discontinued antidepressant therapy during the study and the number of total relapses increased. Although current recommendations limit antidepressant use in bipolar disorder, our results suggested that the antidepressant therapy did not increase the manic relapses during the 24-month period. Further controlled trials would be required to test this observation.

Limitations of this study are the naturalistic design, which makes it impossible to establish causality factors but, on the other hand, allows the investigation of antidepressant prescription patterns in a large bipolar I sample with good representativeness.

In summary, our findings suggest that antidepressant treatment during a manic episode is often maintained despite the absence of evidence to support such practice and that this practice may be influenced by local prescription patterns across Europe. Patients with lower education levels are more likely to receive antidepressants, suggesting that patients with higher education levels may get psychoeducation or at least some information relevant to the convenience of stopping antidepressants. The use of antidepressants in manic patients seems to be more likely in patients with a heavy load of depressive features, either cross-sectionally (mixed-state patients) or in the past (rapid cyclers, depressive predominant polarity). The use of antidepressants does not seem to be directly related to suicide risk or comorbidity with other *DSM-IV* conditions, but they could be related to anxiety as a symptom. The fact that anxiety as a symptom was retained in the model is not actually surprising, as clinicians have been reported to treat symptoms rather than syndromes, and dimensions may be clinically more useful than categories under certain circumstances.[49] These findings suggest that there is an unmet need to treat effectively the depressive burden within bipolar disorder, even during manic episodes, and that clinicians (regardless of whether they are right or wrong) use what they think might help, even against all the evidence.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), citalopram (Celexa, Lexapro, and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), venlafaxine (Effexor and others).

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