Risk Factors for Antidepressant-Related Switch to Mania

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ABSTRACT

Objective: Treatment of bipolar depression with antidepressants is strongly debated on the basis of the methodologically poor and insufficient data supporting their use and the widely held belief that antidepressants can induce new episodes of abnormal mood elevation or accelerate the rate of cycling. The present study aimed at identifying clinical risk factors for switch into hypomania, mania, or mixed states, within 8 weeks after introduction of an antidepressant or after increasing its dosage, in a prospective, longitudinal design.

Method: 221 consecutive *DSM-IV-TR* depressed bipolar I and II disorder patients were treated with antidepressants, which were added to previously prescribed mood stabilizers and/or atypical antipsychotics. No patient was on antidepressant monotherapy. The patients were enrolled from October 2005 through January 2010. The primary outcome was the assessment of switch to mania or hypomania within 8 weeks after the introduction or dose increase of an antidepressant. Both groups were compared with analysis of variance and χ^2 procedures.

Results: Treatment-emergent affective switch was detected in 54 patients (24.4%) (switch group) while 167 patients (75.6%) (nonswitch group) did not experience a treatment-related switch. The main clinical differences significantly associated with the occurrence of an antidepressant-related switch, after performing logistic regression analysis, were higher rate of previous switches ($P < .001$) in the switch versus the nonswitch group, lower rate of responses to antidepressants ($P < .001$) in the switch versus the nonswitch group, and earlier age at onset ($P = .026$) in the switch versus the nonswitch group.

Discussion: Bipolar patients with an earlier age at onset and an illness course characterized by lower rate of response to antidepressants and higher rate of switches into mania or hypomania were found to be the ones with higher switch risk. Nevertheless, a greater number of previous antidepressant exposures was not associated with the occurrence of an antidepressant-associated switch.

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Although mood elation is the main clinical feature that distinguishes bipolar disorder from recurrent major depressive disorder, depression, rather than mania, is the leading cause of impairment and death among patients with bipolar disorder.[1,2] Moreover, bipolar disorder patients spend much more time experiencing depressive symptoms than manic ones.[3] The treatment of bipolar depression is difficult and the number of evidence-based options is very limited.[4]

Treatment of bipolar depression with antidepressants is strongly debated for 2 main reasons.[5] First, the data supporting their use in bipolar depression are methodologically poor and insufficient. Second, the widely held belief that antidepressants can induce new episodes of abnormal mood elevation (hypomanic or manic switch) or accelerate the rate of cycling has been neither confirmed nor refuted by placebo-controlled studies.

The US Food and Drug Administration (FDA) has not approved any standard antidepressant drug for the treatment of bipolar depression. The same applies to the European Medicines Agency. However, the combination of olanzapine, a second-generation antipsychotic, with the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine is actually FDA-approved—on the basis of positive placebo-controlled data[6]—in the United States for the acute treatment of bipolar depression.

In clinical practice, antidepressants are frequently used either as monotherapy or as adjuncts to mood-stabilizing medication for the treatment of bipolar depression, despite the limited evidence of the short- and long-term benefits and potential risks (treatment-emergent hypomania, mania, or mixed episode, cycle acceleration). In fact, the most common treatment of bipolar depression in clinical practice appears to be antidepressant monotherapy,[7] and many clinicians maintain antidepressants for long-term treatment and even during mania.[8]

Tondo et al,[9] in a very large (N = 114,521) meta-analysis, found an average overall risk of mania with antidepressants of 12.5% and without antidepressants of 7.5% among patients diagnosed with bipolar disorder and major depressive disorder. They concluded that the use of antidepressants in patients with these disorders approximately doubled moderate spontaneous risk of hypomania or mania. The antidepressant-associated mania was more frequent in bipolar disorder than major depressive disorder patients, but it presented a higher increase in the latter group. Tricyclic antidepressants bore higher risk than SSRIs, while data for other types of antidepressants were inconclusive. They also concluded that mood stabilizers had little preventive effect against mood elevation during antidepressant treatment.

While most treatment guidelines and experts agree that antidepressant monotherapy should not be recommended in bipolar depression, there is a debate between clinicians who believe that they do more harm than good, even when used as adjuncts to antimanic treatments, and those who do not.[10–18]

Regardless of whether switch into mania and hypomania is a truly antidepressant-related phenomenon or rather a result of the natural course of illness, and irrespective of the arguable effectiveness of antidepressants in bipolar depression, the identification of risk factors for

Clinical Points

- In clinical practice, up to one-quarter of patients with bipolar depression may have a switch into mania, hypomania, or mixed episodes during treatment with any type of antidepressant, even in the context of concomitant antimanic treatment.
- Antidepressant-associated switch risk into mania, hypomania, or mixed episodes is more likely to occur in patients with an earlier age at onset and an illness course characterized by lower rate of response to antidepressants and higher rate of previous switches. Greater number of previous antidepressant exposures was not associated with the occurrence of an antidepressant-associated switch.
- A history of psychosis may actually protect against switch.

antidepressant-associated switch is extremely relevant from the clinical point of view. No risk factors have been replicated so far, partly due to the lack of agreement on what is a "switch."[15] The present study aimed at identifying clinical risk factors for switch into mania, hypomania, and mixed states, using a standardized definition of switch in a prospective, longitudinal design.

METHOD

Study Design and Participants

This was a prospective, naturalistic cohort study conducted on a sample of 221 consecutive bipolar I and II disorder outpatients, recruited among patients participating in the systematic follow-up of the Bipolar Disorder Program of the Hospital Clinic and University of Barcelona.[19] Approximately 60% of the patients attending the program belong to a specific catchment area from the city of Barcelona, Catalonia, Spain, whereas 40% are sent from other areas as a reference center for difficult-to-treat patients.[20] Hence, the sample may have an overrepresentation of treatment-resistant patients.

Inclusion criteria comprised *DSM-IV-TR* criteria for bipolar I or II disorder, current major depressive episode, a 17-item Hamilton Depression Rating Scale (HDRS-17)[21] score over 20, and agreement to initiate treatment with any antidepressant combined with treatment-as-usual (ie, lithium, anticonvulsants, and/or antipsychotics), as decided by the treating psychiatrist. As this was a naturalistic study, the antidepressant compound was chosen by the treating psychiatrist on the basis of each patient's clinical profile, preferences, and, eventually, previous response. Patients with major medical comorbidities were excluded from the study. All patients received full information on the study procedures and provided signed informed consent. The enrollment for this study started in October 2005 and finished in January 2010. The design of the study was approved by the Ethics and Research Committee of the Hospital Clinic of Barcelona. The study is registered at clinicaltrials.gov (identifier: NCT01503489).

The follow-up comprised 6 months, with visits on days 1, 7, 14, 21, 28, 35, 42, 49, and 56 and afterward every 2 weeks. After 6 months, the sample was divided into 2 groups according to antidepressant-emergent affective switch (switch group) or the absence of antidepressant-emergent affective switch (nonswitch group).

Treatment-emergent affective switch, according to the International Society for Bipolar Disorders (ISBD) nomenclature task force,[22] was defined as fully syndromic hypomanic, manic, or mixed episode, following *DSM-IV-TR* criteria, Young Mania Rating Scale (YMRS)[23] score > 12 and an increase of 5 points or more compared to the last assessment for hypomanic/manic features, and YMRS *and* HDRS-17 scores > 14 for a mixed episode. The above-mentioned alterations needed to occur within 8 weeks after introduction of the antidepressant or after increasing the dosage.

Procedures and Outcomes

To confirm diagnosis, we used the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I)[24] and for *DSM-IV* Axis II Disorders (SCID-II).[25] Several variables were obtained from structured interviews with both patients and their relatives, medical records, and data register of the Barcelona Bipolar Disorders Program prospective follow-up survey. These included sociodemographic data collection and an exhaustive register including number and polarity of lifetime episodes, hospitalizations, age at onset, age at first hospitalization, age at bipolar disorder diagnosis, diagnostic delay, years of follow-up, lifetime history of psychotic symptoms, suicidal behavior, number of antidepressants during illness, mean duration of treatment with antidepressants, presence and number of previous responses to antidepressants, presence and number of previous relapses with antidepressants, and presence and number of previous switches with antidepressants. All patients were assessed at each visit with the HDRS-17[21] and YMRS,[23] Spanish validated versions,[26,27] administered by trained raters to assess depressive and manic symptoms, respectively.

Operational definitions of symptomatic response, symptomatic remission, recovery, subsyndromal depression, relapse, recurrence, and treatment-emergent mood switch according to the task force of the ISBD nomenclature[22] were used in order to define specific course and outcome indicators, both during the illness and at the index episode.

Predominant polarity was attributed to a patient if at least two-thirds of all his/her past mood episodes were of the same sign—depressive versus hypomanic or manic—according to its validated operational definition.[28]

Suicidality was measured by the number of attempts and by the presence or absence of suicidal ideation (by the suicide item of the HDRS-17 and specific assessment during the interview).

The primary outcome of the study was the assessment of switch to mania or hypomania within 8 weeks after the introduction or dose increase of an antidepressant and the

Table 1. Demographic, Global Social Functioning, and Clinical Qualitative Features Differentiating Patients With Antidepressant-Associated Switch at the Index Episode and Patients With No Antidepressant-Associated Switch at the Index Episode

Variable	Total Sample (N = 221), n (%)	Switch Group (n = 54), n (%)	Nonswitch Group (n = 167), n (%)	χ^2	*P*
Male gender	101 (45.7)	28 (51.9)	73 (43.7)	1.089	NS
Education, qualified	130 (58.8)	31 (57.4)	99 (59.3)	0.059	NS
Active work	90 (40.7)	24 (44.4)	66 (39.5)	0.410	NS
Autonomy, good	186 (84.2)	47 (87.0)	139 (83.2)	0.443	NS
Bipolar I disorder	144 (65.2)	32 (59.3)	112 (67.1)	1.095	NS
First episode depression	153 (69.2)	39 (72.2)	114 (68.3)	0.300	NS
Psychotic symptoms at first episode	53 (24.0)	10 (18.5)	43 (25.7)	1.170	NS
Psychotic symptoms during illness	124 (56.1)	24 (44.4)	100 (59.9)	3.948	.058
Mixed episodes during illness	60 (27.1)	18 (33.3)	42 (25.1)	1.382	NS
Predominant polarity	98 (44.3)	19 (35.2)	79 (47.3)	2.429	NS
Type of predominant polarity, depressive	73 (74.5)	14 (73.7)	59 (74.7)	0.008	NS
Family history of bipolar disorder	82 (37.3)	20 (37.0)	62 (37.3)	0.002	NS
Seasonal pattern	64 (29.0)	20 (37.0)	44 (26.3)	2.267	NS
Rapid cycling	41 (18.6)	13 (24.1)	28 (16.8)	0.230	NS
Melancholic depression	92 (41.6)	20 (37.0)	72 (43.1)	0.431	NS
Psychotic depression	40 (18.1)	8 (14.8)	32 (19.2)	0.520	NS
Atypical depression	108 (48.9)	31 (57.4)	77 (46.1)	2.085	NS
Suicidal ideation	102 (46.2)	23 (42.6)	79 (47.3)	0.365	NS
Suicidal attempts	52 (23.5)	13 (24.1)	39 (23.4)	0.012	NS
Treatment adherence, good	166 (75.1)	43 (79.6)	123 (73.7)	0.780	NS
Axis II comorbidity	59 (26.7)	13 (24.1)	46 (27.5)	0.251	NS
Anxiety comorbidity	79 (35.7)	22 (40.7)	57 (34.1)	0.776	NS
Substance abuse comorbidity	51 (23.1)	14 (25.9)	37 (22.2)	0.327	NS
ECT	36 (16.3)	12 (22.2)	24 (14.4)	1.844	NS
Antidepressant in first depression	135 (61.1)	28 (51.9)	107 (64.1)	2.563	NS
Mood stabilizer in combination at first depression	56 (25.3)	10 (18.5)	46 (27.5)	1.757	NS
First antidepressant					
TCA	89 (43.2)	25 (46.3)	64 (38.3)	1.078	NS
SSRI	117 (52.9)	28 (51.9)	89 (53.3)	0.034	NS
SNRI	15 (6.8)	2 (3.7)	13 (7.8)	1.074	NS
TCA antidepressant during illness	125 (56.6)	34 (63.0)	91 (54.5)	1.192	NS
SSRI during illness	197 (89.1)	52 (96.3)	145 (86.8)	3.780	NS
SNRI during illness	117 (52.9)	29 (53.7)	88 (52.7)	0.017	NS
Previous relapse with antidepressant	138 (62.4)	30 (55.6)	108 (64.7)	1.146	NS
Previous response to antidepressant[a]	202 (91.4)	42 (77.8)	160 (95.8)	16.882	< .001
Previous switch with antidepressant[a]	151 (68.3)	53 (98.1)	98 (58.7)	29.367	< .001
Depression with atypical features index	90 (40.7)	25 (46.3)	65 (38.9)	0.919	NS
TCA prescribed in index episode	36 (16.3)	9 (16.7)	27 (16.2)	0.007	NS
SSRI prescribed in index episode	135 (61.1)	33 (61.1)	102 (61.1)	0.000	NS
SNRI prescribed in index episode	62 (28.1)	17 (31.5)	45 (26.9)	0.416	NS

[a]Variables with significant differences between the 2 groups after performing a logistic regression analysis.
Abbreviations: ECT = electroconvulsive therapy, NS = not significant, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

comparison of the group who switched with the group who did not, for which we examined demographic, clinical, and treatment history features.

Statistical Analysis

We used the Statistical Package for Social Sciences v.16 for Windows (SPSS, Inc; Chicago, Illinois) for statistical analysis. Patients in the switch group and those in the nonswitch group were compared for clinical and sociodemographic characteristics by analysis of variance for continuous variables and the χ^2 test for qualitative variables, as appropriate.

A logistic regression was performed using entry method by assuming antidepressant-emergent affective switch at index episode as the dependent variable. The variables that were considered to be potentially relevant to the model and those with *P* values ≤ .05 were entered as independent factors in the multivariate analysis.

RESULTS

Switch Rates and Sample Characteristics

The study cohort presented with moderate to severe bipolar depressive episodes, according to HDRS-17 baseline scores. Mean ± SD initial HDRS-17 score was 23.9 ± 3.6.

Among the 221 bipolar patients included in the final sample, 54 (switch group, 24.4%) showed an antidepressant-associated switch to mania, hypomania, or mixed episode, according to the definition described above, while 167 (nonswitch group, 75.6%) did not experience any antidepressant-associated switch within the 8-week period. Switch rates were similar across bipolar subgroups (bipolar I disorder, 32/144 [22.2%]; bipolar II disorder, 22/77 [28.6%]; *P* value was nonsignificant). The mean age of the sample was 49 years (SD = 13.8). Mean age at onset of bipolar disorder was 29.2 years (SD = 11.4). The mean duration of illness was 19.7 years (SD = 10.8), with a mean diagnostic delay of bipolar disorder of 7.2 years (SD = 8.3). Mean duration of follow-up was 9.53 years (SD = 5.2). Mean duration of antidepressant add-on for the specific index episode was 4.9 months (SD = 1.7).

Among specific antidepressant classes, alone or in combination, the antidepressant class that was most often prescribed was SSRIs (61%, n = 135), followed by serotonin-norepinephrine reuptake inhibitors (SNRIs) (28.2%, n = 62), and tricyclic antidepressants (16.3%, n = 36).

Concerning baseline maintenance treatment at the time that the antidepressant was added, 63.3% (n = 140) of patients were taking lithium; 31.6% (n = 70), an atypical antipsychotic; 27.1% (n = 60), valproate; 13.0% (n = 29), carbamazepine; 10.8% (n = 24), lamotrigine; and 2.8% (n = 6), oxcarbazepine.

Study Outcomes and Differences Between Antidepressant Switchers and Non-Antidepressant Switchers at Index Episode

The 2 groups were comparable in terms of education and job qualification. Demographic and clinical qualitative and quantitative characteristics of the 2 groups are shown in Tables 1 and 2.

Table 2. Demographic and Clinical Quantitative Features Differentiating Patients With Antidepressant-Associated Switch at the Index Episode and Patients With No Antidepressant-Associated Switch at the Index Episode

Variable	Total Sample (N = 221), Mean (SD)	Switch Group (n = 54), Mean (SD)	Nonswitch Group (n = 167), Mean (SD)	*F*	*P*
Age at onset, y[a]	29.22 (11.4)	26.2 (9.9)	30.2 (11.7)	5.016	.026
Age at first antidepressant prescription, y	33.5 (11.8)	30.3 (10.7)	34.5 (11.9)	5.493	.02
Diagnostic delay, y	7.2 (8.3)	8.07 (9.9)	6.9 (7.7)	0.774	NS
Years of illness	19.7 (10.8)	20.5 (12.1)	19.4 (10.4)	0.411	NS
Years of follow-up	9.53 (5.2)	8.7 (5.2)	9.8 (5.2)	1.545	NS
Total no. of episodes	15.14 (14.4)	20.8 (21.6)	13.3 (10.6)	11.629	.001
No. of depressive episodes	8.5 (8.8)	11.7 (13.7)	7.4 (6.3)	10.232	.002
No. of manic episodes	2.2 (3.1)	2.5 (3.7)	2.1 (2.9)	0.509	NS
No. of hypomanic episodes	3.85 (5.3)	5.9 (7.7)	3.2 (4.1)	11.518	.001
No. of mixed episodes	0.6 (1.37)	0.6 (1.4)	0.6 (1.2)	0.020	NS
No. of hospitalizations	2.1 (2.5)	2.2 (2.4)	1.8 (2.7)	0.586	NS
No. of suicide attempts	0.43 (0.9)	0.4 (0.9)	0.5 (1.0)	0.441	NS
No. of depressive episodes for which an antidepressant was prescribed for the first time	1.9 (1.8)	2.3 (2.6)	1.7 (1.5)	3.647	NS
No. of antidepressants	3.7 (2.4)	3.8 (2.3)	3.6 (2.6)	0.280	NS
Duration of antidepressant treatment, mo	10.6 (9.4)	9.5 (12.4)	10.9 (12.3)	0.481	NS
No. of relapses with antidepressants	3.05 (9.4)	5.6 (18.0)	2.2 (3.2)	5.450	.02
No. of responses to antidepressants	3.1 (3.5)	3.7 (5.7)	2.9 (2.3)	1.940	NS
No. of antidepressant-associated switches	1.9 (2.6)	3.09 (3.05)	1.5 (2.3)	16.931	< .001
Age, y	42.0 (13.6)	39.7 (13.8)	42.7 (13.4)	1.982	NS
No. of antidepressants during the index episode	1.1 (0.31)	1.1 (0.34)	1.1 (0.30)	0.324	NS

[a]Variables with significant differences between the 2 groups after performing a logistic regression analysis.
Abbreviation: NS = not significant.

Table 3. Results From Logistic Regression Analysis Showed That Only Rate of Previous Antidepressant-Associated Switches, Rate of Previous Responses to Antidepressants, and Age at Onset Were Significantly Associated With the Occurrence of an Antidepressant-Related Switch

Variable	β	Wald	*P*	OR
Rate of previous antidepressant-associated switches	3.423	10.679	.001	30.652
Rate of previous responses to antidepressants	−2.406	13.300	< .001	0.090
Age at onset	−0.038	3.903	.048	0.963
Psychotic symptoms during the illness[a]	−0.676	3.076	.079	0.509

[a]The presence of psychotic symptoms during the illness did not reach statistical significance, but it showed a trend: $R^2 = 0.391$ (Nagelkerke R^2); model $\chi^2_6 = 67.228$, $P < .001$.

The group that did not experience a switch during the index episode showed a trend toward higher lifetime history of psychotic symptoms than the switch group (59.9% vs 44.4%, $P = .058$). Regarding the course of the illness, the switch group showed a lower percentage of lifetime response or responses to antidepressants (77.8% vs 95.8%, $P < .001$) and a greater percentage of lifetime switch or switches with antidepressants (98.1% vs 58.7%, $P < .001$).

Among quantitative features, the switch group compared to the nonswitch group had a significantly lower mean age at onset (26.2 vs 30.2, $P = .026$) and a lower age at first antidepressant prescription (30.3 vs 34.5, $P = .02$).

The switch group compared to the nonswitch group presented a greater mean number of total episodes (20.8 vs 13.3, $P = .001$), as well as a higher mean number of depressive episodes (11.7 vs 7.4, $P = .002$) and a greater overall mean number of hypomanic episodes (5.9 vs 3.2, $P = .001$), but not a greater number of manic and mixed episodes.

Regarding the course of the illness, the switch group compared to the nonswitch group showed a higher mean number of depressive relapses with antidepressants (5.6 vs 2.2, $P = .02$), as well as a greater number of antidepressant-associated switches (3.09 vs 1.5, $P < .001$), but we did not find differences regarding number of episodes responding to antidepressants.

The sociodemographic and clinical characteristics that had displayed the most significant differences ($P \leq .058$) between the switch and nonswitch groups, during the index follow-up period, were treated as independent variables (age at onset, age at first antidepressant prescription, number of previous episodes, number of previous depressions, number of previous hypomanias, number of previous depressive relapses, number of previous antidepressant-associated switches, psychotic symptoms during the illness [yes/no], previous antidepressant-associated switches [yes/no], and previous responses to antidepressants [yes/no]).

Results from logistic regression analysis showed that only rate of previous antidepressant-associated switches, rate of previous responses to antidepressants, and age at onset were significantly associated with the occurrence of an antidepressant-related switch. The presence of psychotic symptoms during the illness did not reach statistical significance, but it showed a trend ($P = .079$). The model explained 39.1% of the variance ($\chi^2_6 = 67.228$; $P < .001$). The results are displayed in Table 3.

DISCUSSION

The purpose of this study was to examine the risk factors for antidepressant-associated switch from depression to hypomania, mania, or mixed episode during the 8 weeks after the introduction of an antidepressant or after increasing the dosage of baseline antidepressant treatment during a breakthrough depressive episode.

One of the most surprising findings of this study, and apparently in contradiction with previous literature,[29] was the unexpectedly high rate of antidepressant-related switch (24.4%) observed during the 8 weeks after the prescription of the drug. However, it is likely that switch rates are higher in naturalistic settings as compared to clinical trial samples, which are generally milder and free of substantial comorbidity and suicide risk. A second explanation may have to do

with the definition of switch used in this study, which was much more sensitive than that used in most clinical trials, which are generally not specifically designed to assess switch. A third explanation could be that our program includes mainly difficult-to-treat bipolar patients, with presumably worse outcome and perhaps at higher risk to experience a switch after adding an antidepressant. It is important to remark that 100% of the patients were on an antimanic drug besides the antidepressant; had this not been the case, the switch rate might have been even higher.

In our study, several indicators of longitudinal severity of the disease were associated with switch risk, such as higher number of total affective episodes, higher number of depressive episodes, higher number of hypomanic episodes, higher number of relapses with antidepressants, and higher number of antidepressant-associated switches during the illness. The following indicators were especially associated with switch risk after we performed a logistic regression: higher rate of antidepressant-associated switches during the illness, lower rate of responses to antidepressants, and earlier age at onset.

Our study does not replicate early findings on higher switch rates with SNRIs compared to SSRIs,[30] which were confirmed in another randomized clinical trial.[31,32] The possibility that the group with switch during the index episode might have more frequently used SSRIs, but not other antidepressants, was not due to comorbidity with anxiety disorders, because the prevalence of anxiety disorders did not differ between the 2 groups. However, because the investigators were likely aware of the reported switch risk associated with SNRIs, it is possible that they were slightly less inclined to prescribe SNRIs to subjects perceived as "at risk."

After performing a logistic regression, lifetime history of psychotic symptoms showed a trend toward the absence of antidepressant-related switches. Likewise, Mazzarini et al,[33] in an Italian cohort of 164 bipolar II disorder patients, found that the presence of psychotic symptoms was associated with lower episode frequency, thus better longitudinal outcome. It seems that acute severity may be inversely correlated with longitudinal severity. Adjunctive antidepressants may be safely prescribed in patients with psychotic depression or history of psychosis.

Furthermore, the switch group had a greater number of total episodes, depressions, and hypomanic episodes, but not a higher number of manic and mixed episodes. We did not find a relationship between the number of antidepressants used during the illness and the occurrence of an antidepressant-related switch, at least during the index episode. This may be surprising since a greater number of previous depressive episodes are expected to be associated with higher antidepressant exposure and thus, eventually, higher switch risk. This finding may indicate that the switching depended on the illness course rather than being antidepressant-induced. This is in agreement with findings by Licht et al,[17] who hypothesized that, in bipolar disorder, switch commonly occurs as a natural course of the illness.

The only study that has specifically examined switch rates and risk factors in a large cohort of bipolar depressed patients is the one by Perlis et al[34] in the context of the STEP-BD study. They used survival analysis to examine time to transition to mania, hypomania, or mixed state among 2,166 bipolar I and II disorder individuals in a major depressive episode. They found that 21.3% transitioned to a mania, hypomania, or mixed state before remission. Among the group treated with antidepressants (1,475 of 2,166) the percentage was 19.6%. As we found, greater number of past depressive episodes and history of switch while treated with antidepressants were 2 clinical features associated with greatest transition hazard. Consistent with their findings, our results also indicate that certain clinical features may be associated with greater risk of transition from depression to manic, hypomanic, or mixed states, but the majority of them are not specific to antidepressant-treated patients, with the only exception being the timing of antidepressant prescription.

In accordance with our conclusion that greater number of prior episodes represents a risk factor for poor outcome, Ghaemi et al,[35] in a recent study, found higher relapse rates into depression during treatment with antidepressant in rapid-cycling patients when compared to nonrapid cyclers.

The results from multivariate analysis showed that rate of previous antidepressant-associated switches, rate of previous responses to antidepressants, and age at onset were the variables that best predicted the occurrence of an antidepressant-related switch in our sample. The multivariate model explained up to 40%.

Limitations of this study include its unicentric nature, which might limit the generalizability of the findings, and the fact that this was not a clinical trial (absence of randomization and placebo arm) due to its naturalistic design. However, the naturalistic design of the study, which implies the participation of several potentially confounding variables, is justified by the fact that the study was precisely designed to ascertain the variables associated with emergence of antidepressant-related switch in routine clinical practice. In fact, clinical trial samples exclude most of the relevant variables to ensure internal validity, and switch has never been the primary outcome of any trial in bipolar disorder. In one of the few placebo-controlled trials[36] of an antidepressant in bipolar depression, the switch rate on paroxetine monotherapy was relatively low (10%) and similar to placebo.

The main strengths of this study include the long-term, prospective design combined with retrospective, standardized assessment of some specific variables, the use of a sensitive definition of switch as the one proposed by the ISBD, and the systematization of outcomes, all of which result in sufficient statistical power that enables detection of differences between switch and nonswitch groups. The results of our study may provide important suggestions for daily clinical practice.

Bipolar patients with a worse outcome and an illness course characterized by multiple episodes were found to have higher switch risk. However, we did not find that patients with higher switch risk were those with a greater number of previous antidepressant exposures. Our results suggest that, although the overall switch risk might be higher than generally reported in controlled trials, no specific antidepressant subtype seemed

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to be associated with higher switch risk. Early prescription of antidepressants may be associated with higher switch risk, suggesting that other options should take precedence in the youth. One of the main predictors of switch was actually previous switch, its prominence emphasizing how important it is to capture that feature when interviewing patients with bipolar disorder. The controversy around the use of antidepressants in bipolar depression is likely to continue.

Drug names: carbamazepine (Carbatrol, Equetro, and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), paroxetine (Paxil, Pexeva, and others).

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