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Predictors of Depressive Switch in Patients With Bipolar I Disorder Who Initiated or Changed Pharmacologic Treatment for Mania or Mixed-Mania:

A Prospective Observational Study

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ABSTRACT

Objective: To evaluate the prevalence and the predictors of depressive switch in patients with bipolar I disorder (BD-I) requiring the initiation or change (but not a dose change) of treatment with oral antipsychotics or mood stabilizers for mania or mixed-mania.

Methods: This was a 3-month, prospective, noninterventional study conducted in 34 Italian psychiatric centers from April 2012 to April 2013. The study sample comprised 234 patients aged 18 years or older presenting with a manic episode according to *DSM-IV-TR* criteria. Patients were assessed at baseline and at follow-up visits by a variety of measures, including the Clinical Global Impressions scale for use in bipolar illness (CGI-BP). The primary outcome measure was depressive switch, which was defined a posteriori on the basis of a Montgomery-Åsberg Depression Rating Scale total score ≥ 15 and a Young Mania Rating Scale total score < 10 at week 12. A stepwise backward logistic regression model was used to explore the effect of clinical variables on the occurrence of depressive switch.

Results: According to the definition used in this study, 26 (11.1%) of 234 patients switched to depression. The variables associated with a depressive switch were prescription of both first- and second-generation antipsychotics ($P = .017$), depressive-predominant polarity ($P = .012$), CGI-BP total score at baseline evaluation ($P = .024$), depressive temperament ($P = .063$), and age at evaluation ($P = .020$).

Conclusions: Depressive switch was observed in about 1 of 10 of the BD-I patients. Our results suggest an association between the depressive switch and treatment with both first- and second-generation antipsychotics, depressive-predominant polarity, greater severity of the symptomatology, and older age at evaluation. Further randomized controlled studies are needed to confirm possible predictors of a depressive switch during mania.

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Bipolar disorder (BD) is a chronic illness characterized by recurrent manic and depressive episodes, multiple medical and psychiatric comorbidities, significant functional impairment, high cost to the patient and to the health care system, and high rates of suicide.[1] A significant proportion of patients with BD can show switches from depression to mania or vice versa.[2] The switch phenomenon is characterized by a transition from a mood episode to another episode of the opposite polarity; this particular feature distinguishes BD from all other psychiatric disorders[3] and is associated with a poor long-term outcome.[4]

In the past 30 years, patients' switching from depression to mania has been a widely studied issue that originated a great debate on the possible trigger role of antidepressant drugs,[5,6] particularly when they are used in monotherapy.[7] However, the switch from mania to depression has been poorly investigated, and few studies have explored factors that may be associated with an increased risk of this particular phenomenon.[8–10]

In a 2-year, prospective, observational study[8] in which the primary outcome measure was depressive switch in patients with a manic/mixed episode,switching to depression was defined a posteriori using Clinical Global Impressions (CGI) scale for use in bipolar illness (CGI-BP)[11] mania and depression score as a change from manic and not depressed to depressed but not manic over 2 consecutive observations within the first 12 weeks of follow-up. This criterion excluded those patients who already had clinically significant depressive symptoms since baseline during acute mania. According to this very narrow definition, only 120 (5.0%) of 2,390 patients switched to depression within the first 12 weeks. Factors positively associated with depressive switch included a history of previous depressive episodes, comorbidity with substance abuse, greater overall severity of bipolar disorder, and use of benzodiazepines, while those negatively associated with depressive switch were CGI-BP depression score, Young Mania Rating Scale (YMRS)[12] severity score, and atypical antipsychotic use. The authors

Clinical Points

- In patients with bipolar disorder, switches from mania to depression have been poorly investigated.
- In this sample, depressive switch was observed in about 1 of 10 patients who initiated or changed treatment with oral antipsychotics or mood stabilizers.
- Depressive-predominant polarity and the combination of first- and second-generation antipsychotics may play a role in increasing the risk of switch from mania to depression, and this relationship should be further studied.

concluded that an appropriate pharmacologic strategy in manic patients might reduce the risk of switching to depression. However, the exclusion of mixed patients, who are known to be more likely to switch,[13] and the use of a narrow definition based on the absence of depression before and on the remission of mania after the switch, limit the interpretation of the results. In other words, the negative association of atypical antipsychotics with the presence of depressive switch may be related to a selection bias or to other confounding factors rather than to a therapeutic effect.

The Observational Study to Evaluate factors predicting Remission in Bipolar I patients experiencing manic episode (OSTER)[14] was a prospective observational study conducted in a sample of bipolar patients who required the initiation or change of oral medications for an acute manic episode. Over a 12-week observational period, the changes from baseline in manic and/or depressive symptoms, functioning, and quality of life were recorded. The primary objective of the original study was to identify the possible factors predicting remission during a manic episode. The aim of the present post hoc analysis was to identify internal and external factors that could predict depressive switch at the final evaluation.

METHODS

Study Design and Sample

This multicentric, prospective, longitudinal, noninterventional study was conducted in 34 recruiting Italian psychiatric centers, representative of the entire national territory, from April 2012 to April 2013. The study population included inpatients or outpatients aged 18 years or older presenting with a manic episode in the context of bipolar I disorder (BD-I), diagnosed according to *DSM-IV-TR* criteria,[15] and requiring the initiation or a change (but not a dose change) of treatment for mania with oral antipsychotics or mood stabilizers. The assignment of the patients to a particular therapeutic strategy was independent of the decision to include the patient in the study. According to his or her clinical experience and treatment guidelines, the treating psychiatrist made therapeutic choices in a naturalistic setting. Patients not able to read or understand the informed consent, pregnant or breast-feeding women, subjects participating in a separate study that had an interventional design, and site personnel or their immediate family members were not eligible for participation.

The study duration was 3 months for each patient and included 5 visits: screening for inclusion in the study and baseline assessment were concomitants; follow-up visits were at weeks 1, 3, 8, and 12 (±1 week). Demographic data, medical and psychiatric history, disease characteristics, past and current treatment prescriptions for BD, and other comorbidities were recorded at study entry. During all the course of the study, any change in drug regimen or doses was recorded, as was any nonpharmacologic treatment. At each visit, adherence to medication was systematically assessed by interviewing patients and cohabitants, when available. If necessary, plasma levels of drugs were monitored, as routinely performed in observational naturalistic studies.

At baseline, at regular times of follow-up, and at the last evaluation (week 12), BD patients were assessed by the YMRS,[12] the Montgomery-Åsberg Depression Rating Scale (MADRS),[16] the CGI-BP,[11] and the Functioning Assessment Short Test (FAST).[17] At week 12, the brief version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego—Münster version (briefTEMPS-M)[18] was also administered.

All patients gave their written informed consent prior to the start of any study-related procedure. The study protocol was approved by the reference Ethic Committee of each study site.

Assessment Tools

The diagnosis of manic episode in BD-I patients was made by the treating psychiatrist according to *DSM-IV-TR* criteria.[15]

Manic symptoms were quantitatively and qualitatively assessed through the YMRS.[12] Depressive symptoms were investigated by the MADRS,[16] which was expressly created to be sensitive to the evolution of depressive symptoms over time. The assessment of depressive symptoms is thought to be relevant also during manic phases owing to the possible occurrence of dysphoria and switching toward a mixed state. The global psychopathology was evaluated by the CGI-BP,[11] a version of CGI that preserves the fundamental assets of the original global rating instrument focusing on the specific components of BD.

Psychosocial functioning was assessed through the administration of the FAST.[17] The FAST is organized in 6 clusters (autonomy, occupational functioning, cognitive functioning, financial management, social functioning, and leisure time) whose items are evaluated from absence of difficulty to high difficulty. The FAST shows strong psychometric properties, and it is sensitive to different mood states.

The assessment of temperamental characteristics was performed by use of the briefTEMPS-M.[18] The briefTEMPS-M includes 5 temperamental subscales: depressive, cyclothymic, hyperthymic, irritable, and anxious. All of the briefTEMPS-M temperaments correlate quite well (Pearson *r*, 0.49–0.72) with the original, longer version of the TEMPS-M.

To minimize the influence of the acute manic symptomatology, the brief TEMPS-M was administered at week 12.

Definition of Switching From Mania to Depression

Switching from mania to depression was defined a posteriori on the basis of a MADRS total score ≥ 15 and a YMRS total score < 10 at week 12. The definition of switch used in this study was aimed at targeting those patients who would actually go from mania to depression after the initiation or change of treatment for mania with oral antipsychotics or mood stabilizers. We included also those patients who already had clinically significant depressive symptoms at baseline evaluation (mixed-mania).

Statistical Analyses

We used *t* test and χ^2 test, respectively, for comparison of continuous and parametric variables between patients with a depressive switch (DS) and with no DS (NDS). Owing to the exploratory nature of the study, we considered levels of significance of $P < .05$, without applying any correction for multiple comparisons.

A stepwise backward logistic regression model was then used to explore the effect of clinical variables on the depressive switch of manic or mixed-manic patients 12 weeks after the initiation or change of treatment with oral antipsychotics or mood stabilizers. An α of .05 in the univariate comparison was used as the cutoff for the inclusion of a variable in the regression model. The stepwise modeling procedure started with the full model and, for each step, continued by eliminating the last statistically significant variable from the model and recomputing the revised model, until all remaining variables were $P < .1$. Odds ratios with 95% confidence intervals were used for observed associations.

We used the statistical routines of SPSS Statistics version 22.0 for Mac (IBM Corporation; Armonk, New York).

RESULTS

Overall, 245 BD-I manic patients were screened and 243 of them were included in the study. Two patients were excluded from the evaluable population due to their not switching therapy for BD-I. Our analyses were performed on the 234 patients who completed the MADRS at final evaluation. Among them, remission of manic symptoms at week 12 was achieved in 191 patients (81.6%), while a reduction of ≥ 50% in YMRS total score from baseline to week 12 was observed in 195 patients (83.3%). The mean ± SD change in YMRS total score from baseline to week 12 was 22.0 ± 10.7. The mean MADRS total score also progressively decreased from baseline to week 12, with a mean ± SD change of 6.1 ± 8.2; the mean ± SD change in CGI-BP total score from baseline to week 12 was 4.5 ± 3.4, while FAST total score mean ± SD change from baseline to week 12 was −17.5 ± 17.3. As assessed by the MADRS total score ≥ 15 and by the YMRS total score < 10 at 12 weeks after the initiation or change of treatment with oral antipsychotics or mood stabilizers, only 26 patients (11.1%) showed a depressive switch.

Table 1. Demographic and Clinical Features of 234 Patients With Bipolar I Disorder Experiencing a Manic or Mixed-Manic Episode[a]

Characteristic	NDS[b,c] (n = 208)	DS[b,d] (n = 26)	χ^2/t	P[e]
Female	115 (55.3)	13 (50.0)	0.261	.610
Age, y	47.82 ± 13.61	53.62 ± 11.85	−2.076	**.039**
Age at first episode, y	32.62 ± 12.87	40.27 ± 14.82	−2.809	**.005**
First-degree family history for BD	81 (38.9)	7 (26.9)	1.423	.233
Total number of previous:				
Depressive episodes	2.93 ± 4.78	4.92 ± 5.97	−1.947	.053
Manic episodes	3.85 ± 4.66	2.65 ± 1.62	2.625	**.010**
Mixed episodes	1.05 ± 2.45	0.77 ± 2.08	0.565	.573
Hypomanic episodes	1.63 ± 4.52	2.42 ± 4.16	−0.855	.393
History of psychotic features	135 (64.9)	13 (50.0)	2.208	.137
History of suicide attempts	35 (16.8)	6 (23.1)	0.625	.429
Rapid cycling course	9 (4.3)	0	1.170	.279
Depressive-predominant polarity	32 (15.4)	10 (38.5)	8.357	**.004**

[a]Comparisons are between patients with no depressive switch (NDS) and with a depressive switch (DS) 12 weeks after the initiation or change of treatment with oral antipsychotics or mood stabilizers.
[b]Values are n (%) or mean ± SD.
[c]No depressive switch is defined as a MADRS total score ≤ 14 at week 12.
[d]Depressive switch is defined as a MADRS total score ≥ 15 and a YMRS total score < 10 at week 12.
[e]Boldface type indicates statistical significance.
Abbreviations: BD = bipolar disorder, DS = depressive switch, MADRS = Montgomery-Åsberg Depression Rating Scale, NDS = no depressive switch, YMRS = Young Mania Rating Scale.

The comparisons of the demographic and clinical variables between NDS and DS patients are reported in Table 1. The 2 groups presented similar sex distribution (female, respectively, 55.3% vs 50.0%), while DS patients presented higher mean age at the moment of the evaluation than NDS subjects (mean ± SD, respectively, 53.62 ± 11.85 vs 47.82 ± 13.61; $P = .039$). Likewise, DS patients showed higher mean age at onset of mood disorder compared with the NDS group (mean ± SD, respectively, 40.27 ± 14.82 vs 32.62 ± 12.87; $P = .005$). NDS and DS patients did not show significant differences in the rates of first-degree family history for BD; in the history of psychotic features and suicide attempts; in the rates of rapid cycling course; and in the total number of previous depressive, mixed, and hypomanic episodes. Conversely, compared with the NDS group, DS patients presented a lower total number of previous manic episodes (mean ± SD, respectively, 2.65 ± 1.62 vs 3.85 ± 4.66; $P = .010$) and a higher rate of depressive-predominant polarity, defined as at least two-thirds of a patient's past episodes fulfilling criteria for major depressive episodes[19] (respectively, 38.5% vs 15.4%; $P = .004$).

Regarding psychometric scales (Table 2), DS patients presented higher scores compared with NDS subjects on the CGI-BP at baseline evaluation (mean ± SD, respectively, 12.12 ± 2.75 vs 10.54 ± 2.43; $P = .002$). Conversely, there were no significant differences between the 2 groups in YMRS, MADRS, and FAST total scores at baseline. The DS group showed higher scores on the depressive temperamental subscale than the NDS group (mean ± SD, respectively, 20.60 ± 6.94 vs 16.77 ± 6.07; $P = .004$),

Table 2. Mean Psychometric Scale Scores of 234 Patients With Bipolar I Disorder Experiencing a Manic or Mixed-Manic Episode[a]

Measure	NDS[b,c] (n = 208)	DS[b,d] (n = 26)	χ^2/t	P[e]
MADRS total score at baseline	13.00 ± 6.44	13.38 ± 6.49	−0.291	.772
YMRS total score at baseline	28.24 ± 9.45	28.81 ± 9.69	−0.290	.772
CGI-BP total score at baseline	10.54 ± 2.43	12.12 ± 2.75	−3.079	**.002**
FAST total score at baseline	40.08 ± 16.46	39.92 ± 12.81	0.046	.963
BriefTEMPS-M subscale score				
Depressive temperament	16.77 ± 6.07	20.60 ± 6.94	−2.891	**.004**
Cyclothymic temperament	18.08 ± 6.62	19.38 ± 8.55	−0.867	.387
Hyperthymic temperament	19.76 ± 6.13	18.58 ± 6.93	0.867	.387
Irritable temperament	15.44 ± 5.61	16.84 ± 8.84	−0.767	.449
Anxious temperament	13.89 ± 5.69	16.16 ± 6.71	−1.816	.071

[a]Comparisons are between patients with no depressive switch (NDS) and with a depressive switch (DS) 12 weeks after the initiation or change of treatment with oral antipsychotics or mood stabilizers.
[b]All values are mean ± SD.
[c]No depressive switch is defined as a MADRS total score ≤ 14 at week 12.
[d]Depressive switch is defined as a MADRS total score ≥ 15 and a YMRS total score < 10 at week 12.
[e]Boldface type indicates statistical significance.
Abbreviations: briefTEMPS-M = brief version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego–Münster version; CGI-BP = Clinical Global Impressions scale for use in bipolar disorder; DS = depressive switch; FAST = Functioning Assessment Short Test; MADRS = Montgomery-Åsberg Depression Rating Scale; NDS = no depressive switch; SD = standard deviation; YMRS = Young Mania Rating Scale.

Table 3. Psychiatric Comorbidity of 234 Patients With Bipolar I Disorder Experiencing a Manic or Mixed-Manic Episode[a]

Comorbidity	NDS[b,c] (n = 208)	DS[b,d] (n = 26)	χ^2/t	P
Anxiety disorders	55 (26.4)	11 (42.3)	2.873	.090
Eating disorders	15 (7.2)	0	2.003	.157
Alcohol-Substance use disorders	66 (31.7)	12 (46.2)	2.163	.141
Borderline personality disorder	10 (4.8)	1 (3.8)	0.048	.827

[a]Comparisons are between patients with no depressive switch (NDS) and with a depressive switch (DS) 12 weeks after the initiation or change of treatment with oral antipsychotics or mood stabilizers.
[b]All values are n (%).
[c]No depressive switch is defined as a MADRS total score ≤ 14 at week 12.
[d]Depressive switch is defined as a MADRS total score ≥ 15 and a YMRS total score < 10 at week 12.
Abbreviations: DS = depressive switch, MADRS = Montgomery-Åsberg Depression Rating Scale, NDS = no depressive switch, YMRS = Young Mania Rating Scale.

Table 4. Pharmacologic Treatment of Patients With Bipolar I Disorder Experiencing a Manic or Mixed-Manic Episode[a]

Medication	NDS[b,c] (n = 208)	DS[b,d] (n = 26)	χ^2/t	P[e]
SGAs	195 (93.8)	25 (96.2)	0.237	.626
Asenapine	73 (35.1)	8 (30.8)	…	…
Olanzapine	44 (21.2)	6 (23.1)	…	…
Quetiapine	41 (19.7)	5 (19.2)	…	…
Risperidone	30 (14.4)	4 (15.4)	…	…
Aripiprazole	21 (10.1)	3 (11.5)	…	…
Others	11 (5.3)	2 (7.7)	…	…
FGAs	125 (60.1)	22 (84.6)	5.949	**.015**
Haloperidol	41 (19.7)	10 (38.5)	…	…
Clotiapine	36 (17.3)	7 (26.9)	…	…
Chlorpromazine	30 (14.4)	5 (19.2)	…	…
Others	22 (10.6)	5 (19.2)	…	…
Both FGAs and SGAs	116 (55.8)	21 (80.8)	5.952	**.015**
Mood stabilizers	194 (93.3)	25 (96.2)	0.321	.571
Lithium carbonate	88 (42.3)	14 (53.8)	…	…
Valproate sodium	129 (62.0)	18 (69.2)	…	…
Antidepressants	28 (13.5)	7 (26.9)	4.026	**.045**

[a]Most common (≥ 10% of patients) prescribed medications (ATC drug class and generic name) at final evaluation. Comparisons are between patients with no depressive switch (NDS) and with a depressive switch (DS) 12 weeks after the initiation or change of treatment with oral antipsychotics or mood stabilizers.
[b]All values are n (%).
[c]No depressive switch is defined as a MADRS total score ≤ 14 at week 12.
[d]Depressive switch is defined as a MADRS total score ≥ 15 and a YMRS total score < 10 at week 12.
[e]Boldface type indicates statistical significance.
Abbreviations: ATC = anatomic therapeutic chemical classification system, DS = depressive switch, FGA = first-generation antipsychotic, MADRS = Montgomery-Åsberg Depression Rating Scale, NDS = no depressive switch, SGA = second-generation antipsychotic, YMRS = Young Mania Rating Scale.

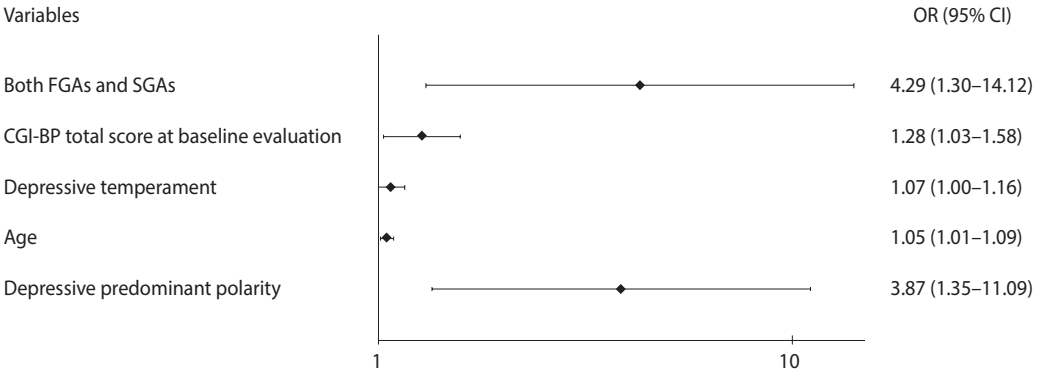
while the scores on the cyclothymic, anxious, hyperthymic, and irritable temperamental subscales were similar in the 2 groups.

Considering comorbidity with other mental disorders, DS and NDS patients showed no significant differences in the rates of anxiety, eating, alcohol-substance use and borderline personality disorders (Table 3).

Regarding psychopharmacologic treatment (Table 4), almost all the patients (more than 90%) in both groups received mood stabilizers and second-generation antipsychotics (SGAs), with no statistically significant differences between the 2 groups. Conversely, when compared with the NDS group, the DS group was significantly more frequently treated with first-generation antipsychotics (FGAs) (respectively, 60.1% vs 84.6%; $P = .015$) or with a combination of both FGAs and SGAs (55.8% vs 80.8%, $P = .015$). At baseline evaluation, 61.5% of DS and 40.9% of NDS patients were on antidepressant treatment, while at final evaluation, 26.9% and 13.5% of patients, respectively, were taking antidepressants. The most commonly prescribed medications, ie, in at least 10% of patients, are listed in Table 4.

In the logistic regression model (Figure 1), the variables associated with depressive switch were the prescription of both FGAs and SGAs ($P = .017$), the depressive-predominant

Figure 1. Logistic Regression Backward Procedure of Clinical Variables on the Occurrence of Depressive Switch 12 Weeks After the Initiation or Change of Treatment With Oral Antipsychotics or Mood Stabilizers in Patients With Bipolar I Disorder Experiencing a Manic or Mixed-Manic Episode[a]



[a]Wald = 24.567. $P = .000$. Variables not in the equation: FGAs, antidepressants, age at first episode, total number of previous manic episodes.
Abbreviations: CGI-BP = Clinical Global Impressions scale for use in bipolar illness, FGAs = first-generation antipsychotics, OR = odds ratio, SGAs = second-generation antipsychotics.

polarity ($P = .012$), the CGI-BP total score at baseline evaluation ($P = .024$), the depressive temperament ($P = .063$), and the age at evaluation ($P = .020$).

DISCUSSION

In this multicentric, prospective, longitudinal, observational study conducted on BD-I manic or mixed-manic patients, the initiation or change of therapy with oral antipsychotics or mood stabilizers was associated with rapid and marked improvement, and more than 80% of the patients achieved remission of manic symptoms after 12 weeks. This high rate of response is not unexpected and is consistent with the results of the controlled and naturalistic studies[20] showing the efficacy of different mood stabilizers and antipsychotic agents in controlling acute mania and the relatively good response of manic episodes compared with depressive and mixed/cycling ones.[21,22]

Most importantly, 26 (11.1%) of the 234 patients included in the present analysis, after recovering from mania, switched into depression at the end of the 12-week observation period. In our sample, the rate of depressive switches is higher than that reported in the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study,[8] in which only 5.0% of patients switched to depression within the first 12 weeks. The discrepancy between the results of the 2 studies can be explained by differences in the sample selection criteria and in the definition of depressive switch. In the EMBLEM study, switching to depression was defined using CGI-BP mania and depression scores: "Patients changed from manic and not depressed to depressed but not manic over two consecutive observations within the first 12 weeks of follow-up."[8(p.1)] This definition precluded patients with mixed-mania from inclusion in the depressive switch group.

In our study, switching from mania to depression was defined on the basis of a MADRS total score ≥ 15 and a YMRS total score < 10 at week 12, including also those patients who already had clinically significant depressive symptoms at baseline evaluation (mixed-mania). In addition, the MADRS seems to be more sensitive than the CGI-BP mania and depression subscales in assessing depressive symptomatology over time. The decision to also evaluate patients with mixed-mania was taken because of the high risk of switching to depression in such patients.[13,23]

The rate of depressive switches in our sample is similar to that observed in the naturalistic McLean-Harvard First-Episode Mania Study,[24] in which 22 (13.3%) of 166 patients with a first hospitalization for a manic/mixed episode switched to depression over 2 years of follow-up; in that study, switching is defined as an early phase shift to depression without an interval of recovery from the index episode and, like in our study, mixed-manic patients were included in the sample.

A series of clinical variables were distributed differently in our patients with or without depressive switch. CGI-BP total score at baseline, age, age at onset, and rate of depressive temperament were higher in patients with depressive switch than in those without. In addition, patients with depressive switch showed a lower total number of previous manic episodes and higher rates of depressive-predominant polarity compared with the rest of the sample. These data are consistent with the results of the EMBLEM study,[8] in which depressive switches were positively associated with age at bipolar onset, high number of previous depressive episodes, and severe CGI-BP score.

Our patients with and without depressive switch did not show significant differences in prescription of mood stabilizers and SGAs. Interestingly, our study pointed out a significant association of depressive switch with the prescription of both FGAs and a combination of FGAs and SGAs. This observation is consistent with several studies showing that SGAs may be less likely to induce a depressive switch compared with FGAs.[8–10,25] Furthermore, in comparison with the rest of the sample, patients with depressive switch were significantly

more frequently treated with antidepressants at the study entry. This observation is consistent with previous reports[8] and may reflect the tendency of patients with depressive switch toward a high number of previous depressive episodes and a prevalent depressive course of the illness.

The multivariate logistic regression included among the possible predictors of depressive switch the prescription of both FGAs and SGAs, the presence of a depressive-predominant polarity, the CGI-BP total score at baseline evaluation, the presence of a depressive temperament, and the age at evaluation. These clinical features could be important in choosing a treatment strategy for mania or mixed-mania and should be further evaluated in future randomized controlled clinical trials. Given the naturalistic approach of our study and the generalization of pharmacologic classes used, we cannot draw conclusions about the causal connection between antipsychotics and development of a depressive switch. However, our results highlight the need for further studies investigating this topic and focusing on how the within-class differences among FGAs and SGAs, with respect to possible antidepressant, depressogenic, or depression-neutral effects, impact the occurrence of depressive switches.

Although predominant polarity seems to be clinically relevant to predict the outcome and the polarity of the forthcoming episode in some patients, this illness course specifier is still missing in the major diagnostic systems (*DSM* and *ICD*); our study seems to support the utility of this construct. In patients with depressive-predominant polarity, the use of FGAs and, in particular, the combination of FGAs and SGAs, seems to be associated with higher rates of switching to depression and, consequently, with worse outcomes.

The present observational study is limited by the noncontrolled and nonrandomized design and by the fact that it was not designed a priori to examine the impact of pharmacotherapy on switch events. Furthermore, this study was designed with few restrictive inclusion and exclusion criteria to ensure as wide of a representation as possible of BD-I patients receiving pharmacologic treatment with oral antipsychotics or mood stabilizers for acute mania or mixed-mania. Thus, many factors may have played a confounding role in the results of the present study (eg, the interruption of antidepressant therapy, the possible other pharmacologic treatments). Moreover, the sample size could not be adequately powered to draw a reliable conclusion on the predictors of switching from mania to depression. For the same reason, the comparisons between manic and mixed-manic patients, and the prediction of switch rates on the basis of the different prescribed medications, were not possible. In addition, our definition of depressive switch is different from those of previous studies, limiting the comparability with other research. Finally, the relatively short duration of the observation period may influence the switch rates that could increase with time. On the other hand, this approach limited the possibility of confounding switches with recurrences. Despite the many limitations, we believe that this kind of study could highlight important aspects in everyday clinical practice.

In conclusion, while manic/hypomanic switches (particularly those induced by antidepressant treatments) have been widely studied, the switch from mania to depression still remains a poorly investigated issue, as do the clinical features potentially associated with this particular phenomenon. In our BD-I patients treated for mania or mixed-mania, 12 weeks after the initiation or change of treatment with oral antipsychotics or mood stabilizers, depressive switch has been observed in about 1 of 10 patients. Several demographic, psychopathological, and pharmacologic variables seemed to be associated with the switch from mania to depression, such as age, severity of symptoms at baseline, a course characterized by depressive-predominant polarity, and mostly, treatment with a combination of FGAs and SGAs. Prospective randomized controlled studies are now needed to formally test hypotheses about the causal relationship between antipsychotic use and mania-to-depression polarity conversion. Furthermore, longer-term follow-up studies comprising wider samples of patients may yield further information on rates and predictors of depressive switches, the understanding of which may help clinicians in the long-term management of BD.

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