Antidepressant-Induced Mania in Bipolar Patients: Identification of Risk Factors

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Background: Concerns about possible risks of switching to mania associated with antidepressants continue to interfere with the establishment of an optimal treatment paradigm for bipolar depression.

Method: The response of 44 patients meeting DSM-IV criteria for bipolar disorder to naturalistic treatment was assessed for at least 6 weeks using the Montgomery-Asberg Depression Rating Scale and the Bech-Rafaelson Mania Rating Scale. Patients who experienced a manic or hypomanic switch were compared with those who did not on several variables including age, sex, diagnosis (DSM-IV bipolar I vs. bipolar II), number of previous manic episodes, type of antidepressant therapy used (electroconvulsive therapy vs. antidepressant drugs and, more particularly, selective serotonin reuptake inhibitors [SSRIs]), use and type of mood stabilizers (lithium vs. anticonvulsants), and temperament of the patient, assessed during a normothymic period using the hyperthymia component of the Semistructured Affective Temperament Interview.

Results: Switches to hypomania or mania occurred in 27% of all patients (N = 12) (and in 24% of the subgroup of patients treated with SSRIs [8/33]); 16% (N = 7) experienced manic episodes, and 11% (N = 5) experienced hypomanic episodes. Sex, age, diagnosis (bipolar I vs. bipolar II), and additional treatment did not affect the risk of switching. The incidence of mood switches seemed not to differ between patients receiving an anticonvulsant and those receiving no mood stabilizer. In contrast, mood switches were less frequent in patients receiving lithium (15%, 4/26) than in patients not treated with lithium (44%, 8/18; p = .04). The number of previous manic episodes did not affect the probability of switching, whereas a high score on the hyperthymia component of the Semistructured Affective Temperament Interview was associated with a greater risk of switching (p = .008).

Conclusion: The frequency of mood switching associated with acute antidepressant therapy may be reduced by lithium treatment. Particular attention should be paid to patients with a hyperthymic temperament, who have a greater risk of mood switches.

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There have been many studies concerning the acute treatment of mania and prophylaxis for bipolar disorder. In contrast, few studies have been devoted specifically to treatment strategies for depression in bipolar patients, and the results of such studies have been limited or inconclusive.[1] Most of what is known about the treatment of depression is derived from clinical trials that systematically exclude depressed bipolar patients. The section of the National Institute of Mental Health (NIMH) workshop report dealing with the treatment of depressed bipolar patients has stressed the need for more research in this field.[2] Depressive episodes in bipolar disorder are associated with considerable morbidity and mortality. The mean duration of bipolar depressive episodes is far longer than that of manic episodes, and more than 20% of bipolar depressive episodes have a chronic course.[3] In addition, 19% of bipolar patients kill themselves.[4] However, concerns about the risks of antidepressant treatment, such as manic episodes and rapid cycling, continue to interfere with the establishment of an optimal treatment paradigm for bipolar depression. Indeed, bipolar patients taking antidepressants alone or in conjunction with mood stabilizers have been observed to have a high rate of switching to manic states, with a particular risk in the first few weeks of therapy.[5–7] This high rate seems to occur frequently with tricyclic antidepressants (TCAs).[8]

If antidepressants are required, guidelines for the acute treatment of bipolar depression suggest bupropion or a selective serotonin reuptake inhibitor (SSRI) as first-line treatments.[9,10] Nevertheless, there have been no studies focusing on the risk of switching to mania in depressed bipolar patients treated with SSRIs in combination with various mood stabilizers. Some studies[11–13] have reported the rate of mood switching with SSRIs in bipolar patients

Table 1. Characteristics of Patients (N = 44)

Characteristic	N	%
Sex		
Male	13	30
Female	31	70
Education (< 12 y)	21	48
Occupational status (currently working, student, retired)	26	59
Marital status (always been single)	14	32
Diagnosis		
Bipolar I	31	70
Bipolar II	13	30
	Mean	SD
Age, y	42.7	12.6

but did not consider this rate a function of the use and type of mood stabilizer. In addition, little is known about the clinical features of patients prone to switching. These characteristics might be useful for predicting manic episodes.

Therefore, this study was designed to address these questions by focusing on the occurrence of switches to hypomanic or manic states through the follow-up of a group of depressed bipolar patients receiving naturalistic treatment.

METHOD

Forty-four bipolar patients who were experiencing a DSM-IV–diagnosed major depressive episode were recruited from January 1995 to May 1999 from consecutive admissions to the psychiatric inpatient clinic or visits to the outpatient center of Charles Perrens Hospital, Bordeaux, France. The same physician (C.H.) made the treatment decision and supervised the systematic assessment of each bipolar disorder patient. Each patient was included only once.

All patients gave informed written consent. Patients were interviewed by trained psychiatrists (F.S. and J.L.) with a French version of the Diagnostic Interview for Genetic Studies,[14] providing DSM-IV Axis I diagnoses. The clinical state of hospitalized patients was assessed daily, and outpatients were assessed once per week. In all cases, the Montgomery-Asberg Depression Rating Scale (MADRS)[15] and the Bech-Rafaelsen Mania Rating Scale[16] were used weekly to measure longitudinal changes in individual patients. If a switch occurred, the mood elation was assessed during the first 3 days. Serum levels of mood stabilizer were determined at the onset of the episode and were regularly followed thereafter. All associated treatments given during the depressive episodes in addition to mood stabilizers and antidepressants were recorded.

The following criteria were used for an antidepressant-induced hypomanic or manic switch: (1) the hypomanic or manic episodes must fulfill DSM-IV criteria and duration, and (2) patients must be followed for at least 6 weeks after beginning antidepressant treatment, because most switches occur during this period.[17] The switch had to be a direct switch from depression to mania or hypomania, with no remission prior to switching.

Patients who met these criteria were identified and compared with patients who did not switch to mania or hypomania on several variables including age, sex, diagnosis (bipolar I vs. II), number of previous manic episodes, type of antidepressant (electroconvulsive therapy [ECT] vs. chemical antidepressant, and more specifically, SSRIs), use and type of mood stabilizer (lithium vs. anticonvulsant), and the temperament of the patient assessed during a normothymic period. Patients were excluded from this study if they met criteria for rapid-cycling bipolar disorder (more than 4 episodes per year) to avoid the confound of spontaneous switches.

Temperament was assessed using the French version of the Semistructured Interview for Hyperthymic Temperament criteria developed by Akiskal and Mallya.[18] This interview consists of 22 items concerning usual mood, cognition, psychomotor activity, personal relationships, sleep needs, sexual appetite, and attitudes toward social norms. Answers were selected by the patient and not by the scorer, and the interview was administered when patients were euthymic. One point was counted per positive item. This characterization of temperament was used as a dimension rather than a category.[19]

Statistical Analysis

Dichotomous variables were compared using chi-square analysis or the Fisher exact probability test, and a t test was used for continuous variables. All continuous variables are expressed as mean ± SD. We used a t test to compare the hyperthymic score in switchers versus that in nonswitchers. We treated the hyperthymic score as a continuous variable, as in a previous article.[19] Statistical analysis was carried out using Statview software (Abacus Concepts Inc., Berkeley, Calif.)

RESULTS

Sample Characteristics

Forty-four patients met the inclusion criteria. The sample consisted of 13 men (30%) and 31 women (70%), with a mean age of 42.7 ± 12.6 years (range, 18–72 years). Most patients were bipolar type I (70%; N = 31), but 13 patients (30%) were bipolar type II (Table 1).

Educational level was less than baccalaureate level (< 12 years of education) for 21 patients (48%) and baccalaureate level or higher (≥ 12 years of education) for 22 patients (50%). Occupational status was "unemployed or disability pension" for 17 patients (39%), and "currently working, student, or retired" for 26 patients (59%) (data missing for 1 patient). Concerning marital status, 14 patients (32%) had always been single, and 29 patients (66%) were married, divorced, or widowed (data missing for 1 patient).

Table 2. Major Depressive Episode Features[a]

Variable	N	%
Major depressive episode	44	100
With psychotic features	14	32
With melancholic features	6	14
With catatonic features	1	2
Suicide attempt during current episode	4	9
Inpatient status	36	82
	Mean	SD
Length of stay, wk	7.2	3.5
MADRS score before antidepressant treatment	30.6	7.8

[a]Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Table 3. Treatment[a]

Variable	N	%
Mood stabilizer received prior to admission	33	75
Lithium only	18	41
Carbamazepine	2	5
Valproic acid	4	9
Lithium and carbamazepine	7	16
Lithium and valproic acid	1	2
Valproic acid and carbamazepine	1	2
Additional medication during the episode	26	59
Type of antidepressant therapy		
Antidepressant medication	33	75
ECT	11	25

[a]Abbreviation: ECT = electroconvulsive therapy.

Major Depressive Episode Characteristics

All depressive episodes met the DSM-IV criteria for a major depressive episode, and 14 (32%) met the criteria for a major depressive episode with psychotic features. Six patients (14%) had an episode of melancholia, and 1 patient (2%) was catatonic (Table 2). The intensity of episodes, assessed before the beginning of treatment, was moderate to severe, with a mean MADRS score of 30.6 ± 7.8. Most of the patients (82%; N = 36) were inpatients, and 9% (N = 4) attempted suicide during this episode. The mean duration of hospitalization was 7.2 ± 3.5 weeks (range, 1–14).

Treatment Characteristics

Seventy-five percent of patients (N = 33) received baseline mood stabilizers alone or in combination (lithium [N = 18], carbamazepine [N = 2], valproic acid [N = 4], lithium and carbamazepine [N = 7], lithium and valproic acid [N = 1], valproic acid and carbamazepine [N = 1]) (Table 3). During the major depressive episode, all patients had serum levels of mood stabilizer in the therapeutic range, with a mean of 0.72 ± 0.11 mEq/L for lithium, 5 to 10 mg/L for carbamazepine, and over 50 μg/mL for valproic acid. Twenty-six subjects (59%) were given additional medication during the episode. The medication given included benzodiazepines and sedative neuroleptics. Antidepressant therapy usually consisted of a chemical antidepressant (75%; N = 33), with ECT necessary in some cases (N = 11; 25%). The mean number of ECT treatments was 8.6 (range, 3–21).

Risk Factors for Switches to Hypomania or Mania

Switches to hypomania or mania occurred in 12 (27%) of the 44 bipolar depressed patients, with 7 manic episodes (16%) and 5 hypomanic episodes (11%). All switches occurred shortly after the start of antidepressant or ECT treatment (mean = 5.8 weeks; range, 3–10), and 8 (66%) of 12 patients experienced mood elation before 6 weeks of antidepressant treatment was completed. The mean score on the Bech-Rafaelsen Mania Rating Scale was 17.8 (range, 10–30).

Sex, age, and diagnosis (bipolar I vs. bipolar II) did not affect the risk of switching (Table 4). Neither MADRS score (p = .13) nor frequency of severity symptoms such as psychotic, melancholic, and catatonic symptoms (p = .18) differed significantly between patients who did and did not switch, but the sample size was small and significant results might have been obtained with a larger sample.

There was no significant difference in the risk of inducing mania (or hypomania) by ECT or chemical antidepressant (p = .46). Switches to hypomania or mania occurred with a frequency of 24% (8/33 patients) with antidepressant drugs and 36% (4/11 patients) with ECT. The use of an additional treatment did not affect the risk of switching (p = .73). SSRIs (fluvoxamine, fluoxetine, and paroxetine) induced 26% of switches (8/30). In the chemical antidepressant group, most of the patients were treated with SSRIs (90%), and it was therefore impossible to make comparisons with other types of medication. Within the SSRI group, there was no difference in the incidence of switches for fluvoxamine (33%; 4/12), fluoxetine (25%; 2/8), and paroxetine (20%; 2/10).

The incidence of mood switching did not differ between patients receiving anticonvulsants (43%; 3/7) and patients receiving no mood stabilizer (45%; 5/11) (Fisher exact, p > .999). In contrast, mood switches tended to be less frequent in patients receiving lithium only (11%; 2/18) than in patients receiving no mood stabilizer (45%; 5/11) (Fisher exact, p = .07). They were also less frequent in patients given lithium (alone or in combination with anticonvulsants) (15%; 4/26) than in patients not given lithium (44%; 8/18) (Fisher exact, p = .04) (Figure 1). The difference in the frequency of switches between patients treated with lithium only (11%; 2/18) and those treated with anticonvulsants only (43%; 3/7), although large, was not statistically significant (Fisher exact, p = .11).

The number of previous manic episodes did not affect the probability of switching (p = .38), but a high score on the hyperthymic temperament scale was associated with a greater risk of switching (p = .008).

Table 4. Predictive Factors for Switching Among 12 of 44 Bipolar Patients[a]

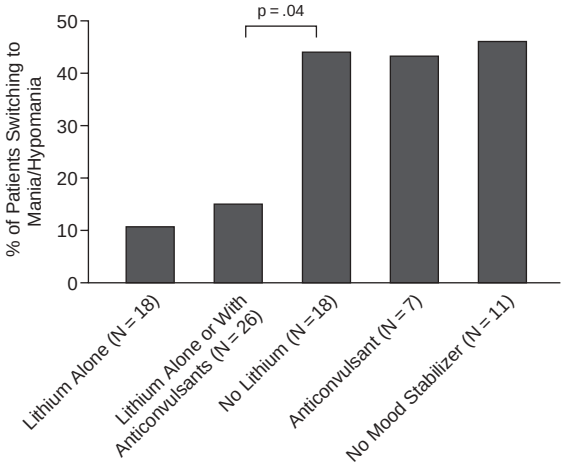
Variable	Nonswitchers (N = 32) Mean	SD	Switchers (N = 12) Mean	SD	p Value
Age, y	42.4	13.1	43.7	11.7	NS
MADRS score before antidepressant treatment	28.5	7.9	32.6	7.1	.13
Hyperthymic temperament[b]	8.6	4.9	14.0	5.7	.008 t test
			N	%	
Sex					NS
Male			3/13	23	
Female			9/31	29	
Diagnosis					NS
Bipolar I			9/31	29	
Bipolar II			3/13	23	
Prior mania episodes[c]				24	
Additional treatment (eg, benzodiazepines, neuroleptics)					NS
Yes			8/26	31	
No			4/18	22	
Antidepressant treatment					NS
Antidepressant medication			8/33	24	
ECT			4/11	36	
Type of SSRI					NS
Fluvoxamine			4/12	33	
Fluoxetine			2/8	25	
Paroxetine			2/10	20	
Type of MDE					.17
Without particular features			4/23	17	Fisher
With melancholic, psychotic, or catatonic features			8/21	38	exact test
Type of mood stabilizer					
Lithium (alone or with anticonvulsants)			4/26	15	
No lithium			8/18	44	
Anticonvulsant only			3/7	43	
No mood stabilizer			5/11	45	
Lithium only			2/18	11	
Anticonvulsant only			3/7	43	

[a]Abbreviations: ECT = electroconvulsive therapy, MADRS = Montgomery-Asberg Depression Rating Scale, MDE = major depressive episode, SSRI = selective serotonin reuptake inhibitor.
[b]Score on the Semistructured Interview for Hyperthymic Temperament.
[c]Prior mania episodes among nonswitchers: 32%.

DISCUSSION

In this sample, treatment-induced mood switches occurred in 27% of patients, with manic episodes in 16% and hypomanic episodes in 11%. This is the first study to compare the occurrence of switching induced by ECT and antidepressant drugs and to compare the efficacy of various mood stabilizers in preventing switching. Moreover, this is also the first published prospective comparison, within the same sample, of mania switch rates for various SSRIs, although the sample sizes were too small for meaningful comparisons. We also found that a hyperthymic temperament was associated with a higher risk of switching to mania or hypomania.

Figure 1. Influence of Mood Stabilizers on Switching to Mania or Hypomania[a]



[a]Mood switch frequency was similar in patients treated with anticonvulsants (43%; 3/7) and patients receiving no mood stabilizer (45%; 5/11) (p = .91; Fisher exact, p > .999). Overall, mood switches occurred in 44% of patients receiving no lithium (8/18), whereas switches were less frequent in patients receiving lithium alone (11%; 2/18) or with anticonvulsants (15%; 4/26) (Fisher exact, p = .04).

Switch Rate and Type of Antidepressant

The safety and tolerability of SSRIs have made these drugs the standard first-line treatment for bipolar depression, even if venlafaxine and bupropion are indicated in the treatment of moderate bipolar depression. However, only a few reports have assessed the efficacy of SSRIs in bipolar depression and the associated risk of drug-induced mania.

Pooled data obtained from published studies show that mood switches occur considerably more frequently with TCAs (11.2%) than with SSRIs (3.7%) or placebo (4.2%).[20] However, these low rates of switching should be viewed with caution. These patients were treated in unipolar depression (major depressive disorder) studies in which patients with bipolar I disorder were excluded but some bipolar II patients were included. Thus, patients did not receive mood stabilizers. This previous study therefore indicates the possibility of switching to mania with SSRI monotherapy in patients with bipolar II disorder, but provides no information about bipolar I disorder or the use of SSRIs with mood stabilizers. Himmelhoch et al.[6] have reported the frequency of mood elation to be 21% with a monoamine oxidase inhibitor (MAOI) and 25% with imipramine. These results are similar to those reported by Altshuler et al.,[7] who found in a retrospective study that 35% of 51 patients had antidepressant-induced manic episodes (most treated with MAOIs) and 26% had cycle acceleration. They concluded that it was necessary to explore the impact of SSRIs and mood stabilizers on these switches. Stoll and colleagues[21] analyzed data in a

retrospective study comparing 49 consecutive inpatients in antidepressant-associated manic states with 49 matched inpatients with spontaneous mania. They found that antidepressant-associated mania tended to be milder and of shorter duration than spontaneous mania. They suggested that MAOIs and bupropion trigger manic states milder than those triggered by TCAs and fluoxetine. However, there was no difference among the drug treatment groups in any variable assessed except for the Clinical Global Impressions-Severity of Illness scale score at admission. Sachs et al.,[22] in a double-blind prospective study, reported that bupropion, a new antidepressant, is less likely than desipramine to induce mood elevation.

One prospective study[8] assessed the response to naturalistic treatment of 29 bipolar I patients who experienced a total of 79 depressive episodes. The treatment given consisted principally of mood stabilizers used alone or in combination with antidepressants. The study showed that switches occurred in 28% of patients and were judged to be extremely disruptive in only 10% of patients. In this study, manic or hypomanic episodes had to occur within 2 months of each depressive episode. The results obtained were very similar to our findings. More surprisingly, antidepressant treatment combined with mood stabilizer therapy was not associated with a higher frequency of postdepressive mood elation than mood stabilizer therapy alone. Depressive episodes treated with TCAs or MAOIs were more frequently marked by switching to mania or hypomania than those with fluoxetine. Unfortunately, the episodes studied for fluoxetine were experienced by only 1 patient, who relapsed 8 times. Therefore, this isolated prospective study provides little useful information about switches induced by SSRIs.

There are also some double-blind studies reporting the use of SSRIs in bipolar depression. The first is by Cohn et al. (1989),[11] who compared fluoxetine with imipramine and with placebo in double-blind treatment of bipolar I depression. Unfortunately, few of the patients in this study were on treatment with lithium (about one third of the fluoxetine group and 15% of the imipramine group). This makes it difficult to interpret the risk of mania relative to that associated with the standard use of mood stabilizers with antidepressants. In any case, the mania switch rate was low in all 3 groups in the 6-week double-blind phase, but in the open crossover phase, about 15% of those on fluoxetine treatment switched to mania or hypomania. Thus, this study showed no advantage of fluoxetine over imipramine except that only 7% of fluoxetine-treated patients discontinued treatment due to adverse events, versus 30% of imipramine-treated patients.

The second study, by Young et al.,[12] has not yet been published but was presented at a research meeting. It was a large, multicenter, industry-sponsored clinical trial comparison of paroxetine, imipramine, and placebo as add-ons to lithium in refractory bipolar I depression. No cases of mania were reported with paroxetine, whereas mania occurred in about 10% of patients treated with imipramine.

The third double-blind study[13] compared the addition of paroxetine to a mood stabilizer (divalproex sodium or lithium) with the combination of divalproex and lithium. Significant improvements in depressive symptoms were recorded for both groups during the 6-week trial. However, the dropout rate was significantly higher for the group treated with the 2 mood stabilizers than for the group treated with a mood stabilizer and paroxetine. The addition of paroxetine to the treatment of 11 patients did not lead to the onset of manic symptoms in the 6-week period. Another double-blind study[23] of patients with bipolar II disorder with fluoxetine monotherapy reported a low mania switch rate, but had a number of limitations. It was based on post hoc analyses of data from unipolar depression studies. Mania symptoms were not assessed using prospective rating scales, and "manic switch" was defined not on the basis of DSM-IV criteria, but on clinical definitions.

We should point out that 32% of our patients had psychotic features and that this frequency is higher than the typical percentage seen in major depressive disorder (15%).[4] This suggests that the efficacy of SSRIs should be assessed in bipolar depression in terms of the particular characteristics of this kind of depression.

Switch Rate and Type of Mood Stabilizer

Jann et al.[24] found a significant correlation between low serum lithium levels and switches during antidepressant treatment. Lewis and Winokur[25] confirmed this finding and concluded that lithium and neuroleptic treatment significantly prevented the induction of mania. Rouillon et al.[26] reported switches to hypomania or mania in 21% of patients receiving placebo, 51% receiving imipramine, 21% receiving lithium, and 28% receiving imipramine and lithium. These results suggest that the risk of switching with imipramine monotherapy is about double the natural rate and that this increase in risk is almost completely abolished if lithium is also given. No previous study has compared the efficacy of lithium with that of other mood stabilizers. A placebo-controlled study of maintenance therapy with divalproex sodium and lithium has been recently conducted by Bowden et al.[27] However, Bowden and colleagues' work was not designed to compare the risk of antidepressant-induced mania between the 2 mood stabilizers. We found no difference in switching frequency between patients not receiving a mood stabilizer and patients treated with anticonvulsants. In contrast, lithium prevented mood elation. Although the difference between the 2 mood stabilizer groups in the percentage of patients experiencing mood switches was large, it was not significant, probably due to the small size of the sample of patients treated with anticonvulsants.

Clinical Characteristics of Patients Who Switch to Mania

Few studies have investigated the relationships between the characteristics of bipolar illness and of the patient's personality and the tendency to develop antidepressant-induced mood elevation. One study[6] showed that bipolar I patients present more treatment-induced mood swings than bipolar II patients, but we found no difference in the incidence of switching between bipolar I and bipolar II patients in our sample. Another study[17] showed that patients who switched to mania were significantly younger, had a lower mean age at onset of the illness, and tended to present with more severe illness.

The clinical data for 11 patients who developed mania during treatment with SSRIs show that SSRIs may induce severe mania. This induction is more likely to occur if patients have personal or family histories of hypomania or mania.[28] Boerlin et al.[8] have also reported that larger numbers of past manic episodes are associated with a higher risk of switching. Conversely, Altshuler et al.[7] found that this variable did not predict susceptibility to antidepressant-induced mania.

In our study, we found no correlation between the number of previous manic episodes and the risk of mania induced by antidepressant. However, we did find that hyperthymic temperament was associated with a tendency to switch. The number of manic episodes may have been a less indicative factor, because it is more sensitive than temperament to prophylactic drug treatment. Temperament is thus a more stable dimension. In addition, number of previous manic episodes is not a good predictive factor in patients with a recent onset of the illness. In a previous report, we showed that there is a correlation between temperament subtypes (hyperthymic vs. depressive) and polarity of episodes.[19] Bipolar patients with a hyperthymic temperament in premorbid and intercrisis periods have a tendency to develop mania.[19] This association between hyperthymic temperament and risk of switching is not due to residual symptoms, because temperament was assessed during a normothymic period, during which temperament is stable. Therefore, temperament may be useful for discriminating and identifying subtypes of bipolar illness and for optimizing treatment. This emphasizes the relevance of hyperthymia as a clinical sign of bipolar disorder.

As with many naturalistic studies, our results are limited by a variety of methodological constraints. The most important of these is the nonrandom nature of treatment assignment and the lack of blinding. Another limitation of this study is the small sizes of the subgroups. However, we have been careful to use prospective, standard rating scales. Of course, we cannot exclude the possibility that spontaneous switches occurred, but, to minimize this effect, we took precautions to exclude patients who met criteria for rapid-cycling bipolar disorder.

In conclusion, this study provides the first evidence that (1) lithium may be the most efficient mood stabilizer for preventing antidepressant-induced mania, (2) hyperthymic temperament was predictive of switches, and (3) SSRIs and ECT have similar effects in the induction of mania and hypomania (however, because of the small sample size, we cannot exclude totally the possibility of a type II error). These findings may help us to improve the treatment of bipolar depression, although definitive conclusions must await subsequent investigations including larger numbers of subjects.

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), desipramine (Norpramin and others), divalproex sodium (Depakote), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), valproic acid (Depakene), venlafaxine (Effexor).

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