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# The number of past manic episodes is the best predictor of antidepressant-emergent manic switch in a cohort of bipolar depressed patients



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## ABSTRACT

The present study sought to identify factors associated with the onset of a manic or hypomanic episode during the month following a new antidepressant therapy in depressed bipolar patients. Patients receiving mood stabilizers for  $\geq 3$  months were screened from 400 French centers and were assessed for a 4-week period following prescription of a first or a new antidepressant. Of the 1242 included participants, 4.8% ( $n=60$ ) experienced antidepressant-emergent manic switch (AEMS). AEMS was more frequently associated with lifetime manic, depressive, and total mood episodes, and with past AEMS. A higher score at two items of the Montgomery-Åsberg Depression Rating Scale (pessimistic and suicidal thoughts) were significantly associated with AEMS. Logistic regression analysis showed that the number of lifetime manic episodes and past AEMS were the two most factors associated with an AEMS. Having more than four past manic episodes was associated with a 2.84 fold increased risk of AEMS. Cumulative number of past mood episodes seems to be the most important factor for switching to a manic episode following antidepressants in patients with bipolar disorder. Longer-term studies are required to further delineate antidepressant causality from natural disease course.

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## 1. Introduction

Bipolar disorder is a common, chronic, intermittent, and disabling psychiatric illness associated with high levels of functional impairment, morbidity, and mortality. Bipolar depression causes more disability than any other manifestation of the illness (Judd et al., 2002). Patients with bipolar disorder spend up to three times longer recovering from the depressive phase of the disease than the manic phase, and are at significant risk of suicide (Lopez et al., 2001).

The lack of a consensus between guidelines on the treatment of bipolar depression reflects the paucity of data in this area. Lithium is considered a standard mood-stabilizing therapy for bipolar disorder (Sachs, 1996). However, up to one-half of patients effectively maintained with lithium therapy may be unresponsive to its antidepressant effects (Gershon et al., 1997). Despite the safety of antidepressant treatment in bipolar depression being controversial treatment of bipolar patients with antidepressants alone or in combination with mood stabilizers or atypical antipsychotics is common (Frye et al., 2009), occurring in approximately 15–20% of patients (Goldberg et al., 2003).

Manic episodes occur in the natural course of bipolar disorder (American Psychiatric Association, 2002). Clinical experience shows that a mood stabilizer does not always protect against the occurrence of mania during the natural course of illness or during antidepressant therapy. Moreover, not every bipolar patient

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becomes hypomanic or manic during antidepressant therapy. Although rarely reported, mania and hypomania have been precipitated by sudden or gradual discontinuation of antidepressant therapy in bipolar disorder regardless of whether the patient was taking a mood stabilizer (Fava et al., 2003; Goldstein et al., 1999; Kora et al., 2008).

A switch to hypomania, mania, or rapid cycling in bipolar patients treated with antidepressants has been reported with virtually every class of antidepressant medication (Montgomery et al., 2000). The risk of antidepressant-emergent manic switch is estimated to be between 20% and 40% in bipolar disorder patients (Goldberg et al., 2003), although this figure is based on a relatively small sample size. Switching has also been reported during combination anticonvulsant therapy with valproate and carbamazepine, even with serum levels within the standard therapeutic range (Stoner et al., 2001).

The prevalence of manic or hypomanic episodes, and the risk of accelerating frequency of cycles during antidepressant treatment are unknown (Wehr and Goodwin, 1979; 1987), because of a poor design of the study in this area. Prior studies suggest that antidepressant-emergent manic switch may be due to a milder intensity and shorter duration than spontaneous mania (Boerlin et al., 1998). The role of mood stabilizers in preventing antidepressant-emergent manic switch has been studied, but with mixed results (Henry et al., 2001; Mundo et al., 2001). Among the different risk factors of antidepressant-emergent manic switch proposed in the literature, the number of past mood episodes is shared by many and seems to be the most relevant (Boerlin et al., 1998; Truman et al., 2007). Besides, it has been shown that predictors of antidepressant-emergent manic switch in children and adolescents bipolar patients were concomitant antipsychotics and family history of other psychiatric disorder (Park et al., 2014). A higher risk of manic switch associated with antidepressant monotherapy than with second generation of antipsychotic monotherapy in pediatric patients with bipolar depression (Bhowmik et al., 2014). Antidepressants are associated with the potential risk for treatment-emergent mania or hypomania, particularly in bipolar patients with short illness duration, multiple past antidepressant trials, and past experience of switch with at least one antidepressant (Truman et al., 2007).

The aim of the present study was to evaluate the socio-demographic and clinical factors associated with antidepressant-emergent manic switch after 4 weeks of antidepressant treatment in depressed bipolar patients receiving mood stabilizers in everyday practice. For this purpose, we focused on bipolar patients already treated with a mood stabilizer and for whom the psychiatrist decided that an antidepressant treatment was required for a depressive episode. We hypothesized that patients with more past episodes (acquired vulnerability) and with a type II bipolar disorder would be the more frequent group of patients for whom the prescription of an antidepressant treatment would be quickly followed by a new manic episode.

## 2. Materials and methods

### 2.1. Study design and patient population sample

Patients with bipolar depression were recruited between November 2006 and March 2007 from 400 French centers. Each center was required to recruit at least 4 patients. The sample was drawn from French-speaking patients, aged between 18 and 65 years old attending regular scheduled visits. Patients were receiving mood stabilizers (lithium, valproate, or carbamazepine) for at least 3 months, and were treated with antidepressant therapy, either for the first time for the current episode, or were being switched to a new antidepressant treatment. All antidepressant classes were included in the study. Exclusion criteria were organic brain disease, chronic medical illness, comorbid mental disorder, current alcohol or drug abuse, pregnancy or lactation, and electroconvulsive therapy within the past 6 months.

All patients were given a full explanation of the collection of clinical data and procedures, and written informed consent was obtained from each participant. The study protocol was approved by the local ethics committee.

### 2.2. Clinical assessments

Sociodemographic data and records of illness history and psychotropic treatment administered throughout the preceding year were both collected during the screening phase. Patients included in the study were assessed at baseline (visit 1) and after 1 month (visit 2). Present analyses are restricted to the first visit following the prescription of an antidepressant (visit 2), to reduce other confounding factors between initial prescription and potential onset of a manic episode.

Diagnosis of bipolar disorder was carried out according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (American Psychiatric Association, 1994), using the MINI 5.0.0 (Sheehan et al., 1998) and any other available information.

It was a clinical, prospective, observational, study. Patients signed an informed consent for two visits at the first visit, and as the clinician had to collect different information, with no requirement for prescription, apart from the fact that the patients had to be treated by a mood-stabilizer.

At visit 1, sociodemographic and clinical data were collected, and the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery et al., 1979) was filled.

At visit 2, MADRS and Young Mania Rating Scale (YMRS) (Young et al., 1978) scores, and data on concomitant medication were collected. The antidepressant-emergent manic switch was assessed using the MINI questionnaire (a section of which enables screening for mood episodes). A treatment-emergent manic switch was defined as a full syndromic hypomanic, manic, or mixed episode, lasting at least two consecutive days with daily occurrence of symptomatic periods lasting more than 50% of time each day and starting within eight weeks after start (or change) of treatment. In current practice, "switchers" and "non-switchers" are used. Here, both term, "switchers" and "antidepressant-emergent manic switch", was used interchangeably.

The reliability measure regarding the MINI, MADRS, and YMRS has been done for all investigators in one national information session. Data from the MINI, YMRS, and MADRS, were used for determination of clinical status, severity of illness (depression and antidepressant-emergent manic switch), and the number of mood episodes.

### 2.3. Statistical analysis

Continuous variables were analyzed using Student's *T*-test, while categorical variables were analyzed using the chi-square test. Predictors of manic switch were examined using step-wise logistic regression analyses using odds ratios (ORs) and 95% confidence intervals (CI); prescribed treatments were not taken into account. The alpha level of significance was set at 0.05; all variables are expressed as mean  $\pm$  standard deviation. Variables were checked for normality of distribution before using parametric statistics. Analysis was conducted with Statistical Package for the Social Sciences (SPSS) software for personal computers (PC); version 17.

A systematic review found that the risk of antidepressant-emergent manic switch was 14.2% and 7.1% for bipolar I and bipolar II disorders, respectively, (Bond et al., 2008) and that the type of bipolar patient was the most frequently detected risk factor. In order to demonstrate that such a risk factor is significant in our prospective study, 330 patients were needed. To account for an expected excess of patients with bipolar I disorder, the attrition rate and analysis of factors other than type of bipolar disorder, we planned to include a sample size that was three times larger.

The ability of the number of past mood episodes to predict AEMS at the second visit was evaluated through construction of receiver operating characteristics (ROC) curves.

## 3. Results

### 3.1. Baseline characteristics

Of the first 1442 patients screened, 1242 patients were eligible for inclusion in the study. Among the 200 patients excluded from the study, the majority was due to the presence of one or more exclusion criteria (mainly comorbid addictive disorders), and the remainder because they refused to participate. Three hundred and ninety different centers participated to this study, as each clinician could include up to 6 patients, therefore the between centers heterogeneity is not easy to demonstrate concerning the event we analyzed, namely AEMS (60 cases out of 1220 subjects).

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