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Factors associated with initial treatment response with antidepressants in bipolar disorder

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Abstract

Introduction: Controversy in antidepressant (AD) use in bipolar depression relies in its potential induction of mood switches and ineffectiveness. Responders to acute AD add-on treatment maintain response with continued treatment, whilst partial/non-responders fail to reach remission despite continuation treatment. We aimed to identify response predictors to acute AD addition in bipolar depression in order to optimize treatment choice in bipolar depression and avoid unnecessary AD exposure of people unlikely to respond. *Methods:* Two hundred and twenty-one DSM-IV-TR depressed bipolar – type I and II – patients were treated with AD on an observational study. AD response was defined as an at least 50% drop from baseline of their HDRS17 score after 8 weeks of treatment. One hundred and thirty-eight patients (138, 62.4%) fulfilled response criteria (RI) whilst 83 patients (37.6%) did not (NRI). In all cases AD therapy was on top of previously prescribed stabilizers and/or atypical antipsychotics. *Results:* RI patients were more likely to have had previous response to ADs, whereas NRI had a higher number of previous mood switches with ADs during past depressive episodes. Psychotic symptoms were more frequent amongst RI, whilst lifetime history of atypical depression was more frequent amongst NRI. NRI had more total, depressive, and hypomanic, but not manic or mixed, episodes in the past than RI. Analyzed through a logistic regression, higher previous response to ADs and lower rate of past hypomanic episodes in RI were the variables explaining intergroups (RI vs. NRI) differences. *Discussion:* Taking into account the proper caution in the use of Ads in bipolar disorder, there is a subgroup of bipolar patients who might benefit from adjunctive Ads. Looking at specific clinical factors during the course of the illness could help physicians in deciding whether to use an antidepressant in a bipolar depressed patient already treated with mood stabilizers.
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1. Introduction

The role of antidepressants (ADs) in the treatment of bipolar depression is highly controversial, both in terms of safety and efficacy. Indeed, ADs have been associated with hypo/manic or mixed switch and cycle acceleration (Vieta et al., 2002; Gijsman et al. 2004; Post et al., 2006; Sachs et al., 2007; Vieta, 2008; Grunze, 2008; Licht et al., 2008; Ghaemi et al., 2004, 2008, 2010; Pacchiarotti et al., 2009; Amsterdam and Shults, 2010) and recent studies argue against their effectiveness in treating bipolar depression, with the doubtful short-term efficacy vanishing at the long-term (Ghaemi et al., 2004, 2008, 2010).

Bipolar depression is linked to higher rates of initial nonresponse to ADs compared with unipolar depression (Ghaemi et al., 2004), and with higher recurrence rates (Post et al., 2003). However, some other studies do not support these findings (Bottlender et al. 2002).

Nevertheless, data on the clinical response to ADs in bipolar depression are still scanty, compared to the evidence obtained in unipolar depression (Rush et al., 2006; Smith et al., 2009; Seemüller et al., 2010).

As a consequence, the risk-benefit ratio associated with AD use in bipolar disorder (BP) remains, at least, unclear and ADs continue to be widely prescribed by psychiatrists as initial therapy in the treatment of bipolar depression, mostly as adjunct to mood stabilizers that were unsuccessful in treating the acute depressive episode, but also in monotherapy and as a long-term treatment strategy (Baldessarini et al., 2007; Ghaemi et al., 2006).

Even more striking, despite the general consensus in advising ADs discontinuation during a manic/mixed episode, the results from a large 2-year follow-up prospective observational study conducted by the European mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) have shown that 14% of bipolar manic/mixed patients were maintained with ADs by clinicians, especially those patients with mixed episodes, rapid cyclers, anxiety, and with more previous depressive episodes (Rosa et al., 2010).

Routine clinical practices show that physicians still tend quite often to endorse AD use for BP depression, regardless regulatory recommendations and randomized controlled trial data. This fact only stresses that there is need for clarifying whether there is a rationale for the use of ADs in bipolar depression, at least in the short-term and in specific subgroups of bipolar patients.

Regarding the clinical implications of initial response to AD treatment, a recent study of a representative sample of 842 inpatients on a major depressive episode (recurrent unipolar or bipolar depression) identified early partial response (within the first 2 weeks) as the most relevant predictor of remission (80% of the sample showed initial response and 57.9% obtained remission at discharge) (Hennings et al., 2008).

Similarly, the results from a large naturalistic cohort of inpatients with major depression (N=795) supported that early improvement within the first two weeks might the most sensitive predictor of later response and remission, even in hospitalized patients suffering from more severe depression (Henkel et al., 2009).

Hence, there is need to better identify potential socio-demographic and clinical predictors of acute AD response in bipolar depression in order to optimize their prescription.

Most studies assessing this issue have been conducted in samples of patients with unipolar depression or in mixed samples with a minority of bipolar patients (Hennings et al., 2008; Smith et al., 2009; Seemüller et al., 2010).

The aim of the present study is to assess the initial AD treatment response rate and to identify clinical factors potentially associated with response/nonresponse to ADs in a sample of acutely BP depressed patients.

2. Methods

2.1. Study design and participants

This is a prospective naturalistic cohort study conducted on a sample of bipolar I and II outpatients (N=221), recruited from those participating in the systematic follow-up of the Bipolar Disorder Program of the Hospital Clínic and University of Barcelona.

Inclusion criteria comprised DSM-IV diagnosis of Bipolar type I (BP-I) or II (BP-II) Disorder current major depressive episode, Hamilton Depression Rating Scale-17 (HDRS17) over 20, and having initiated treatment with any antidepressant on their ongoing treatment (i.e., lithium, anticonvulsants and/or antipsychotics), prescribed 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 condition. Patients with major medical comorbidities were excluded from the study. All patients provided signed informed consent. The enrolment 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 Clínic.

The follow-up comprised 6 months with visits on days 1, 7, 14, 21, 28, 35, 42, 49 and 56, and afterwards every 2 weeks.

After 6 months, the sample was split in two groups according to response (RI group) or lack of response (NRI group) to treatment. Response was defined as a drop of at least 50% from baseline on HDRS17 scores after 8 weeks of treatment).

2.2. Procedures and outcomes

To confirm diagnosis, we used both the Structured Clinical Interview for DSM-IV I and II (SCID-I and SCID-II) (First et al., 1997a,b). Several variables were obtained both from structured interviews with patients and their relatives, medical records and data registrar of the Barcelona Bipolar Disorders prospective follow-up. These included the usual socio-demographic collection, and an exhaustive register including number and polarity of lifetime episodes, hospitalizations, age at onset, age at first hospitalization, age at BP diagnosis, diagnostic delay, years of follow-up, lifetime history of psychotic symptoms, suicidal behavior, number of ads during illness, mean duration of ADs treatment, presence and number of previous responses to ads, presence and number of previous relapses with ADs, presence and number of previous switch with ADs. Besides the 17-item Hamilton Depression Rating Scale (HDRS17) (Hamilton, 1967), all patients were assessed at each visit with the Young Mania Rating Scale (YMRS) (Young et al., 1978), Spanish validated versions (Bobes et al., 2003; Colom et al., 2002) administered by trained raters to assess depressive and manic symptoms, respectively.

To define specific course and outcome indicators, both during the illness and at the index episode, we chose operational definitions of symptomatic response, symptomatic remission, recovery, subsyndromal depression, relapse, recurrence and treatment-emergent mood switch almost identical to those developed by the Task Force of the International Society for Bipolar Disorders (ISBD) (Tohen et al., 2009) (see Table 1).

Predominant polarity (DPP) was attributed to a patient if at least two-thirds of all his/her past mood episodes were of the same sign-depressive versus (hypo)manic-, according to its validated operational definition (Colom et al., 2006).

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