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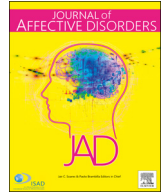
Short communication

Does recent mania affect response to antidepressants in bipolar disorder? A re-analysis of STEP-BD data

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ABSTRACT

Background: One previous study suggested that the presence of a manic episode before bipolar depression is related to worse response to antidepressants.

Method: To examine this effect in a larger sample, we used data from the large, multi-site STEP-BD study. We hypothesized that among persons treated with antidepressants for bipolar depression, manic or mixed episodes before depression onset (as compared to euthymia) would predict lower rate of recovery, more sustained depressive symptoms and higher rate of switching into mania/hypomania after antidepressant treatment of bipolar depression. 320 participants were available for analyses (140 male) diagnosed with bipolar I, bipolar II, cyclothymia, bipolar disorder not otherwise specified, or schizoaffective disorder bipolar subtype. Patients were randomly assigned to 3 treatment randomization strata (placebo, bupropion, and paroxetine) as adjuncts to mood stabilizers.

Results: Analyses were conducted to examine the effect of episode status before the depressive episode on the degree of change in depressive symptoms at 3 and 6 months, the likelihood of depression recovery and the likelihood of anti-depressant induced switching.

Presence of a manic episode before depression in patients with bipolar disorder did not significantly predict response to antidepressants.

Limitations: The study was limited by a high rate of attrition, and consideration of only two antidepressant medications.

Conclusions: Our findings are in agreement with other past studies suggesting that mania and depression may operate separately for those with bipolar disorder, with differential predictors of the onset and offset of mania versus depression. Future directions may consider vulnerability for these episodes separately.

Bipolar disorder is a highly recurrent psychiatric illness with estimated annual costs of US $151 billion (Dilsaver, 2011). Although the disorder is defined on the basis of manic episodes, depressive episodes are present for most people with this disorder and are a major determinant of impairment (Perlis et al., 2006; Mitchell and Malhi, 2004), suicidal ideation, attempts and related deaths (Mitchell and Malhi, 2004; Weinstock et al., 2016). Depressive episodes are also more frequently recurrent than manic episodes are among those diagnosed with bipolar I disorder (Mitchell and Malhi, 2004). Despite widespread use, concerns have been raised about the use of antidepressants in bipolar depression, including the possibility that they can trigger switch into mania (Bhowmik et al., 2014; Goldberg and Truman, 2003; although see Licht et al., 2008 for evidence to the contrary), and lack of efficacy when administered as adjuncts to lithium or anti-seizure medications.

Although many predictors of antidepressant response have been

considered within bipolar disorder (Tada et al., 2015), we focus here on whether antidepressant effects may be influenced by episode status before bipolar depression. Several early investigations placed focus on the sequence in which depression and manic episodes occurred as an important clinical characteristic (Winokur et al., 1969; Angst, 1978; Kukopulos et al., 1980; Roy-Byrne et al., 1985). In one previous study of 42 patients, episode status before onset of a depressive episode robustly affected the response to treatment of bipolar depression (MacQueen et al., 2002). The authors differentiated biphasic depressive episodes, in which the depressive episodes were preceded by mania or hypomania from those in which the prior mood state was euthymia. Biphasic depressions were less than half as likely to attain recovery (27.9%) in the next 3 years, as other depressive episodes (62.5%) (MacQueen et al., 2002). In addition, mania preceding the depression predicted other poor outcomes such as a three-fold greater risk of switch from depression into mania. Although this

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suggests that manic symptoms preceding episode could be a robust predictor that should shape treatment expectations, a second naturalistic study of 72 people found no significant effects of manic symptoms preceding the depression on recovery or switch into mania (Gitlin et al., 2003). Nonetheless, both studies were limited by the small samples and the lack of control over medication.

Given the pressing need to improve bipolar depression treatment, we aimed to address these limitations using a large representative sample of patients with bipolar disorder who were randomly assigned to treatment conditions and conducting more detailed analyses to examine the presence and degree of recovery, and switch into mania/hypomania. To do so, we employed data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (Sachs et al., 2003). We hypothesized that manic or mixed episodes before depression onset compared to euthymic periods would predict lower rate of recovery, more severe depressive symptoms and higher rate of switching into mania/hypomania after antidepressant treatment of bipolar depression.

1. Method

1.1. Study overview and participants

The STEP-BD was a double-blind, randomized controlled study of treatment via standard antidepressants as adjuncts to mood stabilizers. Inclusion criteria included age of at least 18 years old, being in treatment at one of 22 study sites in the United States and diagnosis of bipolar I, bipolar II, cyclothymia, bipolar disorder not otherwise specified, or schizoaffective disorder bipolar subtype (for more information, see Sachs et al., 2003).

The present analysis examined outcomes among the subset of participants who were randomly assigned to treatment during a major depressive episode. Treating psychiatrists could choose from three randomization strata (placebo vs. bupropion, placebo vs. paroxetine, and placebo vs. either antidepressant) as adjuncts to mood stabilizers (lithium, valproate, carbamazepine, or other FDA-approved antimanic agents) (Sachs et al., 2003, 2007). Previous STEP-BD publications have shown that antidepressants did not perform better than placebo in reducing depression regardless of bipolar subtype (Sachs et al., 2007).

1.2. Procedures and measures

The Affective Disorder Evaluation (ADE) interview and Mini-International Neuropsychiatric Interview (MINI) were administered at study entry to assess diagnosis. Both the ADE and MINI included assessment of lifetime and recent course of illness, including number of lifetime episodes, age of onset and previous episode status. Consensus diagnosis of bipolar disorder on both the MINI and ADE was required for study inclusion. The MINI has been shown to produce diagnoses concordant with those obtained using the SCID and has shown high inter-rater reliability, kappa above 0.75 (Sheehan et al., 1998).

At each follow-up visit, participants were assessed using Clinical Monitoring Form, a standardized, validated semi-structured interview, which includes subscales to evaluate depression (SUM-D) and mania severity (SUM-ME) and current medications (Sachs et al., 2002). SUM-D (range 0 to 22) and SUM-ME (range 0 to 16) subscales cover the DSM symptom criteria, and have shown robust correlations with the Montgomery-Asberg Depression Rating Scale (MADRS $r = 0.88$; Sachs et al., 2002) and the Young Mania Rating Scale (YMRS $r = 0.84$; Sachs et al., 2002), respectively.

The MADRS, a 10-item questionnaire (max score = 60) was used to assess depressive symptom severity at each three-month outcome point, and to check the validity of interview-based data (p.1032).

Recovery, as defined by STEP-BD and the NIMH Collaborative Depression Study, was operationalized as the presence of two or fewer present affective symptoms for at least 8 consecutive weeks (SUM-D <

3 & SUM-M < 3) (Perlis et al., 2006; Sachs et al., 2003). Switch into mania/hypomania was operationalized by the presence of three or more manic symptoms at any point within the 6-month follow-up period (SUM-M > 2).

1.3. Statistical analyses

Analyses were conducted to examine the effect of episode status before the depressive episode (manic/mixed vs. euthymic) on four outcomes: the degree of change in depressive symptoms at 3 and 6 months, the likelihood of recovery from depression and the likelihood of antidepressant-induced switching. All analyses considered the effects of bipolar diagnosis (Bipolar I versus other types) and medication (placebo, Paroxetine, Bupropion).

To assess degree of change, a two-way (previous episode status, medication) repeated measures analysis of variance (ANOVA) was conducted to assess change in depression symptoms from baseline to follow-up. Because fewer participants completed the 6-month follow-up, separate, parallel ANOVAs were conducted to examine the 3 versus 6-month follow-ups. To assess episode status as a predictor of recovery (yes/no) and switch into mania/hypomania, we conducted two separate binary regression models with Wald chi-square statistics accompanied by 95% confidence intervals (CIs). All statistical tests were two-tailed, with alpha = 0.05.

2. Results

Of the 366 participants randomized to treatment, 38 were excluded from all analyses for missing data, and 8 because their initial SUM-D score < 3, leaving 325 participants available for analyses (140 male). Relevant to the ANOVA analyses, 81 were missing MADRS scores at 3-month, and 32 more at 6-month follow-up. There were 272 participants available for binary regression analysis for switching into mania/hypomania episode. 104 (38.2%) of the participants were coded as switching into a manic or hypomanic episode during the first 6 months. See Table 1 for sample characteristics.

A two-way repeated measures analysis of variance (ANOVA) was conducted to evaluate episode status before the depressive episode (manic or mixed episode vs. euthymia preceding depression), Bipolar I status (Bipolar I versus other types) and medication as predictors of depression (MADRS) at 3 month as compared to baseline ($N = 244$). There was a significant effect of time on depression, $F (1, 232) = 19.880$, $p < .001$, $\eta_{p2} = 0.079$, indicating decline in depressive symptoms from baseline (M = 20.93, SD = 10.66) to 3 months (M = 17.03, SD = 10.72). Contrary to our hypothesis, previous episode status did not predict change in depressive symptoms in that the interaction of Previous episode status x Time was not significant, $F (1,$

Table 1
Clinical and demographic characteristics at study entry.

Variable	N	%
Previous mood state		
Manic or Mixed	147	45.2
Euthymic	176	54.2
Antidepressant medication		
Placebo	168	51.7
Paroxetine	82	25.2
Bupropion	75	23.1
Bipolar disorder diagnosis		
Bipolar I disorder	214	65.8
Bipolar II disorder	104	32.0
Bipolar NOS & Schizoaffective BP	7	2.1
Recovered		
Yes	237	74.1
Switch into a manic or hypomanic episode		
Yes	104	38.2

Table 2

Summary of logistic regression analysis for variables predicting recovery from bipolar depression (N = 320).

Predictor	B	SE B	OR	95% CI OR
Constant	−0.952	.448	.386*	
Medication status				
Paroxetine	.122	.310	1.130	(0.616–2.074)
Bupropion	.166	.321	1.181	(0.629–2.218)
Bipolar I vs. other subtypes	.452	.284	1.572	(0.902–2.741)
Manic/mixed episode before depression	−0.265	.261	.767	(0.460–1.278)
Block 2				
Manic or mixed episode preceding depression x Medication				
Manic or mixed episode preceding depression x Paroxetine	.717	.643	2.048	(0.580–7.229)
Manic or mixed episode preceding depression x Bupropion	.462	.655	1.588	(0.439–5.737)
Bipolar I x Medication				
Bipolar I x Paroxetine	.636	.737	1.889	(0.445–8.015)
Bipolar I x Bupropion	.221	.725	1.248	(0.301–5.169)
Bipolar I x Manic or mixed episode preceding depression	.661	.610	1.938	(0.587–6.402)
Block 3				
Bipolar I diagnosis x Manic/mixed episode before depression x Medication status				
Bipolar I by Manic or mixed episode preceding depression x Paroxetine	−1.856	1.552	.156	(0.007–3.275)
Bipolar I by Manic or mixed episode preceding depression x Bupropion	−1.336	1.524	.263	(0.013–5.214)

Note. *$p < .05$.
Block one: $chi^2 (4) = 3.989$, $p = 0.407$.
Block two: $chi^2 (9) = 7.946$, $p = 0.540$.
Block three: $chi^2 (11) = 9.649$, $p = 0.562$.

Table 3

Summary of logistic regression analysis for variables predicting switch into Mania/Hypomania (N = 272).

Predictor	B	SE B	OR	95% CI OR
Constant	−0.192	.441	.825	
Medication status				
Paroxetine	−0.290	.314	.748	(0.405–1.384)
Bupropion	.101	.308	1.106	(0.605–2.022)
Bipolar I vs. other subtypes	.212	.273	1.236	(0.724–2.110)
Manic/mixed episode before depression	−0.273	.256	.761	(0.461–1.258)
Block 2				
Manic or mixed episode preceding depression x Medication				
Manic or mixed episode preceding depression x Paroxetine	.062	.651	1.064	(0.297–3.809)
Manic or mixed episode preceding depression x Bupropion	.306	.626	1.358	(0.398–4.633)
Bipolar I x Medication				
Bipolar I x Paroxetine	−1.013	.685	.363	(0.095–1.391)
Bipolar I x Bupropion	−0.535	.677	.586	(0.155–2.208)
Bipolar I x Manic or mixed episode preceding depression	.209	.572	1.233	(0.402–3.781)
Block 3				
Bipolar I diagnosis x Manic/mixed episode before depression x Medication status				
Bipolar I by Manic or mixed episode preceding depression x Paroxetine	−1.669	1.444	.188	(0.011–3.195)
Bipolar I by Manic or mixed episode preceding depression x Bupropion	−1.208	1.393	.299	(0.019–4.585)

Note. *$p < .05$.
Block one: $chi^2 (4) = 2.939$, $p = 0.568$.
Block two: $chi^2 (9) = 5.614$, $p = 0.778$.
Block three: $chi^2 (11) = 7.203$, $p = 0.782$.

$232) = 0.0$, $p = .987$, $\eta_{p2} = 0.0$. As has been reported previously, the interaction of Time x Antidepressant was not significant, $F (2, 232) = 0.144$, $p = .866$, $\eta_{p2} = 0.001$, nor Time x Bipolar type, $F (1, 232) = 0.046$, $p = .831$, $\eta_{p2} = 0.0$ or Time x Previous episode status x Medication, $F (2, 232) = .306$, $p = .736$, $\eta_{p2} = 0.0$.

A parallel two-way repeated measures ANOVA was conducted to evaluate MADRS scores at 6-month follow-up as compared to baseline ($N = 213$). The results also indicated a significant effect of time on depression, $F (1, 201) = 19.516$, $p < .001$, $\eta_{p2} = 0.089$. Again, episode status did not predict change in symptoms, with no significant interactions observed of Time x Previous episode status, $F (1, 201) = 0.667$, $p = .415$, $\eta_{p2} = 0.003$, Time x Bipolar type, $F (1, 201) = 1.003$, $p = .318$, $\eta_{p2} = 0.005$, Time x Antidepressant, $F (2, 201) = 2.848$, $p = .060$, $\eta_{p2} = 0.028$, nor Time x Previous episode status x Antidepressant groups, $F (2, 201) = .214$, $p = .808$, $\eta p2 = .002$.

A logistic regression analysis was conducted to predict depression recovery using previous episode status, bipolar diagnosis and medication status, and their interactions, as predictors. Prediction success overall was 74.1% (100% for nonrecovery and 0% for recovery, $N = 320$). The main effects of the three predictors as a set did not significantly predict recovery, with a low effect size, Nagelkerke's $R^2 = 0.018$.

To predict antidepressant-induced switching to mania/hypomania, a parallel logistic regression analysis was conducted using bipolar diagnosis, previous episode status and medication status, and their interactions, as predictors. Prediction success overall was 61.8% (100% for no switch and 0% for switch, $N = 272$). The main effects of the three predictors as a set did not significantly predict antidepressant induced switching, with a low effect size, Nagelkerke's $R^2 = 0.015$.

3. Discussion

Findings of one previous study indicated that biphasic depressions, that is, depressions that occurred after mania, appeared less treatment-responsive (MacQueen et al., 2002). However, the Macqueen study, as well as one non-replication (Gitlin et al., 2003), used small samples. The present analysis had the advantage of a larger sample, random assignment to treatment, and long-term (6-month) follow-up. Despite the strengths of the study, presence or absence of a manic episode before depression in patients with bipolar disorder did not significantly predict response to antidepressants. We found this across four strong statistical tests examining 3-month follow-up, 6-month follow-up, odds of recovery and switch into mania/hypomania.

The lack of effect of manic symptoms on depression response fits with models that emphasize the differential processes involved in depression versus mania. That is, some have argued that mania and depression may operate separately for those with bipolar disorder, with differential predictors of the onset and offset of mania versus depression (Johnson and Kizer, 2002).

It is important to note several limitations. First, as is typical of medication studies in bipolar disorder, the high rate of attrition may have affected the results. Second, we were unable to consider other possible factors influencing recovery, such as life events or number of previous cycles. Third, current analyses only considered two antidepressant medications, and antidepressants may differ in their interactions with mania, as previous work indicates differential switch rates (Licht et al., 2008).

In summary, although one previous study noted robust effects, results from this study found no significant effects of manic or mixed episodes before a depressive episode on the rate and degree of recovery to antidepressant treatment among persons with bipolar depression. Future research would do well to consider other potential predictors of depressive course, such as the number of previous episodes, or the presence of rapid cycling.

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Author contribution

DL generated the hypothesis and provided background literature for the paper, ZM conducted literature review, SJ and ZM collaborated on analyses and writing, all edited and approved the manuscript.

Conflict of interest

None.

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