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# Transition to Mania During Treatment of Bipolar Depression

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Some individuals with bipolar disorder transition directly from major depressive episodes to manic, hypomanic, or mixed states during treatment, even in the absence of antidepressant treatment. Prevalence and risk factors associated with such transitions in clinical populations are not well established, and were examined in the Systematic Treatment Enhancement Program for Bipolar Disorder study, a longitudinal cohort study. Survival analysis was used to examine time to transition to mania, hypomania, or mixed state among 2166 bipolar I and II individuals in a major depressive episode. Cox regression was used to examine baseline clinical and sociodemographic features associated with hazard for such a direct transition. These features were also examined for interactive effects with antidepressant treatment. In total, 461/2166 subjects in a major depressive episode (21.3%) transitioned to a manic/hypomanic or mixed state before remission, including 289/1475 (19.6%) of those treated with antidepressants during the episode. Among the clinical features associated with greatest transition hazard were greater number of past depressive episodes, recent or lifetime rapid cycling, alcohol use disorder, previous suicide attempt, and history of switch while treated with antidepressants. Greater manic symptom severity was also associated with risk for manic transition among both antidepressant-treated and antidepressant-untreated individuals. Three features, history of suicide attempt, younger onset age, and bipolar subtype, exhibited differential effects between individuals treated with antidepressants and those who were not. These results indicate that certain clinical features may be associated with greater risk of transition from depression to manic or mixed states, but the majority of them are not specific to antidepressant-treated patients.

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> [W]e find in manic-depressive insanity a certain group of clinical manifestations that alternate, and we have no right to trace these endless varieties of the clinical pictures back to fundamentally different basic mechanisms. On the contrary, we should classify every single fragment of a clinical course into the broad frame of manic-depressive insanity. (Kraepelin E. Edition VI, pp 368–369)

## INTRODUCTION

Kraepelin (1899) noted that some individuals with bipolar disorder transition directly from depressive to manic or mixed states without an intervening period of euthymia. The extent of this risk has been difficult to quantify reliably and it is unclear what treatments or clinical features might increase this risk, though concern about inadvertently precipitating a manic episode may significantly influence the clinician behavior. Early studies suggested that monoaminergic antidepressants might increase the risk of transition to mania (Bunney *et al*, 1972, 1970), or accelerate the frequency of cycling (Wehr and Goodwin, 1987, 1979; Wehr *et al*, 1988). Older studies examining antidepressant-treated patients with bipolar disorder, which included subjects not treated with mood-stabilizing medication, suggested that a transition directly to mania was observed in up to 50% of the cases (for a synopsis see Calabrese *et al*, 1999). For second-generation antidepressants combined with mood stabilizers, a more recent large study suggested switch rates of 12–22% during acute treatment, depending on the definition of mania used (Altshuler *et al*, 2006; Leverich *et al*, 2006). In contrast, multiple recent

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randomized placebo-controlled trials indicate that the risk of transition during an acute treatment trial is less than 10% when antidepressants are combined with mood stabilizers—rates that are comparable to or lower than those found in placebo control conditions (Keck *et al*, 2005; Nemeroff *et al*, 2001; Sachs *et al*, 2007).

Recent investigations have focused on identifying features that may predict polarity transition risk specifically among antidepressant-treated patients. A secondary analysis of randomized data from the Stanley Foundation cohort ($n = 176$) found that the greater the number of manic symptoms manifest during a depressive episode, the more likely a bipolar patient is to become syndromally manic/hypomanic or mixed following antidepressant treatment (Frye *et al*, 2009), broadly consistent with a previous investigation (Goldberg *et al*, 2007). The Stanley Foundation study, however, did not examine a comparison group of subjects not treated with antidepressants, so the treatment specificity of risk could not be determined. That is, it could not determine whether the risk factors associated with transition were specific to antidepressant-treated patients or to bipolar patients as a whole. A recent statement by the International Society of Bipolar Disorders (ISBD) nomenclature task force emphasizes the importance of recognizing that transitions to mania, even those which occur within the first 8 weeks of treatment, do not necessarily represent treatment-induced phenomena (Tohen *et al*, 2009).

Thus, despite a wealth of previous investigation focused on the magnitude of risk specifically associated with antidepressants, three clinically relevant questions remain unanswered. First, what is the incidence of transition directly to manic/mixed/hypomanic states among depressed bipolar I and II patients in large clinical cohorts, rather than randomized clinical trials? Second, are there clinical and sociodemographic features that identify individuals at greatest risk for such transition? Third, if so, do particular risk factors pertain to all patients, or do they convey differential risk among antidepressant-treated patients? To address these questions, we examined outcomes during up to 2 years of follow-up in a large, naturalistic cohort study, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), conducted at multiple US sites. The broadly inclusive design of STEP-BD, incorporating minimal inclusion and exclusion criteria and allowing for any clinical interventions felt to be appropriate by the study clinician, provides a unique opportunity to address these clinically controversial aspects of illness course and treatment outcome.

## METHODS

### Study Overview

STEP-BD was a multicenter study, conducted in the US between 1999 and 2005, which evaluated prospective outcomes among individuals with bipolar disorder treated according to contemporary practice guidelines. Methods for the STEP-BD study as a whole are detailed elsewhere (Perlis *et al*, 2006; Sachs *et al*, 2003).

### Participants

Study participation was offered to all bipolar patients seeking outpatient treatment at any of the participating study sites. Entry criteria included meeting DSM-IV criteria for bipolar disorder I, II or not otherwise specified, cyclothymia, or schizoaffective disorder bipolar type, and ability to provide informed consent. (The present report includes only those with bipolar I and II disorder, because of its focus on transition from major depressive episodes to mania/hypomania). For individuals aged 15–17, a written assent was also required from the parents or guardian. Hospitalized individuals were eligible to enter this study following discharge.

### Assessments

Bipolar diagnosis was determined using mood and psychosis modules from the SCID as incorporated in the Affective Disorders Evaluation (ADE), and confirmed by a second clinical rater using the Mini International Neuropsychiatric Interview (MINI) (Sheehan *et al*, 1998). Comorbid axis I diagnoses were also determined using the MINI. At each visit, clinicians assigned current mood status on the basis of the Clinical Monitoring Form (Sachs *et al*, 2002), which assesses DSM-IV criteria for depressive, manic, hypomanic or mixed states in the prior 14 days. Each criterion is scored on a 0–2 scale, where 1 represents 'threshold' by DSM-IV mood episode criteria; fractional scores are used to indicate subthreshold symptoms. For example, a patient with insomnia less than half the time would receive a '0.5' rather than a '1' on the sleep item.

Additional details of patient retrospective course on entering STEP-BD were collected by the clinician on the ADE, including proportion of time in the preceding year with depressive, manic and anxious symptoms, as well as number of episodes of each type.

Rating scales for depressive and manic symptoms were completed at study entry, every 3 months for the first year, and every 6 months thereafter. Thus, in the present report these assessments were available only for the subset of patients in a major depressive episode at study entry. Depressive symptoms were quantified using the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), and manic symptoms using the Young Mania Rating Scale (YMRS; Young *et al*, 1978).

### Intervention

Study clinicians in STEP-BD were trained to use model practice procedures, which included published pharmacotherapy guidelines (Sachs *et al*, 2003), but they could prescribe any treatment, which they felt to be indicated, including psychosocial interventions. Elsewhere, we have reported high concordance between treatment selection and guideline recommendations, indicating that patients received standard-of-care treatment when entering STEP-BD (Dennehy *et al*, 2007).

### Outcomes

Because STEP-BD was intended to mimic clinical practice, participants were seen as frequently as clinically indicated.

The Clinical Monitoring Form (CMF) (Sachs *et al*, 2003), which includes a clinician-rated assessment of DSM-IV mood state criteria, was completed at each visit. At each visit, current medications and dosages were also recorded using the CMF. Remission was defined consistent with prior reports as at least 8 weeks of euthymia; consistent with standard DSM-IV criteria for partial or full remission and with criteria used in the earlier NIMH Collaborative Study of Depression (Keller *et al*, 1993), this was operationalized as two or fewer syndromal features of mania, hypomania or depression. Transition to mania was defined as transition to a DSM-IV-defined manic, hypomanic, or mixed state, as recorded on the CMF. (For consistency with the ISBD statement on antidepressant-associated mania, we refer throughout to 'transition to mania' rather than 'switch into manic, hypomanic, or mixed state', as we examined outcomes beyond the ISBD's 8-week threshold and did not focus on causation by antidepressants).

Syndromal rather than rating-scale based definitions were applied for consistency with the STEP-BD protocol and previous publications (Sachs *et al*, 2007). The relatively long intervals between collection of MADRS and YMRS (every 3 or 6 months, as above) precluded their application as outcome measures for this analysis, though they were include as potential predictors of outcome.

### Statistical Analysis

In total, 3640 subjects entered STEP-BD and returned for at least one follow-up visit, and 2166 were diagnosed with bipolar I or II, and had at least one prospectively observed depressive episode. Clinical details of the STEP-BD cohort have been described elsewhere (Perlis *et al*, 2009).

Primary analyses used survival analysis examining time from first visit at or after study entry at which subjects met DSM-IV criteria for a major depressive episode, until transition to mania. Data was censored after completion of 2 years of follow-up, last recorded visit, or achievement of remission and whichever came first. (A sensitivity analysis also examined the effects of censoring subjects who reached any period of euthymia, rather than remission. As these results were essentially the same as those for the primary outcome definition, they are not presented here). Baseline variables were examined using Cox regression after confirmation that the proportional hazards assumption was met by incorporating a variable-by-time term in regression models, and by visual inspection of hazard plots. All analyses were adjusted for site of participation, on the basis of the four largest STEP-BD sites. For socio-demographic and clinical features, Bonferroni corrected $p$-value $< 0.05$ (ie, uncorrected $p < 0.00167$ for $\sim 30$ comparisons) was considered to be statistically significant.

To examine heterogeneity of effects between individuals exposed to, or not exposed to, antidepressants, a Cox model was fit incorporating each predictor, as well as a term for antidepressant use at the previous visit, and the interaction of antidepressant use with the predictor being investigated. Where the term for treatment-group-by-predictor interaction was significant, indicating such heterogeneity, Cox regression models were fit separately for these two groups. All analyses were conducted using Stata 10.0 (College Station, TX).

## RESULTS

The full STEP-BD cohort included 3640 subjects with 48 287 follow-up visits; among these, 2166 (69.3% bipolar I, 59.3% female) experienced at least one major depressive episode and were considered in these analyses. In the depressed cohort, total follow-up was 13 406 visits, or 395 275 days: mean number of visits was 6.2, median 4; mean follow-up duration was 182.5 days, median 126.

We first investigated prevalence of manic transition and differences by treatment groups. During follow-up, 461/2166 subjects (21.3%) transitioned directly from depression to a manic ($n = 106$; 4.9%), hypomanic ($n = 185$; 8.5%), or mixed ($n = 170$; 7.8%) state without reaching remission; for these subjects, median time to transition was 74 (IQR 31–160) days after first observed depressive visit. These 461 included 289/1475 (19.6%) who transitioned among antidepressant-exposed subjects, and 172/691 (24.9%) among antidepressant-unexposed subjects. The cohort included 266 subjects (12.3%), who did not receive lithium, valproate, carbamazepine or an antipsychotic during the index episode—in this group, 25/105 (23.8%) antidepressant-unexposed subjects, and 23/161 (14.3%) of antidepressant-exposed subjects, experienced transition directly to mania/hypomania.

Next, we sought to identify general predictors of transition risk, independent of treatment type, among bipolar individuals. Results of Cox regression examining association of sociodemographic and clinical features with transition risk are summarized in Table 1. These features are sorted by magnitude of effect, in terms of hazard ratio, with greatest effect at the top. So, for example, individuals with rapid cycling were $\sim 44\%$ more likely to experience transition to mania. After Bonferroni correction, features significantly associated with greater hazard for transition included younger age, earlier age of illness onset, history of rapid cycling in the past year, history of suicide attempts and greater proportion of days elevated, irritable, or anxious in the past year. In a Cox regression model simultaneously incorporating all of these terms, all except proportion of days anxious and onset age remained nominally significantly associated with risk for transition. Incorporating overall clinician-rated severity at study entry and first depressed visit (in terms of CGI) did not meaningfully change individual results (results not shown).

As greater manic symptom severity during depressive episodes has been proposed as a predictor of risk (Frye *et al*, 2009), we next examined the risk associated with mania severity, and individual mania symptoms, based on the YMRS. As the YMRS was collected at study entry and quarterly follow-up, this analysis included only 1888/2166 (87.2%) subjects who were in a major depressive episode at study entry, but not the 278 (12.8%) who experienced onset during follow-up. As expected, greater baseline severity of manic symptoms, including individual items on the YMRS, was associated with significantly greater transition risk (Table 2). After adjusting for total YMRS severity, decrease in sleep was significantly associated with greater hazard for transition, as was greater insight (ie, lower score on the insight item). Using the alternative definition of transition to mania yielded essentially identical results in all cases (results not shown). An analysis of total MADRS score in

**Table 1** Hazard for Manic Transition Associated with Individual Sociodemographic and Clinical Features at Baseline

| Feature | Full cohort | | Interaction with antidepressant status |
|---|---|---|---|
| | HR | 95% CI | $p<0.05$ |
| Previous depressions, 2+ | 2.63 | 1.18–5.90 | |
| Rapid cycling, past year | 1.44 | 1.20–1.74** | |
| History of suicide attempt | 1.44 | 1.20–1.73** | # |
| Current alcohol use disorder | 1.40 | 1.07–1.81 | |
| Previous depressions, 3+ | 1.40 | 0.89–2.19 | |
| Rapid cycling, lifetime | 1.29 | 1.04–1.61 | |
| Current drug use disorder | 1.27 | 0.91–1.76 | |
| Gender: Male | 0.80 | 0.66–0.96 | |
| Antidepressant-associated 'switch' | 1.23 | 1.01–1.49 | |
| Race: Caucasian | 0.82 | 0.61–1.11 | |
| Graduated high school | 0.82 | 0.49–1.38 | |
| Age (per decade) | 0.82 | 0.76–0.89** | |
| Age at onset (per decade) | 0.82 | 0.73–0.92** | # |
| DSM–IV manic symptoms | 1.20 | 1.11–1.31** | |
| Subtype: bipolar I | 1.17 | 0.95–1.44 | # |
| Previous manias, 3+ | 1.15 | 0.84–1.56 | |
| CGI overall (study entry) | 1.15 | 1.06–1.24** | |
| Previous manias, 2+ | 1.14 | 0.76–1.70 | |
| Days elevated, past year (per 10%) | 1.12 | 1.07–1.16** | |
| DSM–IV depressive symptoms | 1.12 | 1.05–1.20** | |
| Polarity of onset: mania | 1.11 | 0.89–1.40 | |
| Any current anxiety disorder | 1.10 | 0.91–1.33 | |
| Employed | 0.91 | 0.75–1.10 | |
| CGI (1st depressed visit) | 1.09 | 0.98–1.22 | |
| Days irritable, previous year (per 10%) | 1.08 | 1.05–1.12** | |
| Married now | 1.07 | 0.88–1.30 | |
| Ethnicity: Hispanic | 0.94 | 0.59–1.51 | |
| Days anxious, past year (per 10%) | 1.04 | 1.02–1.07** | |
| Days depressed, past year (per 10%) | 1.02 | 0.99–1.05 | |

Abbreviations: 95% CI, confidence interval around hazard ratio; HR, hazard ratio.
**Significant at Bonferroni-corrected $p<0.05$.
#$p$-value of test for predictor-by-antidepressant treatment status interaction $<0.05$.

**Table 2** Hazard for Manic Transition Associated with Rating Scale Scores at First Depressed Visit

| Feature | Full cohort | | Interaction with antidepressant status |
|---|---|---|---|
| | HR | 95% CI | $p<0.05$ |
| Elevated mood | 1.13 | 0.94–1.35 | |
| Increased motor | 1.13 | 0.97–1.32 | |
| Sexual interest | 1.03 | 0.82–1.30 | |
| Amount of sleep | 1.16 | 1.02–1.34* | |
| Irritability | 1.07 | 0.97–1.17 | |
| Speech | 1.02 | 0.92–1.12 | |
| Language | 1.01 | 0.84–1.20 | |
| Thought content | 1.07 | 0.98–1.17 | |
| Disruptive behavior | 1.05 | 0.94–1.16 | # |
| Appearance | 1.01 | 0.83–1.24 | |
| Insight | 0.42 | 0.19–0.94* | |
| YMRS total score | 1.06 | 1.04–1.08* | |
| MADRS total score | 1.06 | 1.04–1.09* | |

Abbreviations: CI, 95% confidence interval around hazard ratio; HR, hazard ratio.
*Significant at uncorrected $p<0.05$.
#$p$-value of test for predictor-by-antidepressant treatment status interaction $<0.05$.
Items on Young Mania Rating Scale are listed in the order they appear on the scale.

this cohort likewise indicated greater severity to be associated with greater transition risk.

We then explored whether any of clinical features were associated with differential risk for antidepressant-exposed *vs*—unexposed subjects—that is, we sought to identify predictor-by-treatment status interactions. Additional columns in Tables 1 and 2 indicate the significance of a test for such an interaction; where this interaction was statistically significant, hazard ratios by treatment status are presented in Table 3. The interaction term was significant for two predictors demonstrating effects in the full cohort: onset-age and history of suicide attempt. For onset age (in decades), the hazard ratio was 0.91 (0.79–1.04) among antidepressant-exposed patients, and 0.67 (0.53–0.84) among antidepressant-unexposed patients—ie, the hazard appeared to be present solely or largely among untreated patients. For lifetime suicide attempts, the hazard ratio was 1.69 (1.34–2.13) among antidepressant-exposed patients, and 1.07 (0.79–1.46) among antidepressant-unexposed patients—ie, the hazard was present among antidepressant-treated patients. A third predictor, which did not demonstrate significant effects in the full cohort did demonstrate differential effects depending on antidepressant exposure: bipolar I subtype was associated with numerically greater risk (a result which was not statistically significant) among antidepressant-exposed patients, but not among antidepressant-unexposed patients.

Table 2 reports the same analysis for individual YMRS items, and for YMRS and MADRS total scores. Significant interaction between manic symptoms and treatment status (ie, antidepressant or no antidepressant) was identified only for disruptive behavior, suggesting that in general the association with greater hazard of transition to mania is not a treatment-specific phenomenon.

## DISCUSSION

In this analysis of prospective data from more than 2100 bipolar I and II patients followed for up to 2 years, transition from depression directly to manic, hypomanic or mixed states was common, observed in 21.3% of individuals prospectively observed for a single episode. This incidence is broadly similar to that observed in other longitudinal

**Table 3** Hazard for Manic Transition Associated with Individual Sociodemographic and Clinical Features at Baseline: Predictor-by-Treatment-Interactions

| Feature | Full cohort | | AD exposure (+) | | AD exposure (−) | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Subtype: Bipolar I | 1.17 | 0.95–1.44 | 1.28 | 0.98–1.67 | 0.84 | 0.60–1.18 |
| History of suicide attempt | 1.44 | 1.20–1.73[a] | 1.69 | 1.34–2.13 | 1.07 | 0.79–1.46 |
| Age at onset (per decade) | 0.82 | 0.73–0.92[a] | 0.91 | 0.79–1.04 | 0.67 | 0.53–0.84 |
| YMRS: Disruptive behavior | 1.05 | 0.94–1.16 | 1.12 | 0.99–1.25 | 0.86 | 0.69–1.07 |

Abbreviation: YMRS: Young Mania Rating Scale.
[a]Bonferroni-corrected $p<0.05$ (for full cohort only).

studies such as the Stanley Foundation cohort (Frye *et al*, 2009; Leverich *et al*, 2006) when that study examined postacute treatment outcomes. Not surprisingly, rates were about twice than those observed in randomized, placebo-controlled studies (Keck *et al*, 2005; Nemeroff *et al*, 2001; Sachs *et al*, 2007), which considered only short-term transition to mania.

We also sought to extend previous reports of association between manic symptom severity and risk for transition to mania (Frye *et al*, 2009), or greater manic symptomatology (Goldberg *et al*, 2007). In a recent report, Frye and colleagues examined outcomes among 176 antidepressant-treated depressed bipolar patients randomized to one of three antidepressants. Risk factors for transition to mania included greater total YMRS at study entry, with greatest risk associated with motor activation, pressured speech, and racing thoughts (Frye *et al*, 2009). In a similar vein, we had previously reported a subset of 445 STEP-BD subjects with bipolar I, II, or NOS, where an interaction was noted between number of threshold or subthreshold manic symptoms, and antidepressant cotreatment in YMRS mania severity at 3 months (Goldberg *et al*, 2007). However, the interaction noted there was far from straightforward: subjects with 3+ manic symptoms at entry who received antidepressants actually had numerically lower YMRS scores at 3 months, whereas those with 0 manic symptoms who received antidepressants had numerically greater scores; moreover, differences in transition to mania were not examined.

In this study, which was intended to address a different question and explicitly considered manic/hypomanic transition, we examined a substantially larger cohort with longer-term follow-up. As expected, we found that individuals with more manic symptoms at entry (ie, closer to being syndromally manic or mixed) are in general at greater risk for syndromal manic, hypomanic, or mixed states during treatment. Importantly, we found that these predictors were not specific to antidepressant-treated patients—regardless of antidepressant treatment status, for each 1-point increase in YMRS score, hazard for manic transition increased by ~6%. Whether higher-risk individuals might benefit from, for example, closer monitoring or greater antimanic prophylaxis awaits further investigation. Based on our results, however, it cannot be concluded that individuals with greater subthreshold manic severity should not receive antidepressants, as these individuals appear to be at elevated risk, which is independent of, and not increased by, treatment status.

From a clinical perspective, our results do offer a number of illness features to consider in stratifying risk for transition to mania or hypomania beyond current symptomatology. When overall magnitude of effect is considered, a history of a greater number of previous depressive episodes, previous suicide attempt, and current or lifetime rapid cycling may all be indicative of greater risk. As we previously reported (Ostacher *et al*, 2010), current substance use disorder, particularly alcohol abuse, also appears to be associated with greater risk. Other predictors, while of lesser absolute magnitude, may also merit consideration, such as earlier age at illness onset, and younger age overall.

Several previous studies investigated clinical predictors of switch risk. In one, risk factors among 416 bipolar patients included older age, absence of delusions, depressive onset, fewer manic episodes, and bipolar I subtype (Serretti *et al*, 2003). In a matched case–control study including 24 patients, risk factors included being older and having a longer duration of illness and more previous episodes (Tamada *et al*, 2004). A meta-analysis of both major depressive disorder and bipolar disorder studies suggested greater risk among bipolar I than bipolar II patients (Bond *et al*, 2008).

Taking these studies together, the most consistent predictor identified has been bipolar I status (Bond *et al*, 2008, Serretti *et al*, 2003); although we identified a numerically greater risk in this group (HR 1.17, 95% CI 0.95–1.45), it did not reach statistical significance. Identification of a statistically significant treatment-by-predictor interaction suggested that, among antidepressant-treated but not -untreated patients, bipolar 1 status is associated with greater switch risk. Still, caution is warranted in interpreting this finding, as confidence intervals for both antidepressant-treated and untreated patients cross one, indicating that we cannot exclude the possibility of no effect in either group. Among other previously reported risk factors, for age, we observed greatest risk among younger rather than older patients, in contrast to some prior descriptions (Serretti *et al*, 2003; Tamada *et al*, 2004).

We examined predictor-by-treatment effects in an effort to understand which predictors might be specific to antidepressant-treated patients. This analysis is noteworthy primarily for a relative paucity of effects: that is, most of the predictors we identify appear to have similar effects regardless of antidepressant treatment status. Notable

exceptions are lifetime history of suicide attempt and the disruptive behavior item on the YMRS, which, like bipolar I status, are associated with significantly greater switch risk only among antidepressant-treated patients. History of suicide attempt may represent a marker for impulsivity or affective instability, which might be exacerbated by antidepressant use. Emergence of disruptive behavior may likewise indicate an underlying diathesis. On the other hand, earlier illness onset appears to confer risk primarily among antidepressant-unexposed patients, which is difficult to interpret, but could suggest that antidepressants actually help to neutralize an underlying vulnerability among early-onset bipolar patients. If confirmed in future investigations, these features may be useful in identifying individuals at particularly high risk of manic transition with antidepressant treatment.

From a broader perspective, our finding underscore that risk of transition from depression directly to manic/mixed states is a characteristic of the disorder itself, and thus may not always be directly related to antidepressant treatment. The finding that such transitions is common even in the absence of antidepressant treatment is entirely consistent with original descriptions of bipolar disorder in the modern era (Kraepelin, 1899), but in no way detracts from the seminal studies which established that, in some cases, antidepressants may be associated with elevated switch or cycling risk, particularly in the absence of antimanic treatment (Bunney *et al*, 1972, 1970; Wehr and Goodwin, 1987, 1979; Wehr *et al*, 1988).

Still, a central problem in interpreting clinical outcomes in psychiatry is the potential logical fallacy of '*post hoc*, ergo propter hoc' (after this, therefore because of this): it is assumed that when a phenomenon follows the initiation of a treatment, that phenomenon is precipitated by the treatment. Kraepelin observed 'spontaneous' transition to mania during depressive episodes in some patients, more than 50 years before the introduction of antidepressant medications. Spontaneous transitions could explain reports of mania being precipitated by agents subsequently shown to be potent antimanic treatments (Rachid *et al*, 2004). Given the likelihood of medication changes during mood episodes in bipolar disorder, and the relatively high incidence of transition directly to mania without intervening recovery, it follows that some medication changes will often precede emergence of mania, but may not directly contribute to it.

We emphasize that this analysis is not intended to address the absolute increase in risk, if any, associated with antidepressant treatment, because of the substantial risk of confounding-by-indication. In other words, requirement for an antidepressant could be a marker for more severe illness course, which could lead us to conclude falsely that antidepressants increase risk. (In fact, in absolute terms, fewer subjects experienced transition to mania/hypomania among the antidepressant-exposed group). To confidently assess the risk associated with antidepressant use, randomized, double-blind, placebo-controlled trials are necessary. Of note, such trials consistently indicate risks equivalent to placebo when antidepressants are given in conjunction with antimanic treatments (Nemeroff *et al*, 2001; Sachs *et al*, 2007; Tohen *et al*, 2003). Similarly, risk for confounding precludes drawing conclusions about the impact of co-treatments such as antimanic agents. Instead, we sought to identify risk factors in the STEP-BD cohort as a whole, which might be independent of treatment, then explored potential interactive effects with treatment.

In summary, our results suggest that transition directly to mania during major depressive episodes in bipolar disorder is common and associated with defined risk factors beyond subthreshold manic/mixed symptoms and substance use disorders (Frye *et al*, 2009; Goldberg *et al*, 2007). The majority of these appear to be treatment nonspecific, however, rather than tied to antidepressant treatment *per se*. All bipolar patients merit close follow-up during treatment of depressive episodes.

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## DISCLOSURE

Dr Perlis has received research support from Eli Lilly, Elan/Eisai; Advisory/Consulting fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Pfizer; Speaking Fees or Honoraria from AstraZeneca, Bristol-Myers Squibb Company, Eli Lilly, GlaxoSmithkline, Pfizer; and has Equity Holdings and Patents for Concordant Rater Systems.

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