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Abstract

Aims: Antidepressant use is common in bipolar disorder (BD), but controversial due to questionable efficacy/psychiatric tolerability. We assessed associations between baseline antidepressant use and longitudinal depressive burden in BD. Methods: Stanford BD Clinic outpatients enrolled during 2000-2011 were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation and monitored longitudinally for up to two years with the STEP-BD Clinical Monitoring Form while receiving naturalistic expert treatment. Prevalence and clinical correlates of baseline antidepressant use in recovered (euthymic ≥8 weeks) and depressed patients were assessed. Kaplan-Meier survival analyses assessed times to depressive recurrence and recovery in patients with versus without baseline antidepressant use, and Cox Proportional Hazard regression analyses assessed covariate effects. Results: Baseline antidepressant use was less among 105 recovered (31.4%) versus 153 depressed (44.4%) patients (p=0.04), and among recovered patients was associated with Caucasian race, and higher rates of lifetime anxiety and eating disorders, and bipolar II disorder, earlier onset age, and worse Clinical Global Impression scores, and hastened depressive recurrence (only if mood elevation episodes were not censored), driven by lifetime anxiety disorder. Baseline antidepressant use among depressed patients was associated with older age, female gender, and higher anxiolytic and complex pharmacotherapy use rates, but no other unfavorable illness characteristic/current mood symptom, and not time to depressive recovery. Limitations: American tertiary BD clinic referral sample receiving open naturalistic expert treatment. Conclusions: Additional research is required to assess the complex associations between baseline antidepressant use and longitudinal depressive burden in BD.

Keywords	bipolar disorder; antidepressant; longitudinal; depression; illness characteristics

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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
The data that has been used is confidential

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Editor, Journal of Affective Disorders

Dear Editor,

We would like to submit for your consideration the enclosed manuscript "Antidepressants Have Complex Associations with Longitudinal Depressive Burden in Bipolar Disorder" for publication as an original article in the *Journal of Affective Disorders.* This manuscript is not under consideration by any other journal.

Although the role of antidepressants in bipolar disorder has been an ongoing controversy, longitudinal studies of this issue are very limited. We believe that our observed association between baseline antidepressant use and hastened depressive recurrence only if mood elevation episodes are *not* censored is noteworthy, consistent with the complexity of the relationship between baseline antidepressant use and longitudinal depressive burden in patients with bipolar disorder. We believe that the relationship between baseline antidepressant use and hastened depressive recurrence emphasizes the need to further our understanding of the role of baseline antidepressant use in bipolar disorder longitudinal depressive burden.

All authors have made substantial contributions to conception and design or analysis and interpretation of data, and substantial contributions to drafting the article or revising it critically for important intellectual content, have given final approval of the version submitted, and have approved transfer of copyright of this work.

Disclosures for the last 36 months are as follows: Drs. Hooshmand, Gershon, Park, and Wang as well as Dennis Do, Saloni Shah, and Laura Yuen report no financial relationships with commercial interests. Dr. Dell'Osso has received grant/research support from Cyberonics, Inc. and AstraZeneca and Lundbeck and Lecture Honoraria from AstraZeneca and Lundbeck. Dr. Miller has received grant/research support from Merck and Company and Sunovion, Inc. Dr. Ketter has received grant/research support from the Agency for Healthcare Research and Quality, AstraZeneca Pharmaceuticals LP, Cephalon Inc., Eli Lilly and Company, National Institute of Mental Health, Pfizer Inc., and Sunovion Pharmaceuticals; Consultant Fees from Allergan, Inc., Avanir Pharmaceuticals, Bristol-Myers Squibb Company, Cephalon Inc., Forest Pharmaceuticals, Janssen Pharmaceutical Products, LP, Merck & Co., Inc., Neurocrine Biosciences, Sunovion Pharmaceuticals, and Teva Pharmaceuticals; Lecture Honoraria from Abbott Laboratories, Inc., AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, and Otsuka Pharmaceuticals; and Publication Royalties from American Psychiatric Publishing, Inc. In addition, Dr. Ketter's spouse is a former employee of and still holds stock in Janssen Pharmaceuticals. In addition, Dr. Ketter's spouse is an employee of and holds stock in Janssen Pharmaceuticals.

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This article will likely be of considerable interest to readers of the *Journal*. I hope you find it appropriate for publication, and I look forward to hearing from you.

Sincerely,

Terence Ketter, MD

Highlights

Antidepressant use in Bipolar Depression is controversial

Antidepressants in Bipolar Depression can yield treatment-emergent manic switch (TEAMS)

Baseline antidepressant use was associated with TEAMS only if manic prior to depressive episodes were *not* censored

Thus, antidepressants have complex associations with longitudinal depressive burden in bipolar disorder

Aims: Antidepressant use is common in bipolar disorder (BD), but controversial due to questionable efficacy/psychiatric tolerability. We assessed associations between baseline antidepressant use and longitudinal depressive burden in BD.

Methods: Stanford BD Clinic outpatients enrolled during 2000-2011 were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation and monitored longitudinally for up to two years with the STEP-BD Clinical Monitoring Form while receiving naturalistic expert treatment. Prevalence and clinical correlates of baseline antidepressant use in recovered (euthymic ≥8 weeks) and depressed patients were assessed. Kaplan-Meier survival analyses assessed times to depressive recurrence and recovery in patients with versus without baseline antidepressant use, and Cox Proportional Hazard regression analyses assessed covariate effects.

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Limitations: American tertiary BD clinic referral sample receiving open naturalistic expert treatment.

Conclusions: Additional research is required to assess the complex associations between baseline antidepressant use and longitudinal depressive burden in BD.

Antidepressants Have Complex Associations with Longitudinal Depressive Burden in Bipolar Disorder

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Disclosure of Financial Relationships (past 36 months)

Drs. Hooshmand, Gershon, Park, and Wang as well as Dennis Do, Saloni Shah, and Laura Yuen report no financial relationships with commercial interests. Dr. Dell'Osso has received grant/research support from Cyberonics, Inc. and AstraZeneca and Lundbeck and Lecture Honoraria from AstraZeneca and Lundbeck. Dr. Miller has received grant/research support from Merck and Company and Sunovion, Inc. Dr. Ketter has received grant/research support from the Agency for Healthcare Research and Quality, AstraZeneca Pharmaceuticals LP, Cephalon Inc., Eli Lilly and Company, National Institute of Mental Health, Pfizer Inc., and Sunovion Pharmaceuticals; Consultant Fees from Allergan, Inc., Avanir Pharmaceuticals, Bristol-Myers Squibb Company, Cephalon Inc., Forest Pharmaceuticals, Janssen Pharmaceutical Products, LP, Merck & Co., Inc., Sunovion Pharmaceuticals, and Teva Pharmaceuticals; Lecture Honoraria from Abbott Laboratories, Inc., AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, and Otsuka Pharmaceuticals; and Publication Royalties from American Psychiatric Publishing, Inc. In addition, Dr. Ketter's spouse is an employee of and holds stock in Janssen Pharmaceuticals.

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Limitations: American tertiary BD clinic referral sample receiving open naturalistic expert treatment.

Conclusions: Additional research is required to assess the complex associations between baseline antidepressant use and longitudinal depressive burden in BD.

Keywords: bipolar disorder; antidepressant; longitudinal; depression; illness characteristics.

Introduction

Although antidepressants (with the exception of fluoxetine combined with olanzapine) are not FDA approved for treatment of bipolar disorder (BD) (Ketter, 2015), they have been among the most common medications prescribed for treatment of BD, used twice as often as mood stabilizers (Baldessarini et al., 2007). The wide use of antidepressants in BD could be due to unmet pharmacological needs in treatment of depressive morbidity in BD (Frye et al., 2009; Goldberg, 2012; Kasper et al., 2008), as well as tolerability limitations of the three FDA-approved bipolar depression treatments, all of which have an antipsychotic component (Ketter, 2015; McIntyre et al., 2013).

Multiple previous studies do not support the efficacy of antidepressants in treatment of acute bipolar depression (Bauer et al., 2012; McElroy et al., 2010; Sachs et al., 2007; Sidor & Macqueen, 2011), and antidepressant monotherapy (i.e. without an antimanic agent) is commonly considered contraindicated in bipolar I disorder patients as well as certain bipolar II disorder patients due to concerns for increased risk of mood elevation and/or rapid cycling (Frye et al., 2009; Pacchiarotti et al., 2013; Prien et al., 1984; Vieta, 2005). Attributing the direction of causality between antidepressant use and emergence of hypomanic, manic, and mixed states, rapid cycling, and depression itself remains controversial because of the highly variable natural course of BD which makes it difficult to distinguish spontaneous from antidepressant-induced mood changes (Licht et al., 2008) and associations of mixed and rapid cycling presentations with treatment-resistant depression which could itself result in antidepressant administration.

Although available data support faster short-term recovery from depression with the olanzapine-fluoxetine combination (Tohen et al., 2003), other studies show highly variable acute and longer-term effects when antidepressants are used (either as monotherapy or in combination with mood stabilizers) for the treatment of bipolar depression (Altshuler et al., 2017; Ghaemi et al., 2008; Goldberg et al., 2007; McElroy et al., 2010; Sachs et al., 2007; Sidor & Macqueen, 2011).

Data on the efficacy and tolerability of long-term use of antidepressants in BD are inadequate, with some (but not all) studies suggesting that adjunctive antidepressant use is associated with increased switch to mania/hypomania and only variable protection from depression (Amsterdam et al., 2015; Ghaemi et al., 2008). Other studies have reported increased depressive recurrence with longer-term antidepressant treatment (Ghaemi et al., 2004; Sachs et al., 2007). In contrast, one observational study found that among the limited percentage (approximately 15%) of BD patients who initially uneventfully (i.e., without emergence of mood elevation symptoms) remitted from a major depressive episode while taking antidepressants added to mood stabilizers, those who continued compared to those who discontinued antidepressants within 6 months of remission had an approximately 50% lower rate of depressive recurrence (Altshuler et al., 2003; Amsterdam et al., 2015; Pacchiarotti et al., 2013). Indeed, although the International Society for BD guidelines for the short-term treatment of bipolar depression appear clinically useful, the potential role of antidepressants in the longer-term management of BD remains to be established (Tundo et al., 2015).

In summary, the association between antidepressant use and illness course remains controversial in BD. In this prospective study, we examined longitudinal relationships

between baseline antidepressant use and episode recurrence and recovery in BD patients.

Methods

Outpatients referred to the Stanford BD Clinic from 2000 to 2011 were assessed using the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation (Sachs et al., 2002; Sachs et al., 2003), which included the Structured Clinical Interview for the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (SCID for DSM-IV) (First et al., 1997) mood disorders module and the Clinical Global Impression for BD-Overall Severity (CGI-BP-OS) score (Spearing et al., 1997). The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was also performed in order to confirm bipolar and comorbid psychiatric disorder diagnoses. Patients were followed prospectively for up to two years, while receiving naturalistic expert-administered treatment with a monthly modal visit frequency. The Clinical Monitoring Form (CMF) (Sachs et al., 2002) was used to assess clinical status at each follow-up visit.

Current (baseline) medication use was based upon patient report and review of medical records at the time of enrollment. Antidepressants included Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), Atypical Antidepressants (AAs, e.g., bupropion, mirtazapine), and First-Generation Antidepressants (FGAs, e.g., heterocyclic antidepressants, monoamine oxidase inhibitors). Mood stabilizers included lithium, valproate, carbamazepine, and lamotrigine. Antipsychotics included the Second-Generation agents olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole. Anxiolytic/hypnotics included benzodiazepine and non-benzodiazepine agents administered for anxiety (e.g., lorazepam, clonazepam, alprazolam, and buspirone) and/or insomnia (e.g., temazepam, zolpidem, and trazodone).

As described below, clinical characteristics of participants were evaluated and prospective clinical course of participants meeting diagnostic criteria for either current recovery (euthymic ≥ 8 weeks) or a current major depressive episode at enrollment were assessed for the primary analyses. Secondary analyses included assessment of participants experiencing a current manic/hypomanic/mixed episode. The Stanford University Administrative Panel on Human Subjects approved the STEP-BD protocol, as well as the subsequent similar Assessment, Monitoring, and Centralized Database protocol specific to Stanford University. Both protocols conformed to the standards of the Helsinki Declaration as revised in 1989, and all subjects provided verbal and written informed consent before participating in the study.

Trained medical and research staff collected data on 6 demographic parameters and 25 illness characteristics/current mood symptoms/current (baseline) medications. The demographic parameters assessed were: (A) Age (in years); (B) Gender; (C) Race/Ethnicity; (D) Education; (E) Marital Status; and (F) Employment status. The illness characteristics/current mood symptoms/current (baseline) medications assessed were: (1) Lifetime anxiety disorder; (2) Lifetime alcohol/substance use disorder; (3) Lifetime eating disorder; (4) Lifetime personality disorder; (5) Bipolar II Disorder; (5A) Lifetime psychosis (which is very commonly associated with Bipolar I Disorder); (5B) Lifetime prior psychiatric hospitalization (which is also very commonly associated with Bipolar I Disorder); (6) ≥ One first-degree relative with mood disorder; (7) Onset age (in years); (8) Childhood (age < 13 years) onset; (9) Illness duration (in years); (10) Long illness duration (≥ 15 years); (11) Episode accumulation (≥ 10 prior mood episodes); (12) Lifetime suicide attempt; (13) Rapid cycling (≥ 4 episodes) in prior year; (14) current CGI-BP-OS; current (i.e., any in the prior 10 days); (15) Sadness; (16) Anhedonia; (17) Euphoria; (18) Irritability; and (19) Anxiety; and current (baseline) (20) Mood stabilizer use; (21) Antipsychotic use; (22)

Antidepressant use; (23) Anxiolytic/Hypnotic use; (24) Complex Pharmacotherapy (≥ 4 mood stabilizers, antipsychotics or antidepressants); and (25) Number of Core Psychotropics (mood stabilizers, antipsychotics, antidepressants).

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 23.0 software (IBM Corp.; Armonk, NY) on an Apple MacBook Air computer (Apple Corporation, Cupertino, CA). Prevalence and clinical correlates of baseline antidepressant use were examined in currently recovered (i.e., euthymic ≥ 8 weeks) and currently depressed (i.e., with a current major depressive episode) patients, as well as patients experiencing a current mood elevation (manic/hypomanic/mixed) episode. Analytical statistics included Fisher's Exact test comparisons of categorical data and independent-sample t-test comparisons of continuous variables. In addition, binary logistic regression was used to adjust for potential confounding variables.

Primary longitudinal analyses consisted of Kaplan-Meier survival analyses (Log-Rank tests), which compared times to depressive recurrence and recovery in patients with and without baseline antidepressant use. We used for the primary recurrence analyses the novel approaches of not censoring patients with mood elevation episode prior to depressive episode recurrence in assessing time to depressive recurrence, and not censoring patients with depressive episode prior to mood elevation episode recurrence in assessing time to mood elevation recurrence, and for secondary recurrence analyses the more conventional approaches of censoring patients with mood elevation prior to depressive recurrence in assessing time to depressive recurrence, and censoring patients with depressive prior to mood elevation recurrence in assessing time to mood elevation recurrence (Tohen et al., 1990). We used for the primary recovery analyses the novel approaches of not censoring patients with mood elevation episode prior to depressive episode

recovery in assessing time to depressive episode recovery, and not censoring patients with depressive episode prior to mood elevation episode recovery in assessing time to mood elevation recovery, and for secondary analysis, the more conventional approaches of censoring patients with mood elevation episode prior to depressive episode recovery in assessing time to depressive recovery, and censoring patients with depressive episode prior to mood elevation episode recovery in assessing time to mood elevation recovery. Secondary metrics included for baseline antidepressant use and depressive longitudinal severity were Kaplan-Meier estimated recurrence/recovery rates for significant longitudinal depressive associations. Additional secondary analyses included Cox proportional hazard analyses (hazard ratios (HRs) and 95% confidence intervals (CIs)) of depressive recurrence and recovery, as well as of potential mediators of statistically significant longitudinal depressive illness severity findings. To select parameters for entry into mediator models, univariate Cox proportional hazard analyses were performed for all statistically significant clinical correlates of current antidepressant use. Parameters with $p < 0.05$ were entered into a forward stepwise procedure, and covariates were included in the model if $p < 0.05$. Additionally, Cox proportional hazard analyses with time-dependent covariates were used to further characterize associations between current antidepressant use and depressive recurrence and recovery. Finally, among recovered patients, we assessed changes from baseline to depressive recurrence/endpoint (last visit if no recurrence) in antidepressant status (i.e. numbers of patients continuing same antidepressants, switching antidepressants, and discontinuing antidepressants). Throughout analyses, we used a two-tailed significance threshold with $p < 0.05$, with no correction for multiple comparisons.

Results

Table 1 includes demographics, illness characteristics, current mood symptoms, and baseline medications in currently recovered and currently depressed BD outpatients, stratified by the presence or absence of baseline antidepressant use. In our overall sample of 503 outpatients with bipolar I disorder or bipolar II disorder, 105 (20.9%) were currently recovered and 153 (30.4%) were currently depressed. The prevalence of baseline antidepressant use was significantly lower among recovered versus depressed (31.4% versus 44.4%, Chi-square = 4.4, df = 1, p = 0.04) patients.

Demographics and Illness Characteristics/Current Mood Symptoms/Baseline Medications in Recovered Patients With Versus Without Baseline Antidepressant Use.

Among recovered patients, presence compared to absence of baseline antidepressant use was significantly less common by more than one-half (31.4% versus 68.6% were and were not currently taking antidepressants, respectively, Binomial test p = 0.0002). Indeed, recovered patients with versus without baseline antidepressant use had significantly higher rates of Caucasian race (90.9% versus 69.4%, Chi-square = 5.3, df = 1, p = 0.02), lifetime anxiety (69.7% versus 36.1%, Chi-square = 10.3, df = 1, p = 0.002), and eating (21.2% versus 4.2%, Chi-square = 7.6, df = 1, p = 0.01) disorders, bipolar II disorder (57.6% versus 30.6%, Chi-square = 6.9, df = 1, p = 0.01), and baseline antidepressant use (by definition, 100.0% versus 0.0%, Chi-square = 105.0, df = 1, p < 0.0001), as well as significantly lower mean ± SD onset age (16.9 ± 8.3 versus 20.6 ± 9.0, t = -2.0, df = 102, p = 0.046), and significantly higher CGI-BP-OS scores (2.4 ± 0.8 versus 2.1 ± 0.8, t = 2.3, df = 103, p = 0.02), and number of core psychotropics used (partially by definition, 2.4 ± 0.8 versus 1.3 ± 0.8, t = 6.5, df = 103, p < 0.0001). Although baseline antidepressant use was inversely associated with history of psychiatric hospitalization (24.2%

versus 56.9%, Chi-square = 9.7, df = 1, p = 0.003) rate, this relationship was mediated by the association of bipolar I subtype with history of psychiatric hospitalization. All of the above-mentioned significant relationships between baseline antidepressant use and other illness characteristics/current mood symptoms/baseline medications in recovered patients remained significant after covarying for race. No other demographic parameter and no other clinical characteristic in Table 1 was significantly associated with baseline antidepressant use among recovered patients.

INSERT TABLE 1 ABOUT HERE

Demographics and Illness Characteristics/Current Mood Symptoms/Baseline Medications in Depressed Patients With Versus Without Baseline Antidepressant Use.

Among currently depressed patients, presence compared to absence of baseline antidepressant use was only non-significantly less common (44.4% versus 55.6% had and lacked baseline antidepressant use, respectively, Binomial test p = 0.20). Nevertheless, baseline antidepressant use was significantly associated with a higher mean ± SD age (38.8 ± 13.7 versus 34.1 ± 12.8, t = 2.2, df = 151, p = 0.03) and rate of female gender (72.1% versus 52.9%, Chi – square = 5.8, df=1, p = 0.02), as well as significantly higher rates of baseline antidepressant (by definition, 100.0% versus 0.0%, Chi-Square = 153.0), df = 1, p < 0.0001), anxiolytic/hypnotic (50.2% versus 22.4%, Chi-square = 12.8, df=1, p = 0.0006), and complex pharmacotherapy (partially by definition, 42.6% versus 17.6%, Chi-square = 18.6, df=1, p < 0.0001) use, as well as more core psychotropics used (partially by definition, 2.3 ± 1.1 versus 1.1 ± 1.1, t = 6.7, df = 151, p < 0.0001). No other demographic parameter and no illness characteristic in Table 1 was

significantly associated with baseline antidepressant use among depressed patients. Higher rates of baseline anxiolytic/hypnotic and complex pharmacotherapy use in depressed patients with versus without baseline antidepressant use were driven by age, but not by gender. In contrast, no demographic drove the higher number of core psychotropics in patients with versus without baseline antidepressant use. No illness characteristic drove higher rates of anxiolytic or complex pharmacotherapy use, or higher number of core psychotropics in depressed patients with versus without baseline antidepressant use.}

Baseline Antidepressant Use in Relationship to Time to Recurrence.

Baseline antidepressant use was significantly associated with hastened depressive recurrence (Log-Rank p = 0.033) in 33 vs. 72 recovered patients with versus without baseline antidepressant use, only if the 3 (9.1%) versus 16 (22.2%) with mood elevation episodes prior to depressive episode recurrence were not censored (Figure 1). Indeed, censoring patients with mood elevation episodes prior to depressive episode recurrence reduced the relationship between baseline antidepressant use and hastened depressive recurrence to a trend-level (Log-Rank p = 0.08).

Insert Figure 1 About Here

Baseline antidepressant use was also associated with hastened depressive recurrence using Cox Proportional Hazard analysis (HR = 1.9; 95% CI 1.0-3.5; p = 0.036), once again only if mood elevation episode prior to depressive episode recurrence were not censored. Hastened depressive recurrence among patients with baseline antidepressant use was driven by lifetime

anxiety disorder (HR = 2.8; 95% CI 1.4 - 5.4; p = 0.003). However, the Kaplan-Meier estimated depressive recurrence rate was only non-significantly higher among patients with (70.3%; 95% CI 52.5 - 88.1) compared to without (42.7%; 95% CI 28.8 - 56.6) baseline antidepressant use.

In contrast, baseline antidepressant use only non-significantly tended to be associated with time to mood elevation recurrence (Log-Rank p > 0.05 and < 0.10) in 33 vs. 72 recovered patients with versus without baseline antidepressant use, whether or not depressive episodes were censored (not illustrated). Also, baseline antidepressant use was not significantly associated with time to any mood episode recurrence (Log-Rank p = 0.70) in 33 vs. 72 recovered patients with versus without baseline antidepressant use (not illustrated).

Among recovered patients taking baseline antidepressants with (N = 24) versus without (N = 9) antimanic (second-generation antipsychotics, lithium, valproate, and carbamazepine (but NOT lamotrigine)) agents, times to depressive (with or without censoring prior mood elevation episodes) and mood elevation (with or without censoring prior depressive episodes) recurrence were not significantly different.

Baseline Antidepressant Use in Relationship to Time to Recovery.

Baseline antidepressant use was not significantly related to time to recovery whether or not opposite pole mood episode prior to recovery was censored in 68 vs. 85 depressed patients with versus without baseline antidepressant use, and in 13 versus 41 manic/hypomanic/mixed patients with versus without baseline antidepressant use (not illustrated). Also, times to recovery from any mood episode, in 81 versus 126 syndromal mood episode patients with versus without baseline antidepressant use were not significantly different (not illustrated).

Among patients taking baseline antidepressants with versus without antimanic agents, times to recovery from depression (N = 45 and 23, respectively; with or without censoring mood elevation) and from mood elevation (N =12 and 1, respectively; with or without censoring depression) were not significantly different (not illustrated). Also, among patients taking baseline antidepressants with (N = 57) versus without (N = 24) antimanic agents, times to recovery from any mood episode (without censoring mood elevation or depression prior to recovery) were not significantly different (not illustrated).

Antidepressant Changes in Recovered Patients With and Without Depressive Recurrence.

Among recovered patients taking baseline antidepressants with depressive recurrence (20/33, 60.6%), longitudinal antidepressant use included: continuation of same antidepressant (14/20, 70.0%), discontinuation of antidepressant (5/20, 25%), and switch to a different antidepressant (1/20, 5.0%). Of note, among 5/20 (25%) recovered patients taking antidepressants with a depressive recurrence who had a mood elevation episode prior to the depressive episode; continuation of same antidepressant was observed in 3/5 (60.0%), while antidepressant was discontinued in 2 (40.0%) of these patients. Among recovered patients taking antidepressants without depressive recurrence (13/33, 39.4%), longitudinal antidepressant use included: continuation of same antidepressant (10/13, 76.9%) and switch to a different antidepressant (3/13, 23.1%).

Discussion

We found that among recovered patients, baseline antidepressant use was significantly associated with Caucasian race, lifetime anxiety and eating disorders, bipolar II disorder, worse CGI score, lower onset age, more core psychotropic use, and hastened depressive recurrence (only if prior mood elevation episodes were not censored); driven by lifetime anxiety disorder. Baseline antidepressant use only non-significantly tended to be associated with time to mood elevation recurrence (whether or not depressive episodes were censored). Also, baseline antidepressant use with or without antimanic agents yielded no significant difference in times to recurrence of depression and mood elevation (with or without censoring mood elevation episodes and depressive episodes, respectively). In addition, baseline antidepressant use (with or without antimanic agents) was not significantly associated with time to recovery from depressive or manic/hypomanic/mixed or any mood episode.

Our finding of hastened depressive recurrence among recovered patients taking antidepressants is novel. Although antidepressant use has previously been associated with moderately reduced risk of depressive recurrence (Ghaemi et al.; 2008), it has also been associated with increased risk of switch to mania/hypomania. However, antidepressant use has not previously been significantly associated with hastened depressive recurrence (Amsterdam et al.; 2015,Ghaemi et al.; 2008, Pacchiarotti et al., 2013; Sidor & Macqueen, 2011; Truman et al., 2007 or Bowden et al. 2011), although discontinuation of antidepressants soon after remission has been related to increased depressive recurrence in the 15% of BD patients with very good acute antidepressant responses (Altshuler et al., 2003).

Furthermore, we found that lifetime anxiety disorder, which has been associated with greater risk of depressive recurrence (Perlis et al., 2006; Shah et al., 2017) was a driver of hastened depressive recurrence in patients taking baseline antidepressants. Also, our finding of hastened depressive recurrence in patients taking baseline antidepressants was significant only if prior mood elevation episodes were not censored, highlighting the importance of assessing causality in the relationship between antidepressant use and the risk of mood elevation after depression (Pacchiatotti et al., 2013).

In our study, antidepressant use (with or without anti-manic agents) was only non-significantly associated with mood elevation recurrence despite the previously observed increase in risk of mania related to antidepressant use (Ghaemi et al., 2008). However, available data on association of antidepressant mood switches into manic/hypomanic/mixed states remains highly variable which might be related to use of different definitions of switching (e.g., YMRS (Young Mania Rating Scale) score greater than 8 versus 15) in different studies (Calabrese et al. 1999), differences in switch rates in bipolar I disorder versus bipolar II disorder (Amsterdam et al., 2015, Bond et al., 2008), use of different classes of antidepressants (Post et al. 2001; Vieta et al. 2002), and difficulty in distinguishing spontaneous from antidepressant induced switching (Licht et al., 2008). In our study, antidepressants were used more frequently in depressed than recovered patients and in recovered patients with certain unfavorable illness characteristics (e.g., earlier onset age and worse CGI score), highlighting the need for greater understanding of how more severe BD with worse long-term outcomes could result in antidepressant use.

In contrast, in our study, current antidepressant use was not significantly associated with time to depressive recovery, potentially consistent with the previously observed lack of efficacy of antidepressants for acute treatment of bipolar depression (Sidor & Macqueen, 2011). Except for acute use of the combination of olanzapine/fluoxetine, which is FDA-approved for treatment of acute bipolar depression (Tohen et al. 2003), and a systematic review and meta-analysis of 12 randomized controlled trials published by Gijsman and colleagues in 2004 (which was substantially influenced by the above study) that showed antidepressants were efficacious and safe for treatment of bipolar depression, most controlled studies suggest antidepressants lack efficacy for acute treatment of bipolar depression (Sachs et al. 2007; Sidor & Macqueen, 2011). This may be even more the case for mixed bipolar depression. Indeed, among STEP-BD patients with mixed depression, adjunctive antidepressant treatment neither hastened nor slowed depressive recovery (Goldberg et al. 2007). Nevertheless, in a recent reanalysis of STEP-BD data by Tada, et al. in 2015, using higher doses of antidepressants added to mood stabilizers yielded greater clinical improvement without increasing risk of switch to mania, pointing to the need for further research into the potential utility of antidepressants for bipolar depression (Tada et al., 2015).

We found that antidepressant administration was related to 5 illness characteristics (lifetime anxiety disorder, lifetime eating disorder, bipolar II disorder, earlier onset age, and worse CGI-BP-OS) among recovered patients, but none among depressed patients. This difference was consistent with the notion that administration of antidepressants to recovered versus depressed BD patients may entail more potential illness characteristic

confounds/mediators. Indeed, we found that lifetime anxiety disorder drove hastened depressive recurrence among recovered patients with baseline antidepressant use.

Our study has the strengths of assessing relationships between current antidepressant use and not only hastened depressive recurrence but also delayed depressive recovery, using validated instruments to assess diagnosis and longitudinal course, and having substantial numbers of both well-characterized recovered (N = 105) and depressed (N = 153) BD patients. Furthermore, our rates of depressive recurrence and recovery were comparable to those found in other studies (Vazquez et al. 2015; Otto et al. 2006; Perlis et al. 2006). However, these strengths are accompanied by limitations that include the use of a sample referred to a suburban Northern California BD specialty clinic, limiting the generalizability of our findings in our relatively affluent, well educated but relatively underemployed, predominantly female sample of BD patients with medical insurance, rather than a more heterogeneous mixture of BD inpatients and outpatients being treated in non-specialty clinical settings. Additionally, our sample size, though substantial, had insufficient statistical power to be able to adequately assess relationships between baseline antidepressant use and times to mood elevation recurrence/recovery. In addition, our significant finding of current antidepressant use hastening depressive recurrence could be related to subsequent mood elevation episodes leading to depression, as our significant finding became only a trend when patients with prior manic, hypomanic, and mixed episodes were censored. Additional limitations included: (1) medications being changed during treatment (although our calculations indicated effects of this phenomenon were likely limited); (2) not being able to determine causality regarding the association of antidepressant administration with hastened depressive recurrence (i.e., whether antidepressant administration directly hastened

depressive recurrence, or depression/anxiety prone illness resulted in both hastened depressive recurrence and antidepressant administration, although we hypothesize the latter); (3) potentially heterogeneous reasons for antidepressant administration (e.g., for anxiety versus depression); (4) among recovered patients, we didn't know whether or not antidepressants yielded recovery from the most recent depressive episode or antidepressant withdrawal yielded depressive recurrence; (5) the controversial phenomenon of antidepressant treatment emergent mood elevation was beyond the scope of this paper. Furthermore, mood episode/recovered status duration prior to enrollment was not included in our analyses of mood episode recurrence and recovery. Another limitation was the open naturalistic treatment design, in which patients received diverse uncontrolled (albeit expert-selected, guideline-informed, measurement- and evidence-based) therapies. Finally, we did not correct for multiple comparisons, which particularly limited interpretation of findings with p-values between 0.05 and 0.01. However, this liberal statistical approach increased assay sensitivity with respect to our ability to detect relationships between baseline antidepressant use and depressive recurrence and recovery.

Nevertheless, we contend that our observation of an association between baseline antidepressant use and hastened depressive recurrence suggests an important relationship between baseline antidepressant use and longitudinal depressive burden in BD. Given the commonly inadequate outcomes associated with bipolar depression and antidepressant use, further examination of this relationship is warranted in order to better understand mechanisms and clinical implications.

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Figure Legend

Figure 1. Baseline Antidepressant Use Associated with Hastened Depressive Recurrence in Bipolar Disorder.

Two-year survival analysis of time to depressive recurrence in recovered bipolar disorder patients indicated significantly hastened depressive recurrence in patients with (N = 33, black line on bottom) versus without (N = 72, gray line on top) current antidepressant use (Log-Rank p = 0.033), only if the 3 (9.1%) versus 16 (22.2%) patients with mood elevation episodes prior to depressive episode recurrence were not censored. Baseline antidepressant use was also associated with hastened depressive recurrence using Cox Proportional Hazard analysis (HR = 1.9; 95% CI 1.0-3.5; p = 0.036), once again only if mood elevation episode prior to depressive recurrence were not censored. Hastened depressive recurrence among patients with baseline antidepressant use was driven by lifetime anxiety disorder (HR = 2.8; 95% CI 1.4 - 5.4; p = 0.003).

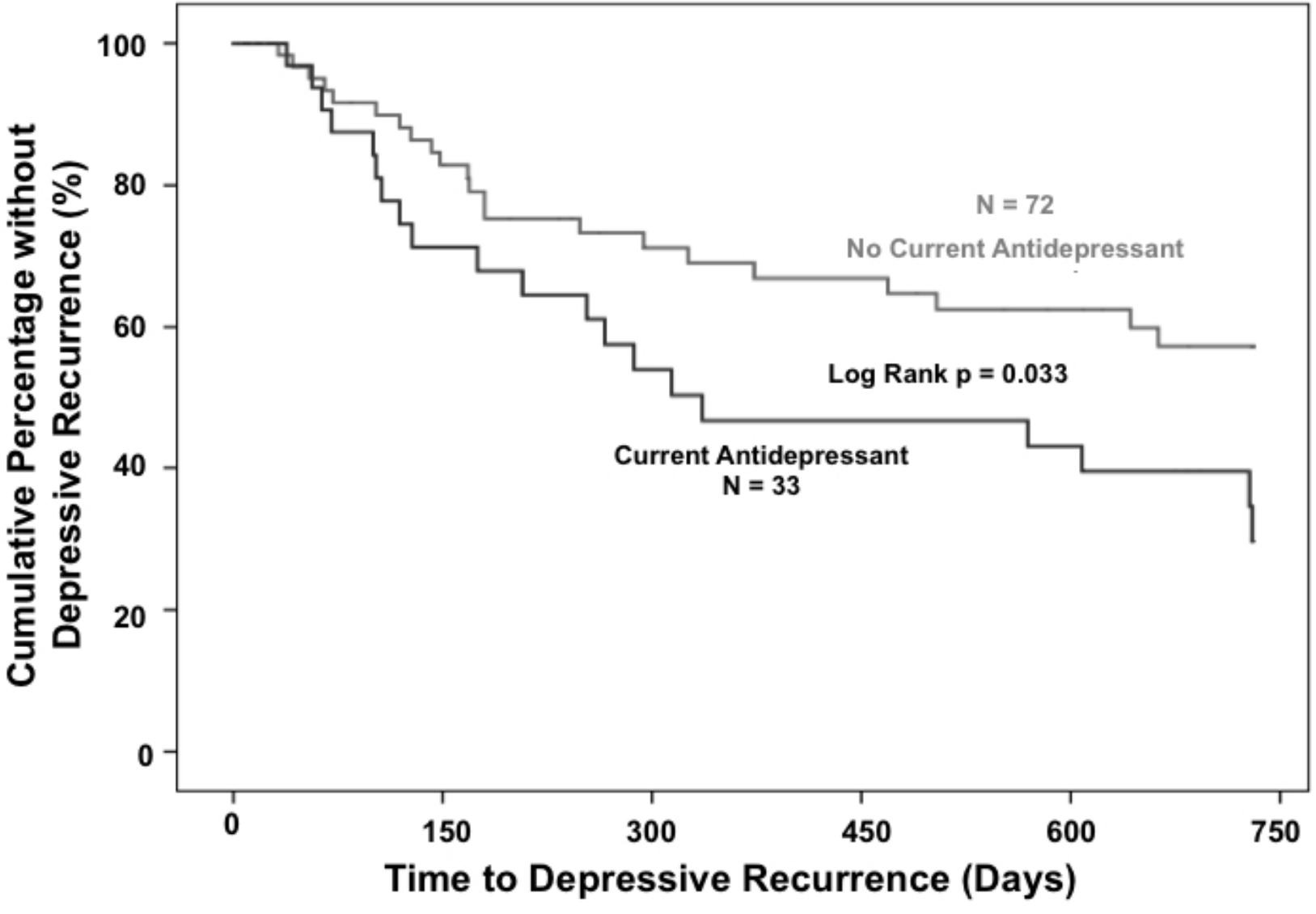
Cumulative Percentage without Depressive Recurrence (%)
100
80
60
40
20
0
N = 72
No Current Antidepressant
Log Rank p = 0.033
Current Antidepressant
N = 33
0
150
300
450
600
750
Time to Depressive Recurrence (Days)

Table 1. Demographics, Illness Characteristics, Current Mood Symptoms, and Baseline Medications in Currently Recovered and Currently Depressed BD Outpatients With Versus Without Baseline Antidepressant Use.

	Recovered w AD	Recovered w/o AD	Depressed w AD	Depressed w/o AD
N (%)	**33 (31.4)^*** **	72 (68.6)	**68 (44.4)**	85 (55.6)
Demographics				
A. Age (years, mean ± SD)	37.0±13.1	35.7 ± 14.0	**38.8 ± 13.7***	34.1 ± 12.8
B. Female (%)	60.6	52.8	**72.1***	52.9
C. Caucasian (%)	**90.9***	69.4	92.6	82.4
D. College degree (%)	69.7	61.1	55.9	40.0
E. Married (current, %)	33.3	37.5	39.7	35.3
F. Full time Employment (current, %)	24.2	37.5	22.1	28.6
Comorbid Disorders (lifetime, %)				
1. Anxiety	**69.7****	36.1	72.1	81.2
2. Alcohol/Substance Use	51.5	50.0	57.4	58.8
3. Eating	**21.2***	4.2	17.6	20.0
4. Personality	9.1	8.3	11.8	16.5
Other Illness Characteristics				
5. Bipolar II disorder (%)	**57.6***	30.6	67.6	56.5
5A. Psychosis (lifetime, %)	*33.3*	*52.8*	*38.2*	*34.1*
5B. Psychiatric Hospitalization (lifetime, %)	*24.2***	*56.9*	*27.9*	*24.7*
6. ≥ One 1° Relative w Mood Disorder (%)	60.6	40.3	63.2	56.5
7. Onset age (years, mean ± SD)	**16.9± 8.3***	20.6 ± 9.0	18.0 ± 8.7	16.4 ± 6.9
8. Childhood (age <13 years) Onset (%)	18.2	8.3	22.1	23.5
9. Illness Duration (years, mean ± SD)	16.6 ± 11.3	17.8 ± 14.4	20.4 ± 13.9	17.4 ± 12.4
10. Long Illness Duration (≥ 15 years, %)	54.5	43.1	56.7	50.6
11. Episode accumulation (≥ 10, lifetime, %)	57.6	38.9	72.7	71.1
12. Suicide Attempt (lifetime, %)	33.3	22.2	40.3	29.4
13. Rapid Cycling (≥ 4 episodes in prior year, %)	6.1	11.1	26.9	31.0
14. CGI-BP-OS (current, mean ± SD)	**2.4 ± 0.8***	2.1 ± 0.8	5.4 ± 0.8	5.3 ± 0.7
Mood Symptoms (any in prior 10 days, %)				
15. Sadness	21.2	18.1	91.2	88.2
16. Anhedonia	15.2	13.9	95.6	94.1
17. Euphoria	21.2	9.7	29.4	27.1
18. Irritability	42.4	33.3	63.2	72.9
19. Anxiety	45.5	31.9	80.9	81.2
Medication Use (current)				
20. Mood Stabilizer (MS, %)	75.8	72.2	67.647	55.300
21. Antipsychotic (AP, %)	39.4	34.7	39.706	30.600
22. Antidepressant (AD, %)	**100.0****	0.0	**100.0****	0.0
23. Anxiolytic/Hypnotic (AN, %)	21.2	15.3	**50.0*****	22.4
25. Complex Pharmacotherapy (≥ 4 MS, AP, AD, %)	24.2	16.7	**42.6*****	17.6

Commented [1]: .024
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Commented [10]: .001
Commented [11]: .001

26. Number of Core Psychotropics (MS, AP, AD, mean ± SD)	**2.4 ± 0.8******	1.3 ± 0.8	**2.3 ± 1.1******	1.1 ± 1.1	

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AD indicates baseline Antidepressant use; CGI-BP-OS indicates Clinical Global Impression for Bipolar Disorder-Overall Severity; SD indicates standard deviation; w indicates with; w/o indicates without.

Boldface font indicates parameters with statistically significant relationships with current antidepressant use not dependent on bipolar subtype. *Italic* font indicates parameter related to bipolar I disorder

Missing data: Recovered: 12.4% for ≥ 10 prior episodes, 0.0%-4.8% for other parameters; Depressed: 7.2% for ≥ 10 prior episodes, 0.0%-1.3% for other parameters.

^ p <0.05 Recovered w AD vs Depressed w AD.

* p <0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001 w vs w/o AD.

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