Differential prevalence and demographic and clinical correlates of antidepressant use in American bipolar I versus bipolar II disorder patients

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Abstract

Aims

Antidepressant use is controversial in bipolar disorder (BD) due to questionable efficacy/psychiatric tolerability. We assessed demographic/clinical characteristics of baseline antidepressant use in BD patients.

Methods

Prevalence and correlates of baseline antidepressant use in 503 BD I and BD II outpatients referred to the Stanford Bipolar Clinic during 2000–2011 were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation.

Results

Antidepressant use was 39.0%, overall, and was higher in BD II versus BD I (46.9% versus 30.5%, $p = 0.0002$). Both BD I and BD II antidepressant compared to non-antidepressant users had higher rates of complex pharmacotherapy (≥ 4 mood stabilizers, antipsychotics, and/or antidepressants) and use of other psychotropics. Antidepressant use in BD II versus BD I was higher during euthymia (44.0% vs. 28.0%) and subsyndromal symptoms (56.1% vs. 28.6%), but not depression or mood elevation.

Limitations

American tertiary BD clinic referral sample receiving open naturalistic treatment.

Conclusions

In our sample, antidepressant use was higher in BD II versus BD I patients, and was associated with markers of heightened illness severity in both BD I and BD II patients. Additional research is warranted to investigate these complex relationships.

Keywords

Bipolar disorderAntidepressant Illness characteristics

1. Introduction

The use of antidepressants in the treatment of bipolar disorder (BD) is a subject of considerable controversy. Data on the efficacy and safety of antidepressants both in acute and long term treatment of BD are commonly variable (Bowden et al., 2012, Sachs et al., 2007, Sidor and Macqueen, 2011, Pacchiarotti et al., 2013). Indeed, an International Society for Bipolar Disorders task force concluded that evidence is lacking to support definitive consensus recommendations on the use of antidepressants in BD, yet cautious antidepressant use may be appropriate for certain BD patients (Pacchiarotti et al., 2013). Nevertheless, despite concerns of mood instability and hypomania/mania associated with antidepressant use (El-Mallakh et al., 2015) and lack of robust efficacy data for treatment of bipolar depression with antidepressants (Sidor and Macqueen, 2011), antidepressants have been the most common medications used in the treatment of BD (Baldessarini et al., 2007). This may be due to unmet pharmacological needs in the 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, Mclntyre et al., 2013).

Research regarding the use of antidepressants in BD has focused more on treatment of bipolar I disorder (BD I) patients (Tohen at al, 2003), leaving questions regarding antidepressant use in bipolar II disorder (BD II) patients (Amsterdam and Brunswick, 2003). The risk of antidepressant associated mood elevation may be lower in BD II versus BD I (Bond et al., 2008, Vohringer et al., 2015); however, the data on effectiveness of antidepressants in BD II are limited and conflicting (Amsterdam et al., 2015, Gijsman et al., 2004, Sidor and Macqueen, 2011). Some data indicate higher rates of treatment-emergent antidepressant switching in BD II versus unipolar major depressive disorder (Peet, 1994) and in BD I versus BDII (Altshuler et al., 2006; Bond et al., 2008; Vasquez et al., 2011; Vohringer et al., 2015), and that antimanic agents may attenuate this risk (Tondo et al., 2010; Pacchiarotti et al., 2011). Few studies have compared BD I versus BD II patients with respect to clinical correlates of antidepressant use (Undurraga et al., 2012, Lorenzo et al., 2012, Vohringer et al., 2015). Understanding the demographic and illness characteristics associated with antidepressant use in BD I versus BD II patients could improve our understanding of how and when antidepressants are used for treatment of BD in clinical practice.

In this paper, we examined prevalence, and demographic and clinical correlates of antidepressant use in BD I versus BD II patients in a tertiary BD outpatient clinic.

2. Methods

We included outpatients with BD I or BD II referred by community practitioners (primarily psychiatrists) to the Stanford University BD Clinic between 2000 and 2011. Patients were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation (Sachs et al., 2003), which included the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (First et al., 1996) mood disorders module and Clinical Global Impression-Bipolar Version-Overall Severity (CGI-BP-OS) score (Spearing et al., 1997). The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was used to confirm bipolar and comorbid psychiatric disorder diagnosis.

Bipolar disorder subtype (BD II vs. BD I) was determined from available medical records and patient and in most cases significant other report, as assessed by the STEP-BD Affective Disorders Evaluation and MINI. Current mood symptoms were determined from patient report, as assessed by the STEP-BD Affective Disorders Evaluation at the time of enrollment, and clinician observation and reflected any mood symptoms in the 10 days prior to enrollment. Current psychotropic medication use was based upon patient report, as assessed by the STEP-BD Affective Disorders Evaluation, and review of medical

records at the time of enrollment. Antidepressants included Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), Atypical Antidepressants (e.g., bupropion, mirtazapine), and First-Generation Antidepressants (e.g., heterocyclic antidepressants, monoamine oxidase inhibitors).

As described below, demographic and clinical characteristics of participants were evaluated. The STEP-BD protocol and the subsequent similar Stanford-specific Assessment, Monitoring, and Centralized Database protocol were approved by the Stanford University Administrative Panel on Human Subjects, and patients provided verbal and written informed consent prior to participation. Trained medical and research staff collected data on six demographic parameters and 25 illness characteristics/current mood symptoms/current psychotropic medications. The demographic parameters assessed were (A) Age (in years); (B) Gender; (C) Race/Ethnicity; (D) Education; (E) Marital Status; and (F) Employment status. Illness characteristics/current mood symptoms/current psychotropic medications assessed were (1) lifetime anxiety disorder; (2) lifetime alcohol/substance use disorder; (3) lifetime eating disorder; (4) lifetime personality disorder; (5) bipolar disorder subtype (BD I versus BD II); (5A) lifetime psychosis (which is very commonly associated with BD I); (5B) lifetime prior psychiatric hospitalization (which is also very commonly associated with BD I); (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 (MS, lithium, valproate, carbamazepine, and/or lamotrigine) use; (21) antipsychotic (AP) use; (22) antidepressant (AD) use; (23) anxiolytic/hypnotic (AN) use; (24) complex pharmacotherapy (≥ 4 MS, AP, or AD); and (25) number of core psychotropics (MS, AP, or AD).

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 23.0 software (IBM Corp.; Armonk, NY, USA) on an Apple MacBook Air computer (Apple Corporation, Cupertino, CA, USA). Prevalence and clinical correlates of baseline antidepressant use stratified by bipolar subtype were examined. 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. Results were presented both with and without Bonferroni adjustment for multiple comparisons, with significance thresholds of $p < 0.0007$ (based on 70 comparisons) and $p < 0.05$, respectively.

3. Results

3.1. Overall demographics and illness characteristics

Table 1 includes demographics, illness characteristics, and current mood symptoms/psychotropic medications of BD patients with and without current antidepressant use stratified by bipolar subtype. Among 503 bipolar disorder outpatients referred to the Stanford University Bipolar Disorder Clinic, 243 (48.3%) had BD I and 260 (51.7%) had BD II. Data were missing for 10.5% of patients with respect to having had at least 10 prior mood episodes, but only for 0.0–6.0% for each of the other individual parameters in Table 1. Among all patients, mean ± SD age was 35.6 ± 13.1 years, 58.3% were female, mean bipolar illness duration was 17.7 ± 13.1 years, current mean CGI-BP-OS score was 3.9 ± 1.5, and current mean number of core psychotropics (MS, AP, AD) was 2.3 ± 1.6.

Table 1. Demographics and Illness Characteristics in BD Patients With Versus Without Antidepressant Use.

	BP I	BP I	BP II

	w/ AD	w/o AD	w/ AD
N (%)	**74 (30.5)****	169 (69.5)	122 (4
Demographics			
A. Age (years, mean ± SD)	35.1±12.8	35.0 ± 13.4	**38.4 ±**
B. Female (%)	59.5	51.5	68.0
C. Caucasian (%) (	**85.1***	71.6	85.2
D. College degree (%)	32.4	30.0	**23.0***
E. Married (current, %)	36.5	33.1	40.2
F. Full time Employment (current, %)	32.4	25.4	32.0
Comorbid Disorders (lifetime, %)			
1. Anxiety	63.5	56.2	76.2
2. Alcohol/Substance Use	85.1	74.6	75.4
3. Eating	**23.0***	10.1	18.0
4. Personality	9.5	6.5	16.4
Other Illness Characteristics			
5. Bipolar II disorder (%)	0.0	0.0	100.0
5A. Psychosis (lifetime, %)	64.9	64.0	13.1
5B. Psychiatric Hospitalization (lifetime, %)	63.5	69.8	11.5
6. ≥ One 1° Relative w Mood Disorder (%)	**66.2****	46.2	62.3
7. Onset age (years, mean ± SD)	18.4 ± 8.2	19.1 ± 8.1	17.1 ±
8. Childhood (age <13 years) Onset (%)	21.6	20.7	32.8
9. Illness Duration (years, mean ± SD)	16.8 ± 12.8	15.9 ± 13.1	**21.1 ±**
10. Long Illness Duration (≥ 15 years, %)	43.1	36.4	**61.2***
11. Episode accumulation (≥ 10, lifetime, %)	58.2	47.8	80.7
12. Suicide Attempt (lifetime, %)	**47.3*****	24.9	31.2
13. Rapid Cycling (≥ 4 episodes in prior year, %)	18.9	10.1	27.0
14. CGI-BP-OS (current, mean ± SD)	**4.0 ± 1.5***	3.5 ± 1.6	4.0 ± 1
Mood Symptoms (any in prior 10 days, %)			
15. Sadness	29.7	19.5	33.6
16. Anhedonia	**44.6****	24.8	**42.6***
17. Euphoria	21.6	21.9	16.4
18. Irritability	28.4	40.2	**40.2****
19. Anxiety	59.5	53.8	72.1
Medication Use (current)			
20. Mood Stabilizer (MS, %)	83.7	89.3	**68.9***
21. Antipsychotic (AP, %)	54.1	51.5	27.0
22. Antidepressant (AD, %)	100.0	0.0	100.0
23. Anxiolytic/Hypnotic (AN, %)	9.5	5.9	10.7
25. Complex Pharmacotherapy (≥ 4 MS, AP, AD, %)	**50.0****	21.9	**45.1****
26. Number of Core Psychotropics (MS, AP, AD, mean ± SD)	**3.7 ± 1.6****	2.3 ± 1.4	**3.5 ± 1**

CGI-BP-OS indicates Clinical Global Impression for Bipolar Disorder-Overall Severity; SD indicates standard deviation; w indicates with; wo indicates without.

Boldface font indicates parameters with statistically significant relationships with antidepressant use.

Missing data: 10.5% for ≥ 10 prior episodes, 0.0–6.0% for other parameters.

*

$p < 0.05$.

**

$p < 0.01$.

***
$p < 0.001$.
****
$p < 0.0001$ for those taking versus not taking antidepressants.

3.2. Prevalence and demographic and clinical characteristics of patients with current antidepressant use, stratified by bipolar subtype

A description of overall prevalence and demographics and illness characteristics of BD patients in the sample taking and not taking at least one antidepressant, stratified by bipolar subtype, is shown in Table 1. The overall rate of current antidepressant use was 196/503 (39.0%). 137 patients (27.2% of all patients, 69.9% of patients with current antidepressant use) took antidepressants in combination with at least one antimanic agent (i.e. lithium, valproate, carbamazepine, and/or antipsychotic).

Among BD I patients, baseline antidepressant users compared to nonusers were fewer (30.5% vs. 69.5%, Chi-square = 74.3, df = 1, $p < 0.0001$); whereas in BD II patients, there was no significant difference between percentages of (baseline antidepressant users and nonusers (46.9% vs. 53.1%)). Indeed, BD II patients compared to BD I patients were significantly more often taking baseline antidepressant (46.9% vs. 30.5%, Chi-square = 14.3, df = 1, $p = 0.0002$) (Fig. 1). In contrast BD I compared to BD II patients were significantly more often taking baseline antipsychotics (50.0% versus 28.3%, Chi-square = 25.9, df = 1, $p < 0.0001$), mood stabilizers (76.1% versus 59.6%, Chi-square = 15.6, df = 1, $p < 0.0001$), and valproate (35.9% versus 11.3%, Chi-square = 43.0, df = 1, $p < 0.0001$) (not illustrated). All of these findings retained statistical significance after adjusting for multiple comparisons.

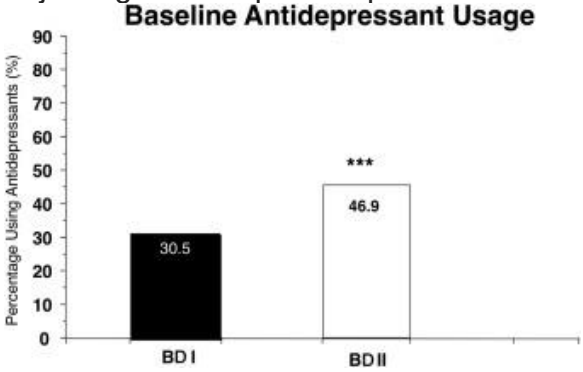

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Fig. 1. Baseline Antidepressant Use Stratified by Bipolar Subtype. ****$p = 0.0002$ versus BD I. BD I indicates bipolar I disorder; BD II indicates bipolar II disorder.

Regarding socio-demographics, BD I (but not BD II) antidepressant users (N= 74) versus nonusers (N= 169) were more often Caucasian (85.1% vs. 71.6%, Chi-square = 5.1, df = 1, $p = 0.02$), whereas BD II (but not BD I) antidepressant users (N= 122) versus nonusers (N = 138) were older (38.4 ± 13.2 vs. 34.0 ± 13.4, $t = 2.6$, df = 258, $p = 0.009$) and less likely to have had a college degree (23.0% vs. 35.5%, Chi-square = 4.9, df = 1, $p = 0.03$). None of these socio-demographic differences retained significance after adjusting for multiple comparisons.

As for illness characteristics, BD I (but not BD II) antidepressant users versus non-users more often had lifetime eating disorder (23.0% vs. 10.1%, Chi-square= 7.1, df = 1, $p = 0.01$), at least one first-degree relative with mood disorder (66.2% vs. 46.2%, Chi-square = 8.3, df = 1, $p = 0.005$), and prior suicide attempt (47.3% vs. 24.9%, Chi-square = 12.0, df = 1, $p = 0.0009$) and had higher CGI-BP-OS scores (4.0 ± 1.5 vs. 3.5 ± 1.6, $t = 2.3$, df = 241, $p = 0.02$). BD II (but not BD I) antidepressant users versus non-users had longer illness duration (21.1 ± 13.5 vs. 17.3 ± 12.4, $t = 2.3$, df = 258, $p = 0.02$) and were

more likely to have long illness duration (more than 15 years) (61.2% vs. 48.5%, Chi-square = 4.1, df = 1, p = 0.045). Among both BD I and BD II antidepressant users versus non-users, there were higher rates of current anhedonia (44.6% vs. 24.8%, Chi-square = 9.4, df = 1, p = 0.003; and 42.6% vs. 28.1%, Chi-square = 5.9, df = 1, p = 0.02, respectively). BD II (but not BD I) antidepressant users versus non-users also had a lower rate of current irritability (40.2% vs. 59.4%, Chi- square = 9.6, df = 1, p = 0.003). With respect to current psychotropic use, BD II (but not BD I) antidepressant users versus nonusers were more often taking a mood stabilizer (68.9% vs. 53.6%, Chi-square = 6.3, df = 1, p = 0.02), whereas both BD I and BD II antidepressant users versus nonusers were more often taking complex pharmacotherapy (Goldberg et al., 2009) (50.0% vs. 21.9% in BDI, Chi-square = 19.2, df = 1, p < 0.0001; and 45.1% vs. 17.4% in BD II, Chi-square = 19.2, df = 1, p < 0.0001, respectively) and were taking more core psychotopics (MS, AD, AP) (3.7 ± 1.6 vs. 2.3 ± 1.4, t = 6.9, df = 241, p < 0.0001 in BDI; and 3.5 ± 1.6 vs. 1.7 ± 1.7, t = 8.8, df = 258, p < 0.0001 in BDII). After adjusting for multiple comparisons with respect to illness characteristics, only the findings that BD I and BD II antidepressant users versus nonusers were more often taking complex pharmacotherapy, and were taking more core psychotropics, retained statistical significance.

3.3. Current antidepressant use in BD I versus BD II stratified by mood state

In our sample of 503 bipolar patients at enrollment, 207 (41.2%) patients were euthymic (107 BD I and 100 BD II), 153 (30.4%) were depressed (59 BD I and 94 BD II), 76 (15.1%) had subsyndromal symptoms (35 BD I and 41 BD II), and 54 (10.7%) met criteria for mood elevation (33 BD I and 21 BD II).

Fig. 2 depicts antidepressant usage in BD II versus BD I, stratified by current mood state. Antidepressant use in BD II versus BD I was significantly higher in euthymic patients and patients with subsyndromal symptoms (44.0% vs. 28.0%, Chi-square = 5.7, df = 1, p = 0.02; and 56.1% vs. 28.6%, Chi-square = 5.8, df = 1, p = 0.02), though these findings were no longer significant after adjusting for multiple comparisons. Antidepressant use in BDII versus BDI did not significantly differ during depression (49.0% vs. 37.3%) or mood elevation (28.6% vs. 30.3%, Fig. 2). Current antidepressant use in BDII was only non-significantly lower when elevated (28.6%) compared to when euthymic (44.0%), depressed (49.0%), or with subsyndromal symptoms (56.1%). Finally, current antidepressant use in BD I was only non-significantly higher when depressed (37.3%) compared to when euthymic (28.0%), with subsyndromal symptoms (28.6%), or elevated (30.3%).

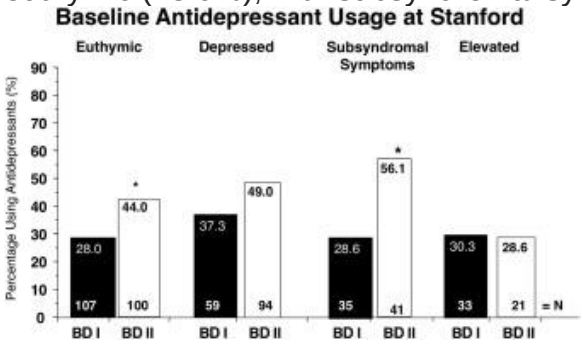

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Fig. 2. Baseline Antidepressant Usage in BD I versus BD II with Baseline Euthymia, Depression, Subsyndromal Symptoms, and Mood Elevation. *p < 0.05 versus BD I. BD I indicates bipolar I disorder; BD II indicates bipolar II disorder.

4. Discussion

Antidepressant use in the treatment of BD remains controversial. Some randomized, controlled studies have suggested that antidepressants may yield benefit for acute bipolar depression, either as monotherapy in bipolar II disorder (Amsterdam and Shults, 2010) or

added to an antipsychotic in bipolar I disorder (Tohen et al., 2003). Another study that was randomized, but not placebo-controlled, suggested similar efficacy of antidepressant and lithium monotherapy for longer-term relapse prevention in bipolar II disorder patients (Amsterdam et al., 2015). Overall, however, there are few adequately powered, randomized, controlled studies investigating the efficacy of antidepressants for the treatment of BD, and many of these failed to demonstrate superiority of antidepressants over placebo (Pacchiarotti et al., 2013). Despite the limited evidence base to support their utility, antidepressants are commonly prescribed for BD patients (Baldessarini et al., 2007), thus warranting an examination of clinical factors associated with antidepressant use in BD patients and how such factors may differ across bipolar subtypes.

The overall use of antidepressants in our sample was 39.0%. Rates of antidepressant use in prior studies range between 30% and 80% (Baldessarini et al., 2007, Carta et al., 2012, Ghaemi et al., 2000, Lorenzo et al., 2012). The higher prevalence of antidepressant use in earlier studies could reflect prior under diagnosis of BD (Ghaemi et al., 2000) and the lack of separate FDA-approvals for bipolar versus unipolar depression prior to 2003 (Tohen et al., 2003), while the lower prevalence of antidepressant use in our study was more consistent with other studies (Baldessarini et al., 2007, Carta et al., 2012) and may be related to the relative reluctance of community based providers practicing near an academic tertiary center to prescribe antidepressants for BD patients.

Several of our findings on clinical variables, particularly with respect to increased rate of complex pharmacotherapy and increased number of core psychotropics associated with antidepressant use, are consistent with overall higher severity of illness in BD patients taking versus not taking antidepressants. The heightened severity associated with antidepressants may reflect greater utilization of antidepressants during depressed mood states, (Ketter, 2015, Mclntyre et al., 2013, Pacchiarotti et al., 2013) and greater illness burden associated with depression rather than mood elevation (Miller et al., 2014). Indeed, BD patients appear to experience depressive symptoms three times more often than they do manic or hypomanic symptoms (Judd et al., 2002); and can take twice as long to recover from depression compared to mania, (Hlastala et al., 1997), often necessitating use of agents such as antidepressants despite their lack of robust efficacy data in BD (Pacchiarotti et al., 2013).

Our results show that BD II patients referred to our clinic were more often taking antidepressants compared to BD I patients. This might be due to lower clinician concern for degree of severity or risk of treatment-emergent antidepressant associated mood elevation in BD II compared to BD I, as shown in prior studies (Bond et al., 2008, Vieta et al., 2002; Altshuler et al., 2006). Increased use of antidepressants in BD II is further supported by research demonstrating that antidepressants may have similar prophylactic effectiveness compared to mood stabilizers in preventing depressive relapses in BD II (Amsterdam et al., 2015). Moreover, our data are consistent with previous research suggesting antidepressants should be used more cautiously in BD I due to concerns of the risk of serious mood elevation (Vohringer et al., 2015, Vieta et al., 2002, Altshuler et al., 2006).

We also showed that antidepressant use tended to be higher in BD II vs BD I patients during euthymic and subsyndromal mood states, but was not significantly different when patients were depressed or elevated. This finding could be related to increased use of antidepressants during depression in BD I patients and decreased use of antidepressants during mood elevation in BD II patients (Fig. 2).

Our study has the strengths of assessing demographics and illness characteristics in a substantial sample of well-characterized BD I and BD II patients taking antidepressants referred to a tertiary academic clinic. 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 and well-educated but 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. Another limitation is the open naturalistic cross-sectional (rather than longitudinal) treatment design, in which patients received diverse uncontrolled therapies. Also, we were not able to determine causality regarding associations between baseline antidepressant use and clinical correlates (e.g., whether antidepressant administration increased rate of current anhedonia or vice versa), nor were we able to determine potentially heterogeneous reasons for antidepressant administration (e.g., for anxiety versus depression).

5. Conclusion

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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Disclosure of financial relationships (past 36 months)

Drs. Hooshmand, Gershon, Park, Kim, and Wang as well as Dennis Do, Saloni Shah, and Laura Yuen report no financial relationships with commercial interests. Dr. Miller has received grant/research support from Merck and Company and Sunovion, Inc. Dr. Dell'Osso has received grant/research support from Cyberonics, Inc. and AstraZeneca and Lundbeck and Lecture Honoraria from AstraZeneca and Lundbeck. 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 was an employee of and holds stock in Janssen Pharmaceuticals.

Authors statement

All authors have seen and approved the final version of the manuscript being submitted to *Journal of Affective Disorders*, titled "Differential Prevalence and Demographic and Clinical Correlates of Antidepressant Use in American Bipolar I versus Bipolar II Disorder Patients." The authors certify that the submitted manuscript represents their original work, has not received prior publication, and is not under consideration for publication elsewhere.

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