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Research paper

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.

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

Abbreviations: BD, bipolar disorder; BD I, bipolar I disorder; BD II, bipolar II disorder; CGI-BP-OS, Clinical Global Impression for Bipolar Disorder-Overall Severity; df, degrees of freedom; MINI, Mini International Neuropsychiatric Interview; SCID for DSM-IV, Structured Clinical Interview for the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders; SD, standard deviation; SPSS, Statistical Package for the Social Sciences; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder

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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.

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.

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.