Journal of Affective Disorders 155 (2014) 283–287

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

Trends in pharmacotherapy in patients referred to a bipolar specialty clinic, 2000–2011

Farnaz Hooshmand [a], Shefali Miller [a,b], Jennifer Dore [a], Po W. Wang [a], Shelley J. Hill [a], Natalie Portillo [a], Terence A. Ketter [a,*]

[a] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305-5723, USA
[b] Sierra Pacific Mental Illness Research Education and Clinical Centers, Palo Alto VA Health Care System, Palo Alto, CA, USA

ARTICLE INFO

Article history:
Received 20 April 2013
Received in revised form
15 October 2013
Accepted 22 October 2013
Available online 21 November 2013

Keywords:
Lamotrigine
Lithium
Valproate
Quetiapine
Aripiprazole
Olanzapine

ABSTRACT

Objective: To assess mood stabilizer (MS) and second-generation antipsychotic (SGA) prescribing trends in bipolar disorder (BD) outpatients referred to a bipolar disorder specialty clinic over the past 12 years.
Method: BD outpatients referred to the Stanford University Bipolar Disorder Clinic during 2000–2011 were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation. Prescription rates for MSs and SGAs were compared during the first (2000–2005) and second (2006–2011) six years.
Results: Among 597 BD patients (mean ± SD age 35.4 ± 8.6 years; 58.1% female; 40.7% Type I, 43.6% Type II, and 15.7% Type Not Otherwise Specified; taking 2.6 ± 1.7 prescription psychotropic medications), lamotrigine, quetiapine, and aripiprazole usage more than doubled, from 14.7% to 37.2% ($p < 0.0001$), 7.2% to 19.7% ($p < 0.0001$), and 3.1% to 10.9% ($p = 0.0003$), respectively, while olanzapine and risperidone use decreased by more than half from 15.0% to 6.6% ($p = 0.0043$), and from 8.7% to 3.8% ($p = 0.039$), respectively. SGA use increased from 34.1% to 44.8% ($p = 0.013$), although MS use continued to be more common (in 65.2% for 2006–2011). Use of other individual MSs and SGAs and MSs as a class did not change significantly.
Conclusions: Over 12 years, in patients referred to a BD specialty clinic, lamotrigine, quetiapine, and aripiprazole use more than doubled, and olanzapine and risperidone use decreased by more than half. Tolerability (for lamotrigine, aripiprazole, olanzapine, and risperidone) more than efficacy (for quetiapine) differences may have driven these findings. Additional studies are needed to explore the relative influences of enhanced tolerability versus efficacy upon prescribing practices in BD patients.

1. Introduction

Bipolar disorder is a common recurrent mood disorder (Merikangas et al., 2007), associated with high levels of disability, comorbidity and suicidality (Judd et al., 2008). For much of the 1970s and 1980s, the mood stabilizer lithium was considered the foundational agent for the long-term management of bipolar disorder, whereas antidepressants and first-generation antipsychotics (FGAs) were considered short-term adjuncts for the treatment of acute bipolar depression and mania, respectively (Goodwin and Jamison, 1990).

Since that time, the United States Food and Drug Administration (US FDA) approved 10 new treatments, which provided important new management options for bipolar disorder (Ketter, 2010). In North America and in German speaking European countries, the mood stabilizer valproate overtook lithium by the late-1990s (Blanco et al., 2002, Goodwin et al., 2003; Fenn et al., 1996; Shulman et al., 2003; Wolfsperger et al., 2007; Baldessarini et al., 2007; Greil et al., 2012; Citrome et al., 1998; Walpoth-Niederwanger et al., 2012).

In at least some jurisdictions, lamotrigine appeared to move towards overtaking lithium and valproate in the mid-2000s (Bramness et al., 2009; Greil et al., 2012; Reimers, 2009; Centorrino et al., 2010; Depp et al., 2008; Walpoth-Niederwanger et al., 2012). In addition, several second-generation antipsychotics (SGAs) overtook FGAs in the 2000s (Wolfsperger et al., 2007; Bowers et al., 2004; Greil et al., 2012; Hayes et al., 2011; Depp et al., 2008; Pillarella et al., 2012; Yang et al., 2008; Wilting et al., 2008; Walpoth-Niederwanger et al., 2012).

By the 2010s, clinicians had a substantial armamentarium of US FDA approved treatments for bipolar disorder, including the MSs lithium, valproate, and lamotrigine, and the SGAs. In order to understand the impact of the above developments upon prescribing

* Correspondence to: Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Room 2124, Stanford, CA 94305-5723 USA. Tel.: +1 650 723 2515; fax: +1 650 723 2507.
E-mail address: tketter@stanford.edu (T.A. Ketter).

0165-0327/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2013.10.054

practices of psychiatrists treating bipolar disorder, we assessed trends in MS and SGA use in patients referred to a bipolar disorder specialty clinic between 2000 and 2011.

2. Method

The current analysis included outpatients with bipolar I disorder, bipolar II disorder, or bipolar disorder not otherwise specified (NOS) referred by community practitioners (primarily psychiatrists) to the Stanford University Bipolar Disorder Clinic between 2000 and 2011. In order for the analysis to reflect pharmacotherapy trends as encountered in the community (as opposed to as encountered in a bipolar disorder research clinic), patients referred from the Stanford University Bipolar Disorder Research Program or previously treated in the Stanford University Bipolar Disorder Clinic were excluded. Patients were assessed with the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Affective Disorders Evaluation (Sachs et al., 2002, 2003), which included the mood disorders module of the Structured Clinical Interview for DSM (First et al., 1996) and Clinical Global Impression for Bipolar Disorder-Overall Severity (CGI-BP-OS) score (Spearing et al., 1997). The STEP-BD protocol and a 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.

Demographics, illness characteristics, and rates of psychotropic drug usage were compared during the first (2000–2005) and second (2006–2011) 6-year epochs of the period from 2000 to 2011 for patients with bipolar I disorder, bipolar II disorder, and bipolar disorder NOS considered in aggregate as well as separately.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 20, Release 20.0.0 (IBM Corporation, Somers, NY) software on an Apple MacBook Pro Computer (Apple Corporation, Cupertino, CA). Analytic statistics included unpaired *t*-tests for comparisons of continuous variables, and Chi-Square tests or Fisher's exact tests as indicated for comparisons of categorical variables. Corresponding non-parametric tests were used when indicated. A two-tailed significance level was used with $p < 0.05$, not adjusted for multiple comparisons.

3. Results

3.1. Demographics and illness characteristics

Over 12 years, 714 bipolar outpatients were referred to the Stanford University Bipolar Disorder Clinic. In order to better reflect pharmacotherapy trends in the community (rather than in a university specialty research clinic setting), the current analysis excluded 33 patients referred from the Stanford University Bipolar Disorder Research Program, as well as 84 patients previously treated in the Stanford University Bipolar Disorder Clinic. Thus, 597 outpatients (69.3% (414/597) referred during 2000–2005 and 30.7% (183/597) referred during 2006–2011) with bipolar I disorder, bipolar II disorder, and bipolar disorder NOS from the Stanford University Bipolar Disorder Clinic were included in the current analysis. A description of the demographics and illness characteristics of the sample is provided in Table 1. Data were missing for only 0.2% to 2.7% of each of the individual parameters in Table 1. Among these patients, the mean ± SD age was 35.4 ± 8.6 years, 58.1% were female, 79.7% were Caucasian, 40.7% had bipolar I disorder, 43.6% had bipolar II disorder, and 15.7% had bipolar disorder NOS, mean bipolar illness duration was 17.4 ± 13.3 years, and the mean number of prescription psychotropic medications was 2.6 ± 1.7. CGI-BP-OS score was 3.9 ± 1.5, with 43.6% of patients being euthymic, 37.0% having syndromal/subsyndromal depression, and 18.8% having syndromal/subsyndromal mood elevation. Among these patients, 13.2% (79/597) were not taking any prescription psychotropic medications, but as the pattern of findings was not influenced by excluding such patients, these patients were included in all analyses.

Table 1
Sample demographics and bipolar illness characteristics in 597 patients.

	Mean ± SD or %
Age (years)	35.4 ± 8.6[a]
Female (%)	58.1
Ethnicity (%)	
Caucasian(%)	79.7
Hispanic (%)	4.2
Black (%)	3.0
Asian (%)	10.2
Other (%)	2.5
Marital status (%)	
Single (%)	50.1[a]
Married (%)	37.5
Divorced (%)	11.2
Widowed (%)	1.0
Employment (%)	
Full time (%)	31.8
Part time (%)	8.9
Unemployed (%)	34.0
Student (%)	24.8[a]
Education (%)	
High school (%)	8.3
College/some college (%)	35.0
Bachelor's degree (%)	30.8
Graduate degree (%)	25.3
Diagnosis (%)	
Bipolar I disorder (%)	40.7
Bipolar II disorder (%)	43.6
Bipolar disorder not otherwise specified (%)	15.7
Lifetime co-morbidities (%)	
Any psychiatric disorder (%)	82.9
Any anxiety disorder (%)	64.0[b]
Alcohol use disorder (%)	35.2
Substance use disorder (%)	37.4
Eating disorder (%)	14.4
Personality disorder (%)	12.2
Other clinical characteristics	
Onset age (years)	18.0 ± 8.6
Illness duration (years)	17.4 ± 13.3[a]
Psychosis (lifetime) (%)	36.3[a]
Psychiatric hospitalization (lifetime) (%)	36.3
Suicide attempt (lifetime) (%)	29.3
Number of prescription psychotropics	2.6 ± 1.7
CGI-BP-OS	3.9 ± 1.5
Clinical status	
Euthymic (%)	43.6
Syndromal/subsyndromal depression (%)	37.0
Syndromal/subsyndromal mood elevation (%)	18.8

All parameters had 0.0–2.7% missing data.

[a] Parameters with statistically significant differences between 2000–5 versus 2006–11.

[b] Parameter with trend towards difference between 2000–5 versus 2006–11.

Five of the demographic and illness characteristic parameters in Table 1 differed for the second compared to first 6-year epoch. Thus, patients in the second compared to first epoch were significantly younger (32.3 ± 11.9 versus 37.1 ± 13.3 years, $t=3.9$, df=595, $p=0.0001$), more often single (60.0% versus 45.9%, Chi-square=9.9, df=1, $p=0.0018$), more often students (31.3% versus 22.1%, Chi-square=5.8, df=1, $p=0.018$), with shorter illness duration (14.5 ± 13.2 versus 18.7 ± 13.2 years, $t=3.4$, df=582, $p=0.0007$), and less often lifetime history of psychosis (30.1% versus 40.0%, Chi-square=5.1, df=1, $p=0.025$), and tended to