Journal of Affective Disorders 144 (2013) 129–133

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

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

Research report

Predictors of later bipolar disorder in patients with subthreshold symptoms

Gregory G. Homish [a,b], Dori Marshall [b,c], Steven L. Dubovsky [b,c,*], Kenneth Leonard [b,c,d]

[a] Department of Community Health and Health Behavior
[b] University at Buffalo, 462 Grider St, Room 1182, Buffalo, NY 14215, USA
[c] Department of Psychiatry, University at Buffalo, 462 Grider St, Room 1182, Buffalo, NY 14215, USA
[d] Research Institute on Addictions

ARTICLE INFO

Article history:
Received 24 March 2012
Accepted 13 June 2012
Available online 28 July 2012

Keywords:
Bipolar disorder
Epidemiology
Subthreshold
Prodromal

ABSTRACT

Introduction: The clinical significance of subthreshold bipolar disorder (SBD), which is characterized by an insufficient number or severity of hypomanic symptoms to qualify for a formal bipolar disorder diagnosis, remains to be determined.
Methods: We examined the outcomes three years later (2004–2005; Wave 2) of 40,512 civilian, non-institutionalized subjects who endorsed elation and/or irritability but did not meet full criteria for lifetime mania or hypomania in 2001–2002 (Wave 1).
Results: The likelihood of developing a clear episode of mania or hypomania by Wave 2 was significantly increased in subjects with elation or only irritability at Wave 1 compared with subjects who did not endorse either (OR 2.8, $p < 0.01$ for each). Endorsement of both symptoms at Wave 1 increased the likelihood of a new episode of mania or hypomania 4.6 times, which was significantly higher than for those with only elation or irritability ($p < .05$ for each).
Limitations: SBD was not limited to depression, reducing comparability to previous studies. Despite the large sample size, there were not enough subjects to determine the impact of different numbers and types of additional symptoms on bipolar outcome. Although the majority of subjects were followed between the two Waves, the total duration of follow-up was probably too short to determine the long-term conversion rate to mania or hypomania.
Conclusions: Elation and/or irritability, especially if accompanied by trouble concentrating, racing thoughts or hyperactivity, may represent a prodrome of formal bipolar disorder that indicate close follow-up and cautious use of antidepressants.

1. Introduction

Bipolar disorder causes more disability than cancer, epilepsy and Alzheimer's disease (Kleinman et al., 2003; Merikangas et al., 2011). People with bipolar disorder have high rates of suicide, substance use, obesity, heart disease, smoking, and sedentary lifestyle, with consequent increased morbidity and mortality (Jansen et al., 2011). In 2009 the direct and indirect costs, respectively, of bipolar I and bipolar II disorder were $30.7 and $120.3 billion, respectively (Dilsaver, 2011).

Unrecognized bipolar disorder is an important clinical problem. Around 20–28% of depressed patients taking antidepressants in primary care practices have been found to have clear cut bipolar disorder, and in these cases the diagnosis is rarely made by the primary care physician (Das et al., 2005; Dubovsky et al., 2011; Hirschfeld et al., 2005; Olfson et al., 2005; Shi et al., 2004). In one study, patients with unrecognized bipolar depression were almost four times more likely to attempt suicide and 50% more likely to be hospitalized as unipolar depressed patients (Shi et al., 2004). Most of these patients are treated with antidepressants, which have not been found to be more effective than placebo for bipolar depression (Ghaemi et al., 2003; Sachs et al., 2007) and which have the potential to destabilize bipolar disorder, especially if any residual hypomanic symptoms are present (Ghaemi et al., 2003; Schneck et al., 2008; Shi et al., 2004).

The combined prevalence of bipolar I and II disorders has generally been estimated to range roughly between 0.5% and 2% (Bauer and Pfennig, 2005; Dunner, 2003; Grant et al., 2005; Judd and Akiskal, 2003; Pini et al., 2005; Weissman et al., 1996), although a single study reported a lifetime prevalence of mania and hypomania of 7.5% and 5.3%, respectively (Jansen et al., 2011). A number of investigators have suggested that bipolar disorder comprises a larger spectrum of conditions causing clinically significant morbidity (Akiskal, 1996; Angst et al., 2011). One proposed subtype has been called subthreshold bipolar disorder

* Corresponding author at: University at Buffalo, Psychiatry, 462 Grider St, Room 1182, Buffalo, NY 14215, US. Tel.: +1 716 898 5940; fax: +1 716 898 4538.
E-mail address: dubovsky@buffalo.edu (S.L. Dubovsky).

0165-0327/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2012.06.020

(SBD), in which features of bipolar I or II disorder are present, but without sufficient duration or a sufficient number of symptoms to qualify for a formal bipolar diagnosis (Akiskal et al., 2000; Angst et al., 2003). Compared with unipolar depression, SBD has been thought to be associated with more suicide attempts, greater familial loading for bipolar disorder, more comorbidity with anxiety, impulse control and substance use disorders, and a higher rate of conversion to frank bipolar disorder (Angst et al., 2010), as well as similar degrees of role impairment to bipolar I and II disorder (Merikangas et al., 2007).

The National Comorbidity Survey Replication (NCS-R), utilizing the WHO Composite International Diagnostic Interview (CIDI), defined SBD as major depression with subthreshold hypomania (hypomania without impairment, or the presence over at least several days of persistent elation or irritability with three or more manic symptoms but an insufficient number of symptoms to meet full criteria for hypomania (Angst et al., 2010). In the overall household population, lifetime and 12-month prevalences of bipolar I, bipolar II, SBD and major depressive disorder (MDD) were 0.7% and 0.3%, 1.6% and 0.8%, 6.7% and 2.2%, and 10.2% and 5.4%, respectively (Angst et al., 2010). The NCS-R also found either recurrent subthreshold or frank hypomania without depression in 2.4% of respondents (Merikangas et al., 2007). SBD was associated with more comorbidity with anxiety and substance use disorders and more "behavioral problems" than MDD, but less than bipolar II disorder. Although severity and family history of depression were similar in SBD and MDD, SBD was associated with significantly more lifetime depressive episodes, and a younger age of onset of depression (Angst et al., 2010); 41% of subjects with SBD had made suicide attempts (Angst et al., 2010). The CIDI equivalent of DSM-IV rapid cycling occurred in 1/3 of subjects with lifetime bipolar disorder and half of those with any 12-month bipolar disorder, including SBD (Nierenberg et al., 2010).

In the Epidemiologic Catchment Area (ECA) study, the prevalence of the "bipolar spectrum" (bipolar I, bipolar II and subthreshold bipolar disorder) was 6.4% of the general population (Judd and Akiskal, 2003). In an international study, 61,392 adults underwent structured diagnostic interviews in their homes in the United States, Mexico, South America, Eastern Europe, Asia, Lebanon and New Zealand to determine the lifetime and 12-month prevalence of the bipolar spectrum (Merikangas et al., 2011). In the pooled sample, lifetime and one-year prevalence was 0.6 and 0.4% for bipolar I disorder, 0.4 and 0.3% for bipolar II disorder, and 1.4 and 0.8% for SBD. Lifetime and 12-month rates of all bipolar spectrum disorders were highest in the United States (4.4% and 2.8%, respectively). Within the bipolar spectrum, 3/4 of patients also met criteria for another lifetime disorder, and more than half of these had three or more comorbid disorders, especially panic attacks, behavior disorders, and substance use disorders. Although symptom severity and suicidality increased from SBD to bipolar II to bipolar I disorder, the risk of significant role impairment was statistically similar in all subtypes (29–57%). Among subjects with subthreshold bipolar disorder, 36% reported suicidal ideation in the past 12 months, 15% had a plan, and 9.5% had made a suicide attempt.

As is true of bipolar disorder in general, the prevalence of SBD would be expected to be higher in depressed patients. In the NCS-R, subthreshold hypomania was present in 39% of patients with a diagnosis of MDD (Angst et al., 2010). Similarly, 31% of a clinical sample of depressed patients in two primary care practices being treated with antidepressants met NCS-R criteria for SBD (Dubovsky et al., 2011). A multicenter study conducted in Asia, Europe and Africa of 5635 adults with a current major depressive episode examined by practicing psychiatrists found that 16% met formal criteria for bipolar disorder (12.2% bipolar I and 3.9% bipolar II), while another 31% met "bipolarity specifier" criteria, which were defined as depression with a history of an episode of elevated mood, irritable mood, or increased activity with at least 3 DSM-IV-TR Criterion B symptoms and producing uncharacteristic change in or impairment of functioning or requiring treatment (Angst et al., 2011). Features associated with a DSM bipolar or a bipolarity specifier diagnosis included more than two prior mood episodes, mood lability, mania or hypomania on an antidepressant, earlier age of onset, and current mixed state; psychotic features also discriminated DSM-IV-TR bipolar but not bipolarity specifier patients. A total of 79% of patients meeting DSM bipolar criteria and 85% of those meeting bipolarity specifier criteria were taking antidepressants, while 69% and 61%, respectively, were taking mood stabilizers.

These kinds of results suggest that SBD, which predominantly but not universally has been reported to include depressive episodes, is a clinically important subtype that is not captured by current bipolar disorder criteria and that is often mistaken for MDD (Angst et al., 2010). To address the question of whether SBD is a distinct and stable subtype or a precursor of other forms of bipolar disorder, we utilized a prospective household survey that obtained data about SBD and DSM-IV bipolar disorder on two occasions, three to four years apart.

2. Methods

2.1. Study sample

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) has been previously described in detail (Grant and Kaplan, 2005; Grant et al., 2003b, 2004). Briefly, two waves of data, in 2001–2002 (Wave 1), and 2004–2005 (Wave 2; 81% of the original sample), were obtained from 43,093 civilian, non-institutionalized adults in the United States. Based on the 2000 Decennial Census, sample selection was adjusted according to socio-demographic variables to ensure a representative sample of the United States population. For both waves, surveys were administered face-to-face, using computer-assisted interviews described below. African Americans, Hispanics, and young adults were oversampled, and the data were weighted to adjust for non-response at the household and individual levels. The present report excludes the 2581 subjects who met full criteria for lifetime mania or hypomania, leaving an initial sample size of 40,512. All data were de-identified and the study was determined to be exempt.

2.2. Measures/analyses

The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV) was administered to generate DSM-IV diagnoses for lifetime alcohol abuse and dependence, generalized anxiety disorder, major depressive disorder, mania, and hypomania (Grant et al., 2003a, 1995). In the present study, we included all subjects who endorsed the screening symptoms for bipolar disorder (elation and/or irritability) at Wave 1 but did not meet full criteria for mania or hypomania. The outcome variable was a first episode of DSM-IV mania or hypomania that occurred after Wave 1 and was identified at Wave 2. Logistic regression was used to examine the relation between Wave 1 predictors of identification of a new episode of mania or hypomania at Wave 2. All analyses accounted for the complex sampling design of the NESARC survey and were adjusted for age, gender, and race/ethnicity.