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ScienceDirect
Psychiatry Research 160 (2008) 63–71
PSYCHIATRY RESEARCH
www.elsevier.com/locate/psychres

Impact of remitted substance use disorders on the future course of bipolar I disorder: Findings from a clinical trial

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Received 12 September 2006; received in revised form 26 March 2007; accepted 27 May 2007

Abstract

Given the high lifetime prevalence rates of bipolar disorder and comorbid substance use disorders (SUDs), the aim of the study was to examine the effect of a *remitted* SUD on the future course of bipolar I disorder in patients taking part in a clinical trial. Patients with bipolar I disorder were enrolled in a larger study examining the effects of pharmacotherapy plus family interventions. These patients were recruited during an acute mood episode and their mood symptoms and substance abuse were assessed longitudinally for up to 28 months. Patients with a remitted SUD showed a poorer acute treatment response, a longer time to remission of their acute mood episode, and a greater percentage of time with subthreshold but clinically significant depression and manic symptoms over follow-up compared to those without this comorbidity pattern. Subsequent substance abuse during follow-up could not fully account for the poorer course of illness. As remitted SUDs appear to negatively predict treatment outcome, current findings have implications for both clinical trials of bipolar patients as well as clinical practice.

Keywords: Bipolar disorder; Course of illness; Subtance use; Comorbidity; Clinical trial

1. Introduction

Bipolar disorder (BP) is one of the top 10 leading causes of disability worldwide in those ages 15–44 (Murray and Lopez, 1996). The direct treatment cost of bipolar disorder was $7.6 billion annually in the U.S. in 1990, and 8% of this figure was accounted for by substance abuse treatment (Wyatt and Henten, 1995). The substantial resources devoted to the treatment of drug and alcohol problems in bipolar patients are not surprising given the high co-occurrence between these disorders. Epidemiological research suggests that the lifetime prevalence of substance use disorders (SUDs) is higher in bipolar disorder than in any other psychiatric disorder, including unipolar depression (Goldberg, 2001). The National Comorbidity Survey found an 8 to 10 fold greater risk of substance or alcohol dependence in bipolar patients (Kessler et al., 1997). Brown et al. (2001) reported rates of SUDs in bipolar patients ranging from 14 to 65% in inpatient and outpatient treatment settings. Conversely, epidemiological studies indicate that individuals with SUDs have a 5 to 8 times greater risk of bipolar disorder (Kessler et al., 1997; Regier et al., 1990). Rates of bipolar disorder in samples

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0165-1781/$ - see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2007.05.014

from drug and alcohol clinics have ranged from 2 to 31% (Salloum and Thase, 2000).

In their review, Salloum and Thase (2000) reported that bipolar disorder and a comorbid SUD are associated with an earlier age of bipolar illness onset, higher frequency of mood episodes, greater persistence of significant symptoms between mood episodes, delayed time to recovery and shortened time to bipolar relapse, greater depression and manic severity, more mixed and rapid cycling episodes, greater disability, and higher mortality rates. Research also has shown that "bipolar substance abuse" (Weiss, 2004) is associated with increases in violence (Salloum et al., 2002) and psychiatric rehospitalizations (Cassidy et al., 2001), as well as poorer psychosocial outcomes (Tondo et al., 1999) when compared to patients with bipolar disorder and no SUD. Even more disturbing, patients with bipolar substance abuse are twice as likely to attempt suicide (Dalton et al., 2003). Comorbid SUDs also have been shown to predict lower medication compliance in numerous studies (Lingam and Scott, 2002). For example, Keck et al. (1998) prospectively followed 134 bipolar patients following hospitalization and found that patients without comorbid SUDs were almost twice as likely to be adherent to medications (58% versus 32%).

Most previous studies on bipolar patients with comorbid SUDs have focused either on samples that included individuals with a current SUD diagnosis or that combined patients with current and past SUDs. Given the high lifetime prevalence of SUDs in bipolar patients and the known negative impact of substance abuse, a post hoc analysis of a larger clinical trial was conduced to examine the potential impact of a past SUD history on the longitudinal course of illness of bipolar I disorder when individuals were currently SUD asymptomatic (i.e., in remission for at least 1 year prior to study entry). Although many clinical trials of bipolar patients exclude those with current SUD diagnoses, a substantial proportion of these patients are likely to have a past SUD history. In addition, if a past SUD history can be shown to negatively impact the future course of illness, there are important clinical implications for the routine screening and treatment of bipolar patients. Given the known negative effects of comorbid SUDs on the course of bipolar illness and the results from previous studies of bipolar patients with current or past SUDs, we hypothesized that bipolar I patients with a remitted SUD would show a poorer acute treatment response, have a longer time to remission from their acute mood episode, and spend a greater percentage of time symptomatic over a 28-month follow-up period compared with patients without a SUD history.

2. Methods

2.1. Participants

Ninety-two patients were enrolled in the larger clinical trial assessing pharmacotherapy versus pharmacotherapy plus family therapy for bipolar disorder (study recruitment period: 1992–1997). Please refer to the original study for a detailed description of the trial (Miller et al., 2004a,b). Patients were enrolled during an acute mood episode, and the vast majority of the original sample was recruited during an index hospitalization (96%). Inclusion criteria for the "parent" clinical trial were: 1) diagnosis of bipolar I disorder (current episode manic, depressed, or mixed) according to the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al., 1990); 2) age 18 to 75; 3) fluency in English; and 4) regular contact with a significant other. Exclusion criteria were: 1) diagnosis of alcohol or drug *dependence* during the past year; 2) a mood disorder due to a medical condition or substance; 3) a medical illness severe enough to contraindicate the use of mood stabilizing medication; or 4) or pregnancy or inadequate contraception use. Current or past substance *abuse* was permitted in the clinical trial if determined at the time of enrollment to be secondary to bipolar disorder, but these patients were excluded from current analyses ($n=7$). Past substance *dependence* was diagnosed according to the SCID and must have been in full remission for at least 1 year prior to study entry.

2.2. Assessments

The SCID (Patient Edition) for DSM-III-R (Spitzer et al., 1990) was used to determine current and lifetime diagnoses. The Bech–Rafaelsen Mania Scale (BRMS) (Bech et al., 1979) is an 11-item interviewer-rated scale used to assess the severity of manic symptoms. The Modified Hamilton Rating Scale for Depression (MHRSD) (Miller et al., 1985) is a 25-item interviewer-rated instrument that was used to assess depression severity. The MHRSD is an adapted form of the original scale that includes standardized question prompts to increase reliability. The commonly used 17-item total was used in analyses. The Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al., 1987) is a clinical interview that was used to determine if patients met the criteria for a SUD during the follow-up period. All interviewers were trained to proficiency on assessment devices and blind to treatment conditions. LIFE interviewers were certified by the developers of the instrument. Raters were trained to initial interrater reliability