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More stressors prior to and during the course of bipolar illness in patients from the United States compared with the Netherlands and Germany

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ABSTRACT

Considerable data suggest that compared to some European countries, in the U.S. there are more childhood onset bipolar disorders, more adverse courses of illness, and greater treatment resistance. Psychosocial variables related to these findings have not been adequately explored. Therefore we analyzed psychosocial stressors in three time domains: childhood; the year prior to illness Onset; and the Last Episode from questionnaires in 968 outpatients (mean age 41) with bipolar I or II disorder; 676 from four sites in the U.S. and 292 from three in the Netherlands and Germany (abbreviated here as Europe). Compared to the Europeans, those from the U.S. had significantly more stressors in childhood and prior to the last episode. Stressors prior to the last episode were related to: childhood stressors; an earlier age at illness onset; anxiety and substance abuse comorbidity; lower income; both parents having an affective illness; and feeling more stigma. These data suggest a greater prevalence of adverse life events in childhood and over the course of bipolar illness in the U.S. compared to the Netherlands and Germany. Clinical, therapeutic, and public health approaches to these illness-relevant stressors require further exploration.

1. Introduction

Bipolar outpatients in the U.S. appear to have a more pernicious course of bipolar illness compared with those from Germany and the Netherlands (Post et al., 2008, 2011). Patients from the four sites in the U.S. (Los Angeles, Dallas, Cincinnati, and Bethesda) had a significantly earlier age at onset of illness compared with those from three sites in Utrecht, the Netherlands and Freiburg and Munich, Germany (Post et al., 2010a).

These findings have recently been replicated using U.S. patients from the Pittsburgh case registry compared to a multi-country European consortium (Bellivier et al., 2011). Consistent with the earlier age at onset in our U.S. cohort, there were also a significant increase in two vulnerability factors for early onset: (1) parental loading for affective disorder (Post et al., in press); and (2) childhood adversity (Leverich et al., 2002; Post et al., 2010a, 2013a).

In addition, in those from the U.S. the retrospective course of illness was characterized by more anxiety and substance abuse comorbidity, an increased incidence of having had 20 or more prior episodes, and more rapid cycling compared with Germany and the Netherlands (hereafter referred to Europe) (Post et al., 2011). Following Network entry during largely naturalistic treatment, those from the U.S. also showed more long-term treatment non-response than those from Europe (Post et al., 2010b).

Given these apparent greater illness-related difficulties in the U.S. vs. the European Network patients, we here examine the occurrence of psychosocial stressors occurring in three temporal domains: in

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childhood (prior to age 13); in the year prior to illness Onset; and in the year prior to the Latest Episode. We had previously observed that the occurrence of psychosocial adversity in childhood in the form of physical or sexual abuse (in a subset of 525 of these patients who were followed for at least 1 year in the Network) was associated with many adverse illness characteristics (Leverich et al., 2002). Here, we extend the observations to include verbal abuse and utilize the entire Network population of more than 900 patients.

Stressors in childhood have been well documented to contribute to the onset of depression following stressors in adulthood (Kendler et al., 2000, 2001; Caspi et al., 2003; Danese et al., 2009; Risch et al., 2009; Rutter et al., 2009; Karg et al., 2011) and are related to adult medical and psychiatric difficulties in the general population (Shonkoff and Garner, 2012).

We hypothesized, based on the relationships of early adversity to later adversity, that those from the U.S. compared to Europe would also have an increased incidence of multiple different types of stressors, including those related to loss of social support, employment, and economic issues, and that these in turn would be related to indices of a more complex course of bipolar disorder. Given the known differential national health care coverage in Europe compared with the U.S., we also postulated that health care access would be a contributor to the greater stressor burden.

2. Methods

Patients ($N=968$) with bipolar illness were recruited into the Stanley Foundation Bipolar Treatment Outcome Network funded by the Stanley Medical Research Institute from 1995 to 2002 (Post et al., 2001, 2011) and now continuing as the Bipolar Collaborative Network. They gave oral and written informed consent for participation in the naturalistic component of the research network, as well as separate consents for any potential participation in naturalistic treatment or clinical drug evaluations as outlined elsewhere (Post et al., 2006). The criteria for patient entry were broad and patients were excluded only for current active major medical comorbidities that would preclude participation in pharmacotherapy clinical trials or for acute alcohol or substance abuse that required treatment in another facility.

Six hundred and seventy six patients were from the U.S. sites, which included (1) UCLA and the VA in Los Angeles; (2) Dallas; (3) Cincinnati; and (4) Bethesda. Two hundred and ninety two patients were from three European sites, which included (1) Utrecht, the Netherlands, (2) Freiburg, and (3) Munich, Germany.

A diagnosis of bipolar disorder was validated with SCID interview and prospective assessment of the NIMH-LCM (Post et al., 2010a, 2010b, 2011). Patients completed a detailed questionnaire about demographic and prior illness characteristics, as well as stressors. For age at onset, patients were asked for the year of life in which a first hypomanic or manic episode occurred, or a first episode of depression that was associated with dysfunction (so that it would likely approximate DSM IV requirements).

Questions were asked about the frequency (on a 0–3 point scale) of verbal, physical, and sexual abuse in childhood prior to age 13. The questionnaire also included ratings of the occurrence of 14 listed stressors and their potential impact (on a four-point scale). These were based on events previously linked to the onset or recurrent of episodes of unipolar depression or bipolar disorder in other studies (Kendler et al., 2000, 2001; Caspi et al., 2003; Danese et al., 2009). For each stressor, ratings of none or mild were considered as stressor absent, while a moderate or severe rating was considered as stressor present. Each specific stressor was rated in the year prior to illness Onset, and again in the year prior to the most Recent (Last) Episode prior to Network entry. Seven stressors were in the general realm of lack of psychosocial support; four pertaining to financial and employment difficulties; and three about medical comorbidities and health care coverage and access.

2.1. Statistics

The occurrence of verbal, physical, and sexual abuse in childhood was listed for patients in the U.S. and the Netherlands and Germany. The frequencies of each kind and their relationships to other types of abuse were also evaluated as well as the correlation among them. Major course of illness variables was reported as a function of continent (U.S. vs. Europe) and the presence of any abuse in childhood.

The 14 different stressors rated in the year prior to illness Onset and prior to the Latest Episode were examined in those from the U.S. vs. Europe and tested with χ^2 with $p<0.05$ considered significant. Mean number of stressors at each illness time point were reported in U.S. vs. Europe for each item, as well as those grouped as relating to social support; financial and work distress; and medical illness and health care access.

A logistic regression was employed to predict a history of childhood physical, sexual or verbal abuse from demographics and course of illness variables. "Predict" here does not imply causality, but only that if, for example, a patient had a rapid cycling course they would be more likely to have had childhood adversity. Variables in the regressions included: country of origin, rapid cycling, early age of onset (18 or less), ability to work, number of mood episodes, anxiety disorder, alcohol and drug abuse, and parental history of mood disorders. The regression illustrated in Table 2B was checked for specification errors, multi-collinearity (VIF < 1.6), and non-linear predictors using a Box–Tidwell model. Age of onset was non-linear if not transformed into an early/late dichotomy at age 19 as previously used by our group and Perlis et al. (2004). A Hosmer and Lemeshow's test indicated our model fit the data fairly well ($p=0.654$). Very slight improvements in the goodness of fit could be obtained by removing the non-significant predictors from the regression. As the inability of these variables to predict childhood abuse was of interest, they were left in the regression.

Similar statistical diagnostics were employed for stressors at illness Onset and prior to the Last episode. Only minor violations were found, which were dealt with by using robust standard errors and transforming age into the log of age. A robust linear regression related a variety of illness and demographic factors to the number of stressors occurring at illness Onset and again for stressors occurring prior to the Latest Episode (Tables 5A and 5B).

3. Results

3.1. Childhood adversity

Table 1 shows the incidence and the relationships of different types of abuse in childhood in the entire sample. About half the patients experienced verbal abuse, one-quarter physical abuse, and one-fifth sexual abuse in childhood. Each type of abuse occurred more often in the U.S. compared to Europe. The presence of these variables was moderately inter-correlated. Verbal abuse was related to physical abuse ($r=0.50$) and sexual abuse ($r=0.28$), and physical abuse was related to sexual abuse ($r=0.32$; all correlations $p<0.001$).

Selective demographic and course of illness variables of the subjects included in the study are listed in Table 2A. In each instance, these variables are listed as the function of whether or not there was any type of abuse in childhood. With the exception of not being able to work, all the other variables were higher in the U.S. than in Europe, and were also higher when there had been any type of child abuse present compared to absent. Fig. 1 shows the increased incidence of these childhood stressors in the U.S. compared with Europe.

Table 2B illustrates the logistic regression linking a history of any abuse in Childhood independently to: being from the U.S; having an earlier age at onset of bipolar disorder; an anxiety disorder comorbidity; and a positive parental history of a mood disorder.

By logistic regression (data not illustrated), the occurrence of verbal abuse in childhood was independently related to being from the U.S. and having one or more parents with affective illness or substance abuse problems. In contrast, the risk of having had physical or sexual abuse related only to being from the U.S. and parental variables were not contributory.

Table 1
Incidence type of abuse in childhood by continent.

	Incidence of childhood abuse						
	Total	Overall		U.S.		Europe	
	N	Yes *N*	Yes %	Yes *N*	Yes %	Yes *N*	Yes %
No abuse	948	412	43.5	233	35.5	176	61.5
Verbal only	948	201	21.2	156	23.7	45	15.7
Any verbal	942	474	50.3	386	58.8	88	46.2
Any physical	942	231	24.5	191	29	40	14
Any sexual	936	205	21.9	168	36	37	12.9
All three	943	100	10.6	88	13.4	12	4.2