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Review article

More illness in offspring of bipolar patients from the U.S. compared to Europe

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ABSTRACT

Background: Evidence suggests that patients with bipolar disorder from the United States have an earlier age of onset and a more difficult course of illness than those from Germany and the Netherlands. These characteristics were related to a greater family burden of psychiatric illness and the experience of more psychosocial adversity in childhood. We hypothesized that this greater illness burden would extend to the offspring of the US patients.

Methods: 968 outpatients (average age 41) with bipolar illness gave informed consent for participation in a treatment outcome network and filled out a detailed questionnaire about their illness and family history of illness, including whether their offspring had a diagnosis of depression, bipolar disorder, alcohol or substance abuse, suicide attempt or "other" illness. Of those with children, 356 were from the US and 132 were from Europe.

Results: Compared to the Europeans, offspring of patients from the US had significantly ($p < 0.001$) more depression, bipolar disorder, drug abuse, and "other" illnesses. The number of illnesses in the offspring was related to the bipolar parent being from the US, having had childhood adversity, more than 20 prior episodes, and more parental psychiatric illness.

Conclusions: While the findings are limited by their basis on self report, the distribution of the percentages in the US offspring are similar to those of Axelson et al. (2015) who used direct interviews. The higher burden of illness in the offspring and their in direct progenitors from the US compared to Europe warrant new attempts at better treatment and prevention.

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1. Introduction

Compared to Europeans patients with bipolar disorder from the United States (US) have an earlier age of onset of their illness (Bellivier et al., 2014; Etain et al., 2012; Post et al., 2014b,2011,2014a). Across multiple studies an early age of onset is associated with a more difficult or severe course of illness (Birmaher et al., 2009,2014; Carlson et al., 2002; Carter et al., 2003; DelBello et al., 2007; Ernst and Goldberg, 2004; Perlis et al., 2004; Post et al., 2014b,2014a,2010b), and accordingly, patients from the US have a higher incidence of factors associated with a poor prognosis, including: childhood adversity; anxiety and substance abuse comorbidity, rapid cycling, and more with 20 or more prior episodes, as well as poor response to long term naturalistic treatment (Post et al., 2014b).

Earlier age of onset and more severe illness characteristics appear to have a genetic/familial basis as parents and grandparents of the US patients have more mood and substance abuse disorders than these relatives of the European patients, and this burden of illness in the family is associated with an earlier age of onset and more difficult illness course in our bipolar probands (Post et al., 2015).

Given these findings we hypothesized that the offspring of the bipolar patients for the US would have a higher incidence of these same illnesses that characterized the prior generations (i.e., the probands parents, and their grandparents) than those from the Netherlands and Germany. These included depression, bipolar disorder, suicide attempts, alcohol abuse and substance abuse, and "other" illnesses. We also hypothesized the more difficult illness characteristics in the patients themselves would be associated more illness in the offspring.

2. Methods

968 outpatients (average age 41) with bipolar disorder (75% BP I) diagnosed by SCID interview were recruited from advertisements and local clinics in four cities in the United States (Los Angeles, Dallas, Cincinnati, Bethesda) and three in Europe (Utrecht, the Netherlands and Freiburg and Munich, Germany) from 1995 to 2002. Patients gave informed consent for participation in the network and completed self-rated questionnaires on family history, psychosocial adversity in childhood, and their retrospective course of illness (Leverich et al., 2002; Post et al., 2014b,2013a,2010a,2014a,2010b).

The following diagnoses were queried on the offspring: unipolar depression, bipolar disorder, history of a suicide attempt or completed suicide, alcohol abuse, drug abuse, and "other illness" including for example an anxiety disorder. Each diagnosis of a family member was rated by the proband as definite, likely, unlikely, or not present, and a definite or likely rating was taken as a positive diagnosis for that relative (Post et al., 2014b,2014a). The questionnaire also elicited answers pertaining to the adult patients' demographics, stressors in childhood, and course of illness characteristics, including the age of onset of bipolar disorder. This was described as the age of onset of the first major depression associated with dysfunction or the first manic or hypomanic episode. Stressors in childhood included a total score for the report of verbal, physical, and sex abuse, each rated as never=0, rarely=1, occasionally=2, and frequently=3 (Leverich et al., 2002; Post et al., 2014c).

Patients were asked about the number of offspring that they had and whether the offspring had any of the above diagnoses. 488 patients indicated that they had children. Of these 356 were from the US and 152 were from Europe. Age of the children was not elicited, and age of onset of the psychiatric disorders they may have had was not obtained.

The incidence of the psychiatric difficulties in the offspring of those from the US was compared with those from Europe by chi-square test and $p < 0.05$ was considered significant. The presence or absence of each type of illness in the offspring was related to their parents' (the proband) illness characteristics by a chi-square, except where a low N required a Fisher's Exact Test. These characteristics included: early onset (before age 19); presence of any abuse in the proband's childhood; a history of rapid cycling (4 or more episodes/year) and 20 or more episodes prior to Network entry; a history of any anxiety disorder, alcohol, or drug abuse comorbidity; and a positive family history of psychiatric illness in the proband's parents.

A linear regression with robust standard errors was run on the proband's adverse illness characteristics (poor prognosis factors, PPFs) to see whether they were independently related to the number of psychiatric diagnoses their offspring had (Table 2). After examing parents ppf's on the total number of child psychiatric diagnoses we looked at each psychiatric diagnosis separately. For each psychiatric diagnosis a logistic regression was run to see the relationship of each of the specified diagnoses to their parents PPFs, and each regression is reported for each offspring illness in Table 3 (A)–(F). Table 4 illustrates the independent effect of being from the US as opposed to Europe when all of the patient differences in PPFs were taken into account. It summarizes the results of 6 separate regressions and only reports on the independent effect of country.

3. Results

The demographics of the parents who had children ($N=488$) were very similar to those in the entire network ($N=968$) and are summarized in Table 1. Each of what might be considered a poor

Table 1
Demographics of parents' adverse bipolar illness characteristics (what have been termed poor prognosis factors, or PPFs).

	US ($n=356$) % positive	Europe ($n=132$) % positive	chi	p
Early onset	68.8	37.1	40.4	0.00
Childhood abuse	70.8	46.2	25.3	0.00
Number of episodes	60.7	27.3	43.0	0.00
Rapid cycling	75.8	47.0	36.9	0.00
Anxiety disorder	48.3	28.8	15.0	0.00
Drug or alcohol abuse	50.0	25.8	23.0	0.00
Parental history or uni or bipolar disorder	60.1	37.9	19.2	0.00

% positive is the precent of probands positive for the listed ppf in the specified country.
Statistic is a chi square.

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