Journal of Affective Disorders 207 (2017) 313–319

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Illnesses in siblings of US patients with bipolar disorder relate to multigenerational family history and patients severity of illness

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ARTICLE INFO

Keywords:
Depression
Alcohol abuse/dependence
Substance abuse/dependence
Suicide attempts
Anxiety disorder
Transgenerational vulnerability
Illness differences across countries

ABSTRACT

Background: Patients with bipolar disorder from the US have more early-onset illness and a greater familial loading for psychiatric problems than those from the Netherlands or Germany (abbreviated here as Europe). We hypothesized that these regional differences in illness burden would extend to the patients siblings.

Methods: Outpatients with bipolar disorder gave consent for participation in a treatment outcome network and for filling out detailed questionnaires. This included a family history of unipolar depression, bipolar disorder, suicide attempt, alcohol abuse/dependence, drug abuse/dependence, and "other" illness elicited for the patients' grandparents, parents, spouses, offspring, and siblings. Problems in the siblings were examined as a function of parental and grandparental problems and the patients' adverse illness characteristics or poor prognosis factors (PPFs).

Results: Each problem in the siblings was significantly ($p < 0.001$) more prevalent in those from the US than in those from Europe. In the US, problems in the parents and grandparents were almost uniformly associated with the same problems in the siblings, and sibling problems were related to the number of PPFs observed in the patients.

Limitations: Family history was based on patient report.

Conclusions: Increased familial loading for psychiatric problems extends through 4 generations of patients with bipolar disorder from the US compared to Europe, and appears to "breed true" into the siblings of the patients. In addition to early onset, a variety of PPFs are associated with the burden of psychiatric problems in the patients' siblings and offspring. Greater attention to the multigenerational prevalence of illness in patients from the US is indicated.

1. Introduction

Similarly to patients with bipolar disorder, siblings should be at increased risk for psychiatric illness because of the shared genetic and environmental risk factors. In our international network we have observed that patients with bipolar disorder from the United States (US) have multiple characteristics of more severe illness than those from the Netherlands and Germany (abbreviated here as Europe) (Post et al., 2014a, 2011). Sites in the US included Los Angele, Dallas, Cincinnati, and Bethesda; those from Europe included Utrecht, Freiberg, and Munich. Differential illness characteristics include more: early onset bipolar disorder, adversity in childhood, anxiety and substance abuse/dependence comorbidity, rapid cycling and greater than 20 prior episodes, and treatment resistance during prospective

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http://dx.doi.org/10.1016/j.jad.2016.09.042
Received 18 July 2016; Received in revised form 7 September 2016; Accepted 27 September 2016
Available online 06 October 2016
0165-0327/

naturalistic follow up (Post et al., 2010b). This difficult course of illness was related to greater genetic/familial history for bipolar disorder and other psychiatric problems in the patients' parents and grandparents (Post et al., 2015a, 2015c). More environmental vulnerability was also evident from psychosocial stressors, both abuse during childhood and more stressors in the year prior to illness onset and prior to the last episode just before Network entry at average age 40 (Post et al., 2013a, 2015b).

In addition, compared to the Europeans, the patients from the US had offspring that were more ill than those from the Europeans (Post et al., 2016b). Given this evidence of multiple generations of those from the US having more psychiatric illness and more vulnerability factors for early onset, it was appropriate to further validate these differences in other relatives in the same generation as the patients, i.e. their siblings. Siblings have been widely used in genetic studies, and the data of Lin et al. (2006) suggested, based on data in siblings, that early onset bipolar disorder and substance abuse/dependence were genetically linked.

We hypothesized that, like the patients with bipolar disorder from the US, their siblings would have more psychiatric problems than those from Europe. Moreover, as observed in the patients' offspring (Post et al., 2016b), we predicted that psychiatric problems in the patients' parents and grandparents would be associated with the same type of problems seen in the siblings. The number of adverse illness characteristics or poor prognosis factors (PPFs) in the patients was used as an indirect index of illness burden and severity in the patient and the number of PPFs was also hypothesized to be related to the psychiatric problems manifest in the siblings.

2. Methods

979 patients with bipolar disorder were enrolled into the Stanley Foundation Bipolar treatment outcome Network (SFBN) from 1995 to 2002 (Kupka et al., 2007; Post et al., 2014a, 2011, 2014b, 2010b, 2001). 75% had bipolar I disorder, 21% had bipolar II disorder, and 4% had bipolar not otherwise specified (BP-NOS) or schizoaffective disorder bipolar subtype. They gave informed consent for their participation and completed a comprehensive battery of diagnostic and follow up evaluations. This included Structured Clinical Interview for the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (SCID-DSM-IV) interview (First et al., 1997) to confirm the diagnosis, as well as at each visit cross sectional ratings on the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Inventory for Depressive Symptoms (IDS) (Rush et al., 1986), and Clinical Global Impression scale for Bipolar Disorder (CGI-BP) (Spearing et al., 1997). In addition, patients were rated on a daily basis using the National Institute of Mental Health (NIMH)-Life Chart Method (NIMH-LCM) (Denicoff et al., 1997) by trained clinicians. Once funding for patient enrollment and study ended in 2002, data analysis continued under the auspices of the Bipolar Collaborative Network (BCN) to further examine US versus European differences (Post et al., 2014a, 2016b, 2015b, 2011, 2015c).

Upon enrollment, patients completed a detailed questionnaire that included data on: demographics; clinical course of illness; family history of psychiatric problems; and psychosocial stress in childhood, at illness onset, and prior to the most recent episode. It also included information about comorbid anxiety, substance abuse/dependence, and medical conditions. Age of illness onset the patients' bipolar disorder was acquired from both a SCID interview and the patient questionnaire in response to the inquiry about the age of onset of the first hypomanic or manic episode or the first episode of depression that was associated with dysfunction (to approximate DSM criteria).

Upon network entry, a subset of 529 patients who were rated daily in the network for at least 1 year. Those who entered the network ill (as opposed to euthymic), were characterized as long-term (greater than 6 months) responders or non-responders based on their ability to achieve and maintain a much improved or very much improved clinical status on the CGI BP based on visual examination of the daily NIMH-LCM ratings (Post et al., 2010a).

The patients six adverse illness characteristics, that we label poor prognosis factors (PPFs) based on the literature and findings in our own cohort, included: early age of onset (prior to age 19), a history of adversity in childhood, an anxiety disorder; substance abuse/dependence comorbidity, rapid cycling (4 or more episodes in any given year), and the experience of 20 or more prior episodes.

The following psychiatric problems were queried on the patients' siblings, parents, and grandparents: unipolar depression, bipolar disorder, history of a suicide attempt or completed suicide, alcohol abuse/dependence, drug abuse/dependence, and "other illness" including for example an anxiety or other disorder. Each psychiatric problem 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 evidence of that psychiatric problem for that relative (Post et al., 2014a, 2014b). 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., 2015b). A positive rating included verbal abuse rated a 3, or physical or sexual abuse rated a 2 or 3.

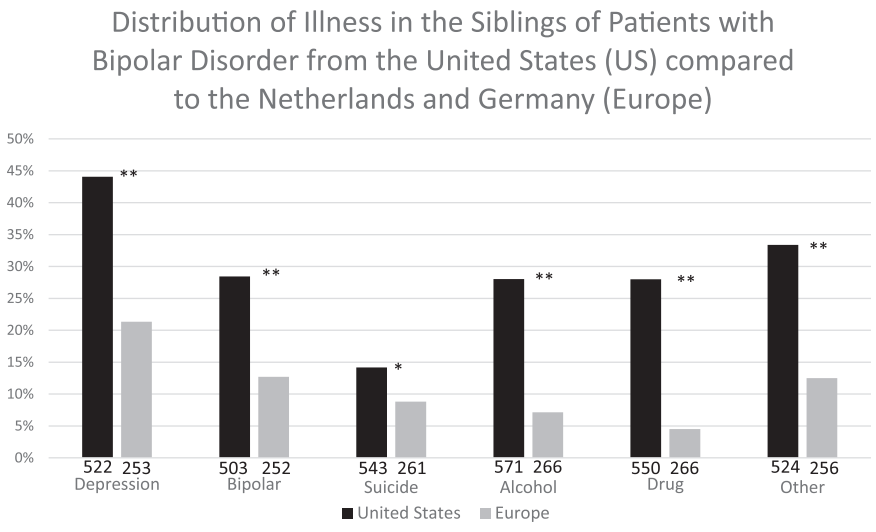

Fig. 1. Distribution of Illness in the Siblings of Patients with Bipolar Disorder from the United States (US) compared to the Netherlands and Germany (Europe). *p=0.03; **p < 0.001; numbers below each bar=number of siblings in each group.