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

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Journal of Affective Disorders 191 (2016) 180–186

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Review article

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

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ARTICLE INFO

Article history:
Received 29 July 2015
Received in revised form
22 October 2015
Accepted 22 November 2015
Available online 26 November 2015

Keywords:
Depression
Substance abuse
Anxiety disorder
Family history
Suicide attempt

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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http://dx.doi.org/10.1016/j.jad.2015.11.038
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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.

Table 2
Logistic Regression for the Number of illnesses in the offspring as predicted by probands' poor prognosis factors ($N=488$).

	Odds ratio	Std. err.	z	p	[95% conf. interval]	
Country	-0.39	0.08	-4.78	0.000	−0.56	−0.23
Age of onset	0.00	0.00	0.18	0.855	−0.01	0.01
Childhood abuse	0.29	0.09	3.26	0.001	0.12	0.47
Number of episodes > 20	0.37	0.11	3.43	0.001	0.16	0.59
Anxiety disorder	0.30	0.12	2.6	0.010	0.07	0.53
Parental history	0.29	0.10	2.91	0.004	0.10	0.49

The number of illnesses in the offspring was significantly related to each PPF with the exception of early Age of Onset of bipolar disorder

prognosis factor for long term outcome of bipolar disorder was highly significantly more prevalent in the US than in the Netherlands or Germany (Europe). These patients had an average of 1.97 and a median of 2 offspring, and this did not differ between those from the US versus Europe.

The burden of offspring illness was substantial and included 20.3% with depression, 13.5% with bipolar disorder, 5.3% with a suicide attempt, 5.9% with alcohol abuse, 9.8% with drug abuse, and 20.5% with "other" illness. As shown in Fig. 1, compared to Europeans the offspring of patients with bipolar illness from the US had significantly more of each diagnosis ($p < 0.001$), with the exception of a history of alcohol abuse (p,0.01), or suicide attempt (ns) and schizophrenia where the incidence of these in the offspring was low.

Table 2 illustrates the linear regression with robust standard errors of the number of diagnoses in the offspring as related to parental illness characteristics $F\ (6,481)=13.17$, $p < 0.001$. The parents emanating from the US as opposed to Europe, having had abuse during childhood, having had 20 or more episodes, an anxiety disorder comorbidity, and more psychiatric illness in their parents (the grandparents of the offspring) were significantly independently related to the number of diagnoses in the offspring. Neither the proband's income level or level of educational attainment related to the presence or absence of the offsping's diagnosis of depression or bipolar disorder (data not illustrated).

As illustrated in Table 3 each type of psychiatric difficulty in the offspring was related to various aspects of the patients' (parents') illness characteristics as described in the paragraph below. In addition in Table 4 is the summary of six logistic regressions indicating that the country of origin (US vs Europe) was significantly related to each of the offspring's difficulties independently of any of the parent's illness characteristics, listed in Table 3.

The occurrence of depression (3A) or an "other" diagnosis (3F) in the offspring was significantly related to the presence of each of the adverse illness characteristics (poor prognosis factors) in the proband, with the exception of alcohol or drug abuse. Very similarly, a diagnosis of bipolar disorder in the offspring (3B) was related to the probands' early onset, more episodes and rapid cycling, anxiety disorder comorbidity, and a positive parental history of psychiatric illness, but not a history of alcohol or substance abuse and in this instance not the parents's history of abuse in childhood.

Interestingly, even with the very small numbers of offspring positive for a suicide attempt (3C), this was significantly related to the probands' own history of abuse in childhood ($p=0.008$), an anxiety disorder comorbidity ($p=0.05$), and the patients' parents positive history of psychiatric illness ($p=0.046$).

Table 3
Relationship of bipolar patients' illness poor prognosis factors (PPFs) to illness occurring in their offspring.

	Child's depression diagnosis in absence or presence of parental PPF		
3A			
Parents illness PPF	p	No PPF $n=389$	PPF $n=99$
Early onset	0.031	15.5%	23.5%
Childhood abuse	0.014	14.3%	23.6%
20+episodes	0.00	12.3%	27.8%
Rapid cycling	0.002	12.2%	24.1%
Anxiety	0.00	13.7%	29.1%
Alcohol or drug abuse	0.497	19.2%	21.7%
Parental history	0.00	12.1%	27.3%
3B			
	Child's bipolar dx		
	p	No PPF $n=422$	PPF $n=66$
Early onset	0.002	7.7%	17.4%
Childhood abuse	0.198	10.9%	15.0%
20+episodes	0.001	8.1%	18.7%
Rapid cycling	0.022	8.3%	16.0%
Anxiety	0.001	9.0%	19.5%
Alcohol or drug abuse	0.723	13.0%	14.2%
Parental history	0.00	6.7%	19.3%
3C			
	Child's suicide attempt		
	p	No PPF $n=462$	PPF $n=26$
Early onset	0.582	4.6%	5.8%
Childhood abuse	0.008	1.7%	7.4%
20+episodes	0.065	3.4%	7.1%
Rapid cycling	0.062	2.6%	6.6%
Anxiety	0.05	3.6%	7.6%
Alcohol or drug abuse	0.271	4.4%	6.6%
Parental history	0.046	3.1%	7.2%
3D			
	Child's alcohol abuse		
	p	No PPF $n=459$	PPF $n=29$
Early onset	0.076	3.6%	7.5%
Childhood abuse	0.00	0.6%	9.0%
20+episodes	0.001	2.1%	9.5%
Rapid cycling	0.351	4.5%	6.6%
Anxiety	0.173	4.7%	7.6%
Alcohol or drug abuse	0.817	6.2%	5.7%
Parental history	0.005	2.7%	8.7%
3E			
	Child's drug abuse		
	p	No PPF $n=460$	PPF $n=48$
Early onset	0.205	11.2%	7.7%
Childhood abuse	0.00	2.9%	13.7%
20+episodes	0.001	5.1%	14.3%
Rapid cycling	0.039	5.8%	11.8%
Anxiety	0.051	7.6%	12.9%
Alcohol or drug abuse	0.203	8.3%	11.8%
Parental history	0.032	6.7%	12.5%
3F			
	Child's "Other" diagnosis		
	p	No PPF n-388	PPF $n=100$
Early onset	0.00	12.4%	25.9%
Childhood abuse	0.00	8.0%	27.5%
20+episodes	0.00	10.6%	29.8%
Rapid cycling	0.00	9.6%	25.6%
Anxiety	0.00	12.2%	31.4%
Alcohol or drug abuse	0.563	19.6%	21.7%
Parental history	0.007	15.2%	25.0%

Table 4

Influence of Country on disorders in children of bipolar patients controlling for proband ppfs*

	OR	SE	z	p	[95% conf. interval]		Regression N	Regression LR	Regression p
Depression	0.43	0.16	-2.3	0.022	0.21	0.88	488	46.53	0.00
Bipolar	0.29	0.15	-2.46	0.014	0.11	0.78	488	41.39	0.00
Suicide	0.62	0.42	-0.71	0.48	0.16	2.36	488	15.15	0.0563
Alcohol	0.35	0.28	-1.31	0.19	0.07	1.69	488	36.19	0.00
Drug	0.27	0.17	-2.08	0.038	0.08	0.93	488	33.09	0.0001
Other	0.28	0.12	-2.94	0.003	0.12	0.65	488	74.41	0.00

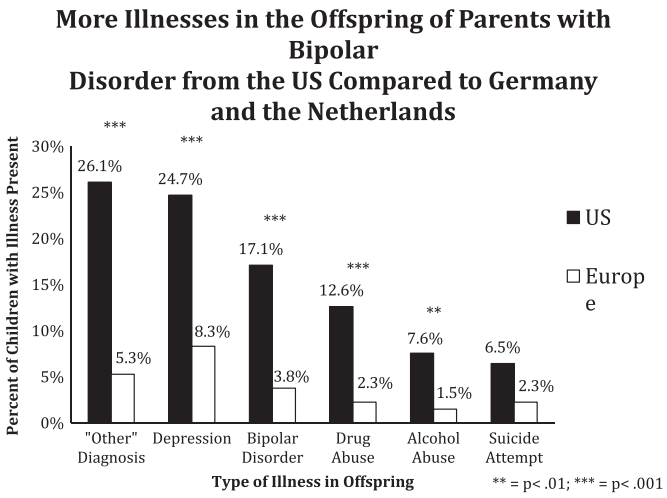

Fig. 1. The total sample of all patients who responded to whether their child had a disorder was 488; of these 356 were from the US and 132 were from Europe.

A diagnosis of alcohol abuse (3D) and of drug abuse (3E) in the offspring were both related to a history of the parents history of abuse in childhood ($p < 0.001$), the occurrence of 20 or more episodes ($p = 0.001$), and the parental loading for psychiatric illness, but interestingly not the probands' history of either type of substance abuse.

Table 4 summarizes the results of 6 separate regressions illustrating that offspring in the US compared to Europe had significantly more of each type of illness (except suicide attempt) even after all of the differences in the patients PPFs were taken into account.

4. Discussion

Each psychiatric diagnosis was more common in the offspring of patients with bipolar illness from the US compared to those from the Netherlands or Germany (for convenience abbreviated here as Europe). Particularly striking were the high levels and significant US vs Europe differences in the offsprings' incidence of depression (25% vs. 8%), bipolar disorder (17% vs. 4%), and "other" psychiatric disorders (26% vs. 5%) and drug abuse (12% vs 2%),.

The number of illnesses in the offspring was also significantly related to country (US > Germany and the Netherlands). This difference remained significant even when the other poor prognosis factors were taken into account in the linear regression in Table 2. Most of the probands' poor prognosis factors (with the notable exception of drug or alcohol abuse comorbidity) were significantly related to an increased incidence of offspring depression, bipolar disorder, and "other" illness in the whole sample. These included; the patient's own parental history of psychiatric illness, an early age of onset (before age 19), a history of an anxiety disorder comorbidity, and 20 or more episodes and rapid cycling. A history of abuse in childhood was related to depression and "other" illness in the offspring, but not to bipolar disorder in the offspring. When separate logistic regressions were run including country as well as all other illness characteristics (poor prognosis factors) of the parents, in each instance the greater amounts of illness in the offspring in the US compared to Europe were significant (Table 4) and could not be explained by any of the difference in the patients poor prognosis factors (listed in Table 1)

The relationship of more severe illness characteristics in the adult patient (probands) themselves to the occurrence of depression, bipolar, and "other" illness in the offspring suggest strong transgenerational transmission of not only bipolar disorder, but also depression and "other" psychiatric illness in the offspring. These findings are consistent with our previous observations that parents and grandparents of the US probands had more psychiatric illness burden than the European probands (Post et al., 2014a), and that this total family loading was associated with an earlier age of onset of bipolar disorder in the probands (Post et al., 2015).

The occurrence of psychosocial adversity in the proband's childhood was likewise higher in the US than Europe (Post et al., 2013a), and this interacted with the degree of family loading to convey the earliest ages of onset of bipolar disorder in our probands (Post et al. 2015). The proband's early age of onset was related to their offsprings diagnoses of depression, bipolar disorder, and "other" illness, but early age of onset was not a predictor of the overall number of illnesses the offspring had in the multiple regression. This relationship of parental early onset illness to the occurrence of bipolar illness in the offspring is consistent with the findings of (Preisig et al., 2015) that early onset bipolar disorder (and not bipolar disorder in general) was the significant risk factor for the offspring in their study to develop bipolar disorder.

4.1. Caveats, limitations and counter arguments

Before with further discussing these findings and their potential implications, several caveats are in order. Most of the data presented rest on answers by the proband to a detailed patient questionnaire and were not directly cross validated by other sources.

However, a number of factors in the literature suggest that these finding are likely valid. Most telling are the recent finding of Axelson et al. (2015) in high risk children (because of a parent with bipolar disorder) who had increased risk of bipolar spectrum disorder, depression, anxiety and other disorders compared to community controls upon a 6.7 year prospective follow up with systematic diagnositic assessments. The incidence of these disorders was even higher in the offspring in the Axelson et al. (2015) study compared to our offspring. While our study and that of Axelson et al. (2015) are not directly comparable in age of the children, duration of time of observation or follow up, or methods of diagnosis, the findings show substantial similarities in the

distribution and moderately high incidence of these childhood disorders. In our study, a positive offspring diagnosis was counted only once even in families with 2 or more children suggesting that the percent of illness in the individual children of our patients could be somewhat lower than stated.

The findings also bare some similarity to those in other prospective high risk studies in the literature conducted in the US which showed a higher incidences of childhood onset bipolar disorder than those conducted in Canada, the Netherlands, or Switzerland (Post et al., 2014b). In the review of epidemiological studies of childhood onset bipolar disorder, Van Meter et al. (2011) found higher rates of bipolar disorder in the US than many other countries when studies that included BP-NOS in the assessments were compared.

The very substantially earlier age of onset of bipolar disorder in the US in our studies (Post et al., 2014b,2008) have been replicated by others (Bellivier et al., 2014; Post et al., 2008). The earlier the age of onset of illness in our patients (probands) was associated with higher incidence of a diagnosis of bipolar disorder, as well as depression and "other" illness in the offspring.

4.2. Clinical Implications

Given the data from studies in the literature in addition to our own reported here, there is considerable evidence that bipolar illness in the US has an earlier age of onset and more adverse course than in many other countries. In addition there appears to be an excess of family history positivity for a number of illnesses in 4 generations of those from the US compared to Germany and the Netherlands. In particular a substantial portion of a new generation of offspring from parents with bipolar illness have already progressed from an "at high risk" status to already having multiple actual difficult-to-treat childhood disorders as seen here and in the study of Axelson et al. (2015) and the other high risk studies particularly in the US but also in Europe.

This large burden of illness is also consistent with the findings supporting the existence of a year of birth or cohort effect where each generation from the early 1900s has had an increased incidence and earlier age of onset of unipolar and bipolar disorder (Lange and McInnis, 2002). A cohort effect is also present for ADHD where there is a higher incidence in more recently born children that in older children, an effect that is not related to differences in diagnostic criteria (Thomas et al., 2015). Thus, pediatricians and psychiatrists need to play a key role not only recognizing the impact of childhood adversity on subsequent medical and psychiatric illness (Shonkoff and Garner, 2012), but also of the range of psychiatric illnesses beginning in childhood and adolescence in both high risk and community-based populations (Axelson et al., 2015) that require careful evaluation, treatment, and referral if necessary.

This transgenerational transmission in our results and in the literature would appear to have both genetic and environmental (epigenetic) bases. As in the classic cross-fostering studies of Meaney and associates (Weaver et al., 2004,2006), the biochemical and behavioral signature of high licking and grooming dams is passed to the next generation based on the licking and grooming behavior the pups received and not on genetic inheritance of traits. In addition to these well-accepted environmental experience-induced epigenetic mechanisms, new data suggest the possibility of a third form of transmission, where a father's lifetime experience with and reactivity to stressors and some drugs of abuse is passed on to the next generation in the absence of any contact with the offspring. These altered behavioral reactivities are thought to be mediated by the persistence of epigenetic chemical marks on the gametes (ova and sperm) that are passed to the next generation (Bale, 2014; Dias and Ressler, 2014; Szutorisz et al., 2014; Vassoler et al., 2014). This mechanism is of particular interest in relationship to the findings in our study of the parents' own experience of abuse in childhood being related to the occurrence of each diagnosis in the offspring (except bipolar disorder) as well as to the number of psychiatric difficulties in the offspring.

Whatever the precise genetic, neurobiological, and psychosocial mechanisms of transgenerational transmission, this problem of a high multigenerational increased illness burden in the US deserves replication with more precise prospective measures and epidemiologically sound methodology, as well as attempts at amelioration and prevention. Miklowitz et al. (2013) reported that high risk children by virtue of a positive family history of bipolar disorder who had a diagnosis of depression, anxiety, or cyclothymia did significantly better with family focused therapy (FFT) than treatment as usual (TAU) in most aspects if symptomology and the effects were the largest in families with high negative expressed emotion. Thus it would appear that FFT or some related therapy (Fristad et al., 2009) would be of great importance in approaching early mood and anxiety symptoms that may or not be precursors to bipolar disorder (Axelson et al., 2015). Since early childhood onsets of unipolar and bipolar disorder both have a less positive outcome than adult onset 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) at least in part driven by the increased duration of time lag before treatment is commenced (Post et al., 2010b), approaching this lag as a remediable risk factor deserves special attention.

Little systematic data are available to guide clinical therapeutics in childhood bipolar disorder or in the youngest children who often present with BP-NOS, which is itself is highly disabling, difficult to treat, and a precursor to full bipolar in about 50% of the children who also have a positive family history of bipolar disorder (Axelson et al., 2015; Birmaher et al., 2009). A new vital treatment research agenda is indicated, so that the very large groups of children who have the multiple illnesses seen in our US cohort and that of Axelson et al. (2015) and others (Birmaher et al., 2009,2014; Perlis et al., 2004; Post et al., 2015,2010) have the best information for optimized care. There are multiple safe candidate agents that could readily be studied in practical (open randomized) clinical trials including omega 3 fatty acids (Nemets et al., 2006; Wozniak et al., 2007) (Ratheesh and McGorry, 2014), vitamin D3 (Gracious et al., 2012), N-acetylcysteine (Berk et al., 2013; Hardan et al., 2012), and perhaps even EM Power, and minocycline that could be explored (Post et al., 2013) in parallel to studies of agents already found effective in adults.

In light of the paucity of data about how very young child with mood and behavioral disorders are currently being treated in the community, we have started a Child Mood Disorder Initiative for parents of children (2–12) with these illnesses (or at risk for them by virtue of a positive parental history of a mood disorder) to rate the severity of symptoms on a weekly basis on a secure web site. The observational protocol is approved by the IRB of John Hopkins School of Medicine in collaboration with the PI Robert Findling. Information about the Network and an informed consent document are available at www.bipolarnews.org. Parents will be able to print out the longitudinal weekly ratings of depression, anxiety, ADHD, oppositional behavior and mania which should assist them and their child's clinicians in better defining illness course and response to treatment. We hope this Child Network will add a modicum of treatment-related knowledge in very young children as the field awaits more systematic data from randomized studies. In the meantime the message from our studies and those in the literature is that in addition to a general trend in the population seen in the cohort effect, children at high risk for illness because of

a positive family history of bipolar, especially in the US but also elsewhere, deserve special attention, monitoring, and in many instances specific treatment for their varied disorders. With early recognition and intervention, these illnesses will hopefully have a more benign course (Correll et al., 2007; McNamara et al., 2010; Post, 2009; Post et al., 2013c; Post and Kowatch, 2006; Ratheesh and McGorry, 2014).

Acknowledgments

We acknowledge the support of the Stanley Medical Research Institute for the collection of the patient data from June, 1995 to December, 2002.

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