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Research report

Role of childhood adversity in the development of medical co-morbidities associated with bipolar disorder

Robert M. Post [a,*], Lori L. Altshuler [b], Gabriele S. Leverich [a], Mark A. Frye [c], Trisha Suppes [d], Susan L. McElroy [e,f], Paul E. Keck Jr.[e,f], Willem A. Nolen [g], Ralph W. Kupka [h], Heinz Grunze [i], Mike Rowe [a]

[a] Bipolar Collaborative Network, 5415 West Cedar Lane Suite 201B, Bethesda, MD 20814, USA
[b] UCLA Mood Disorders Research Program and VA Medical Center, Los Angeles, CA, USA
[c] Mayo Clinic Department of Psychiatry and Psychology, Mayo Clinic Depression Center, USA
[d] Stanford University School of Medicine and V.A., Palo Alto Health Care System, Palo Alto, CA, USA
[e] Lindner Center of Hope, Mason, OH, USA
[f] Biological Psychiatry Program, University of Cincinnati Medical College, Cincinnati, OH, USA
[g] University Medical Center Groningen (UMCG), University of Groningen, Groningen, The Netherlands
[h] VU University Medical Center, Department of Psychiatry, Amsterdam, The Netherlands
[i] Newcastle University, Institute of Neuroscience, Newcastle upon Tyne, UK

ABSTRACT

Objective: A role for childhood adversity in the development of numerous medical conditions in adults has been described in the general population, but has not been examined in patients with bipolar disorder who have multiple medical comorbidities which contribute to their premature mortality.
Methods: More than 900 outpatients (average age 41) with bipolar disorder completed questionnaires that included information about the occurrence of verbal, physical, or sexual abuse in childhood and whether their parents had a mood or substance abuse disorder, or a history of suicidality. These factors were combined to form a total childhood adversity score, which was then related to one or more of 30 medical conditions patients rated as present or absent.
Results: The child adversity score was significantly related to the total number of medical comorbidities a patient had ($p < .001$), as well as to 11 specific medical conditions that could be modeled in a logistic regression ($p < .03$). These included: asthma, arthritis, allergies, chronic fatigue syndrome, chronic menstrual irregularities, fibromyalgia, head injury (without loss of consciousness), hypertension, hypotension, irritable bowel syndrome, and migraine headaches.
Limitations: The contribution of parental diagnosis to childhood adversity is highly inferential.
Conclusions: These data link childhood adversity to the later occurrence of multiple medical conditions in adult outpatients with bipolar disorder. Recognition of these relationships and early treatment intervention may help avert a more severe course of not only bipolar disorder but also of its prominent medical comorbidities and their combined adverse effects on patients'health, wellbeing, and longevity.

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1. Introduction

Bipolar disorder is associated with a host of psychiatric and medical comorbidities (Jerrell et al., 2010). These comorbidities have a dramatic effect on behavior, functioning, and longevity. Recent estimates suggest that bipolar disorder, like other major mental disorders, is associated with a marked reduction in years of life expectancy (Osby et al., 2001). In the U.S. these range from 13 years of lost life expectancy in some eastern states such as Virginia

to 30 years in some western states (Colton and Manderscheid, 2006; Newcomer and Hennekens, 2007). While suicide is a factor, medical causes and contributions appear to exert the major effect (Colton and Manderscheid, 2006; Newcomer and Hennekens, 2007; Osby et al., 2001), especially cardiovascular diseases. The presence of childhood adversity appears to exert a negative influence on the earlier onset and adverse course of bipolar disorder (Brown et al., 2005; Garno et al., 2005; Leverich et al., 2002). Whether it also exerts an influence on increased risk for medical comorbidities remains to be studied.

In general medical practices, a history of childhood abuse or neglect is associated with a significant increase in the onset of a variety of medical illnesses, some of which appear predominantly in adulthood (Anda et al., 2006, 2008, 2010; Dube et al., 2009;

Felitti et al., 1998; Shonkoff and Garner, 2012; Wolkowitz et al., 2011). These include: obesity, cancer, stroke, COPD, diabetes, fractures, hepatitis, asthma, headaches, pulmonary disease, and autoimmune disorders, in addition to overall worse health and functional disability (Anda et al., 2009; Walker et al., 1999).

Some of the potential mechanisms of these long-term effects have been revealed in preclinical and clinical studies. In the laboratory, early adversity can be associated with lifelong reductions of BDNF in frontal cortex and hippocampus (Post, 2007; Roceri et al., 2004; Roth et al., 2009), decreases in the set-point for neurogenesis (Gould and Tanapat, 1999), increases in inflammatory cytokines, and evidence of endocrine and behavioral over-reactivity (Champagne and Meaney, 2001; Plotsky et al., 2005; Weaver et al., 2004). Many of these abnormalities have also been documented in human populations exposed to a variety of types of childhood adversity (Dube et al., 2009; Heim et al., 2004; Kauer-Sant'Anna et al., 2007; McGowan et al., 2009).

In this manuscript we explore the relationship of childhood adversity to the occurrence of medical comorbidities in bipolar disorder (Jerrell et al., 2010; McElroy et al., 2001; Osby et al., 2001) and postulate that childhood adversity is a risk factor for the development of a range of subsequent medical comorbidities reported by adult outpatients.

2. Methods

The demographics and clinical characteristics of the outpatients in the former Stanley Foundation Bipolar Treatment Outcome Network, now continuing as the Bipolar Collaborative Network, have been previously detailed (Post et al., 2010a, 2010b, 2001). Briefly, outpatients with Bipolar I, II or schizoaffective disorder, bipolar type, were recruited from four academic sites in the U.S. and three in The Netherlands and Germany. They gave informed consent for detailed documentation of their prior course of illness and prospective evaluation during naturalistic treatment.

The Network recruited over 900 patients from 1995 to 2002 whose diagnoses were validated by SCID interview and confirmed in prospective longitudinal assessments. Participants were excluded only for active substance abuse requiring acute treatment in another setting, or major medical illnesses that would preclude participation in clinical drug treatment evaluations. Upon admission to the Network, patients filled out a detailed patient questionnaire on demographics and course of illness variables that included questions on the occurrence and frequency of physical, sexual, or verbal abuse in childhood; family history of psychiatric disorders; and a personal history of medical conditions.

In medical populations, Felitti et al. (1998) and Anda et al. (2006) utilized an index of total Adverse Childhood Experiences (ACE) that included the presence or absence of abuse and also a positive parental history of psychiatric disorders including alcohol and substance abuse. In our study, we similarly used a total childhood adversity score (tCAS) which included assessments of childhood physical, sexual, or verbal abuse as well as parental psychiatric difficulties. Childhood physical, sexual, or verbal abuse each were scored on a 0–3 scale according to their reported frequency of occurrence (for a maximum score of 9). History of parental psychiatric difficulties was scored as 0,1, or 2, depending on whether neither, one, or both parents had these difficulties. A report of an "absent" or "not likely" diagnosis was scored as a 0, while a "likely" or "definite" rating in the patient questionnaire was scored as present for that parent. Parental history was assessed for the presence of an affective disorder (either unipolar or bipolar); drug abuse; alcohol abuse; and the occurrence of a suicide or major suicide attempt. The maximum score was 8 if both parents were positive for these psychiatric difficulties, yielding a maximum total childhood adversity score (tCAS) of 17.

We then examined the relationship of the tCAS to the patients' report of the lifetime occurrence of 30 medical conditions, each was scored as present if the patient rated it as "likely" or "definite" having that condition, and absent if it was scored as "unlikely" or "not present". These medical conditions were tabulated for the 968 patients who completed the patient questionnaire. If the comorbidity was rare, (i.e., occurring in less than 20 patients), it was dropped from the analysis in this study due to insufficient sample size. The tCAS scores were then compared in the bipolar subjects as a function of the presence or absence of each of the remaining medical conditions. For this calculation we used tCAS scores only for those 904 who answered all of the questions related to childhood adversity burden. The mean tCAS score was 3.74 ± 3.26 for all 968 patients, while it was 3.84 ± 3.27 for the 904 patients answering all questions.

The relationship between the tCAS and each patient's total number of comorbidities was also examined with a multinomial logistic regression with each patient having none (0), few (1–3), or many (4+) comorbidities using the few category as the baseline. Patient's age, gender, body mass index, country of origin and any interactions were included as needed to produce the best model.

Once a relationship between the total number of comorbidities and tCAS was found, each comorbidity was then individually examined for tCAS influence on it. A logistic regression was run for each comorbidity modeling its occurrence as a function of tCAS and age, gender, body mass index and country of origin. Relationships of the different components of the tCAS to the presence of a given medical condition were preliminarily examined.

Table 1
Frequency of comorbidities in bipolar patients: association with higher tCAS.

Medical comorbidity	Obs.	Number present	Percent present (%)	Mean tCAS present	Mean tCAS absent
Allergies	949	353	37.2	4.66	3.31
Arthritis	946	125	13.2	5.23	3.6
Asthma	947	122	12.9	5.03	3.64
Cancer	948	24	2.5	4.63	3.8
Chronic fatigue syndrome	949	58	6.1	5.41	3.72
Chronic menstrual irregularities (no male)	505	140	27.7	5.11	3.79
Diabetes	949	30	3.2	3.89	3.81
Fibromyalgia	947	29	3.1	5.89	3.75
Head injury (with loss of consciousness)	949	134	14.1	4.4	3.72
Head injury (without loss of consciousness)	950	209	22.0	5.81	3.52
Heart disease	949	55	5.8	4.28	3.78
Hypertension (high blood pressure)	953	152	15.9	4.28	3.78
Hyperthyroidism	945	38	4.0	3.5	3.84
Hypoglycemia	952	60	6.3	4.84	3.75
Hypotension (low blood pressure)	952	100	10.5	5.12	3.67
Hypothyroidism	946	142	15.0	4.01	3.79
Irritable bowel syndrome	944	127	13.5	5.15	3.6
Kidney disease	949	29	3.1	3.76	3.82
Liver disease/Hepatitis	950	43	4.5	5.26	3.75
Migraine headache	950	228	24.0	4.94	3.45
other	721	95	13.2	4.09	3.7
Seizure	946	31	3.3	5.63	3.75

This table lists the frequency with which each comorbidity was found in our patient population as well as the mean tCAS for patients with (present) and without (absent) that comorbidity. Encephalitis, hyperadrenalism (Cushing's disease), hypoadrenalism (Addison's disease), meningitis, multiple sclerosis, narcolepsy, Parkinson's disease, and stroke were also queried, but the incidence was less then 2%, and they were not listed in the table or further examined.

3. Results

The number and percentage of patients reporting each of the 22 medical conditions that occurred in more than 20 individuals are listed in Table 1. Among the most prominent were allergies, migraine headache, and head injury (without loss of consciousness), which occurred in 22–37.2% of the patients. These were followed by hypertension, chronic menstrual irregularities, hypothyroidism, head injury (with loss of consciousness), irritable bowel syndrome, arthritis, asthma, and other problems occurring in 12–16%.

The distribution of the tCAS are listed and illustrated in Fig. 1. Nineteen percent had a score of zero, while 47% of the patient population had a score of 4 or greater. As illustrated in Fig. 2, higher tCAS were associated with a higher number of medical comorbidities; these were grouped as none, few (1–3), or many (4 or more) and subjected to multinomial logistic regression which also accounted for age, gender, and country of origin. Significant independent predictors of having 4+ medical comorbidities as compared to 1–3 included higher tCAS score (the best predictor), being from the US, and female gender, but not age. Significant predictors of having 1–3 medical comorbidities as compared to none included higher tCAS score, increased age, and female gender, but not country of origin Fig. 2.

As reported in Table 2, for 11 of the 16 medical conditions that could be modeled by a logistic regression accounting for age, gender, and country of origin, the risk of patients having that specific comorbidity significantly increased as a function of increasing tCAS. These comorbidities included: allergies, arthritis, asthma, chronic fatigue syndrome, chronic menstrual irregularities, fibromyalgia, head injury (without loss of consciousness), hyper- and hypo-tension, irritable bowel syndrome, and migraine headache.

Table 2 (right column) also shows which parts of the tCAS produced the best individual component model of the comorbidities presence. A history of physical abuse in childhood remained related to numerous comorbidities, including allergies, chronic fatigue syndrome, head injury (without loss of consciousness), and hyper- and hypotension. Sexual abuse was only related to irritable bowel syndrome. Verbal abuse was related to arthritis and migraine headaches. However, while the best model was obtained by using the specified abuse type listed, one could typically substitute the other types of abuse with only minor loss in the model's explanatory power. Parental
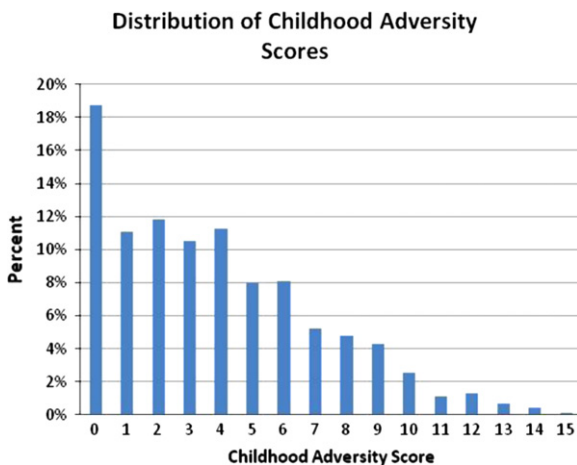
Fig. 1. shows the distribution of childhood adversity scores with the total population ($n=890$). A tCAS of 0 was the most frequent score (18.7%), but then tCAS scores of 1–4 occurred with similar frequency (10.5–11.8%). A little over one third of the population had a tCAS 5 or greater.
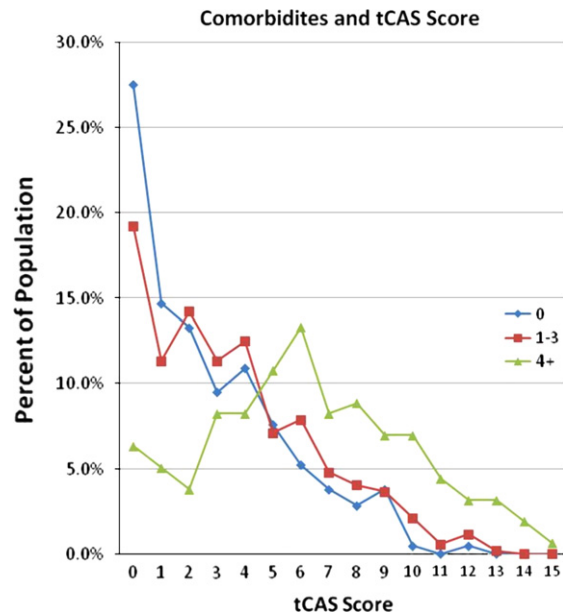
Fig. 2. shows the percent of the population at each tCAS score as a function of having 0 comorbidities, few (1–3), or many (4+). Those with none or few comorbidities had the highest percentage of their populations at 0 tCAS and a rapid dropoff thereafter. In contrast, the 4+ comorbidity category starts with a small percentage of their population at a 0 tCAS and peaks at a relatively high tCAS score of 6 before dropping back down.

	Coef.	RRR	Std. Err.	z	p > |z|	[95% Conf.] Interval	
No comorbidities							
Total Childhood Adversity Score	−0.08	0.92	0.03	−2.61	0.01	−0.14	−0.02
Country	0.19	1.21	0.18	1.07	0.28	−0.16	0.54
Age	−0.02	0.98	0.01	−2.49	0.01	−0.03	0.00
Gender	0.51	1.66	0.17	3.03	0.00	0.18	0.84
4+ comorbidities							
Total Childhood Adversity Score	0.23	1.26	0.03	7.56	0.00	0.17	0.29
Country	−0.55	0.58	0.26	−2.07	0.04	−1.06	−0.03
Age	0.01	1.01	0.01	1.14	0.25	−0.01	0.03
Gender	−0.41	0.66	0.21	−1.99	0.05	−0.82	−0.01

A multinomial logistic regression (above) was used to model the relationship between tCAS score and number of comorbidities using 1–3 comorbidities as a baseline including potential confounds of country of origin, age and gender ($n=890$, likelihood ratio chi-square$=144.27$, $d.f.=8$, $p < .000$). The top row shows that having higher tCAS slightly decreased the likelihood of having 0 comorbidities as opposed to 1–3 (RRR$=0.92$).

However, (bottom rows) increasing tCAS score increased the relative risk of having many (4+) comorbidities as opposed to few (1–3) by a much larger amount (RRR$=1.26$). Patients from the US (as opposed to Europe) were also more likely to have many (4+) comorbidities as compared to few (1–3). Also females were more likely to be in the higher comorbidity group.

history of mood disorder was related to allergies, chronic fatigue syndrome, and menstrual irregularities; parental history of substance abuse to arthritis, head injury, and hypotension; and history of suicidality to fibromyalgia.

4. Discussion

As previously reported in the literature, many medical conditions co-occur in adult outpatients with bipolar disorder (Table 1) whose average age at entry into the Network was just over 40

Table 2
Relationship of total childhood adversity score (tCAS) to 11 medical co-morbidities in adults with bipolar disorder.

Medical comorbidity	Coeff.	Relative increase (%)	Std. Err.	z	P > |z|	95 Conf Int.		n	LR	P	MacFadden's pseudo r2	Individual components
Allergies	0.11	11.0	0.02	4.58	0.00	0.06	0.15	884	49.56	0.00	0.04	Physical abuse, Mother mood disorder
Arthritis	0.11	12.0	0.03	3.57	0.00	0.05	0.18	882	127.72	0.00	0.18	Verbal abuse, Mother drug abuse
Asthma	0.10	10.5	0.03	3.26	0.00	0.04	0.16	882	32.21[a]	0.00	0.05	
Chronic fatigue syndrome	0.16	16.8	0.04	3.64	0.00	0.07	0.24	862	21.57	0.00	0.05	Physical abuse, Mother mood disorder, Father mood disorder
Chronic menstrual irregularities	0.26	30.0	0.11	2.36	0.02	0.04	0.48	500	20.09	0.01	0.03	Verbal abuse, Father mood disorder
Fibromyalgia	0.12	12.9	0.06	2.18	0.03	0.01	0.23	882	48.45	0.00	0.20	Mother suicidal
Head injury Without loss of consciousness	0.13	13.3	0.03	4.86	0.00	0.07	0.18	885	37.34[a]	0.00	0.04	Physical abuse, Mother drug abuse[b]
Hypertension	0.07	6.8	0.03	2.16	0.03	0.01	0.13	867	78.22[a]	0.00	0.10	Physical abuse
Hypotension	0.18	19.3	0.04	4.86	0.00	0.11	0.25	887	65.73	0.00	0.11	Physical abuse, Mother alcohol
Irritable bowel syndrome	0.07	6.7	0.03	2.15	0.03	0.01	0.12	882	85.27	0.00	0.12	Sexual abuse
Migraine headache	0.11	11.9	0.03	4.48	0.00	0.06	0.16	885	72.20	0.00	0.07	Verbal abuse
Not related to tCAS Score												
Diabetes	0.00	0.3	0.06	0.05	0.96	−0.12	0.13	884	39.05	0.00	0.16	Age, BMI
Heart disease	0.09	9.8	0.05	2.05	0.04	0.00	0.18	884	41.65	0.00	0.10	Age
Hypoglycemia	0.03	3.4	0.04	0.82	0.41	−0.05	0.11	886	32.41	0.00	0.08	Age, Country, Gender
Hyperthyroidism	0.00	0.2	0.06	0.03	0.97	−.011	0.11	880	12.56	0.01	0.04	Country, Gender
Kidney disease	0.01	0.5	6.2	0.08	0.93	−0.12	0.13	884	13.14	0.07	0.05	Nonsignificant
Other	0.06	5.8	0.04	1.52	0.13	−0.02	0.13	669	11.99	0.10	0.02	Nonsignificant

This table presents a summary of the influence of tCAS on each comorbidity. Each comorbidity was modeled with a logistic regression as a function of tCAS score accounting for potential effects of country, age, gender, body mass index, and their interaction if needed. Comorbidities which could be successfully modeled with no more then minor speficification errors (as noted) are presented. This shows overall strength of the model (n, LR, p, r2) and the results of the tCAS factor. The other factors included in the model are not shown here. The 11 comorbidities listed at the top of the table were successfully modeled, and all increased significantly as tCAS increased as indicated in the fifth column ($p < (z)$). For these comorbidities, the Individual Components (far right column) shows which parts of the tCAS were significantly related to a given comorbidity when each separate component was used in the logistic regression and the best model selected.

In the bottom rows, the tCAS was not related to diabetes, heart disease, hypoglycemia, hyperthyroidism, even though they were well modeled. Kidney disease and "other" produced non-significant models, while the other comorbidities (Cancer, Head Injury with Loss of Consciousness, Hypothyroidism, Liver Disease/Hepitatis, and Seizure) could not be modeled, as specification errors were too high to be acceptable.

[a] a minor specification error as determined by a linktest with a hat value between .05 and 1.
[b] individual components model slightly better and without specification error.

years. Our study found significant relationships between the total childhood adversity score (tCAS) and the overall number of medical comorbidities a given patient reported (Fig. 1) and to 11 different medical conditions (Table 2), including allergies, arthritis, asthma, chronic fatigue syndrome, chronic menstrual irregularities, fibromyalgia, head injury, hypertension, hypotension, irritable bowel syndrome, and migraine headaches.

4.1. Mechanisms and implications

Both animal models of childhood adversity and clinical data have revealed lasting behavioral, endocrinological, and neurochemical consequences of early stressors in part based on epigenetic mechanisms (Champagne and Meaney, 2001; Meaney and Szyf, 2005; Roth et al., 2009). Early adversity in animals is associated with a decrease in hippocampal glucocorticoid receptors based on increased methylation of the GR promoter. These findings have been replicated clinically in autopsy studies in humans (McGowan et al., 2009, 2008), where reduced glucocorticoid receptors and increased methylation of the promoter have been found in suicide victims with a history of childhood abuse compared with those without such abuse. Similarly, a substantial body of evidence indicates that childhood adversity is associated with increases in inflammatory markers and in the risk for being overweight (Dube et al., 2009; Shonkoff and Garner, 2012), each of which could also contribute to the vulnerability to many of the co-occurring medical conditions. Many biological effects associated with both stress and affective disorders (increases in glucocorticoids, inflammatory markers, oxidative stress, mitochondrial dysfunction, insulin resistance and decreases in neuroprotective factors) could contribute to increases in allostatic load

(Kapczinski et al., 2008; McEwen, 2003, 2004; Post, 2007; Post et al., 2012) and likewise increase the chance of medical illnesses and complications.

Scott et al. (2011) reported in a recently published large international study that both childhood adversity and earlyonset mental disorders (anxiety and depressive disorders) had independent effects in increasing the risk for diverse chronic medical conditions in later life, including the six that they investigated (heart disease, asthma, diabetes, arthritis, chronic spinal pain, and chronic headache). They also found that a history of three or more childhood adversities (such as abuse, neglect, and multiple parental variables) was associated with all six physical conditions with hazard ratios of 1.44–2.19.

The occurrence of bipolar disorder in the absence of a history of childhood adversity is associated with a variety of comorbidities, and many of the same mechanisms noted above have been postulated for such an association. It is clear that there are a rather extraordinarily large number of years of life expectancy lost in those with bipolar disorder and other major psychiatric disorders compared to the general population (Colton and Manderscheid, 2006; Newcomer Hennekens, 2007; Osby et al., 2001). The reason for this early demise appears to be highly attributable to cardiovascular disease, but contributions from other medical comorbidities and suicide are also apparent to a lesser extent. The lack of significant differences in tCAS in those with heart disease in this study may in part be due to the relative low incidence of heart disease (n=55, 5.8%), likely because of the relative young age of our population.

The current findings of an increased burden of medical comorbidities in those subjects with bipolar disorder who have higher tCAS scores suggest the importance of discriminating the

differential contributions of bipolar illness itself and that of a history of childhood adversity on the incidence of various medical comorbidities and their ultimate impact on functional impairment, disability, and mortality. Since recurrence of stressors, substances of abuse, and episodes of affective illness each have been postulated to yield sensitization effects (increased reactivity upon repetition) as well as cross-sensitization to the others in part via epigenetic mechanisms (Post, 2010; Post and Kauer-Sant'Anna, 2010; Post and Miklowitz, 2010; Post et al., 2012), the findings further highlight the importance of early intervention and prevention (Post et al., 2010a, 2010b; Post and Kowatch, 2006). Such early effective treatment might minimize and mitigate the effects of childhood adversity, recurrent episodes of illness, and substances of abuse on subsequent course of bipolar illness, as well as its numerous comorbidities.

The current study also re-enforces the importance of specifically focusing on medical comorbidities and their appropriate treatment in patients with bipolar illness in an effort to decrease the impact and consequences of such medical conditions on health, quality of life, and longevity. Many of the medical comorbidities reported here and in other studies of adults with bipolar disorder were already present at a disproportionately high rate in adolescents (age 13–17) with bipolar disorder compared to a matched control group population (Jerrell et al., 2010). These included obesity, type II diabetes, dyslipidemia, endocrine disorder, organic brain disorder, migraine, epilepsy, cardiovascular disease, and asthma (Jerrell et al., 2010).

Later in life and in the course of bipolar disorder, the burden of cardiovascular disease may be even more apparent than that seen in our study population. A study in Sweden found that bipolar patients and those in the population at large arrived at the same age with heart-related complaints, but compared to those in the general population, the psychiatric patients went on to have fewer invasive corrective interventions, such as angioplasty and bypass surgery, thus potentially accounting for their reduced longevity (Laursen et al., 2009).

We have found that the duration of the interval between the onset of the first episode of bipolar disorder and the first treatment for mania or depression is an independent contributor to an adverse outcome in adulthood (Post et al., 2010b). This time to first treatment was significantly longer in those with a history of childhood physical or sexual abuse compared with those without (Post and Leverich, 2006). Thus, increasing recognition of both the medical and psychiatric difficulties that are associated with a range of childhood adversities may help facilitate earlier and more effective psychosocial and psychopharmacological intervention in these children and adolescents who are at risk for a more adverse course of not only their bipolar disorder but also the emergence of many other medical conditions as well (Shonkoff and Garner, 2012).

Social support, early intervention, and other primary and secondary preventive interventions may also be helpful in those at highest risk for bipolar disorder (Post and Kowatch, 2006; Post and Leverich, 2006;Post and Miklowitz, 2010; Post and Post, 2004). Family psycho-education compared with treatment as usual has consistently been shown to have long-term positive effects in both adults and adolescents with bipolar disorder (Colom and Lam, 2005; Miklowitz et al., 2003a, 2003b; Vieta and Colom, 2004). Part of this education is not only focused on the symptoms of bipolar disorder but also on enhancing interpersonal interactions and intra-family communication and minimizing stressors. Similarly, support by family members, visiting nurse, or a volunteer may be helpful during periods of parental illness and minimize the direct or indirect effects of parental diagnosis on subsequent emergence of medical comorbidities (Eckenrode et al., 2001; Olds et al., 1999).

4.2. Limitations

There are a number of limitations that must be considered in interpreting the findings of this study. The study was based entirely on retrospective and self report data. Self-reports of childhood stressors were based on subjective reports and were not reconfirmed by other informants. However, such self reports and questionnaire methodology are widely used in epidemiological and psychiatric studies (Anda et al., 2006; Brown et al., 2005; Felitti et al., 1998; Garno et al., 2005; Leverich et al., 2002), and some data suggest that they represent conservative estimates of the actual occurrence of childhood adversity, which is often forgotten (Hardt and Rutter, 2004). We also did not have a control group so that whether any of the relationships described may or may not have been specific to this population of bipolar patients is not known.

The classification of parental history of psychiatric illness was also based only on the probands' reports and not confirmed with direct interviews of the family members. Again, some investigators question the reliability of this type of family history, but others indicate that it has considerable reliability and validity (Algorta et al., 2011). However, our exclusive use of a parental history of illness, rather than that of any first-degree relative, may also increase accuracy of reporting.

Another caveat is the utilization of a positive parental history for psychiatric illness as a reflection of potential childhood adversity. The parental status of active illness versus wellness during the early years of the proband's life, which may be an important factor in the relationship to childhood adversity, was not obtained. For example, it is known that treating a mother's depression to remission is associated with less psychiatric illness and externalizing disorders in her children compared to mothers who were similarly diagnosed and treated but did not reach remission (Wickramaratne et al., 2011). Another confounding factor would also be the inability to discriminate whether any contribution of parental psychiatric diagnosis was based on genetic vulnerability or environmental stressors. The medical histories of the parents were also not available.

We decided to include these parental measures and construct a combined tCAS scale in order to closely approximate the measures of adversity used in other studies in the general population (Anda et al., 2006; Felitti et al., 1998). Since these parental variables were indirect and only an indication of potential childhood adversity, these were rated only as present or absent for each parent, and not graded according to frequency or severity, as were the direct reports of verbal, physical, or sexual abuse, which thus were slightly more heavily weighted in the tCAS. However, when we used an un-weighted score of just present or absent for each type of abuse and for either parent having a psychiatric disorder (or suicide attempt), the results were highly similar to those seen when the weighted tCAS was used (analysis not shown). Moreover, in the analysis of the relationship of different components of the tCAS to individual comorbidities, both the childhood abuse and parental variables were found to contribute (Table 2, right column). However, the precise relationships of different components of the tCAS score presented in the Table should be considered highly preliminary and in need of replication as many of the other types of abuse/ adversity would have provided relationships with very little loss of explanatory power. Certainly a larger N would also give more confidence about the relationships described. Although our total childhood adversity scale (tCAS) was similar to the adverse childhood experience (ACE) scale used by Felitti et al. (1998), it was not identical. Moreover, the scale has not been independently validated against other measures in the literature.

Another potential limitation in our study is the reliance on self-report for garnering patients' medical history. The study of

Banks et al. (2006) provides indirect validation of this type of self-report for medical conditions in 55–65 year old white males. In that study, self reports of high blood pressure were validated by actual measures of elevated blood pressure; reports of diabetes by elevated measures of hemoglobin A1C; inflammatory disease processes by elevated c-reactive protein and fibrinogen, and the like. Banks et al. (2006) thus concluded that "Self-reports of disease are not deceiving us about the reality of the situation", and we would assume our similarly acquired data about one's medical conditions would also be reliable especially since they mirror the incidences of these comorbidities reported in other studies and populations of bipolar patients. However, the severity and impact of the medical syndromes listed was not evaluated in our study. Finally, the neurobiological mechanisms underpinning the described relationships were not studied and deserve further exploration, particularly as they might have implications for therapeutics and prevention.

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