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

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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 hypotension, irritable bowel syndrome, chronic fatigue syndrome, irritable bowel syndrome, chronic metabolic syndrome, fibromyalgia, head injury (without loss of consciousness), hypertension, hypopituitarism, 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.

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; Dubé 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

<table>
<thead>
<tr>
<th>Medical comorbidity</th>
<th>Obs. present</th>
<th>Percent present (%)</th>
<th>Mean tCAS present</th>
<th>Mean tCAS absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergies</td>
<td>949</td>
<td>353</td>
<td>37.2</td>
<td>4.66</td>
</tr>
<tr>
<td>Arthritis</td>
<td>946</td>
<td>125</td>
<td>13.2</td>
<td>5.23</td>
</tr>
<tr>
<td>Asthma</td>
<td>947</td>
<td>122</td>
<td>12.9</td>
<td>5.03</td>
</tr>
<tr>
<td>Cancer</td>
<td>948</td>
<td>24</td>
<td>2.5</td>
<td>4.63</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>949</td>
<td>58</td>
<td>6.1</td>
<td>5.41</td>
</tr>
<tr>
<td>Chronic meningitis</td>
<td>905</td>
<td>140</td>
<td>27.7</td>
<td>5.11</td>
</tr>
<tr>
<td>Diabetes</td>
<td>949</td>
<td>39</td>
<td>4.0</td>
<td>3.89</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>947</td>
<td>29</td>
<td>3.1</td>
<td>5.89</td>
</tr>
<tr>
<td>Head injury (with loss of consciousness)</td>
<td>949</td>
<td>134</td>
<td>14.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Head injury (without loss of consciousness)</td>
<td>950</td>
<td>209</td>
<td>22.0</td>
<td>5.81</td>
</tr>
<tr>
<td>Heart disease</td>
<td>949</td>
<td>55</td>
<td>5.8</td>
<td>4.28</td>
</tr>
<tr>
<td>Hypertension (high blood pressure)</td>
<td>953</td>
<td>152</td>
<td>15.9</td>
<td>4.28</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>945</td>
<td>38</td>
<td>4.0</td>
<td>3.84</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>952</td>
<td>60</td>
<td>6.3</td>
<td>4.84</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>952</td>
<td>100</td>
<td>10.5</td>
<td>5.12</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>946</td>
<td>142</td>
<td>15.0</td>
<td>4.01</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>944</td>
<td>127</td>
<td>13.5</td>
<td>5.15</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>949</td>
<td>29</td>
<td>3.1</td>
<td>3.76</td>
</tr>
<tr>
<td>Liver disease/Hepatitis</td>
<td>950</td>
<td>43</td>
<td>4.5</td>
<td>5.26</td>
</tr>
<tr>
<td>Migraine headache</td>
<td>950</td>
<td>228</td>
<td>24.0</td>
<td>4.94</td>
</tr>
<tr>
<td>other</td>
<td>721</td>
<td>95</td>
<td>13.2</td>
<td>4.09</td>
</tr>
<tr>
<td>Seizure</td>
<td>946</td>
<td>31</td>
<td>3.3</td>
<td>5.63</td>
</tr>
</tbody>
</table>

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 than 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 tCAS 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 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
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 than minor specification 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/Hepatitis, and Seizure) could not be modeled, as specification errors were too high to be acceptable.

* a minor specification error as determined by a linktest with a hat value between .05 and 1.
* individual components model slightly better and without specification error.
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 impair-
ment, 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 miti-
gate 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 specific-
cally 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 dis-
order, 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 shown to have long-term positive
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but also the emergence of many other medical conditions as well
(Shonkoff and Garner, 2012).

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 investiga-
tors 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
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 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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Conflict of interest

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Dr. Grunze has received consulting fees and honoraria within the last two years from AstraZeneca, BMS, Eli Lilly, Gedeon Richter, Lundbeck, Merck, Otauka, Servier and UBC.

Dr. McElroy is a consultant to, or member of the scientific advisory boards, in the past year: Alkermes and Shire; is presently or has been in the past year a principal or co-investigator on research studies sponsored by: Agency for Health Care Research & Quality (AHRQ): Alkermes, AstraZeneca, Cephalon, Eli Lilly and Company, Marriott Foundation, NIMH, Orexigen Therapeutics, Inc., Pfizer, Shire, Takeda Pharmaceutical Company Limited, and Transcept Pharmaceutical, Inc.; is also an inventor on U.S. Patent No. 6,323,366 B2. Use of sulfamate derivatives for treating impulse control disorders, and, along with the use of the patent’s assignee, University of Cincinnati, Cincinnati, OH, has received payments from Johnson & Johnson Pharmaceutical Research & Development, L.L.C., which has exclusive rights under the patent.

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Not applicable.