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# CHILDHOOD MALTREATMENT AND THE COURSE OF BIPOLAR DISORDERS AMONG ADULTS: EPIDEMIOLOGIC EVIDENCE OF DOSE-RESPONSE EFFECTS

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## Abstract

**BACKGROUND—**Childhood maltreatment (CM) is highly prevalent among individuals with bipolar disorders (BP); however few studies have examined its potential role in the course and outcome of individuals with BP. We aim to examine the dose response relationship between the number of types of CM and the course of individuals with BP.

**METHODS—**As part of the National Epidemiologic Survey on Alcohol and Related Conditions, 1600 adults who met lifetime *DSM-IV* criteria for BP-I (n=1172) and BP-II (n=428) were included. Individuals were evaluated using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-*DMS-IV* Version and data was analyzed lifetime and from Waves 1 and 2, approximately 3 years apart.



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CONTRIBUTORS

Dr. Sala managed the literature searches, analyses, and wrote the manuscript. Dr. Goldstein reviewed the manuscript. Dr. Wang made the statistical analyses and Dr. Blanco designed the study, implementing quality assurance. All authors contributed to and have approved the final manuscript.

CONFLICT OF INTEREST

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**RESULTS—**Around half of individuals with BP had a history of at least one type of CM. Overall, there was a clear dose-response relationship between number of CM and severity of BP across several domains, including clinical characteristics, probability of treatment, lifetime prevalence of psychiatric comorbidity, incidence of anxiety disorders, substance use disorder, and nicotine dependence, and level of psychosocial functioning.

**LIMITATIONS—**The interviews were conducted by lay professional interviewers rather than clinicians, use of retrospective report to determine CM in individuals with BP, and not all respondents from Wave 1 were able to be interviewed in Wave 2.

**CONCLUSIONS—**The number of types of CM confers developmental differences in the course of BP with a worse course and outcome of BP. Early identification and treatment of CM are warranted to improve the course and outcome of individuals with BP.

### Keywords

bipolar disorder; childhood maltreatment; dose-response; course; epidemiology

## INTRODUCTION

Bipolar disorder (BP) is a prevalent disabling disease with high morbidity rates that causes significant burden to patients, families and society (Begley et al., 2001; Gonzalez-Pinto et al.; McIntyre and Konarski, 2004; Moreno et al.). Recent research suggests that sexual, physical and emotional abuse and neglect frequently co-occur and confer increased risk for multiple psychiatric diagnoses including BP (Keyes et al., 2012; McLaughlin et al., 2010). Because childhood emotional, physical and sexual abuse are highly prevalent among individuals with BP (Brown et al., 2005; Leverich et al., 2002), an important question is whether childhood maltreatment (CM), beyond increasing the risk of BP, also worsens its course and prognosis. Another important question is whether there is a dose-response relationship. That is, are number of subtypes of CM associated with increasingly severe clinical characteristics?

A few clinical studies have examined the potential role of CM in the course and outcome of individuals with BP (Brown et al., 2005; Garno et al., 2005; Leverich et al., 2003; Leverich et al., 2002; Post et al., 2003). For example, in a study of 100 adults with BP, a history of severe CM was found in approximately half of adults with BP, with multiple forms of abuse having occurred in about a third (Garno et al., 2005). In another clinical sample, CM was reported by 48.3% of 330 veterans with BP and found that individuals with physical and sexual abuse were more likely to have current post-traumatic stress disorder (PTSD) and lifetime diagnoses of panic disorder and alcohol use disorders (Brown et al., 2005). As part of the Stanley Foundation Bipolar Treatment Outcome Network with a sample of 631 adults with BP, a study found that those with childhood physical or sexual abuse had a history of earlier onset of BP, increased number of Axis I and II comorbid disorders, including a higher rate of suicide attempts (Leverich et al., 2003; Leverich et al., 2002; Post et al., 2003). Furthermore, data from the National Comorbidity Survey Replication (NCS-R) indicate that a history of CM predict earlier onset and longer episode duration of BP (Green et al.; McLaughlin et al., 2010).

We sought to build on those prior studies by examining whether findings of clinical samples extended to individuals with BP in the community. In prior cross-sectional studies using data from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), we found that sexual (Perez-Fuentes et al.) and physical (Sugaya et al.) abuse during childhood was associated with increased risk of having BP, with sexual abuse having stronger effect than physical abuse (OR=4.10 vs. OR=3.58). Given the clinical relevance and potential prognostic implications of CM in adults with BP, we sought to examine the clinical characteristics, treatment, lifetime and incidence of psychiatry comorbidity, and functioning of adults with BP-I and BP-II using the NESARC. We hypothesized that among adults with BP there would be a dose response relationship between the number of types of CM and a broad range of variables including age of onset, duration of disorder, rates of comorbidity and rates of treatment seeking for BP.

## METHODS

### Sample

The NESARC (Grant et al., 2005a; Grant et al., 2003b) is a longitudinal nationally representative survey whose target population is the civilian, non-institutionalized population of the 50 United States, age 18 and over. Data collection was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and was conducted in two waves using face-to-face interviews. Wave 1 interviews (n = 43,093) were conducted between 2001 and 2002 by professional interviewers who had an average of five years of experience working on Census and other health-related national surveys (Grant et al., 2003b). The current study utilized data from Wave 1 as well as Wave 2 interviews, which were conducted between 2004 and 2005 with 34,653 of the NESARC Wave 2 respondents (Grant et al., 2005a). After accounting for those ineligible for the Wave 2 interview, the response rate for Wave 2 was 86.7%. The mean interval between Wave 1 and Wave 2 interviews was 36.6 (SD=2.62) months. The research protocol, including informed consent procedures, received full human subjects review and approval from the U.S. Census Bureau and the U.S. Office of Management and Budget. Informed consent was obtained from all participants before beginning the interviews. Detailed descriptions of methodology, sampling, and weighting procedures can be found elsewhere (Grant et al., 2003b).

### Measures

Sociodemographic measures included age, sex, race, marital status, education, employment status and personal income.

All diagnoses were made according to DSM-IV criteria using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-Version for DSM-IV (AUDADIS-IV), a valid, reliable, fully structured diagnostic interview designed for use by non clinician professional interviewers (Grant et al., 2001). Reliability of the BP-I diagnosis ($\kappa$=0.59) is fair and good for BP-II ($\kappa$=0.69) (Grant et al., 2005c), whereas the reliability is excellent for alcohol ($\kappa \geq$ 0.74) and drug use disorders diagnoses ($\kappa \geq$0.79) (Grant et al., 2004). The anxiety disorders included in the present study are panic disorder, social anxiety disorder, specific phobia, generalized anxiety disorder, and PTSD which have fair to good reliability ($\kappa$=0.42-0.52)

(Grant et al., 2004). Attention deficit/hyperactivity disorder (ADHD) was assessed in the Wave 2 NESARC and the test–retest reliability was good (κ=0.71) (Bernardi et al.). Suicide attempts were assessed only in individuals, who reported having been sad, blue depressed or having a period that they did not care about things that they usually enjoyed for at least 2 weeks (Morcillo et al.) In those cases, suicide attempt was assessed and computed for those who reported having attempted suicide during that period. Personality disorders assessed on a lifetime basis at Wave 1 and described in detail elsewhere (Compton et al., 2005; Grant et al., 2005b) included avoidant, dependent, obsessive-compulsive, paranoid, schizoid, schizotypal, narcissistic, borderline, histrionic, and antisocial, grouped in the present study into Clusters A, B, and C to increase statistical power and stability of the estimates. Test-retest reliabilities for AUDADIS-IV personality disorders diagnoses in the general population and clinical settings are fair to good (κ=0.40-0.77) (Canino et al., 1999b; Ruan et al., 2008).

We examined the lifetime clinical characteristics of BP (e.g., age of onset of BP, duration of BP, number of depressive and mania or hypomania episodes, suicidal attempts, psychosis) for individuals with BP with versus without different number of types of CM. In addition, we examined lifetime treatment patterns of individuals with BP (e.g., psychotherapy, medication, hospitalization and emergency room care) for major depressive (MDE) and mania or hypomania episodes and lifetime psychiatric comorbidities. Incidence of comorbid disorders was defined as developing a new disorder between Wave 1 and Wave 2. Psychosocial functioning was assessed at Wave 2 with the mental component summary, social functioning, role of emotional, and mental health of the 12-item Short Form Health Survey, version 2 (SF-12), a reliable and valid measure of disability used in population surveys (Ware et al., 2005).

## Childhood Maltreatment

CM was assessed in Wave 2. All questions about adverse childhood experiences are related to respondents' first 17 years of life. Questions were adapted from the Adverse Childhood Experiences study (Canino et al., 1999a; Grant et al., 2003a; Grant et al., 1995; Hasin et al., 1997; Ruan et al., 2008) and were originally part of an extensive battery of questions from the Conflict Tactics Scale (CTS) (Dong et al., 2003; Dube et al., 2003; Straus M, 1990) and the Childhood Trauma Questionnaire (CTQ) (Straus M, 1990; Straus, 1979). Response categories for most scale items were 1 = never, 2 = almost never, 3 = sometimes, 4 = fairly often, and 5 = very often. Response category values were summed across items to generate scales. The emotional neglect items all required reverse coding. Childhood sexual abuse was defined by four questions developed by Wyatt (1985) (Wyatt, 1985) All sexual abuse questions asked about sexual experiences with an adult or any other person and were restricted to behaviors that respondents did not want and were experienced when respondents were younger than 18 years old. The sexual abuse scale included questions about touching and fondling, touching in a sexual way, and attempting and actually having sexual intercourse (Perez-Fuentes et al.). Physical abuse was defined by two questions from the CTS including the frequency of pushing, grabbing, shoving, slapping or hitting, and hitting so hard that respondents had marks or bruises or were injured were ascertained (Sugaya et al.).

Emotional abuse was defined by three questions from the CTS. For emotional abuse, questions asked how often respondents' parents or caregivers living in their home: (1) swore at, insulted, or said very hurtful things to respondents; (2) threatened to hit or throw something at respondents but didn't; and (3) acted in any other way that made respondents afraid that they would be physically hurt or injured (Ruan et al., 2008). For both emotional and physical neglect, sets of five CTQ items were used. Items assessing physical neglect included the frequency with which respondents: (1) were made to do chores too difficult or dangerous for someone their age; (2) were left alone or unsupervised when they were too young to be alone; (3) went without things they needed like clothing, shoes, or school supplies; (4) went hungry or were not being provided with regular meals; and (5) had parents or caregivers fail to get them medical treatment when respondents were sick or hurt. Items assessing emotional neglect included the following: (1) there was someone in the respondent's family who wanted him or her to be a success; (2) there was someone in the family who helped the respondent feel important or special; (3) the respondent's family was a source of strength and support; (4) the respondent felt that he or she was part of a close-knit family; and (5) someone in the respondent's family believed in him or her (Ruan et al., 2008).

### Statistical analyses

All analyses were performed using SUDAAN (Research Triangle Institute., 2007) to adjust for the complex design of the NESARC. Weighted percentages and means were computed to derive associations with prospectively ascertained clinical characteristics and treatment of individuals with BP, past and incident psychiatric comorbidities, and mental functioning among BP respondents with different number of types of CM. A series of linear $\chi^2$ tests adjusted by age, gender, race, and income were used to examine dose-response relationships between number of types of CM and course of BP by grouping the number of CM into 4 categories: no maltreatment, only 1 type of maltreatment, 2 types of maltreatment, and 3 or more types of maltreatment.

We consider significant odds ratios (ORs) with confidence intervals that do not include 1. All standard errors and 95% confidence intervals (CIs) were estimated using SUDAAN to adjust for the design effects of the NESARC.

## RESULTS

### Prevalence and Sociodemographic Characteristics

Respondents with a lifetime diagnosis of BP-I (n=1172) and BP-II (n=428) in Wave 1 were included in the present study, and were divided into four groups for the purpose of analyses: individuals without CM (45.71%; n=1086), individuals with only one type of maltreatment (23.73%; n=596), individuals with 2 types of maltreatment (12.85%; n=331), and individuals with 3 or more types of maltreatment (17.71%; n=481). Among individuals with BP, 13.57% had physical neglect (PN), 38.44% emotional abuse (EA), 21.68% physical abuse (PA), 25.99% sexual abuse (SA), 14.7% emotional neglect (EN). The co-occurrence between them was 11.01% for PN and EA, 8.62% for PN and PA, 7.59% for PN and SA, 6.2% for PN and EN, 19.79% for EA and PA, 15.47% for EA and SA, 10.14% for EA and

EN, 10.73% for PA and SA, 7.6% for PA and EN, and 7.29% for SA and EN. Among individuals with BP, being older, female, not married/cohabiting, and having lower personal income were significantly associated with having 3 or more types of CM compared to the other groups. In addition, compared to the other groups, those individuals with BP and having 3 or more types of CM had more family history of depression, alcohol abuse or dependence, drug abuse or dependence, and antisocial personality disorders (Table 1).

### Lifetime Clinical Characteristics and Treatment

After adjusting for age, gender, race and income, there was a dose-response relationship between number of types of CM and clinical characteristics of BP so that individuals with greater number of types of CM had earlier age of onset, longer duration of disorders, more BP-I subtype, and higher number of both depressive and manic/hypomanic episodes, were more likely to have a history of suicide attempt, and psychosis (Table 2).

There was also a dose-response relationship between number of types of CM and probability of having received different modalities of treatment for depression, including medication, psychotherapy, hospitalization, and emergency room care, as well as medication, psychotherapy, and hospitalization for mania/hypomania No significant differences were found for emergency room treatment for mania/hypomania (Table 2).

### Lifetime and Incidence of Psychiatry Comorbidities and Functioning

After adjusting for age, gender, race and income, dose-response relationships were also found between number of types of CM and all axis I and II disorders examined. There was also a dose-response relationship between number of types of CM and incidence of anxiety disorders, substance use disorder and nicotine dependence. Furthermore, there was a dose-response relationship between number of types of CM and psychosocial functioning, with individuals having 3 or more type of CM having lower levels of functioning (Table 3).

## DISCUSSION

Around half of individuals with BP had a history of at least one type of CM. Overall, there was a clear dose-response relationship between number of types of CM and severity of BP across several domains, including clinical characteristics, probability of treatment, lifetime prevalence of psychiatric comorbidity, incidence of anxiety disorders, substance use disorder, and nicotine dependence, and level of psychosocial functioning.

In accord with clinical studies in adults (Brown et al., 2005; Garno et al., 2005; Leverich et al., 2003; Leverich et al., 2002; Post et al., 2003), our results showed high rates of CM among individuals with BP. We found that the number of types of CM contribute to extensive psychopathology with an impact on the clinical profile of individuals with BP, increasing their risk for a broad range of psychopathology, including suicide attempts (Leverich et al., 2003; Post et al., 2003) and psychosis (Hammersley et al., 2003). An important new finding of our study was that although some of the associations, such as age of onset or lifetime comorbidity were measured retrospectively, they converged with our prospective findings of increased incidence of comorbid psychiatric disorders, providing

indirect validation for the retrospective results and demonstrating the long-lasting effects of CM.

Several mechanisms may contribute to explain the relationship between number of types of CM and worse course of BP illness. CM may impact the development of physiological stress response systems (Loman and Gunnar). As suggested in the traumatic neurodevelopment model (Read et al., 2001), early trauma may negatively affect the developing brain. Indeed, findings of an association between psychosis and abuse among youth with BP suggest that the adverse neurodevelopmental effects of abuse may already be present before adulthood (Romero et al., 2009). Specifically, hyper-responsivity of the hypothalamic-pituitary-adrenal (HPA) axis may result in altered dopaminergic, noradrenergic, and serotonergic system function, and structural changes to the brain such as hippocampal damage (Ellis et al., 2005; Heim et al., 2000; van der Vegt et al., 2009). This dysregulation may lead to maladaptive emotional and social functioning in adults with BP and history of CM, such as negative expressed emotion (Miklowitz and Hooley, 1998). These long-lasting biological, psychological and social changes may contribute to the ongoing vulnerability to psychopathology among individuals with CM, as indicated by their increased risk of incidence of psychiatric disorders demonstrated in this study, as well as their longer persistence (McLaughlin et al., 2010). Taken together, these findings emphasize the importance of prevention and early intervention to limit the deleterious effects of CM. For example, pharmacological agents that target central CRF systems may reverse the neurobiological consequences of early life stress and therefore be useful in the prevention and treatment of disorders related to CM in children and adults (Binder et al.; Heim and Nemeroff, 2001).

Our findings are consistent with previous work by our group (Perez-Fuentes et al.; Sugaya et al.) and others (Keyes et al., 2012; McLaughlin et al., 2010) documenting the strong association between different number of types of CM with a broad range of disorders. These findings suggest that the deleterious effects of CM are substantial but not specific to one psychiatric disorder. Recent studies (Green et al.; Keyes et al., 2012) have suggested that the effect of CM on psychopathology does not occur at the disorder level, but rather by increasing individuals' liabilities for the broader domains of internalizing and externalizing disorders. Interventions directed towards decreasing those liabilities may be more efficient than those directed at preventing specific disorders.

The potential limitations of this study should be taken into consideration. First, like in all large epidemiological studies, the NESARC interviews were conducted by professional interviewers rather than clinicians. However, the NESARC interviewers received extensive training with a highly structured and well-validated diagnostic assessment instrument (Grant et al., 2003a). Second, the use of retrospective report to determine CM in individuals with BP may be subject to recall bias. However, the proportion of individuals who reported it in our study is similar to the rates reported in clinical studies (Brown et al., 2005; Garno et al., 2005; Leverich et al., 2002). Third, although the reliability of AUDADIS-IV for bipolar disorders is good (Moreno et al., 2012), our data are based on one cross-sectional interview made by trained interviewers. It would be impractical to obtain clinician-administered interviews in such a large sample. Fourth, suicide attempts assessed only among responders

who screened into the depression section of the AUDADIS-IV (i.e., endorsed sadness and/or anhedonia for at least 2 weeks). However, previous research indicates that the percentage of individuals who do not screen into the depression section of the AUDADIS-IV and report a suicide attempt was very low (less than 0.1%) (Baca-Garcia et al., 2010). Finally, not all respondents from Wave 1 could be interviewed in Wave 2. However, statistical adjustments were made for nonresponse to make the reweighted sample representative of the US adult population. Furthermore, although not all respondents were available for re-interview, the response rate of Wave 2 was 86.7%, a much higher figure than other nationally representative surveys (Grant et al., 2008).

Despite these limitations, this is the first representative national study to examine the dose-response relationship between the number of types of CM and the course of BP. Our findings highlight the existence of differences in the course of BP by the number of types of CM conferring further risk for a worse course and outcome of BP, including increased risk for the incidence of comorbid disorders even many years after experiencing the abuse. This study has several clinical implications. First, routine clinical assessment of CM in individuals with BP is warranted. Second, given that individuals with CM have a worse course of BP, they should be more closely monitored. Third, routine screening for suicide risk factors is needed. The present findings highlight the need for careful assessment of CM in individuals with BP, as well as the importance of early identification, intervention, and preventive measures for those at risk. Prompt identification and psychotherapy effort to reverse some of the effects of CM and to prevent victimization or repeated pattern of abuse are needed (Cohen et al., 2012; Mannarino et al., 2012). Prospective studies are necessary to fully understand the impact that CM may have in the course and outcome of individuals with BP.

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**Table 1**

Demographic Characteristics and Family History among individuals with Bipolar Disorder with versus without number of types Childhood Maltreatment

| | **No abuse or neglect** | | **1 type of abuse/neglect** | | **2 types of abuse/neglect** | | **≥3 types of abuse/neglect** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N=1086; %=45.71** | | **N=596; %=23.73** | | **N=331;%=12.85** | | **N=481; %=17.71** | | **Chi-square/F test** | | |
| | MEAN or % | SE | MEAN or % | SE | MEAN or % | SE | MEAN or % | SE | chi- square/F | df | p-value |
| Age | 39.23 | 0.55 | 40.83 | 0.72 | 40.51 | 0.80 | 42.02 | 0.72 | 3.15 | 3 | 0.0308 |
| Sex (female) | 52.14 | 1.88 | 56.98 | 2.26 | 52.82 | 3.46 | 69.75 | 2.47 | 10.20 | 3 | 0.0001 |
| Race | | | | | | | | | 1.50 | 3 | 0.2234 |
| White (ref) | 70.62 | 2.51 | 66.02 | 2.63 | 64.65 | 3.52 | 67.34 | 2.61 | | | |
| Non-White | 29.38 | 2.51 | 33.98 | 2.63 | 35.35 | 3.52 | 32.66 | 2.61 | | | |
| Marital Status | | | | | | | | | 3.19 | 3 | 0.0295 |
| Married/cohabiting (ref) | 50.23 | 1.86 | 50.86 | 2.33 | 55.54 | 2.88 | 60.09 | 2.69 | | | |
| Other | 49.77 | 1.86 | 49.14 | 2.33 | 44.46 | 2.88 | 39.91 | 2.69 | | | |
| Education | | | | | | | | | 0.90 | 3 | 0.4450 |
| High school or less | 43.41 | 1.86 | 44.75 | 2.44 | 47.27 | 3.57 | 48.40 | 2.79 | | | |
| College (ref) | 56.59 | 1.86 | 55.25 | 2.44 | 52.73 | 3.57 | 51.60 | 2.79 | | | |
| Employment Status (employed) | 66.03 | 2.04 | 66.40 | 2.32 | 67.13 | 3.21 | 57.54 | 2.79 | 2.49 | 3 | 0.0681 |
| Personal Income | | | | | | | | | 3.92 | 9 | 0.0005 |
| $0-19,999 (ref) | 53.42 | 1.99 | 53.96 | 2.73 | 56.58 | 3.38 | 67.41 | 2.45 | | | |
| $20,000-34,999 | 23.27 | 1.61 | 24.76 | 2.30 | 19.42 | 2.33 | 21.28 | 2.01 | | | |
| $35,000-69,999 | 18.75 | 1.50 | 14.84 | 1.85 | 18.23 | 2.62 | 9.69 | 1.61 | | | |
| $70,000+ | 4.56 | 0.74 | 6.44 | 1.47 | 5.77 | 1.58 | 1.62 | 0.63 | | | |
| Family History | | | | | | | | | | | |
| Depression | 56.07 | 1.76 | 65.32 | 2.65 | 64.67 | 3.33 | 69.45 | 2.79 | 6.73 | 3 | 0.0005 |
| Alcohol Abuse or Dependence | 43.36 | 1.82 | 52.25 | 2.59 | 54.75 | 3.34 | 69.58 | 2.80 | 18.24 | 3 | 0.0001 |
| Drug Abuse or Dependence | 23.19 | 1.45 | 34.58 | 2.64 | 41.07 | 3.71 | 44.06 | 3.13 | 15.32 | 3 | 0.0001 |
| Antisocial Personality Disorder | 29.63 | 1.82 | 42.67 | 2.58 | 48.35 | 3.69 | 62.25 | 2.86 | 25.04 | 3 | |

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**Table 2**

Lifetime Clinical Characteristics and Treatment among individuals with Bipolar Disorder with vs. without number of types of Childhood Maltreatment

| | No Abuse or Neglect | | 1 type of abuse/neglect | | 2 types of abuse/neglect | | ≥3 types of abuse/neglect | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N=1086; %=45.71 | | N=596; %=23.73 | | N=331;%=12.85 | | N=481;%=17.71 | | Adjusted linear test * | | |
| | MEAN or % | SE | MEAN or% | SE | MEAN or% | SE | MEAN or % | SE | chi-square | df | p-value |
| **Clinical Characteristics** | | | | | | | | | | | |
| BP age of onset | 25.93 | 0.59 | 26.09 | 0.66 | 25.54 | 0.78 | 23.67 | 0.79 | 24.97 | 1 | <0.0001 |
| Duration of BP | 9.44 | 0.37 | 11.07 | 0.60 | 12.55 | 0.75 | 16.20 | 0.87 | 50.68 | 1 | <0.0001 |
| BP diagnosis | | | | | | | | | | | |
| BP-**I** (ref) | 70.59 | 1.73 | 79.72 | 1.86 | 77.50 | 2.91 | 80.36 | 2.04 | | | |
| BP-**II** | 29.41 | 1.73 | 20.28 | 1.86 | 22.50 | 2.91 | 19.64 | 2.04 | 8.05 | 1 | 0.0046 |
| Number of depressive episodes | 6.15 | 0.47 | 6.78 | 0.63 | 8.34 | 1.01 | 9.63 | 0.98 | 10.85 | 1 | 0.001 |
| Number of manic/hypomanic episodes | 5.48 | 0.42 | 5.69 | 0.67 | 6.20 | 0.79 | 6.99 | 0.69 | 5.20 | 1 | 0.0226 |
| **Treatment** | | | | | | | | | | | |
| Any treatment for depression | 51.06 | 2.05 | 58.30 | 2.60 | 56.06 | 3.26 | 69.00 | 2.64 | 14.17 | 1 | 0.0002 |
| Psychotherapy for depression | 44.38 | 1.97 | 50.99 | 2.70 | 51.20 | 3.46 | 64.12 | 2.82 | 20.55 | 1 | <0.0001 |
| Hospitalized for depression | 13.07 | 1.29 | 14.53 | 1.64 | 16.55 | 2.25 | 29.86 | 2.77 | 23.91 | 1 | <0.0001 |
| Emergency room treatment for depression | 11.70 | 1.32 | 15.06 | 1.79 | 16.75 | 2.49 | 26.55 | 2.53 | 20.81 | 1 | <0.0001 |
| Medication for depression | 38.21 | 2.06 | 47.10 | 2.69 | 46.48 | 3.16 | 60.11 | 2.47 | 27.00 | 1 | <0.0001 |
| Any treatment for mania/hypomania | 31.21 | 1.82 | 40.70 | 2.46 | 33.79 | 3.02 | 45.10 | 2.75 | 5.79 | 1 | 0.0161 |
| Psychotherapy for mania/hypomania | 23.02 | 1.51 | 34.82 | 2.38 | 28.12 | 2.68 | 39.15 | 2.68 | 11.59 | 1 | 0.0007 |
| Hospitalized for mania/hypomania | 7.28 | 1.03 | 7.88 | 1.24 | 8.85 | 1.70 | 12.39 | 1.81 | 3.77 | 1 | 0.0523 |
| Emergency room treatment for mania/hypomania | 6.52 | 0.99 | 8.07 | 1.33 | 6.55 | 1.56 | 10.87 | 1.59 | 3.22 | 1 | 0.0729 |
| Medication for mania/hypomania | 22.77 | 1.47 | 31.24 | 2.42 | 26.46 | 2.73 | 38.1* | 2.58 | 11.30 | 1 | 0.0008 |

*Adjusted linear test by age, gender, race, and income

**Table 3**

Lifetime and Incidence of Psychiatry Comorbidity and Functioning among individuals with Bipolar Disorder with vs. without number of types of Childhood Maltreatment

| | No Abuse or Neglect | | 1 type of abuse/neglect | | 2 types of abuse/neglect | | ≥3 types of abuse/neglect | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N=1086; %=45.71 | | N=596; %=23.73 | | N=331;%=12.85 | | N=481;%=17.71 | | Adjusted linear test * | | |
| | %or MEAN | SE | %or MEAN | SE | %or MEAN | SE | %or MEAN | SE | chi-square | df | p-value |
| **Lifetime Psychiatry Comorbidities** | | | | | | | | | | | |
| Any Substance Use Disorder | 64.60 | 1.88 | 71.13 | 2.37 | 75.04 | 3.32 | 77.93 | 2.33 | 38.39 | 1 | <O.0001 |
| Alcohol Use Disorders | 52.09 | 1.89 | 53.97 | 2.68 | 61.90 | 3.77 | 59.70 | 2.87 | 23.68 | 1 | <O.0001 |
| Drug Use disorders | 27.85 | 1.78 | 31.16 | 2.35 | 40.27 | 3.68 | 47.87 | 2.79 | 65.11 | 1 | <O.0001 |
| Nicotine Dependence | 38.82 | 1.77 | 47.65 | 2.77 | 51.90 | 3.89 | 56.10 | 2.80 | 42.38 | 1 | <O.0001 |
| Any Anxiety Disorder | 62.82 | 1.99 | 71.48 | 2.31 | 72.77 | 3.08 | 83.41 | 2.04 | 42.94 | 1 | <O.0001 |
| Panic Disorder | 23.95 | 1.67 | 28.44 | 2.43 | 26.40 | 2.68 | 48.15 | 2.66 | 40.93 | 1 | <O.0001 |
| Social Anxiety Disorder | 21.29 | 1.70 | 25.37 | 2.08 | 27.81 | 3.18 | 41.94 | 2.80 | 34.07 | 1 | <O.0001 |
| Specific Phobia | 31.50 | 1.91 | 38.58 | 2.66 | 38.75 | 3.46 | 50.73 | 2.57 | 25.15 | 1 | <O.0001 |
| Generalized Anxiety Disorder | 26.87 | 1.61 | 34.17 | 2.35 | 34.98 | 3.23 | 45.23 | 2.85 | 21.60 | 1 | <O.0001 |
| Postraumatic Stress Disorder | 15.05 | 1.37 | 21.4 | 2.16 | 23.56 | 2.63 | 38.02 | 2.74 | 39.23 | 1 | <O.0001 |
| ADHD | 7.18 | 1.15 | 10.07 | 1.50 | 17.41 | 2.49 | 24.03 | 2.32 | 59.43 | 1 | <O.0001 |
| Any Personality Disorder | 60.01 | 2.11 | 67.31 | 2.22 | 81.08 | 2.56 | 83.75 | 2.04 | 93.45 | 1 | <O.0001 |
| Cluster A | 31.71 | 1.71 | 38.94 | 2.54 | 52.06 | 3.12 | 59.01 | 2.90 | 71.29 | 1 | <O.0001 |
| Cluster B | 41.29 | 2.07 | 53.36 | 2.61 | 62.59 | 3.04 | 70.89 | 2.58 | 107.93 | 1 | <O.0001 |
| Cluster C | 30.64 | 1.99 | 33.44 | 2.45 | 36.65 | 3.30 | 46.19 | 2.50 | 25.46 | 1 | <O.0001 |
| **Incidence of Psychiatric Comorbidities (since Wave 1)** | | | | | | | | | | | |
| Anxiety Disorders | 28.16 | 2.05 | 33.19 | 2.82 | 37.03 | 3.82 | 53.06 | 3.71 | 23.87 | 1 | <O.0001 |
| Substance Use Disorders | 24.47 | 2.19 | 24.73 | 3.05 | 40.29** | 4.86 | 34.89** | 3.49 | 21.69 | 1 | <O.0001 |
| Alcohol Use Disorder | 18.63 | 1.91 | 16.54 | 2.74 | 26.59** | 4.17 | 18.41** | 2.65 | 3.91 | 1 | 0.0481 |
| Drug Use disorders | 6.64 | 1.11 | 10.66 | 1.83 | 16.71 | 2.95 | 18.12 | 2.56 | 27.01 | 1 | <O.0001 |
| Nicotine Dependence | 8.89 | 1.23 | 13.32 | 2.52 | 16.78** | 3.00 | 16.50** | 2.86 | 7.54 | 1 | 0.0061 |

| | No Abuse or Neglect | | 1 type of abuse/neglect | | 2 types of abuse/neglect | | ≥3 types of abuse/neglect | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N=1086; %=45.71 | | N=596; %=23.73 | | N=331;%=12.85 | | N=481;%=17.71 | | Adjusted linear test * | | |
| | %or MEAN | SE | %or MEAN | SE | %or MEAN | SE | %or MEAN | SE | chi-square | df | p-value |
| **Short-Form 12 norm-based functioning scores (Wave 2)** | | | | | | | | | | | |
| Mental Component Summary | 45.62 | 0.42 | 43.29 | 0.69 | 42.39 | 0.78 | 39.98 | 0.71 | 39.56 | 1 | <O.0001 |
| Social Functioning | 47.61 | 0.47 | 44.95 | 0.70 | 43.81 | 0.82 | 41.20 | 0.62 | 48.38 | 1 | <O.0001 |
| Role of Emotional | 45.15 | 0.46 | 42.98 | 0.66 | 41.95 | 0.70 | 39.14 | 0.75 | 31.88 | 1 | <O.0001 |
| Mental Health | 46.33 | 0.43 | 43.95 | 0.64 | 43.52 | 0.75 | 40.32 | 0.71 | 44.16 | 1 | <O.0001 |

* Adjusted linear test by age, gender, race, and income.

** Pairwise comparison did not show significant differences between "2 types of abuse/neglect" and ">3 types of abuse/neglect"