



Research report

Childhood maltreatment and the course of bipolar disorders among adults: Epidemiologic evidence of dose-response effects

Regina Sala^{a,b,*}, Benjamin I. Goldstein^c, Shuai Wang^a, Carlos Blanco^a^a Department of Psychiatry, New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, New York, NY, USA^b Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London, London, UK^c Department of Psychiatry, Sunnybrook Health Sciences Center, University of Toronto, Toronto, Canada

ARTICLE INFO

Article history:

Received 5 September 2013

Received in revised form

16 April 2014

Accepted 16 April 2014

Available online 23 April 2014

Keywords:

Bipolar disorder

Childhood maltreatment

Dose-response

Course

Epidemiology

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.

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.

© 2014 Elsevier B.V. All rights reserved.

1. 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., 2010; McIntyre and Konarski, 2004; Moreno et al., 2012). 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., 2002, 2003; 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 the 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., 2002, 2003; Post

* Corresponding author at: Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London, Box PO 85, 16 De Crespigny Park, London SE5 8AF, UK. Tel.: +44 207 848 0756; fax: +44 207 708 5800.

E-mail address: regina.sala_cassola@kcl.ac.uk (R. Sala).

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., 2010; 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., 2013) and physical (Sugaya et al., 2012) abuse during childhood was associated with increased risk of having BP, with sexual abuse having stronger effect than physical abuse (OR=4.10 versus 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.

2. Methods

2.1. Sample

The NESARC (Grant et al., 2003b, 2005a) 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).

2.2. 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 ($k=0.71$) (Bernardi et al., 2012). 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., 2010). 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 ($\kappa=0.40-0.77$) (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).

2.3. 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., 1995, 2003a; 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). 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., 2013). 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., 2012).

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 did not; 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).

2.4. 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 χ^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.

3. Results

3.1. 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).

3.2. 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).

Table 1
Demographic characteristics and family history among individuals with bipolar disorder with versus without number of types childhood maltreatment.

	No abuse or neglect N=1086; %=45.71		1 Type of abuse/neglect N=596; %=23.73		2 Types of abuse/neglect N=331; %=12.85		≥ 3 Types of abuse/neglect 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	

Table 2
Lifetime clinical characteristics and treatment among individuals with bipolar disorder with versus 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		Adjusted linear test ^a		
	N=1086; %=45.71		N=596; %=23.73		N=331; %=12.85		N=481; %=17.71		chi-square	df	p-Value
	Mean or %	SE	Mean or %	SE	Mean or %	SE	Mean or %	SE			
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	38.18	2.58	11.30	1	0.0008

^a Adjusted linear test by age, gender, race, and income.

3.3. 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).

4. 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; Garino et al., 2005; Leverich et al., 2002, 2003; 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, 2010). 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., 2010; Heim and Nemeroff, 2001).

Our findings are consistent with previous work by our group (Perez-Fuentes et al., 2013; Sugaya et al., 2012) 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

Table 3
Lifetime and Incidence of Psychiatry Comorbidity and Functioning among individuals with Bipolar Disorder with versus 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		Adjusted linear test ^a		
	N=1086; %=45.71		N=596; %=23.73		N=331; %=12.85		N=481; %=17.71		chi-square	df	p-Value
	% or Mean	SE	% or Mean	SE	% or Mean	SE	% or Mean	SE			
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	< 0.0001
Alcohol use disorders	52.09	1.89	53.97	2.68	61.90	3.77	59.70	2.87	23.68	1	< 0.0001
Drug use disorders	27.85	1.78	31.16	2.35	40.27	3.68	47.87	2.79	65.11	1	< 0.0001
Nicotine dependence	38.82	1.77	47.65	2.77	51.90	3.89	56.10	2.80	42.38	1	< 0.0001
Any anxiety disorder	62.82	1.99	71.48	2.31	72.77	3.08	83.41	2.04	42.94	1	< 0.0001
Panic Disorder	23.95	1.67	28.44	2.43	26.40	2.68	48.15	2.66	40.93	1	< 0.0001
Social anxiety disorder	21.29	1.70	25.37	2.08	27.81	3.18	41.94	2.80	34.07	1	< 0.0001
Specific phobia	31.50	1.91	38.58	2.66	38.75	3.46	50.73	2.57	25.15	1	< 0.0001
Generalized anxiety disorder	26.87	1.61	34.17	2.35	34.98	3.23	45.23	2.85	21.60	1	< 0.0001
Posttraumatic stress disorder	15.05	1.37	21.47	2.16	23.56	2.63	38.02	2.74	39.23	1	< 0.0001
ADHD	7.18	1.15	10.07	1.50	17.41	2.49	24.03	2.32	59.43	1	< 0.0001
Any personality disorder	60.01	2.11	67.31	2.22	81.08	2.56	83.75	2.04	93.45	1	< 0.0001
Cluster A	31.71	1.71	38.94	2.54	52.06	3.12	59.01	2.90	71.29	1	< 0.0001
Cluster B	41.29	2.07	53.36	2.61	62.59	3.04	70.89	2.58	107.93	1	< 0.0001
Cluster C	30.64	1.99	33.44	2.45	36.65	3.30	46.19	2.50	25.46	1	< 0.0001
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	< 0.0001
Substance use disorders	24.47	2.19	24.73	3.05	40.29 ^b	4.86	34.89 ^b	3.49	21.69	1	< 0.0001
Alcohol use disorder	18.63	1.91	16.54	2.74	26.59 ^b	4.17	18.41 ^b	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	< 0.0001
Nicotine dependence	8.89	1.23	13.32	2.52	16.78 ^b	3.00	16.50 ^b	2.86	7.54	1	0.0061
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	< 0.0001
Social functioning	47.61	0.47	44.95	0.70	43.81	0.82	41.20	0.62	48.38	1	< 0.0001
Role of emotional	45.15	0.46	42.98	0.66	41.95	0.70	39.14	0.75	31.88	1	< 0.0001
Mental health	46.33	0.43	43.95	0.64	43.52	0.75	40.32	0.71	44.16	1	< 0.0001

^a Adjusted linear test by age, gender, race, and income.

^b Pairwise comparison did not show significant differences between "2 types of abuse/neglect" and "≥ 3 types of abuse/neglect".

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; Garino 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, the 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 non-response 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.

Role of funding source

The National Epidemiologic Survey on Alcohol and Related Conditions was sponsored by the National Institute on Alcohol Abuse and Alcoholism with supplemental support from the National Institute on Drug Abuse. Work on this manuscript was supported by NIH grants DA019606, DA020783, DA023200, DA023973, MH082773, and the New York State Psychiatric Institute (Dr. Blanco).

Conflict of interest

This study is supported by NIH grants DA019606, DA020783, DA023200, DA023973, MH076051 (Dr. Blanco). The National Epidemiologic Survey on Alcohol and Related Conditions was funded by the NIAAA, with supplemental support from the National Institute on Drug Abuse. Dr. Goldstein is a consultant for and has received travel support from BMS, has received research support from Pfizer, and has received speaker's honoraria from Purdue Pharma. Dr. Sala and Dr. Wang report no financial or other relationship relevant to the subject of this article.

Acknowledgment

The National Epidemiologic Survey on Alcohol and Related Conditions was sponsored by the National Institute on Alcohol Abuse and Alcoholism with supplemental support from the National Institute on Drug Abuse (NIDA), NIH, USA. Work on this manuscript was supported by NIH grants DA019606, DA020783, DA023200, DA023973, and MH082773, and the New York State Psychiatric Institute (Dr. Blanco). Dr. Sala is currently employed by the Department of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College London, London, UK.

References

- Baca-Garcia, E., Perez-Rodriguez, M.M., Keyes, K.M., Oquendo, M.A., Hasin, D.S., Grant, B.F., Blanco, C., 2010. Suicidal ideation and suicide attempts in the United States: 1991–1992 and 2001–2002. *Mol. Psychiatry* 15, 250–259.
- Begley, C.E., Annegers, J.F., Swann, A.C., Lewis, C., Coan, S., Schnapp, W.B., Bryant-Comstock, L., 2001. The lifetime cost of bipolar disorder in the US: an estimate for new cases in 1998. *Pharmacoeconomics* 19, 483–495.
- Bernardi, S., Faraone, S.V., Cortese, S., Kerridge, B.T., Pallanti, S., Wang, S., Blanco, C., 2012. The lifetime impact of attention deficit hyperactivity disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Psychol. Med.* 42, 875–887.
- Binder, E.B., Owens, M.J., Liu, W., Deveau, T.C., Rush, A.J., Trivedi, M.H., Fava, M., Bradley, B., Ressler, K.J., Nemeroff, C.B., 2010. Association of polymorphisms in genes regulating the corticotropin-releasing factor system with antidepressant treatment response. *Arch. Gen. Psychiatry* 67, 369–379.
- Brown, G.R., McBride, L., Bauer, M.S., Williford, W.O., 2005. Impact of childhood abuse on the course of bipolar disorder: a replication study in U.S. veterans. *J. Affect Disord.* 89, 57–67.
- Canino, G., Bravo, M., Ramirez, R., Febo, V.E., Rubio-Stipec, M., Fernandez, R.L., Hasin, D., 1999a. The Spanish Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS): reliability and concordance with clinical diagnoses in a Hispanic population. *J. Stud. Alcohol* 60, 790–799.
- Canino, G.J., Bravo, M., Ramirez, R., Febo, V., Fernandez, R., Hasin, D.S., 1999b. The Spanish alcohol use disorder and associated disabilities interview schedule (AUDADIS): reliability and concordance with clinical diagnoses in a Hispanic population. *J. Stud. Alcohol* 60, 790–799.
- Cohen, J.A., Mannarino, A.P., Kliethermes, M., Murray, L.A., 2012. Trauma-focused CBT for youth with complex trauma. *Child Abuse Negl.* 36, 528–541.
- Compton, W.M., Conway, K.P., Stinson, F.S., Colliver, J.D., Grant, B.F., 2005. Prevalence, correlates, and comorbidity of DSM-IV antisocial personality syndromes and alcohol and specific drug use disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *J. Clin. Psychiatry* 66, 677–685.
- Dong, M., Anda, R.F., Dube, S.R., Giles, W.H., Felitti, V.J., 2003. The relationship of exposure to childhood sexual abuse to other forms of abuse, neglect, and household dysfunction during childhood. *Child Abuse Negl.* 27, 625–639.
- Dube, S.R., Felitti, V.J., Dong, M., Giles, W.H., Anda, R.F., 2003. The impact of adverse childhood experiences on health problems: evidence from four birth cohorts dating back to 1900. *Prev. Med.* 37, 268–277.
- Ellis, B.J., Essex, M.J., Boyce, W.T., 2005. Biological sensitivity to context: II. Empirical explorations of an evolutionary-developmental theory. *Dev. Psychopathol.* 17, 303–328.
- Garno, J.L., Goldberg, J.F., Ramirez, P.M., Ritzler, B.A., 2005. Impact of childhood abuse on the clinical course of bipolar disorder. *Br. J. Psychiatry* 186, 121–125.
- Gonzalez-Pinto, A.M., Dardennes, R., de Zelicourt, M., Lopez, P., Oliveros, R.G., Vieta, E., Barbeito, S., Echevarria, E., Fagnani, F., 2010. In-patient care costs of patients with bipolar I disorder: a comparison between two European centers. *J. Affect Disord.* 121, 152–155.
- Grant, B., Kaplan, K., Moore, T., Kimball, J., 2005a. Source and accuracy statement for the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.
- Grant, B.F., Chou, S.P., Goldstein, R.B., Huang, B., Stinson, F.S., Saha, T.D., Smith, S.M., Dawson, D.A., Pula, A.J., Pickering, R.P., Ruan, W.J., 2008. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *J. Clin. Psychiatry* 69, 533–545.
- Grant, B.F., Dawson, D.A., Hasin, D.S., 2001. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version. National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.
- Grant, B.F., Dawson, D.A., Stinson, F.S., Chou, P.S., Kay, W., Pickering, R., 2003a. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug Alcohol Depend.* 71, 7–16.
- Grant, B.F., Harford, T.C., Dawson, D.A., Chou, P.S., Pickering, R.P., 1995. The alcohol use disorder and associated disabilities interview schedule (AUDADIS): reliability of alcohol and drug modules in a general population sample. *Drug Alcohol Depend.* 39, 37–44.
- Grant, B.F., Hasin, D.S., Blanco, C., Stinson, F.S., Chou, S.P., Goldstein, R.B., Dawson, D.A., Smith, S., Saha, T.D., Huang, B., 2005b. The epidemiology of social anxiety disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J. Clin. Psychiatry* 66, 1351–1361.
- Grant, B.F., Hasin, D.S., Stinson, F.S., Dawson, D.A., June Ruan, W., Goldstein, R.B., Smith, S.M., Saha, T.D., Huang, B., 2005c. Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychol. Med.* 35, 1747–1759.
- Grant, B.F., Kaplan, K., Shepard, J., Moore, T., 2003b. Source and accuracy statement for wave 1 of the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions. National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.
- Grant, B.F., Stinson, F.S., Dawson, D.A., Chou, S.P., Dufour, M.C., Compton, W., Pickering, R.P., Kaplan, K., 2004. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch. Gen. Psychiatry* 61, 807–816.
- Green, J.G., McLaughlin, K.A., Berglund, P.A., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Kessler, R.C., 2010. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: associations with first onset of DSM-IV disorders. *Arch. Gen. Psychiatry* 67, 113–123.
- Hammersley, P., Dias, A., Todd, G., Bowen-Jones, K., Reilly, B., Bentall, R.P., 2003. Childhood trauma and hallucinations in bipolar affective disorder: preliminary investigation. *Br. J. Psychiatry* 182, 543–547.
- Hasin, D., Carpenter, K.M., McCloud, S., Smith, M., Grant, B.F., 1997. The alcohol use disorder and associated disabilities interview schedule (AUDADIS): reliability of alcohol and drug modules in a clinical sample. *Drug Alcohol Depend.* 44, 133–141.
- Heim, C., Nemeroff, C.B., 2001. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol. Psychiatry* 49, 1023–1039.
- Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M., Bonsall, R., Miller, A.H., Nemeroff, C.B., 2000. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *J. Am. Med. Assoc.* 284, 592–597.
- Keyes, K.M., Eaton, N.R., Krueger, R.F., McLaughlin, K.A., Wall, M.M., Grant, B.F., Hasin, D.S., 2012. Childhood maltreatment and the structure of common psychiatric disorders. *Br. J. Psychiatry* 200, 107–115.
- Leverich, G.S., Altshuler, L.L., Frye, M.A., Suppes, T., Keck Jr., P.E., McElroy, S.L., Denicoff, K.D., Obrocea, G., Nolen, W.A., Kupka, R., Walden, J., Grunze, H., Perez, S., Luckenbaugh, D.A., Post, R.M., 2003. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J. Clin. Psychiatry* 64, 506–515.
- Leverich, G.S., McElroy, S.L., Suppes, T., Keck Jr., P.E., Denicoff, K.D., Nolen, W.A., Altshuler, L.L., Rush, A.J., Kupka, R., Frye, M.A., Autio, K.A., Post, R.M., 2002. Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol. Psychiatry* 51, 288–297.
- Loman, M.M., Gunnar, M.R., 2010. Early experience and the development of stress reactivity and regulation in children. *Neurosci. Biobehav. Rev.* 34, 867–876.
- Mannarino, A.P., Cohen, J.A., Deblinger, E., Runyon, M.K., Steer, R.A., 2012. Trauma-focused cognitive-behavioral therapy for children: sustained impact of treatment 6 and 12 months later. *Child Maltreatment* 17, 231–241.
- McIntyre, R.S., Konarski, J.Z., 2004. Bipolar disorder: a national health concern. *CNS Spectr.* 9, 6–15.
- McLaughlin, K.A., Green, J.G., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Kessler, R.C., 2010. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication II: associations with persistence of DSM-IV disorders. *Arch. Gen. Psychiatry* 67, 124–132.
- Miklowitz, D.J., Hooley, J.M., 1998. Developing family psychoeducational treatments for patients with bipolar and other severe psychiatric disorders. A pathway from basic research to clinical trials. *J. Marital Fam. Ther.* 24, 419–435.
- Morcillo, C., Duarte, C.S., Sala, R., Wang, S., Lejuez, C.W., Kerridge, B.T., Blanco, C., 2010. Conduct disorder and adult psychiatric diagnoses: associations and gender differences in the U.S. adult population. *J. Psychiatr. Res.* 46, 323–330.
- Moreno, C., Hasin, D.S., Arango, C., Oquendo, M.A., Vieta, E., Liu, S., Grant, B.F., Blanco, C., 2012. Depression in bipolar disorder versus major depressive disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Bipolar Disord.* 14, 271–282.
- Perez-Fuentes, G., Olsson, M., Villegas, L., Morcillo, C., Wang, S., Blanco, C., 2013. Prevalence and correlates of child sexual abuse: a national study. *Compr. Psychiatry* 54 (1), 16–27.
- Post, R.M., Leverich, G.S., Altshuler, L.L., Frye, M.A., Suppes, T.M., Keck Jr., P.E., McElroy, S.L., Kupka, R., Nolen, W.A., Grunze, H., Walden, J., 2003. An overview of recent findings of the Stanley Foundation Bipolar Network (Part I). *Bipolar Disord.* 5, 310–319.
- Read, J., Perry, B.D., Moskowitz, A., Connolly, J., 2001. The contribution of early traumatic events to schizophrenia in some patients: a traumatic neurodevelopmental model. *Psychiatry* 64, 319–345.

- Research Triangle Institute, 2007. Software for Survey Data Analysis (SUDAAN) version 9.0.3. Research Triangle Park (NC).
- Romero, S., Birmaher, B., Axelson, D., Goldstein, T., Goldstein, B.I., Gill, M.K., Iosif, A. M., Strober, M.A., Hunt, J., Esposito-Smythers, C., Ryan, N.D., Leonard, H., Keller, M., 2009. Prevalence and correlates of physical and sexual abuse in children and adolescents with bipolar disorder. *J. Affect Disord.* 112, 144–150.
- Ruan, W.J., Goldstein, R.B., Chou, S.P., Smith, S.M., Saha, T.D., Pickering, R.P., Dawson, D.A., Huang, B., Stinson, F.S., Grant, B.F., 2008. The alcohol use disorder and associated disabilities interview schedule-IV (AUDADIS-IV): reliability of new psychiatric diagnostic modules and risk factors in a general population sample. *Drug Alcohol Depend.* 92, 27–36.
- Straus M, G.R., 1990. *Physical Violence in American Families: Risk Factors and Adaptations to Violence in 8145 Families*. Transaction Press, New Brunswick.
- Straus, M.A., 1979. Measuring intrafamily conflict and violence: the conflict tactics (CT) scales. *J. Marriage Fam.* 41, 75–88.
- Sugaya, L., Hasin, D.S., Olfson, M., Lin, K.H., Grant, B.F., Blanco, C., 2012. Child physical abuse and adult mental health: a national study. *J. Trauma Stress* 25, 384–392.
- van der Vegt, E.J., van der Ende, J., Kirschbaum, C., Verhulst, F.C., Tiemeier, H., 2009. Early neglect and abuse predict diurnal cortisol patterns in adults: a study of international adoptees. *Psychoneuroendocrinology* 34, 660–669.
- Ware, J., Kosinski, M., Turner-Bowker, D., Gandek, B., 2005. *How to score version 2 of the SF-12 health survey*, Quality Metrics. Lincoln, RI.
- Wyatt, G.E., 1985. The sexual abuse of Afro-American and white-American women in childhood. *Child Abuse Negl.* 9, 507–519.