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Childhood trauma and bipolar affective disorder: Is there a linkage?

ABSTRACT

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Bipolar affective disorder (BPAD) is a major psychiatric illness impairing the quality of life. The etiology of BPAD is influenced by different factors possibly related to gene-environment interactions. Approximately 30% to 50% of individuals with BPAD have experienced some traumatic event in childhood. Serious adverse experiences that children may suffer early in life are often described as childhood trauma (CT). CT is linked with an elevated risk of developing BPAD. Childhood adversities play a role in modulating the early onset of illness, increased number of depressive episodes, increased suicide attempts, and other clinical severity of BPAD. Hospital-based studies comprising heterogeneous populations had researched the specific role of each trauma subtype as a predisposing factor for BPAD. Identifying and addressing CT through early intervention methods may prevent the future development of chronic disorders like BPAD. This review article is an attempt to explore and highlight the existing literature regarding the association of different subtypes of CT with BPAD.

Keywords: Bipolar disorder, childhood trauma, emotional abuse

BPAD is frequently linked to negative effects, such as decreased functioning, lowered quality of life, and an increased risk of suicide.^[1] There is usually full recovery between episodes, and both sexes have higher or nearly equal incidence of other mood disorders.^[2] BPAD is a psychiatric illness that affects more than 1% of the global population.^[1] The etiology of BPAD is influenced by a variety of factors that may involve the interaction of genes and the environment.^[3] CT is more prevalent among people with BPAD than in the general population. According to

many cross-sectional studies, the prevalence rate was as high as 50% to 63%, when a person experiences numerous traumatic episodes.^[2,4]

Serious adverse childhood experiences (ACEs) are frequently used to refer to childhood trauma (CT). It is the most severe and typical cause of stress that young children might experience.^[5] These experiences include

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abuse (physical, emotional, and sexual), neglect (emotional and physical), and dysfunction in the home (such as parental mental health, violence between parents or carers, having a family member in jail, and parental marital strife).^[6] CT subtypes include physical abuse and neglect, emotional abuse and neglect, and sexual abuse. Approximately 30-50% of people with BPAD have experienced a traumatic childhood event.^[7] Therefore, early identification and therapeutic techniques require a better knowledge of the risk factors for bipolar disorder.

There were only few reliable studies identified on CT in BPAD till 2010. Since then more investigations by authors like Watson *et al.* 2013, have strengthened this evidence.^[8] A case-control research comparing 206 patients with BPAD to 94 controls using the Childhood Trauma Questionnaire reveals that patients with BPAD had experienced more traumas than controls (63% vs. 33%).^[9] All trauma subtypes had putative dose effects in bipolar disorder.^[8]

Increased incidence of BPAD has been linked to CT.^[8] Studies conducted across cultures have shown that CT is related to more severe clinical characteristics of bipolar affective disorder (BPAD), such as onset at an early age, elevated risk of suicide attempt, rapid cycling, more frequent mood episodes, and substance abuse.^[10] Early intervention strategies have been suggested to prevent the development of chronic illnesses like BPAD in the future.

The accurate role of each CT subtype is still up for discussion, and it appears that all subcomponents of CT are strongly related to BPAD. CT was previously identified as a risk factor for BPAD, although many gaps still exist. Therefore, this review aims to highlight the association of CT in patients with bipolar disorder.

METHODOLOGY

We did a literature review on CT and its association with BPAD. We used search engines Medline, PubMed, PsycINFO, and Google. We used MeSH words such as CT, child abuse, ACEs, BPAD, mood disorder, and psychiatric disorders.

CHILDHOOD TRAUMA

The word “trauma” is often used to explain negative events that are “emotionally painful” and which overwhelm the coping ability of an individual.^[11] According to the WHO, ACEs encompass the most intense and frequent sources of stress in children. These events have a significant influence on a person’s psychological, physical, and social well-being and may have long-lasting negative repercussions.^[12,13]

Childhood traumatic events are referred as “abuse” incidents when children are left exposed or hurt by those in charge of their care or who have control over them. Such people may be elder siblings, parents, and stepparents of the family. In addition to the home, child abuse can occur in schools, churches, daycare centers, and workplaces. Different studies have classified CT as the following subtypes:^[14]

1. Physical Abuse: It is willful hostility directed toward a child that leads to harm or threat of injury. It includes hitting or beating an infant or treating a youngster roughly in a way that might result in harm or bodily injury. Bruises, scrapes, burns, fractured bones, lacerations, and loss of consciousness are all effects of physical abuse.^[13]
2. Sexual abuse: When a child engages in sexual activity with someone older than them, or someone in a position of control over them, it is a statutory offense.^[15]
3. Emotional Abuse: Often referred to as psychological abuse, this type of abuse is exposing another person to actions that might cause psychological harm. It entails a variety of intentional behaviors that cause children to worry or compromise their sense of self-worth and psychological integrity. It is frequently linked to instances of workplace harassment and abuse. It may also be committed by individuals who engage in torture, other forms of violent behavior, or acute or ongoing violations of human rights, particularly when there is no effective legal recourse such as violations include incarceration without charge or trial, false allegations, erroneous convictions, and excessive defamation when committed by the government or the media.^[1,16]
4. Physical Neglect: Physical neglect is a kind of child abuse that can put children in danger by failing to provide them with the necessary care. Examples include failing to provide a parent or carer with the necessary clothing, food, and shelter; abandoning a kid unattended for long periods; and failing to provide medical assistance when required.^[16]
5. Emotional neglect: Inattention to a child’s emotional and developmental requirements. This also includes permitting certain things like drugs/alcohol, which are considered inappropriate for a child’s development needs. Cultural settings must also be considered in interpretations of emotional neglect since communal or plural caring in particular cultures and societies may permit more diversity in emotional response based on common caregiving practices. More precisely, the caregiving and attachment networks with other carers, such as grandparents, who can sufficiently meet a kid’s requirements, may make up for a parent’s probable lack of attention to a child.^[17]

Childhood trauma as a potential risk factor for mental health issues

Many psychiatric disorders, such as bipolar disorder, depression, substance use disorder, disruptive behavior disorder, antisocial behavior, and psychosis, have been linked to childhood abuse.^[18,19] Studies have shown a strong correlation between childhood trauma/adversity and psychosis, with odds ratios ranging from 2.72 to 2.99.^[20] CT is a risk factor for a more persistent form of depression associated with adult depression.^[21] Recent epidemiologic research indicates that unfavorable childhood experiences are responsible for about one-third of cases of the start of mental illnesses throughout life, highlighting the importance of those exposures for overall public health.^[19] According to the study, links between childhood abuse and various psychiatric outcomes, CT may give a nonspecific risk for psychopathology rather than a risk for specific diseases.

Childhood trauma in bipolar affective disorder

BPAD is a heritable mental disorder, but environmental risk factors also play an important role.^[14,22] Studies have documented that CT is additionally common among people with BPAD, with rates as high as 50% and reaching up to 63% in comparison to the general population.^[23]

Some studies also reported that between all sorts of abuse and neglect, emotional abuse exposure is prevalent in BPAD patients, with a larger odds ratio of 1.88.^[24] These studies confirm that childhood maltreatment, particularly emotional abuse, is a significant risk factor for BPAD.

Early emotional, social, biological, and behavioral development is crucial for healthy coping with challenging circumstances.^[25] Disruption during development coupled with ongoing difficulty in these systems may result in allostatic overload and long-term effects on physical and mental health via biological pathways. Because of neuro-anatomical and neuro-functional alterations brought on by allostatic load, executive processes may be compromised, leading to poor coping mechanisms and affecting one's ability to release tension in stressful situations.^[5] Stressful life event seems to precede and influence the onset and course of BPAD.^[25,26] We can hypothesize that CT enhances stress reactivity, thus leading to an elevated response to negative and positive life situations in the future.^[26,27] Changes in emotion regulation, cognitive functioning, and increased impulsivity with maladaptive coping strategies may influence this. There is a wealth of evidence indicating that early life stress not only affects the chance of developing BPAD but may also impact how the disease manifests or develops in different people.^[28]

Biological underpinnings in the link between childhood trauma and BPAD

Biological systems moderate the effect of early trauma on the likelihood of developing BPAD. To begin with, the Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophic factor that supports adult neuron maintenance and growth throughout brain development. Evidence suggests that individuals with BPAD who have experienced stressful situations have lower levels of BDNF in their blood or mRNA.^[29] Second, CT results in long-term alterations in inflammation processes, such as deviations in C-reactive protein and several cytokines, including Interleukin (IL)-2, 4, 6 receptor and Soluble Tumour Necrosis Factor Receptor Type 1. Studies have also suggested a connection between increased BDNF and pro-inflammatory cytokine levels following trauma.^[30] Additionally, it has been recommended that raising BDNF levels could be an effort to counteract the damaging effects of early stress on the brain.^[31]

The majority of these biological systems may interact and converge in the future to cause BPAD patients to have a heavy physical load and a shorter life expectancy.^[32] Indeed, a meta-analysis by Norman *et al.* in 2012^[33] looked into the long-term effects of CT (abuse and neglect) and discovered connections to bipolar affective illness.

Psychosocial aspects of CT, cognition and brain imaging in bipolar affective disorder

Affective lability is suggested to be a key component of BPAD. Studies in personality disorders and BPAD have connected emotional maltreatment to subsequent affective lability.^[34] It was shown that CT is linked to increased amygdala activity, which controls emotions and fear, strengthening the link between the limbic system, emotional regulation, and childhood.^[35] CT affects how emotions are regulated as well as aspects of aggression or impulsivity, which may raise the likelihood of substance abuse or suicide attempts.^[10] In this sense, it may be connected to how CT affects the brain's inhibitory control network. Patients with BPAD also have cognitive impairments. Although the exact causes of these deficiencies are unknown, genetic and environmental susceptibility factors are probably to blame. According to Bucker *et al.* 2016,^[31] individuals with CT had worse cognitive functioning, as seen by their low IQ, attention, verbal memory, and working memory scores. The clinical overlap between BPAD and other clinical entities (affect dysregulation, impulsivity, suicide behaviors, and substance misuse) is highlighted by the relationships between CT, cognition, and psychopathology. The connections between CT, cognition, and psychopathology highlight the clinical overlap between BPAD and other clinical entities (impulsivity, affect dysregulation, behavior that leads to suicide, and substance

abuse), and they also make people more susceptible to other environmental stressors like cannabis exposure or adult life events.

FACTORS RELATED TO CHILDHOOD TRAUMA IN BIPOLAR AFFECTIVE DISORDER

Age of onset of illness

Beyond genetic risk variations, environmental susceptibility variables are thought to have a role in the pathophysiology of bipolar disorder. At least one form of CT (emotional abuse, sexual abuse, and emotional neglect) was strongly linked to a younger age at which bipolar disease first manifested. Similar findings that family loading and childhood adversity vulnerability characteristics were substantially associated with the age of start of bipolar were repeated by Post *et al.* in 2016,^[36] and their combined effect was considerably greater.

Gender

Studies show that females with BPAD report CT more commonly than males.^[37] Males are more likely than females to report CT, notably physical abuse, whereas females are more likely to report sexual abuse.^[38] Clinical characteristics with CT, which are more prevalent in females than males, include a more significant association with fast cycling, early disease start, a more significant number of episodes of depression, and enhanced suicidal risk. According to Etain *et al.* 2013,^[10] gender had an additive effect on CT, and the link is still significant for BPAD clinical outcomes.

Suicide attempt

In a multivariate analysis of trauma characteristics conducted in 2013, Etain *et al.*^[10] found that CT subtypes (emotional and sexual abuse) were prevalent in most of the cases with a history of suicidal attempts. According to Garno *et al.* 2005,^[39] there is a substantial correlation between severe sexual abuse as a kid and lifelong suicide attempts.

No of hospitalization

Álvarez *et al.* 2011^[40] found that individuals with severe mental illness had a significant frequency of CT. Hospital admissions were twice as common for victims of psychological abuse. Similarly, Marchand *et al.* 2005^[37] reported juvenile bipolar patients may often have adverse events that can harm their prognosis. Adverse occurrences were linked to treatment resistance and inpatient mental stays.

RESPONSE AND DURATION OF TREATMENT

Marchand *et al.* in 2005^[37] retrospectively examined the charts of young people with bipolar illness. 35 out of 66 people (or 53%) had the presence of CT. Most of them showed less therapeutic response as treatment time increased. Adverse

event exposure may be frequent and detrimental to the prognosis in children with bipolar disorder.

Cycling frequencies

Brown *et al.* 2005^[41] examined the relationship between clinical presentation and several categories of CT in a sizable sample of bipolar patients. Compared to individuals who had not been abused, patients with a history of CT showed fast cycling twice as often. Etain *et al.* in 2013^[10] also found that sexual abuse was associated with fast cycling, which elevated the severity of bipolar disorder^[10] (OR = 2.04). Leverich *et al.* in 2002^[42] found individuals who acknowledged having experienced physical or sexual abuse as a child or teenager had a history of quicker cycle frequencies than those who did not.

Delay in diagnosis

Leverich *et al.* in 2002^[42] found that individuals with a childhood history of sexual or physical abuse had an early onset of BPAD and a delayed diagnosis than those without such a history. Romero *et al.* in 2009^[38] found that the abused group among cases of BPAD lasted longer than that of the nonabused group. The prevalence of abuse among the various bipolar disorder subtypes did not differ significantly from one another.

Depressive episode

Garno *et al.* in 2005^[39] assessed the incidence of childhood abuse regarding disease complexity in a sample of 100 patients receiving treatment for BPAD at an academic specialty unit. Results showed a strong correlation between childhood maltreatment and both the average lifetime number of depressive episodes and the severity of current depression symptoms.

Manic episodes

Etain *et al.* in 2013^[10] investigated relationships between clinical manifestations and different categories of CT. The findings showed that greater intensity of manic episodes was independently predicted by both emotional and sexual abuse. Garno *et al.* in 2005^[39] found that people with a history of severe maltreatment began their condition at a younger age and had more severe present manic symptoms than those without such a history.

Psychotic symptoms

Data from the National Comorbidity Survey were used by Shevlin *et al.* in 2007^[43] to calculate the correlation between interpersonal trauma and the propensity to be diagnosed with psychosis. It came to light that physical maltreatment as an adolescent predicted psychosis. Trauma and psychosis had a strong accumulative association, with the likelihood of psychosis rising the more different forms of trauma were encountered.

Substance use disorder

In-depth research by Etain *et al.* in 2013^[10] and Garino *et al.* in 2005^[39] found a connection between severe emotional abuse or neglect and concomitant drug addiction or dependency among BPAD patients. Significant correlations were found between severe emotional maltreatment and concomitant lifelong drug dependence. In comparison to alcohol and any other type of drug, nicotine dependence was more strongly connected with the drugs.

Medical co-morbidities

In 900 outpatients of bipolar disorder, Post *et al.* (2013)^[44] looked for comorbidities that lead to early death. The child adversity score in BPAD patients was significantly correlated with a higher number of medical comorbidities. They also had more medical conditions like “asthma, allergies, chronic fatigue syndrome, menstrual irregularities, fibromyalgia, head injury, hypertension, hypotension, irritable bowel syndrome, migraine, and headaches.” It was suggested that childhood hardship is associated with the development of many medical disorders in adult BPAD outpatients. A more severe course of not just bipolar illness but also its significant medical comorbidities and their combined detrimental impact on patients’ health, well-being, and lifespan may be avoided with recognition of these linkages and early therapeutic intervention.

CLINICAL ASSESSMENT

CT should be routinely assessed in both the initial stages and in cases of BPAD that are already established, as there is a high risk of progression to a more severe form of the illness over time. For subgroups of BPAD patients with early start, comorbidity with suicide attempts or substance abuse, high levels of mood recurrences, or increased mood instability, the evaluation of CT is very important.^[45]

In an interview setting, psychometry assessments can be performed using inventories like Childhood Experience of Care and Abuse (CECA), CT Inventory (CTI), Early Trauma Inventory, Retrospective Assessment of Traumatic Experience, and Traumatic Antecedents Interview. All have a semi-structured format, a manual, and/or require some training, multiple quantitative ratings of trauma (e.g., number of perpetrators), and include a large number of potential trauma areas (at least five different types of traumas).^[46]

The Childhood Trauma Questionnaire (CTQ), the Childhood Abuse and Trauma Scale, and the Assessing Environments III (AEnvIII) all assess five or more different forms of trauma. The test–retest reliability and internal consistency of all three instruments are at least moderately satisfactory.^[46] Using the CTQ to investigate various forms of CT is common in clinical studies on BPAD.

Implication of treatment

Early intervention strategies and approaches focus on addressing CT to stop these people from eventually acquiring a chronic, incurable condition like BPAD.^[14] Psychological therapies like eye-moment desensitization and reprocessing and trauma-focused cognitive behavioral therapy concentrate on the adverse effects of CT.^[46] Early evaluation of CT at baseline is being conducted in further studies to examine how this factor is useful in identifying patients who may or may not respond to therapy.

CONCLUSION

A literature study led to a new understanding of how CT affects psychiatric diseases, particularly BPAD, and the detrimental effects of early life stress. In addition to many severe clinical manifestations throughout time, such as earlier age at commencement, greater frequency of episodes, drug use disorder, and risk of suicide attempt, childhood traumatic events are risk factors for developing bipolar disorders. Emotional abuse has a significant influence on subtypes of CT, which have a strong correlation with BPAD. The intensity and progression of BPAD are recommended to be prevented by screening and early intervention measures.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Etain B, Henry C, Bellivier F, Mathieu F, Leboyer M. Beyond genetics: Childhood affective trauma in bipolar disorder. *Bipolar Disord* 2008;10:867–76.
2. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet* 2016;387:1561–72.
3. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, *et al.* Bipolar disorders. *Nat Rev Dis Primer* 2018;4:18008.
4. Etain B, Mathieu F, Henry C, Raust A, Roy I, Germain A, *et al.* Preferential association between childhood emotional abuse and bipolar disorder: Preferential association between CEA and BD. *J Trauma Stress* 2010;23:376–83.
5. Daruy-Filho L, Brietzke E, Lafer B, Grassi-Oliveira R. Childhood maltreatment and clinical outcomes of bipolar disorder: Childhood maltreatment and bipolar disorder. *Acta Psychiatr Scand* 2011;124:427–34.
6. Pearce J, Murray C, Larkin W. Childhood adversity and trauma: Experiences of professionals trained to routinely enquire about childhood adversity. *Heliyon* 2019;5:e01900.
7. Boullier M, Blair M. Adverse childhood experiences. *Paediatr Child Health* 2018;28:132–7.
8. Watson S, Gallagher P, Dougall D, Porter R, Moncrieff J, Ferrier IN, *et al.* Childhood trauma in bipolar disorder. *Aust N Z J Psychiatry* 2014;48:564–70.
9. Anand A, Koller DL, Lawson WB, Gershon ES, Nurnberger JJ.

- Genetic and childhood trauma interaction effect on age of onset in bipolar disorder: An exploratory analysis. *J Affect Disord* 2015;179:1–5.
10. Etain B, Aas M, Andreassen OA, Lorentzen S, Dieset I, Gard S, *et al.* Childhood trauma is associated with severe clinical characteristics of bipolar disorders. *J Clin Psychiatry* 2013;74:991–8.
 11. Peterson S. The National Child Traumatic Stress Network. About Child Trauma. 2018. Available from: <https://www.nctsn.org/what-is-child-trauma/about-child-trauma>. [Last accessed on 2021 Sep 16].
 12. Treatment (US) C for SA. Trauma awareness. Trauma-Informed Care in Behavioral Health Services. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2014.
 13. Physical Child Abuse: Practice Essentials, Background, Pathophysiology. 2021. Available from: <https://emedicine.medscape.com/article/915664-overview>. [Last accessed on 2021 Sep 16].
 14. Aas M, Henry C, Andreassen OA, Bellivier F, Melle I, Etain B. The role of childhood trauma in bipolar disorders. *Int J Bipolar Disorder* 2016;4:2.
 15. Murray LK, Nguyen A, Cohen JA. Child sexual abuse. *Child Adolesc Psychiatr Clin N Am* 2014;23:321–37.
 16. Myers JEB. Child maltreatment: A collection of readings. SAGE Publications; 2011. p. 385.
 17. Lawler MJ, Talbot EB. Child abuse. In: *Encyclopedia of Human Behavior*. Elsevier; 2012. p. 460–6.
 18. Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, *et al.* Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br J Psychiatry* 2010;197:378–85.
 19. Keyes KM, Eaton NR, Krueger RF, McLaughlin KA, Wall MM, Grant BF, *et al.* Childhood maltreatment and the structure of common psychiatric disorders. *Br J Psychiatry* 2012;200:107–15.
 20. Popovic D, Schmitt A, Kaurani L, Senner F, Papiol S, Malchow B, *et al.* Childhood trauma in schizophrenia: Current findings and research perspectives. *Front Neurosci* 2019;13:274.
 21. Marshall M, Shannon C, Meenagh C, Mc Corry N, Mulholland C. The association between childhood trauma, parental bonding and depressive symptoms, and interpersonal functioning in depression and bipolar disorder. *Ir J Psychol Med* 2018;35:23–32.
 22. Aldinger F, Schulze TG. Environmental factors, life events, and trauma in the course of bipolar disorder. *Psychiatry Clin Neurosci* 2017;71:6–17.
 23. Sala R, Goldstein BI, Wang S, Blanco C. Childhood maltreatment and the course of bipolar disorders among adults: Epidemiologic evidence of dose-response effects. *J Affect Disord* 2014;165:74–80.
 24. Sugaya L, Hasin DS, Olfson M, Lin KH, Grant BF, Blanco C. Child physical abuse and adult mental health: A national study: Child Abuse and Adult Mental Health. *J Trauma Stress* 2012;25:384–92.
 25. Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function, and connectivity. *Nat Rev Neurosci* 2016;17:652–66.
 26. Kemner SM, van Haren NE, Bootsman F, Eijkemans MJ, Vonk R, van der Schot AC, *et al.* The influence of life events on first and recurrent admissions in bipolar disorder. *Int J Bipolar Disord* 2015;3:6.
 27. Koenders MA, Giltay EJ, Spijker AT, Hoencamp E, Spinhoven P, Elzinga BM. Stressful life events in bipolar I and II disorder: Cause or consequence of mood symptoms? *J Affect Disord* 2014;161:55–64.
 28. Aas M, Dazzan P, Fisher HL, Morgan C, Morgan K, Reichenberg A, *et al.* Childhood trauma and cognitive function in first-episode affective and non-affective psychosis. *Schizophr Res* 2011;129:12–9.
 29. Aas M, Haukvik UK, Djurovic S, Tesli M, Athanasiu L, Bjella T, *et al.* Interplay between childhood trauma and BDNF val66met variants on blood BDNF mRNA levels and hippocampus subfields volumes in schizophrenia spectrum and bipolar disorders. *J Psychiatr Res* 2014;59:14–21.
 30. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: A meta-analysis of peripheral C-reactive protein, interleukin-6 and tumor necrosis factor- α . *Mol Psychiatry* 2016;21:642–9.
 31. Bückner J, Fries GR, Kapczynski F, Post RM, Yatham LN, Vianna P, *et al.* Brain-derived neurotrophic factor and inflammatory markers in school-aged children with early trauma. *Acta Psychiatr Scand* 2015;131:360–8.
 32. Kessing LV, Vradi E, McIntyre RS, Andersen PK. Causes of decreased life expectancy over the life span in bipolar disorder. *J Affect Disord* 2015;180:142–7.
 33. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: A systematic review and meta-analysis. *PLoS Med* 2012;9:e1001349.
 34. Aminoff SR, Jensen J, Lagerberg TV, Hellvin T, Sundet K, Andreassen OA, *et al.* An association between affective lability and executive functioning in bipolar disorder. *Psychiatry Res* 2012;198:58–61.
 35. van Harmelen AL, van Tol MJ, Demenescu LR, van der Wee NJA, Veltman DJ, Aleman A, *et al.* Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. *Soc Cogn Affect Neurosci* 2013;8:362–9.
 36. Post RM, Altshuler LL, Kupka R, McElroy SL, Frye MA, Rowe M, *et al.* Age of onset of bipolar disorder: Combined effect of childhood adversity and familial loading of psychiatric disorders. *J Psychiatr Res* 2016;81:63–70.
 37. Marchand WR, Laurel Wirth BS, Cindy Simon MSW. Adverse life events and pediatric bipolar disorder in a community mental health setting. *Community Ment Health J* 2005;41:67–75.
 38. Romero S, Birmaher B, Axelson D, Goldstein T, Goldstein BI, Gill MK, *et al.* Prevalence and correlates of physical and sexual abuse in children and adolescents with bipolar disorder. *J Affect Disord* 2009;112:144–50.
 39. Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Impact of childhood abuse on the clinical course of bipolar disorder. *Br J Psychiatry* 2005;186:121–5.
 40. Álvarez MJ, Roura P, Osés A, Foguet Q, Solà J, Arrufat FX. Prevalence and clinical impact of childhood trauma in patients with severe mental disorders. *J Nerv Ment Dis* 2011;199:156–61.
 41. Brown GR, McBride L, Bauer MS, Williford WO. Impact of childhood abuse on the course of bipolar disorder: A replication study in U.S. veterans. *J Affect Disord* 2005;89:57–67.
 42. Leverich GS, McElroy SL, Suppes T, Keck PE, Denicoff KD, Nolen WA, *et al.* Early physical and sexual abuse is associated with an adverse course of bipolar illness. *Biol Psychiatry* 2002;51:288–97.
 43. Shevlin M, Dorahy MJ, Adamson G. Trauma and psychosis: An analysis of the national comorbidity survey. *Am J Psychiatry* 2007;164:166–9.
 44. Post RM, Altshuler LL, Leverich GS, Frye MA, Suppes T, McElroy SL, *et al.* Role of childhood adversity in the development of medical co-morbidities associated with bipolar disorder. *J Affect Disord* 2013;147:288–94.
 45. Roy CA, Perry JC. Instruments for the assessment of childhood trauma in adults. *J Nerv Ment Dis* 2004;192:343–51.
 46. Ehring T, Welboren R, Morina N, Wicherts JM, Freitag J, Emmelkamp PMG. Meta-analysis of psychological treatments for posttraumatic stress disorder in adult survivors of childhood abuse. *Clin Psychol Rev* 2014;34:645–57.