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BIPOLAR DISORDER AND EARLY AFFECTIVE TRAUMA

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SUMMARY

Background: *Bipolar disorder is a chronic psychiatric disease with a high prevalence and is a major psychosocial and medical burden. The exact etiological pathways of bipolar disorder are not fully understood. Genetic factors are known to play an important role in the etiology of bipolar disorder. However, high rates of discordance among identical twins and a growing body of evidence that environmental factors such as early stress can influence the onset and course of psychiatric diseases underline the importance of additional etiological mechanisms of bipolar disorders. There has been little investigation about early trauma in bipolar disorder. The aim of this study was to review the literature on the association between early traumatic interactions like child neglect, mistreatment, abuse or early parental separation and the occurrence of bipolar disorder in adulthood or impact on the course of the disease.*

Methods: *Studies investigating associations between child neglect, mistreatment, abuse or early parental separation and occurrence of bipolar disorder in adulthood or impact on the course of the disease were searched in the Pubmed database. More than 700 articles were sorted independently by two of the authors using predefined criteria. Only research articles, reviews and meta-analyses were selected for this review.*

Results: *53 articles met the inclusion criteria. To date, four systematic reviews partially addressed our research question. Early trauma is more frequently found in the past of bipolar patients than in the general population. Studies support a harmful effect of childhood trauma on the course of bipolar disease, with more anxious, depressive or psychotic symptoms, an early age of onset and a worse prognosis.*

Conclusions: *Early trauma is more often found in the past of bipolar adult patients than the general population and studies support a harmful effect of childhood trauma on the course of bipolar disease, with more anxious, depressive or psychotic symptoms, an early age of onset and a worse prognosis. In further studies attention should be paid to the age of trauma occurrence and the definition of trauma. The findings also support the importance of additional psychoanalytic oriented psychotherapy for the treatment of bipolar disorder.*

Key words: *early stress – early trauma – bipolar disorder - risk factor*

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INTRODUCTION

Bipolar disorder is a severe and chronic psychiatric disease with a high prevalence which has a major impact on psychosocial and professional functioning. It significantly worsens quality of life and has an important social cost. These reasons underline the need to further study the etiological and risk factors of bipolar disorder.

The exact etiological pathways of bipolar disorder are not fully understood. Genetic factors are known to play a strong role in the etiology of bipolar disorder, and as a result, the majority of the treatments are based on pharmacotherapy and psycho-education.

A recent classical psychoanalytic literature review highlighted the paucity of documents addressing bipolar depression, therefore challenging the role of psychotherapy in the treatment of this disease. Beyond genetic factors, it is important to assess the existence of others mechanisms that could influence the development of bipolar disorder and that could support an improvement of treatment with additional psychoanalytic oriented psychotherapy.

Relatively high rates of discordance among identical twins indicate the influence of additional non genetic mechanisms on the onset of bipolar disorder. Regarding these mechanisms, a growing body of evidence supports the theory that environmental factors such as early stress influence the onset of many psychiatric disorders (Pidsley & Mill 2011). Beyond epidemiologic studies, animal epigenetic studies show the impact of early stress due to inappropriate interactions between the mother and the offspring, in the later development of inappropriate behaviors and inability to cope with daily stress. The choice of epigenetic researchers to study early parental separation as a risk factor for the development of psychiatric disease was inspired by psychoanalytic theories. One of the basic tenets of psychoanalysis holds that a person's development is determined by often forgotten events in early childhood rather than by inherited traits alone.

In animals, Weaver showed that decreased pup licking and grooming and arched-back nursing (when the mother lies over the pups) by rat mothers over the first week of life durably altered the offspring's epigenome at a hippocampus glucocorticoid receptor gene promoter, an epigenetic modification that was associated with anxiety-like behavior in the adult offspring (Weaver et al. 2004). Maternal care influences then hypothalamic-pituitary-adrenal (HPA) function in the rat through epigenetic programming of glucocorticoid receptor expression (Meaney 2001, Liu et al. 1997).

In humans, there is also evidence for decreased hippocampal glucocorticoid receptor expression, conducting to altered HPA stress responses, in several psychopathological conditions associated with suicide, including schizophrenia and mood disorders (Isometsa et al. 1994, Webster et al. 2002). In abused suicide victims, McGowan found the same epigenetic alterations that found in rats. These alterations were not found in suicide victims who were not abused in their past (McGowan et al. 2009). In major depressive disorder, childhood mistreatment predicts an increase in unfavorable course of illness and treatment outcome (Nanni et al. 2012). A meta-analysis studying patients with psychotic disorders concluded that such patients show high rates of self-reported childhood abuse and neglect, ranging from 30% to over 75% (Bonoldi et al. 2013).

Although there is significant evidence that unipolar depression and psychotic disorders are affected by early trauma, there has been little investigation about early trauma in bipolar disorder despite its high prevalence. The aim of this study was to review the literature on the association between early traumatic interactions like child neglect, mistreatment, abuse or early parental separation and the occurrence of bipolar disorder in adulthood or the potential impact of these traumas on the course of the disease. The results of this review could help to clarify the place of psychoanalytic oriented psychotherapy in the treatment of bipolar disorder.

METHODS

The Pubmed database was searched for the terms: "bipolar", "manic", "mania" combined with each of the following terms: "environment", "epigenetic", "epigenetics", "mother", "father", "separation", "separations", "loss", "conflict", "conflicts", "early stress", "trauma", "risk factor", "risk factors", "divorce", "parents", "childhood", "abuse", "neglect", up to December 2015. More than 700 articles were sorted independently by two of the authors using those predefined criteria. Only research articles, reviews and meta-analyses were sorted out for this review. Excluded were theoretical articles, editorials and opinion articles. Selected were only articles that considered adult patients with bipolar disorder as defined by the DSM. Eligibility assessment of titles and abstracts was performed independently by two of the authors and disagreements between reviewers were resolved by consensus with a third author. Pertinent data was further extracted by two of the authors.

RESULTS

53 articles met the inclusion criteria. Extracted data was sorted according to two research questions.

The first research question explored the potential association between early traumatic interactions like child neglect, mistreatment, abuse or early parental separation and the occurrence of bipolar disorder in adulthood.

For this first question, a systematic review focused on the prevalence and social / demographic correlates of child sexual abuse among people with bipolar disorder, without studying an eventual correlational link between both. The estimated prevalence of child sexual abuse among people with bipolar disorder was 24% (Maniglio 2013). Compared to healthy individuals, patients with bipolar disorder reported higher rates of child sexual abuse, but compared to populations with other mental disorders, participants with bipolar disorder reported similar or lower rates of such abuse. Another systematic review looked at the role of environmental risk factors in the development of bipolar disorder (Marangoni et al. 2016), suggesting that exposure to viral infection, substances or trauma (which refers to parental loss, adversities, abuses and brain injury) increase the likelihood of occurrence of bipolar disorder. But the heterogeneity of designs and methodology limited the weight of conclusions.

Although pioneer research suggested that parental death in childhood was no more frequent in bipolar patients than in the general population (Perris 1965), subsequent results demonstrate the opposite. According to Agid, there is a higher rate of early parental loss in patients with bipolar disorder (Agid et al. 1999). When parental loss occurs before the fifth birthday, the occurrence of bipolar disorder is increased four-fold with the loss of the mother and 2.4-fold when the father is lost. For maternal loss only, the risk declines with increasing age of offspring but remains significant throughout childhood (Mortensen et al. 2003). For Paksarian, the number of years of paternal separation was positively associated with bipolar disorder. The risk of bipolar disorder is greater with earlier paternal separation than when it occurred later in childhood (Paksarian et al. 2015). For Alciati, the obese bipolar II subjects reported having experienced childhood parental loss significantly more frequently (45.3%) than the normal weight bipolar controls (20%) (Alciati et al. 2011).

Childhood trauma is frequently assessed using the Childhood Trauma Questionnaire (CTQ, Bernstein et al. 1997). In this tool, trauma is categorized in 5 trauma subtypes, emotional neglect (defined as failure of caretakers to meet children's basic emotional and psychological needs, including love, belonging, nurturance and support), emotional abuse (verbal assaults on a child's sense of worth or well-being or any humiliating or demeaning behavior directed toward a child by an adult or older person), physical neglect (failure of caretakers to provide for a child's basic physical needs, including food, shelter, clothing, safety and health care), physical abuse (bodily assaults on a child by an adult or older person that posed a risk of- or resulted in injury) and sexual abuse (sexual contact or conduct between a child younger than 18 years of age and an adult or older person).

Studies using the Childhood Trauma Questionnaire (Fowke et al. 2012, Etain et al. 2010, Watson et al. 2014) have reported a higher rate of childhood trauma with the reported frequency of childhood emotional abuse and neglect being particularly high. Levels of current internalized shame, defined as a state in which the individual possesses a fundamental sense of incompetence and inferiority and experiences the self as inferior, defective and useless, were significantly higher amongst participants in the bipolar disorder group. Significant correlations were observed between current internalized shame and reports of childhood emotional abuse and neglect. For Noto, history of childhood abuse and neglect was reported by 81.4% of patients with bipolar disorder (Noto et al. 2015). For Russo, 70% suffered from trauma and for Kesebir 35% (Russo et al. 2015, Kesebir et al. 2015).

The second research question addressed the impact of early traumatic interactions, such as child neglect, mistreatment, abuse or early parental separation, on the course of bipolar disorder.

Conflicting results have been published on the impact of child sexual abuse on the course of bipolar disorder. A complicating factor is the heterogeneity of the age of occurrence of the abuse. Nevertheless a systematic review by Maniglio supports the association between child sexual abuse in bipolar patients and a more severe course of the disease (Maniglio 2013). Bipolar patients with a history of sexual abuse are more likely to attempt suicide. They also have comorbid alcohol abuse or dependence, an early age of onset of bipolar disorder, an higher frequency of axis 1 disorder, comorbid cluster A, B or C personality disorders, co-occurring medical conditions, and a longer duration of manic or depressive episodes. Child sexual abuse was strongly associated with posttraumatic stress disorder.

Another systematic review on the impact of childhood trauma on the clinical course of this disease and concludes that in general, childhood mistreatment predicted worsening clinical course of bipolar disorder, being strongly associated to early onset of the disorder, suicidality, and substance abuse disorder (Daruy-Filho et al. 2011).

A series of studies using the Childhood Trauma Questionnaire suggest a correlation between the course of bipolar disorder and childhood trauma (CHT). According to Aas, there is a relationship between childhood trauma (CHT) scores and more severe affective lability in bipolar patients when compared to controls (Aas et al. 2014). Janiri suggests that emotional abuse is an independent predictor of lifetime suicide attempts in bipolar disorder patients (Janiri et al. 2014). Li et al. contradict these findings but their results are subject to the bias related to the use of a retrospective self-report questionnaire and the lack of a control group. Li found a significant association between emotional abuse and emotional neglect and earlier age of onset and a significant correlation between CHT and comorbid PTSD and anxiety (Li et al. 2014). Noto indicates that CHT is associated with specific prodromal features prior to the first major mood episode, social isolation, decrease in functioning and anhedonia (Noto et al. 2015). For Russo, childhood trauma in bipolar disorder patients is correlated to earlier age of onset, longer duration of illness and higher depressive symptoms (Russo et al. 2015). Kesebir reveals that depressive, cyclothymic and anxious temperament scores were higher in bipolar patients with a history of childhood trauma compared with bipolar patients without a childhood history of trauma. Furthermore, resilience scores were higher in bipolar patients without trauma than those with trauma, with a moderate but significant inverse relation between emotional abuse, sexual abuse and emotional neglect, and resilience scores in bipolar patients with childhood trauma (Kesebir et al. 2015). For Pavlova, exposure to mistreatment in childhood is also associated with comorbid anxiety disorders among individuals living with bipolar disorder (Pavlova et al. 2016). Finally, Etain concluded that an effect of childhood trauma on age of onset of bipolar disorder was observed only in patients who carry a specific stress responsiveness-related SLC6A4 promoter genotype (Etain et al. 2015).

In studies using others methods to measure trauma, such as questionnaires or clinical interviews, Neria assessed trauma histories in a cohort of 109 first admission bipolar patients with psychotic features. Childhood trauma was defined as sexual and physical abuse, physical attacks or being threatened with a weapon at or before age 16. Patients exposed to trauma were more symptomatic at each follow-up than those unexposed (Neria et al. 2005). Erten shows that patients who had childhood trauma defined as emotional, physical and sexual abuse or neglect had higher frequencies of depressive episodes, total episodes and attempted suicide more often. Trauma was assessed with the child abuse and neglect questionnaire (Erten et al. 2014). According to Conus, patients with bipolar disorder and childhood and adolescent sexual or physical abuse patients have lower premorbid functional levels and poorer engagement with treatment (Conus et al. 2010). For Upthegrove, significant associations were found between childhood abuse and auditory hallucinations. Strong association was found between sexual abuse and mood congruent or abusive voices. These relationships remain significant even after controlling for lifetime-ever cannabis misuses (Upthegrove et al. 2015). Within a 634 outpatients sample, Post showed that history of physical or sexual abuse or verbal abuse was related to an earlier age of onset of bipolar disorder and other poor prognosis characteristics, including anxiety and substance abuse comorbidity, rapid cycling, and a deteriorating illness course as reflected in ratings of increasing frequency or severity of mania and depression (Post et al. 2015).

DISCUSSION

This review leads us to emphasize the complexity of bipolar disorder which needs to be studied from different perspectives. If early affective trauma was not clearly defined as a risk factor for bipolar disorder, early

adversity is more frequent in this disease and is also frequently found in the past of persons who develop later different psychiatric syndromes (major depression, bipolar disorder, schizophrenia), it is then non-specific of bipolar disorder.

It was impressive to notice the heterogeneity of definitions and ways to measure early trauma, which can refer to traumatic interactions between parents and offspring but also problems at school or brain injury which seem to represent another concepts. It is then complicated to integrate findings using different definitions of early trauma.

A point that seems not enough developed was the time when trauma occurs, as it can have a different impact if it's early or late according to epigenetic and psychoanalytic theories. CTQ is not specific to early childhood, however epigenetic research described the important influence of inappropriate interactions before the first week of life in rats. Mortensen is the only author that considered trauma before the age of 5. Anand considered trauma between 3 and 12 years old and Paksarian between 1 and 15 years old, the others authors from birth to 16 or 18 years old. None of them distinguishes early childhood from adolescence.

Mortensen showed that maternal and paternal loss before the fifth birthday of the offspring increased respectively four-fold and 2.4-fold the risk of bipolar disorder (Mortensen et al. 2003). If we only pay attention to this author that considered childhood trauma before the age of 5, we could consider parental loss as a risk factor for bipolar disorder.

Transversal links can be made between epigenetic research that shows the harmful influence of early affective trauma on the capacity to cope with daily stress, and psychoanalytic theories that consider symptoms (mania, depression, anxiety) as inappropriate defenses against stress. This could inspire further research to pay attention to the age of trauma occurrence and help to rethink a more consensual definition of childhood trauma.

CONCLUSION

It is clear that early traumatic interactions are more often found in the past of bipolar adult patients than general population, even if it is complicated to clarify the nature of the association between both. This potential risk factor seems to be unspecific as it is also found in other frequent psychiatric diseases like unipolar disorder and schizophrenia. Furthermore, studies support a harmful effect of CHT on the course of bipolar disease, with more anxious, depressive or psychotic symptoms, an early age of onset and a worse prognosis.

Findings on the topic are heterogeneous and numerous definitions and tools to conceptualize trauma are applied. According to epigenetic and psychoanalytic theories, it could be interesting to redesign these studies in a transversal way, for example considering only early trauma in first years of life, and considering only interactional or affective trauma instead of problems at school, brain injury or others different events which are not linked to the affective field.

Considering this complexity, we'd like to recommend to researchers and to clinicians an approach that can integrate different dimensions of the disease beyond the syndrome as defined by the DSM IV. We insisted here on the dimension of stress coping influenced by early affective trauma, as a better understanding of the interplay between multiple environmental and genetic factors involved in the pathogenesis of bipolar disorder could provide relevant information for understanding and treating this complex disorder.

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References

1. *Aas M, Aminoff SR, Lagerberg TV, Etain B, Agartz I, Andreassen OA et al.: Affective lability in patients with bipolar disorders is associated with high levels of childhood trauma. Psychiatry Res 2014; 218:252-255.*
2. *Agid O, Shapira B, Zislin J, Ritsner M, Hanin B, Murad H et al.: Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. Mol Psychiatry 1999; 4:163-72.*
3. *Alciati A, Gesuele F, Rizzi A, Sarzi-Puttini P, Foschi D: Childhood parental loss and bipolar spectrum in obese bariatric surgery candidates. Int J Psychiatry Med 2011; 41:155-171.*
4. *Bernstein DP, Ahluvalia T, Pogge D, Handelsman L: Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. J Am Acad Child Adolescent Psychiatry 1997; 36:340-348.*
5. *Bonoldi I, Simeone E, Rocchetti M, Codjoe L, Rossi G et al.: Prevalence of self-reported childhood abuse in psychosis: a meta-analysis of retrospective studies. Psychiatry Res 2013; 210:8–15.*
6. *Conus P, Cotton S, Schimmelmann BG, Berk M, Daglas R, McGorry PD et al.: Pretreatment and outcome correlates of past sexual and physical trauma in 118 bipolar I disorder patients with a first episode of psychotic mania. Bipolar Disord 2010; 12:244–252.*
7. *Daruy-Filho L, Brietzke E, Lafer B, Grassi Oliveira R: Childhood maltreatment and clinical outcomes of bipolar disorder. Acta Psychiatr Scand 2011; 124:427-434.*
8. *Erten E, Funda Uney A, Saatçioğlu O, Özdemir A, Fıstıkçı N, Çakmak D: Effects of childhood trauma and clinical features on determining quality of life in patients with bipolar disorder. J Affect Disord 2014; 162:107-113.*
9. *Etain B, Mathieu F, Henry C, Raust A, Roy I, Germain A et al: Preferential association between childhood emotional abuse and bipolar disorder. J Trauma Stress 2010; 23:376–383.*
10. *Etain B, Lajnef M, Henrion A, Dargel A, Stertz L, Kapczinski F: Interaction between SLC 6A4 promoter variants and childhood trauma on the age at onset of bipolar disorder. Sci Rep 2015; 5:16301.*

11. Fowke A, Ross S and Ashcroft K: Childhood maltreatment and internalized shame in adults with a diagnosis of bipolar disorder. Clin Psychol Psychother 2012; 19:450-457.
12. Isometsa ET, Henriksson MM, Aro HM, Heikkinen ME, Kuoppasalmi KI et al.: Suicide in major depression. Am J Psychiatry 1994; 151:530–536.
13. Janiri D, Sani G, Danese E, Simonetti A, Ambrosi E, Angeletti G et al.: Childhood traumatic experiences of patients with bipolar disorder type I and II. J Affect Disord 2014; 175:92-97.
14. Kesebir S, Ünübol B, Tatlıdil Yaylacı E, Gündoğar D, Ünübol H: Impact of childhood trauma and affective temperament on resilience in bipolar disorder. Int J Bipolar Disord 2015; 3:3.
15. Li XB, Liu JT, Zhu XZ, Zhang L, Thang YL Wang CY: Childhood trauma associates with clinical features of bipolar disorder in a sample of Chinese patients. J Affect Disord 2014; 168:58-63.
16. Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D et al.: Maternal care, hippocampal glucocorticoid receptors and hypothalamic- pituitary- adrenal responses to stress. Science 1997; 277:1659–1662.
17. Maniglio R: Prevalence of child sexual abuse among adults and youths with bipolar disorder: a systematic review. Clin Psychol Rev 2013; 33:561-573.
18. Maniglio R: The impact of child sexual abuse on the course of bipolar disorder: a systematic review. Bipolar Disord 2013; 15:341–358.
19. Marangoni C, Hernandez M, Faedda GL: The role of environmental exposures as risk factors for bipolar disorder: a systematic review of longitudinal studies. J Affect Disord 2016; 193: 165-174.
20. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B et al.: Epigenetic regulation of the glucocor ticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009; 12:3.
21. Meaney MJ: Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu Rev Neurosci 2001; 24:1161–1192.
22. Mortensen PB, Pedersen CB, Melbye M, Mors O, Ewald H: Individual and familial risk factors for bipolar affective disorders in Denmark. Arch Gen Psychiatry 2003; 60:1209-1215.
23. Nanni V, Uher R & Danese A: Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am J Psychiatry 2012; 169:141–151.
24. Neria Y, Bromet EJ, Carlson GA, Naz B: Assaultive trauma and illness course in psychotic bipolar disorder: findings from the suffolk county mental health project. Acta Psychiatr Scand 2005; 111:380–383.
25. Noto MN, Noto C, Caribé AC, Miranda-Scippa A, Nunes SO, Chaves AC et al.: Clinical characteristics and influence of childhood traumaon the prodrome of bipolar disorder. Rev Bras Psi 2015; 37:280-288.
26. Paksarian D, Eaton WW, Mortensen PB, Merikangas KR, Pedersen CB: A population-based study of the risk of schizophrenia and bipolar disorder associated with parent-child separation during development. Psychol Med 2015; 45:2825-37.
27. Pavlova B, Perroud N, Cordera P, Uher R, Dayer A, Aubry JM: Childhood maltreatment and comorbid anxiety in people with bipolar disorder. J Affect Disord 2016; 192:22-7.
28. Perris C: A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. II. Childhood environment and precipitating factors.Acta Psychiatr Scand 1965; 194:45-57.
29. Pidsley R, Mill J: Research Highlights: Epigenetic changes to serotonin receptor gene expression in schizophrenia and bipolar disorder. Epigenomics 2011; 3:537-8.
30. Post RM, Altshuler LL, Kupka R, McElroy SL, Frye MA, Rowe M et al.: Verbal abuse like physical and sexual abuse in childhood is associated with an earlier onset and more difficult course of bipolar disorder. Bipolar Disord 2015; 17:323–330.
31. Russo M, Mahon K, Shanahan M, Solon C, Ramjas E, Turpin J et al.: The association between childhood trauma and facial emotion recognition in adults with bipolar disorder. Psychiatry Res 2015; 229:771-776.
32. Upthegrove R, Chard C, Jones L, Gordon-Smith K, Forty L, Jones I et al.: Adverse childhood events and psychosis in bipolar affective disorder. Br J Psychiatry 2015; 206:191-197.
33. 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.
34. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S et al.: Epigenetic programming by maternal behavior. Nat Neurosci 2004; 7:847-54.
35. Webster MJ, Knable MB, O'Grady J, Orthmann J, Weickert CS: Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. Mol Psychiatry 2002; 7:985–994.

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