

# The frequency of childhood abuse in bipolar disorder and its impact on the clinical course

 Neslihan Cansel<sup>1</sup>,  Nesrin Tomruk<sup>2</sup>,  Nesrin Karamustafalioglu<sup>2</sup>,  Nihat Alpay<sup>3</sup>,  Serhat Citak<sup>4</sup>

<sup>1</sup>Inonu University, Faculty of Medicine, Department of Psychiatry, Malatya, Turkey

<sup>2</sup>Bakırköy Prof. Dr. Mazhar Osman Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, Istanbul, Turkey

<sup>3</sup>T.C. Health Ministry Bakirkoy Mental Health and Neurology Training and Research Hospital, Clinic of Psychiatry, Istanbul, Turkey

<sup>4</sup>Medeniyet University, Faculty of Medicine, Department of Psychiatry, Istanbul, Turkey

Copyright © 2020 by authors and Annals of Medical Research Publishing Inc.

## Abstract

**Aim:** There is a growing awareness of the association between physical and sexual abuse and subsequent development of psychopathology, but little is known about the prevalence and long-term effects of childhood abuse in bipolar disorder. The aim of this study was to investigate the relationship between childhood abuse and adult bipolar disorder.

**Material and Methods:** 50 female and 42 male bipolar I or II disorder out-patients who were in remission were evaluated. Demographic data, comorbid Axis I disorder, history of childhood abuse, family history, suicide attempts and social factors that are associated with the course of illness were investigated.

**Results:** Childhood abuse was reported in 54.3% of the bipolar patients in this study. The incidence of abuse was higher in women. While women were exposed to more sexual abuse, physical abuse was more common in men. The most common type of abuse was neglect. There was no significant difference in sociodemographic variables and family characteristics between patients with history of abuse and patients without history of abuse. Patients who endorsed a history of physical and sexual abuse and neglect compared with those who did not, had an earlier onset of bipolar illness, a higher rate of combined pharmacotherapy and increased number of comorbid disorders, especially post-traumatic stress disorder (PTSD).

**Conclusion:** Greater appreciation of the relationship between early traumatic experiences and an adverse course in bipolar disorder should lead to preventive and early intervention measures that may reduce the associated risk of a poor outcome.

**Keywords:** Bipolar disorder; childhood trauma; treatment

## INTRODUCTION

Bipolar disorder is a severe psychiatric disorder, characterized by biphasic mood episodes of mania or hypomania and depression and is expressed as recurrent episodes of changes in energy levels and behavior (1,2).

Family, twin and genetic studies suggest a strong contribution of genetic factors to the causation of bipolar disorder (3,4). Although bipolar disorder has high heritability, environmental factors that can modify the onset and the course of the disorder should also be taken into consideration. Even though the literature on the role of these factors in bipolar disorders is inadequate, life events, especially childhood abuse, have classically been described as risk factors of bipolar disorders as well as predictors of adverse course (5, 6). It has been estimated that approximately 50% of people with bipolar disorder have been exposed to various forms of childhood abuse (7).

Additionally, it is reported that being exposed to childhood abuse has been associated with unfavorable course and outcomes among patients with bipolar disorder, including earlier age of onset of bipolar disorder (8,9), more frequent relapses (10), increased risk of suicide attempts, frequency of comorbid illnesses (11,12), and substance abuse (13).

In the present study, we attempted to assess the effects of childhood abuse on the course and treatment regimen on bipolar disorder and the risk factors creating the abuse such as sociodemographic characteristics. Elucidating such effects and risk factors could facilitate early identification of individuals most at risk for severe, chronic bipolar illness course, and who are thus important candidates for earlier and more robust interventions to reduce episode recurrence and enhance functioning and quality of life.

**Received:** 12.12.2019 **Accepted:** 02.03.2020 **Available online:** 16.04.2020

**Corresponding Author:** Neslihan Cansel, Inonu University, Faculty of Medicine, Department of Psychiatry, Malatya, Turkey

**E-mail:** neslihancansel@yahoo.com.tr

## MATERIAL and METHODS

### Subjects

This research was conducted in Bakırköy Mental Hospital out-patient clinic between May and June 2003 on 42 male and 50 female patients diagnosed as bipolar disorder according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (14) criteria. Patients were in remission, with seven points in Young Mania Scale (15) and nine points in Hamilton Depression Scale (16). Local ethics committee approved the study and informed consent forms were obtained from all the subjects after explaining the purpose of the study.

The study group consisted of literate patients aged between 18 and 65 years. The patients with mental retardation, dementia, delirium and amnesic disorders and with active alcohol or substance abuse requiring concurrent treatment were excluded. Patients had at least 2-years of bipolar disorder history and were followed in the outpatient clinic for at least a year.

### Materials

Sociodemographic data (i.e. gender, age, education, marital status, occupation, economic status, family history) and clinical data of the patients (i.e. age of onset, duration, number of hospitalizations, total number of manic-depressive-mixed attacks, history of rapid cycling and psychotic episodes, history of electroconvulsive treatment (ECT), medications and treatment compliance) were obtained with two separate forms. Childhood Abuse and Neglect Inventory was used to evaluate the childhood traumas of the patients. This semi-structured scale was developed by Yargıç et al. Physical abuse, emotional abuse, sexual abuse, neglect, frequency of abuse which changes from none to very often, suicide attempts, and self-destructive behaviors were detected with this form (17). Age of abuse (as a child before age sixteen), age of abuser (a person who was at least 5 years older or a family member who was at least 2 years older), abusive behavior were tried to be clarified. While questioning sexual abuse; contact-free situations, experimental sexual activities among peers were excluded. Sexual abuse was defined as sexual conduct or contact between a child and an older person. Physical abuse was defined as bodily assaults (such as repressing several times, slapping, biting, beating with object, kicking, burning and locking) on a child by an older person that posed a risk of injury or resulted in injury. Emotional abuse was defined as severe verbal threats, criticism, and humiliation that endanger the emotional or mental health of the person. Neglect was defined as the failure of caretakers to provide for a child's basic physical and emotional needs, including food, health care, love, and support (18,19). The frequency of abuse was ignored, because of the limitations in sampling. Life-long comorbidities were evaluated with SCID-1 (Structured Clinical Interview for DSM-IV Axis I Disorder) (20).

### Statistical analysis

Ninety-two patients were divided into two groups

according to their abuse history. Abused patients were in group 1, and those without abuse history were in group 2. Statistical analyses were performed between these two groups. SPSS for Windows 11.0 for statistical analysis. Parametric Student t-test was used to compare normal distributed variables and non-parametric Mann-Whitney U-test was used to compare non-normal distributed variables. Categorical variables were compared with chi-square test. The statistical significance was accepted as  $p < 0.05$ .

## RESULTS

Fifty patients were female and 42 were male. Mean age was  $32.8 \pm 9.5$  years. 48.9% of the patients were born in rural areas, 35.9% were primary school graduates, 48.9% were single, 32.6% were housewives, 6.5% were unemployed because of their mental illness, 67.4 % were in the mid-economic level and 5.4% had legal problems. There was homogeneity in patients included in the study in terms of sociodemographic data.

54.3% of the patients had been subject to some kind of abuse (physical, sexual, emotional abuse or physical and emotional neglect). The most frequent type of abuse was neglect (37.0%). Physical abuse (20.7%), sexual abuse (17.4%) and emotional abuse (12.0%) followed neglect. Since some of the patients were subjected to more than one type of abuse; the amount of total abuse was bigger than the number of patients. 66.0% of females and 40.5% of males were abused. The abuse was significantly higher in females than in males ( $p = 0.021$ ) (Table 1).

**Table 1. Abuse characteristics of the sample**

	Female n (%)	Male n (%)	$\chi^2$	P
<b>Abuse present</b>	33 (66.0)	17 (40.5)	5.993	0.021*
<b>Physical abuse</b>	12(36.4)	7(41.2)	1.110	0.740
<b>Sexual abuse</b>	12 (36)	4 (23)	1.397	0.497
<b>Emotional abuse</b>	5 (15.2)	6 (35.3)	2.653	0.103
<b>Neglect</b>	24 (72.7)	10 (58.8)	0.997	0.318

When the relation between the type of abuse and the profile of the abusers was analyzed, it was found that 16.3% ( $n= 15$ ) of the physical abusers were parents, 3.3% ( $n= 3$ ) were foreigners and 1.1% ( $n=1$ ) were second degree relatives and the difference was statistically meaningful ( $\chi^2=6.394$ ,  $P=0.014$ ). Most of the emotional abusers were also parents 7.6% ( $n=7$ ), then foreigners 3.3% ( $n=3$ ) and second-degree relatives 1.1% ( $n=1$ ) ( $\chi^2=1.397$ ,  $P=0.497$ ); while 2.2% ( $n=2$ ) of the sexual abusers were parents, 6.5% ( $n=6$ ) were second-degree relatives and 8.7% ( $n=8$ ) were foreigners ( $\chi^2=0.533$ ,  $P=0.069$ ). There was no significant difference in terms of family history of those patients who were abused and those who were not abused ( $p>0.05$ ).

78.8% (n=41) of the abused group and 85% (n=34) of the non-abused group were brought up by their parents and there was no statistical difference between the two groups in terms of this aspect ( $\chi^2=1.042$ ,  $P=0.549$ ). The rate of divorce of parents in the abused group was 9.6% (n=5) and in the non-abused group was 7.5% (n=3) ( $\chi^2=0.235$ ,  $P=0.628$ ). Apart from these patients, others were brought up by their second-degree family members because of some social reasons (i.e. illness and job). None of the patients grew up in orphanages (n=0).

**Table 2. Comparison of groups according to their clinical features**

	Mean		T	P
	Group 1	Group 2		
Age at onset of disease (years)	20.32	23.33	0.698	0.048*
Illness duration (years)	10.55	9.083	-0.897	0.372
Hospitalization (n)	3.18	3.47	0.422	0.674
Manic phase (n)	3.24	3.92	1.090	0.279
Depressive phase (n)	4.12	3.09	-1.378	0.172
Mixed phase (n)	0.56	0.59	0.188	0.852
Hypomanic phase (n)	2.84	2.54	-0.444	0.658
Total phase (n)	10.78	10.19	-0.376	0.708
Recurrent suicide attempts (n)	0.78	0.35	-1.996	0.049*
ECT treatment (n)	1.40	1.74	-0.685	0.495

**Table 3. Comparison of disease features of groups**

	Group 1 n (%)	Group 2 n (%)	$\chi^2$	P
<b>First attack</b>				
Mania	27 (62.8)	16 (37.2)	2.327	0.312
Depression	22 (46.8)	25 (53.2)		
Mixed	1 (50.0)	1 (50.0)		
Hypomania	0 (0)	0 (0)		
<b>Rapid cycling</b>				
Present	9 (55.6)	7 (43.8)	2.239	0.815
Absent	41 (53.9)	35 (46.1)		
<b>Medications</b>				
Mood stabilizer (MS)	14 (48.3)	15 (51.7)	7.413	0.048*
Antipsychotic (AP)	1 (100.0)	0 (0)		
MS+AP	28 (50.9)	27 (49.1)		
MS+Antidepressant	7 (100.0)	0 (0)		
<b>Treatment compliance</b>				
Regular	43 (56.8)	32 (43.2)	2.284	0.516
Irregular	5 (44.4)	5 (62.5)		
Giving up after active phase	3 (37.5)	5 (55.6)		

When clinical features were compared between the groups, age onset of the disease was significantly earlier in abused patients ( $T=0.698$ ,  $P=0.048$ ). Recurrent suicidal attempts were meaningfully higher in abused patients ( $T= -1.996$ ,  $P=0.049$ ). No difference was found among the number of hospitalizations, total attacks and previously applied ECT regimen amount (Table 2). Abused patients had manic and non-abused patients had depressive episodes initially. Rapid cycling was higher but insignificant in the abused group ( $P>0.05$ ) (Table 3). Abused patients were treated with significantly higher drug combinations ( $P<0.05$ ).

When life-span comorbidities were compared, the abused group had significantly higher comorbid disease ( $\chi^2=14.320$ ,  $P=0.006$ ). The significance was because of the existence of PTSD in the abused group. There was also a high rate of anxiety disorders in the non-abused group (Table 4).

**Table 4. Comparison of comorbidity between groups**

	Group 1 n (%)	Group 2 n (%)	$\chi^2$	P
<b>Life span comorbidity</b>				
Anxiety disorder (except PTSD)	5 (27.8)	13 (72.2)	14.320	0.006*
PTSD	14 (87.5)	2 (12.5)		
<b>Somatization, eating disorder</b>	2 (66.7)	1 (33.3)		
<b>Substance/alcohol abuse</b>	14 (63.6)	8 (36.4)		

## DISCUSSION

Although various studies have explored the long-term effects of childhood abuse on subsequent development of bipolar disorder, the current findings once again revealed important information regarding the underlying effect of childhood abuse on the increased symptomatology and adverse outcome of adult bipolar disorder.

In the present study, the rate of abuse was found to be 54.3% in bipolar disorder. Our results suggest that a history of childhood abuse is found in approximately half of adults with bipolar disorder (7,21). Neglect was found to be the most frequent type of abuse. Regardless of the frequency and type of abuse, there was a higher incidence of lifetime PTSD in especially abused patients compared to non-abused patients (22-24). Although patients with active alcohol or substance abuse requiring concurrent treatment were excluded, abused patients had higher substance abuse history than the non-abused group (13,25). Additionally, a history of childhood abuse was also found to be associated with an increased incidence of repeated suicide attempts (11,26,27). The possible predisposing factors of suicidal behavior is very important in bipolar patients since they are already under higher suicide risk and comorbidity (15-25%). Suicide is among the negative prognostic factors in bipolar disorder and it increases the resistance and interferes with the compliance with treatment (28) and childhood abuse seems to be an

additional risk factor for suicide attempt and comorbidity in bipolar disorder. We also found that abused patients had more polypharmacy. The results could point out that the presence of abuse may not only affect the severity of bipolar disorder but also the treatment cost and social ability.

Negative environmental factors like being female, presence of parental psychiatric disorder or alcohol-substance abuse, divorce, growing up in an orphanage and lack of family support are related not only to increased risk of development of bipolar depression, major depression and anxiety disorders but, they are also strongest predictors of risk of abuse (29). In our study, it was found that the rate of abuse was also higher in women. However, no relation between abuse and growing up in an orphanage could be found as none of the patients grew up in an orphanage. As opposed to the literature, the rate of divorced parents was not different between the abused and non-abused groups. It could be attributed to either (i) a less divorce rate in the studied area, or (ii) a limitation in sampling. It was also found that physical and emotional abuse was mostly done by family members, although sexual abuse was mostly done by foreigners. But, some researches revealed that most of the sexual abuse cases were done by people known to the child, with family members constituting one third to one half of the perpetrators (27). This conflict could either be attributed to (i) a less sexual abuse between the family members in the studied area or (ii) in our country those matters were hardly spoken.

Many studies refer to the relationship between childhood abuse and PTSD. It is stated in the literature that childhood abuse is a risk factor for the development of PTSD later in life. In our study, it was observed that the abused group had a higher comorbid PTSD. One of the causal explanations is that child abuse and neglect can be associated with an impaired and unorganized childhood so, abuse and neglect may share a common resource with the PTSD. According to another view, children who are victims of abuse and neglect may exhibit risky behaviors and show more behavioral disorders since abuse and neglect can lead to pathological dysfunctional behaviors and negativity. Thus, these children have an increased risk for encountering trauma. Childhood trauma also increases the odds of any mood disorders (30). In addition, childhood mania has been shown to be a risk factor for trauma exposure and PTSD. Thus, the frequency of comorbid bipolar disorder and PTSD are reported to be quite high (31,32) like in our study.

Although bipolar disorder is a highly genetic disorder, we found no difference in the family history in our study. But, studies conducted in recent years showed that environmental factors like childhood traumas and repeated exposure to stress may play a role in the emergence of psychiatric disorders such as bipolar disorder (33-37). These studies have shown that traumatic events that exceed the limits of human understanding can result in deterioration of biological and psychological coping

abilities and worsen emotional and behavioral problems in youth (38). Childhood trauma leads to alterations of affect regulation, impulse control, and cognitive functioning (12). So, deterioration of coping abilities in early life time might decrease the ability to cope with later stressors. Moreover; when these stressors cannot be controlled or avoided, they have been shown to cause physiological changes (39,40). These changes include altered hypothalamic-pituitary-adrenal axis activity and neuroplasticity, altered immunological response and chronic inflammation, altered emotion and reward processing circuitry, altered serotonergic transmission and circadian rhythms. These biological changes may decrease the age at the onset of the disorder or increase the risk of suicide and increase resistance to treatment leading to polypharmacy like we found in our study. Additionally, childhood trauma may interact with several genes and epigenetic factors may also be involved in the neurobiological consequences of childhood trauma in bipolar disorder (12). All these negative effects of childhood trauma may affect the clinical course negatively in these bipolar patients. The results obtained in our study support these data.

## LIMITATIONS

There are a number of methodological caveats in interpreting these findings. First, there are many definitions related to childhood abuse depending on social and individual differences. But this is the common problem of related studies. We preferred to use the most common definition in the literature to decrease complexity in definition. Second, the history of childhood abuse was mostly obtained by self-report in an invalidated patient questionnaire instrument rather than a clinician-administered structured interview and thus perhaps subject to greater errors in recall, which could include underreporting or exaggerated recollection. Third, the sample size and retrospective design are the other important limitations. Lastly, as the study is only focused on patients who attended to our clinic, it may not be representative of all the bipolar patients. Hence, replication of our findings in community-based treatment centers would help to establish the representativeness of the study results to a broader community of adults identified as having bipolar disorder. Despite of these limitations, our study represents important findings consistent with previous studies and evaluates the relationship among abuse and course of illness in Turkey.

## CONCLUSION

Finally, although we do not claim childhood abuse as the reason for bipolar disorder, the presence of abuse was related to early onset of the disease, high rate of life-long comorbid illness, more suicidal behaviors, and high use of polypharmacy in treatment. For this reason, we believe that greater appreciation of the relationship between early traumatic experiences and an adverse course in bipolar disorder should lead to preventive and early intervention measures that may reduce the associated risk of a poor outcome.

*Competing interests: The authors declare that they have no competing interest.*

*Financial Disclosure: There are no financial supports.*

*Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.*

Neslihan Cansel ORCID: 0000-0002-5519-205X

Nesrin Tomruk ORCID: 0000-0002-1889-7608

Nesrin Karamustafalioglu ORCID: 0000-0002-2825-3240

Nihat Alpay ORCID: 0000-0001-6481-1054

Serhat Citak ORCID: 0000-0003-1754-8307

## REFERENCES

- Müller JK, Leweke FM. Bipolar Disorder: Clinical Overview. *Med Monatsschr Pharm* Sep 2016;39:363-9.
- Fava GA. Subclinical Symptoms in Mood Disorders: Pathophysiological and therapeutic implications. *Psychol Med* 1999;29:47-61.
- Nurnberger Jr JI, Koller DL, Jung J et al. Identification of pathways for bipolar disorder a meta-analysis. *JAMA Psychiatry* 2014;71:657-64.
- Stahl EA, Breen G, Forstner AJ et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet* 2019;51(5):793-803.
- Bortolato B, Köhler CA, Evangelou E et al. Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. *Bipolar Disord* 2017;19:84-96.
- Jiménez E, Solé B, Bárbara Arias B et al. Impact of childhood trauma on cognitive profile in bipolar disorder. *Bipolar Disord* 2017;19:363-74.
- Garno JL, Goldber Jf, Ramirez PM. Impact of childhood abuse on the clinical course of bipolar disorder course of bipolar disorder. *Nat Genet*;2019;51:793-803.
- Garno JL, Gunawardane N, Goldberg JF. Predictors of trait aggression in bipolar disorder. *Bipolar Disord* 2008;10:285-92.
- Leverich GS, Altshuler LL, Frye MA et al. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. *J Clin Psychiatry* 2003;64:506-15.
- Brown Gr, MC Bride I, Bauer MS et al. Impact of childhood abuse on the course of bipolar disorder: a replication study in USA veterans. *J Affect Disord* 2005;89:57-67.
- Angelakis I, Gillespie EL, Panagioti M. Childhood maltreatment and adult suicidality: a comprehensive systematic review with meta-analysis. *Psychological Medicine* 2019;1057-78.
- Aas M, Henry C, Andreassen OA et al. The role of childhood trauma in bipolar disorders. *Bipolar Disord* 2016;4:2.
- Aas M, Etain B, Bellivier F et al. Additive effects of childhood abuse and cannabis abuse on clinical expressions of bipolar disorders. *Psychol Med* 2014; 44:1653-62.
- American Psychiatric Association. DSM IV: Diagnostic and statistical manual mental disorders, 4th edition. Washington DC: American Psychiatric Association, 1994.
- Young RC, Biggs JT, Ziegler VE et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978;133:429-35.
- Akdemir A, Örsel S, Dağ İ et al. Hamilton depresyon ölçeği (HDDÖ)'nin geçerliliği ve klinikte kullanımı *Psikiyatri Psikoloji Psikofarmakoloji Dergisi* 1996;4: 251-9.
- Yargıç İ, Tutkun H, Şar V. Çocukluk çağı travmatik yaşantıları ve erişkinde disosiyatif belirtiler. *Psikoloji Psikofarmakoloji Dergisi* 1994;1:338-47.
- Bernstein DP, Fink L, Handelsman L et al. Initial reliability and validity of new retrospective measure of child abuse and neglect. *Am J Psychiatry* 1994;151: 1132-6.
- Brown GR, Anderson B. Psychiatry morbidity in adult person with childhood histories of sexual and physical abuse. *Am J Psychiatry* 1991;148:55-61.
- First MB, Spitzer RI, Gibbon M et al. Structured clinical interview for DSM –IV axis I disorder patient (research version, 2/96). New York. Biometrics Research Department, New York State Psychiatric Institute, 1996.
- Leverich Gs, Mcelroy Sl, Suppes T et al. Early physical and sexual abuse associated with and adverse course of bipolar illness. *Biol Psychiatry* 2002;51:288-97.
- Shin LM, Mcnally RJ, Kosslyn SM et al. Regional cerebral blood flow during script-driven imagery in childhood sexual-abuse- related PTSD: a PET investigation. *Am J Psychiatry* 1999;156:575-84.
- Brown GR, Mcbride L, Bauer MS et al. Cooperative studies program 430 Study Team. Impact of childhood abuse on course of bipolar disorder. A replication study in U.S. veterans. *J Affect Disorder* 2005;89:57-67.
- Hammersly P, Dias A, Tood G et al. Childhood trauma and hallucinations in bipolar disorder: preliminary investigation. *Br J Psychiatry* 2003;182:543-7.
- Westermeyer J, Wahmanholm K, Thuras P. Effects of childhood physical abuse on course and severity of substance abuse. *Am J Addict* 2001;10:101-10.
- Leviton RD, Parikh SV, Lesage AD et al. Major depression in individuals with a history of childhood physical and abuse: Relationship to neurovegetative features, mania and gender. *Am J Psychiatry* 1998; 155:1746-52.
- Brown J, Cohen P, Johnson JG et al. Childhood abuse and neglect. Specificity of effects on adolescent and young adult depression and suicidality. *J Am Acad Child Adolesc Psychiatry* 1999;38:1490-6.
- Tamam L, Poyraz N. Comorbidity of anxiety disorder among patients with bipolar disorder in remission. *Psychopathology* 2002;35:203-20933.
- Finkelhor D, Hotaling G, Lewis LA et al. Sexual abuse in national survey of adult man and women: prevalence,

- characteristics and risk factors. *Child Abuse and Neglect* 1990;14:19-28.
30. Sugaya L, Hasin DS, Olfson M et al. Child physical abuse and adult mental health: a national study. *J Trauma Stress* 2012;25:384-92.
  31. Cerimele JM, Bauer AM, Fortney JC et al. Patients with co-occurring bipolar disorder and posttraumatic stress disorder: A Rapid Review of the Literature. *J Clin Psychiatry* 2017;78:506-14.
  32. Gekker M, Coutinho ESF, Berger W et al. Early scars are forever: Childhood abuse in patients with adult-onset PTSD is associated with increased prevalence and severity of psychiatric comorbidity. *Psychiatry Research* 2018;267:1-6.
  33. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol Psychiatry* 2001;49:1023-39.
  34. Bilbo SD, Schwarz JM. Early-life programming of later-life brain and behavior: a critical role for the immune system. *Front Behav Neurosci* 2009;24:3-14.
  35. Knuesel I, Chicha L, Britschgi M et al. Maternal immune activation and abnormal brain development across CNS disorders. *Nat Rev Neurol* 2014;10:643-60.
  36. Post RM, Leverich GS. The role of psychosocial the role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. *Dev Psychopathol* 2006;18:1181-211.
  37. Hyun M, Friedman SD, Dunner DL. Relationship of childhood physical and sexual abuse to adult bipolar disorder. *Bipolar Disord* 2000;2:131-5.
  38. Hanford LC, Eckstrand K, Manelis A et al. The impact of familial risk and early life adversity on emotion and reward processing networks in youth at-risk for bipolar disorder. *PLoS One*. 2019;14:0226135.
  39. Holtzman CV, Shapiro DI, Trotman HD et al. Stress and the prodromal phase of psychosis. *Curr Pharm Des* 2012;18:527-33.
  40. Meyer JS, Hamel AF. Models of stress in nonhuman primates and their relevance for human psychopathology and endocrine dysfunction. *Ilar J* 2014;55:347-60.