

Negative experiences in childhood and the development and course of bipolar disorder

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Summary

The aim of this paper is to review the effects of negative childhood experiences on the development and course of bipolar disorder (BD) and to discuss the involved mechanisms. The negative childhood experiences that may play a role in BD are critical or traumatic events including all kinds of abuse, loss of a parent or parents resulting from death, suicide, separation, divorce or prolonged separation. Previous studies indicate that in BD patients negative childhood events are more frequent than in control group. In BD patients these events are associated with an earlier onset and more severe course of the illness, including more frequent relapses, suicidal behavior, substance abuse and somatic diseases. This paper presents the possibility of the specific impact of individual events on the clinical outcome of BD. Mechanisms explaining the impact of negative childhood events on the development and course of BD include the interaction between biological predisposition and stress factors, the concept of kindling and activation of negative cognitive schemas. Early negative experiences cause a modification of the expression of the mediators of stress and neurotransmitters in certain areas of the brain. The interaction of these mediators with the development of neural networks may lead to longlasting structural and functional changes. Molecular genetic studies indicate the possibility of interactions between environmental factors (stress) and the polymorphisms of serotonin transporter, brain-derived neurotrophic factor (BDNF) and toll-like receptor (TLR2). It has also been hypothesized that childhood experiences affect DNA methylation, acting as a form of molecular memory and modifying brain activity over the next decade.

Key words: negative childhood experiences, violence, bipolar disorder

The pathogenesis and course of bipolar disorder

In the pathogenesis of bipolar disorder (BD) genetic predisposition and neurobiological factors play a significant role. Among other pathogenic factors research

points to the importance of life events. At the same time, a good deal of research in this area is related to recurrent depression but fewer studies have been carried out on bipolar disorder. Previous studies suggest that different types of events in childhood are associated with bipolar disorder in adulthood. Stressful events both in the early stages of development and in adulthood alike may give rise to a predisposition to affective disorders [1].

In the journal "Psychiatria Polska", a recent review of research on the role of life events in bipolar disorder was published in 2013 [2]. The authors discuss the role of life events such as psychological traumas, loss of important members of the family in childhood and adolescence, some years before and immediately preceding the first episode of the illness. In addition to stressful events, positive developments were taken into account, which, according to the authors, may be associated with the occurrence of a manic episode. The relationship between the vulnerability of personality and the presence of stressful events are also described.

The course of bipolar disorder is extremely varied. Kraepelin wrote: "It is possible to give numerous examples of the course of manic-depressive illness but one is never able to fully describe its diversity" (as cited in: [1]). The course of bipolar disorder is influenced by many factors, including genetic predisposition, specific clinical picture, medical treatment as well as family and social circumstances. Many studies have shown, however, that the clinical picture of bipolar disorder may also be affected by childhood trauma [3]. Negative experiences in childhood may be important in the development and clinical course of mental disorders in adulthood and patients with mental disorders often report a history of abuse during childhood [4, 5].

What count as negative events in childhood will vary depending on the theoretical concept. According to Hans Selye's theory of stress, stress is a specific biological reaction common to all organisms, occurring in interaction with various types of environmental stimuli [6]. Traumatic experience is understood as a stressor associated with neurobiological changes in the central nervous system. In modern psychiatry negative childhood experiences are events described as critical, stressful, traumatic or significant [2]. Among these negative events are: the experience of sexual abuse, physical abuse, emotional abuse, loss of parents, as well as other experiences that meet the criteria for the diagnosis of posttraumatic stress disorder (PTSD). At the same time, studies show that trauma is not alone in influencing the formation of mental illness, but experience of neglect and excessive discipline in the family of origin may be relevant stressors to the formation of mental illness [7].

The main aim of this paper is to review the most important research on the role of traumatic childhood experiences in the formation and development of bipolar disorder, published in the last 20 years. The second aim is to discuss mechanisms explaining the impact of negative experiences in childhood on the formation and course of bipolar disorder, in particular, the neurobiological mechanisms. In contrast to the last review

of studies on the role of life events in bipolar disorder, which appeared in 2013, in this paper, only those adverse events that occurred during childhood were taken into account. In addition, the paper includes studies on these events and their mechanisms, which appeared in the last two years.

The impact of negative childhood experiences on the development and course of bipolar disorder

Most research on the role of negative experiences in childhood on bipolar disorder dates back to childhood in a retrospective. This research indicates that different types of events in childhood are associated with bipolar disorder in adulthood.

Many studies have revealed that patients with bipolar disorder experienced negative events in childhood more often than healthy subjects [3–5, 8]. A study on a group of 206 patients with bipolar disorder and 94 control subjects showed that the bipolar patients experienced significantly more complex traumas during childhood (63%) than the control group (33%) [5]. Among the childhood events that may have an impact on the incidence of bipolar disorder are early loss of a parent or prolonged separation from parents. It has been found that such an event increases almost four-fold the risk of depression in the future, and 2.6-fold increase in the risk of developing bipolar disorder. This association was noticed in cases of a parent's death or a patient's separation from a parent before the age of 17 [9].

There are indications that in bipolar disorder, traumatic childhood is associated with different clinical features of the disorder, such as: early onset of the illness, rapid cycling [3, 10], a significant number of mood episodes during lifetime [11], suicidal behavior [3, 10–13] and psychotic symptoms [14, 15]. A systematic review carried out by Daruy-Filho et al. [8] showed that abuse and neglect in childhood in patients with bipolar disorder are associated with an earlier onset of the illness, the occurrence of suicidal behavior and substance abuse. In patients with bipolar disorder (BD) who experienced this kind of negative events as children, more episodes of affective symptoms may be observed in the course of the illness. The episodes were also more severe, there was a greater number of comorbid disorders, and worse response to treatment [8].

There are also reports of a relationship between negative experiences in childhood, and occurrence of suicide attempts [16]. One study conducted by Hoertel et al. showed that all types of adverse experiences in childhood (sexual abuse, physical abuse, emotional abuse, neglect) are associated with the risk of suicide and an early first suicide attempt. At the same time, however, it was sexual abuse that was most strongly associated with the risk of suicide. In this context the importance of epigenetic modification is also stressed as a mechanism that explains the link with the increased risk of suicide in people with a history of childhood trauma [16].

Knowledge regarding the way specific types of negative experiences in childhood are associated with the clinical outcome of the illness remains poor [3] and there is

little research on the role of specific types of emotional abuse and emotional and physical neglect in bipolar disorder [8]. There are many indications that physical and sexual abuse are the strongest predictors of unfavorable clinical outcome of bipolar disorder [8, 17].

Experiencing physical abuse in childhood is probably most strongly associated with an unfavorable course of bipolar disorder [8,17] resulting in, among other things, an earlier onset of the illness, delay in making a diagnosis and beginning treatment as well as rapid-cycling [8, 10, 11, 18, 19]. The relationship between physical abuse, and the occurrence of psychotic symptoms [3, 14, 15] and suicide attempts has been observed [12, 13, 16, 19]. Some researchers suggest that this type of negative experience is associated with more severe manic episodes and more hospitalizations [19]. Patients experiencing physical abuse often suffer from posttraumatic stress disorder (PTSD) [20] and often abuse psychoactive substances [10, 11, 20].

Besides of physical abuse, sexual abuse appears to be a significant predictor of unfavorable clinical outcome of bipolar disorder [8, 17]. Sexual abuse in childhood has been associated with early onset of the illness [3, 19], delayed treatment [19] and BD with rapid cycling [3, 10, 19]. Those who have experienced childhood sexual abuse are more likely to report suicide attempts [3, 10, 12, 13, 16, 19], and their episodes are characterized by a higher incidence of psychotic symptoms [14, 15, 21] and an increased severity of manic episodes [19]. As with physical abuse, sexual abuse is related to comorbidity of PTSD and addiction to psychoactive substances [3, 10, 11, 19, 20, 22].

Another study showed that patients who experienced stressful events in childhood in the form of sexual and physical abuse were characterized by a worse functioning before the onset of the illness and were more likely to discontinue therapy [23]. Etain et al. [3] carried out a study on a group of 587 patients with bipolar disorder, and it showed that the incidence of childhood sexual abuse was associated with an earlier onset of the illness, suicide attempts, rapid cycling and abuse of cannabis [3]. At the same time, Upthegrove et al. [15] studied a group of 2,019 patients and found that the experiences associated with the occurrence of sexual abuse in childhood were associated with a higher incidence of mood-congruent psychotic symptoms.

A review of research carried out by Daruy-Filho et al. suggests that there are few studies that seek to establish a connection between emotional abuse and emotional and physical neglect and the course of bipolar disorder [8]. At the same time, however, the above-mentioned study by Etain et al. suggests that the experience of trauma in childhood is associated with susceptibility to bipolar disorder [5]. In addition, they revealed that the strongest relationship is that between the experience of emotional abuse and bipolar disorder. Patients reported more frequent and more severe forms of negative treatment. The result of this study suggests that this type of experience, in particular emotional abuse, may be a risk factor for bipolar disorder, although a causal relationship cannot be demonstrated [5]. The above-mentioned study showed that

the prevalence of childhood emotional abuse was associated with an earlier onset of the illness, suicide attempts, rapid-cycling, more depressive episodes, more episodes of mania and hypomania and the abuse of cannabis [3]. On the other hand, neglect in childhood was associated with early-onset bipolar disorder [24]. Garino et al. also noted that emotional abuse was related to drug abuse and rapid cycling. Research conducted by Garino et al. showed that 51% of bipolar patients reported childhood abuse and neglect, 37% – experienced emotional abuse, 24% – experienced physical abuse, 24% – experienced emotional neglect, 21% – experienced sexual abuse, and 12% – experienced physical neglect [10].

Research conducted by Kessing et al. on a group of 1,565 patients diagnosed with manic or mixed episode, showed that the suicide of the mother (at least 20 years before the first hospitalization) increased more than five-fold the likelihood of hospitalization for a manic or mixed episode [25].

However, many studies treated various forms of negative experiences as a single phenomenon or did not distinguish forms of abuse [8]. The authors unanimously emphasize that negative experiences in childhood are associated with early-onset bipolar disorder, more episodes of depression and more severe manic and depressive symptoms [10]. In contrast, other studies have shown that negative experiences in childhood in the form of both physical and sexual abuse are associated with a higher incidence of comorbid psychiatric disorders such as alcohol abuse, PTSD or panic attacks [11]. At the same time, however, the researchers emphasize that the experience of physical and sexual abuse is associated with more suicide attempts [13], a poor response to therapy [23, 26] and psychotic symptoms [14]. Etain et al. revealed that the earlier onset of the illness, suicide attempts, rapid-cycling and a greater number of depressive episodes in the course of the illness are associated with the experience of at least one type of trauma be it emotional abuse, sexual abuse or emotional neglect [3]. At the same time, however, multivariate analysis has shown that emotional and sexual abuse are both predictors of an early onset of the illness, suicide and abuse of marijuana, while sexual abuse is the strongest predictor of rapid-cycling, and emotional abuse was associated with more depressive, hypomanic and manic episodes [3].

Bipolar disorder is also linked with comorbid somatic diseases [27]. Post et al. [28] examined the influence of negative childhood events on the development of co-occurring disorders in bipolar patients. The results showed that a history of abuse and neglect in childhood is associated with a significant increase in the occurrence of a variety of somatic diseases in patients with bipolar disorder. An examination of 900 bipolar patients found that negative experiences in childhood, particularly physical, emotional and sexual abuse as well as parental mood disorders, substance abuse and suicidal tendencies are associated with comorbid somatic diseases. Patients with a history of physical abuse were more likely to suffer from: allergies, chronic fatigue syndrome, hypertension and hypotension. They also often experienced head injuries.

Sexual abuse was associated with irritable bowel syndrome. Emotional abuse was associated with arthritis and migraine. These studies have shown a link between the overall result of negative experiences and the total number of somatic diseases, among which allergy, arthritis, asthma, chronic fatigue syndrome, menstrual disturbances, fibromyalgia, head injury, hypertension, hypotension and migraine were numbered [28].

The period between the first episode of bipolar disorder and treatment is an independent factor of adverse clinical outcome. Furthermore, the time between the first episode and treatment was significantly longer in patients with a history of physical and sexual abuse than those without such a history [28]. Better recognition of medical and psychiatric problems in connection with adverse events in childhood can, according to researchers, significantly facilitate early psychosocial and psychopharmacological interventions in children and adolescents at risk of BD and other somatic diseases. The researchers emphasize that social support, early intervention and other preventive procedures may also be helpful for those most at risk of bipolar disorder [28].

A summary of the influence of negative childhood experiences on clinical picture of BD is shown in Table 1 (at the end of the paper).

Mechanisms explaining the impact of the negative childhood experiences

The interaction between a genetic predisposition and environmental factors plays an important role in modulating the early negative childhood experiences in the clinical course of bipolar disorder [29]. These relationships may be explained by the predisposition–stress model. The concept of interaction between predisposition to the disease and stress factors in relation to mental illness implies that initiation, as well as subsequent relapses and exacerbations occur as a result of factors causing mental stress imposed on the shaped predisposition to the illness [30]. Predisposition is mostly connected with genetic background, and under the influence of various factors (stressors), it changes into the biological predisposition [6]. The predisposition–stress model assumes that vulnerability to depression is increased as a result of a confrontation with repeated negative experiences. Chronic induction of stress axis may be understood as a biological exponent of vulnerability to depression. The importance of genetic predisposition and stress experienced in the early stages of development is emphasized, which results in dysregulation of stress axis and increased sensitivity to stressful events later in life [1].

According to Aaron Beck's cognitive theory, depression is caused by dysfunctional cognitions called the "depressive triad", while mania is considered to be a mirror image of depression with a positive triad of the cognitive self, the world and the future, and cognitive distortions. Beck claims that a specific way of thinking of given individual, in combination e.g., with the experience of loss, is a factor that makes a person prone to depression [31]. Studies show that adverse life events exacerbate affective symptoms [32]. Critical events activate dysfunctional cognitive patterns, resulting from negative childhood experiences. Thus, whether the stressful event will result in the occurrence

of depression depends on the extent to which it corresponds with the cognitive schemas of the patient [31].

Another concept of depression is the theory of learned helplessness, originated by American psychologist, Martin Seligman. The learned helplessness model assumes that people with depressive states are characterized by helplessness in choosing the most appropriate response and an inability to avoid situations that entail punishment. According to this theory, a conviction arises in a person that, in difficult and unpleasant situation, they will not be able to deal with it [33]. Negative childhood experiences are a source of a belief that punishment and reward are independent of the choices they make, and therefore they are unable to learn the consequences of their own and other's behaviors. Thus, this theory assumes that what leads to depression are: the expectation of lack of control, the belief that something bad will occur or the belief that something good will not occur [33].

The concept of kindling was the first model of the development of bipolar disorder (BD), which takes into account both psychosocial (stress) and neurobiological factors in triggering episodes of the illness [34]. According to Robert Post, the proponent of the model, stressful events are the primary sensitizing agents. Neurobiological sensitization may thus be the result of childhood abuse or neglect and for further recurrences to occur, increasingly weak external triggers suffice, and finally as the illness progresses, episodes occur spontaneously, without the trigger of stressors. The phenomenon of kindling may in some way explain the relationship between negative childhood experiences and the incidence of depression and bipolar disorder in adulthood [35].

Susceptibility to emotional disorders, including depression results from the interaction between genes and the environment, particularly during developmental years. Negative experiences in early life provoke the release and modification of the expression of stress mediators and neurotransmitters within specific brain regions. The interaction of these mediators with the development of neurons and neural networks may lead to long-term structural and functional alterations [36].

The interaction between a genetic predisposition and stress factors is reflected in molecular-genetic studies. A review conducted by Karg et al [37] focused on the interaction between polymorphisms of the serotonin transporter (5-HTTLPR) gene and stress in the development of depression. The results of these studies suggest that there is a relationship between polymorphisms of this gene and an increased risk of depression due to the stress of maltreatment in childhood [37]. In addition, the interaction between the serotonin transporter gene and negative events causes the development of depression and suicide [38]. Brain-derived neurotrophic factor (BDNF) has been associated with the efficiency of cognitive function and the prevalence of depression due to stress factors [1]. The study also confirms the relationship between the BDNF genotype (Val66Met polymorphism) and stressful life events in bipolar disorder and show that BDNF may have a great impact on sensitivity to stress [39]. It was also

shown that the dysfunction of the immune system may be an important mechanism linking childhood trauma to early-onset bipolar disorder. It was found that the negative impact of sexual abuse on the age of the onset of bipolar disorder may be intensified in carriers of a polymorphism of the TLR-2 rs3804099 gene, which is associated with the activity of the immune system [29].

Canadian researchers have described the concept of neurobiological consequences of negative childhood events associated with aberrant DNA methylation, forming a sort of molecular memory [40]. The researchers showed that the epigenetic mechanisms, and in particular DNA methylation, reflect a molecular form of memory which may modify the function of the brain for a time, and also serve as biomarkers of behavioral phenotypes associated with childhood abuse. DNA methylation is the main substrate that causes neurobiological consequences of negative life experiences, thus exacerbating the negative patterns of behavior and the risk of psychopathology.

Concluding remarks

As it has been shown in this paper, the role of stressors in the form of negative experiences in childhood in the pathogenesis of bipolar disorder is significant. Traumatic experiences in the early stages of development may modulate the functioning of the central nervous system, which, combined with a genetic predisposition may be responsible for the formation and course of bipolar disorder. Negative childhood events may be responsible for more frequent occurrence of bipolar disorder, as well as a number of elements related to a more severe clinical course.

The results of the research point to a necessity to carry out a thorough interview, taking into account negative childhood experience. This is important for the therapeutic management of patients with bipolar disorder. Bear in mind that these patients have a more severe course of the illness (e.g., rapid cycling), early onset of the illness, increased risk of drug and substance abuse and more frequent suicide attempts, are less responsive to treatment, have symptoms of PTSD, and consequently have a greater predisposition to relapse. For this reason, the key issue is to introduce adequate psychotherapy and pharmacotherapy to prevent the development of other disorders and possible subsequent recurrences.

It is necessary to conduct further research on the role of negative childhood experiences in the pathogenesis and course of bipolar disorder integrating both psychological and biological approaches. Particularly interesting are the results of genetic-molecular research which may contribute to a better explanation of the biological mechanisms associated with the impact of traumatic childhood events on the incidence and clinical features of bipolar disorder.

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Table 1. The impact of the negative childhood experiences on the clinical outcome of bipolar disorder

Clinical effect	Total negative experiences	Separation with parents	Physical abuse	Sexual abuse	Emotional abuse	Emotional neglect
The risk of bipolar disorder	[4, 5, 8]	[9]			[5]	
Early onset of bipolar disorder	[3, 10]		[8, 19]	[3, 19]	[3]	[3, 24]
Delay in diagnosis and treatment	[18, 28]		[8, 18, 19, 26, 28]	[19, 28]		
More hospitalizations	[11, 18]		[19, 26]			
More frequent episodes	[8, 10, 11]				[3]	
Severe course	[8]		[8, 17]	[8, 17]		
Increased severity of depression episodes	[3, 3, 10, 18]			[3]	[3]	[3]
Increased severity of mania	[8, 10]		[19]	[19]	[3]	[3]
Rapid cycling	[3, 10]		[8, 10, 11, 19]	[3, 10, 19]	[3, 10]	[3]
Psychotic symptoms	[14, 15]		[3, 14, 15]	[14, 15, 21]		
Suicidal behavior	[3, 10-13, 16]		[12, 13, 16, 19]	[3, 10, 12, 13, 16, 19]	[3, 16]	[3, 16]
Substance abuse	[3, 10]		[10, 11, 20]	[3, 10, 11, 19, 20, 22]	[3, 10]	
Higher incidence of posttraumatic stress disorder	[11, 22]		[11, 20]	[11, 22]		
Increased incidence of somatic diseases	[28]		[28]	[28]	[28]	
Worse response to treatment	[8, 23, 26]		[23, 26]	[23, 26]		[26]