



# Bipolar Disorder: Etiology, Clinical Picture, Prognosis, and Treatment

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## Abstract

Bipolar affective disorder is a chronic and complex mood disorder characterized by the combination of manic (bipolar mania), hypomanic and depressive (bipolar depression) episodes. Damage to emotions is dominant, from which damages to other psychological functions arise. The disease is endogenous with a pronounced hereditary factor. Bipolar affective disorder is one of the leading causes of disability worldwide. It is often associated with severe medical and psychiatric comorbidity, early mortality, high levels of functional disability, and compromised quality of life. Contemporary neuropsychiatry aims to recover from illness and enable a person to lead a satisfying life with maximum functionality in the community. The means used for these purposes are pharmacotherapy, psychotherapy and various psychosocial methods that have shown their usefulness in a series of scientific studies. In this paper, we consider the etiology, clinical picture, course, prognosis, as well as available therapies for the treatment of bipolar affective disorder.

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## Introduction

The term mood disorder refers to mental disorders in which fundamental psychopathological changes occur at the mood level, followed by changes in some other psychological and physical functions [1]. In the tenth revision of the International Classification of Diseases, bipolar affective disorder is located within the group of mood disorders (F30-F39) and is classified under the code F31 [2]. The patient's emotional state oscillates between two extremes: high (mania or hypomania) and low mood (depression). Mood changes are a normal phenomenon in all people, what makes them pathological is their expression and impact on the daily functioning of the patient. In addition to emotional changes, symptoms are also visible in cognitive functioning, behaviour, urges and psychomotor [3]. It is a chronic illness with alternating episodes of mania, hypomania, depression, mixed episodes and euthymia. It is associated with impaired psychosocial functioning, financial dependence on others and earlier mortality [4,5].

When it comes to epidemiology, the frequency of bipolar affective disorder was previously thought to be 1% for both sexes [6], which corresponds to the frequency of schizophrenia, but recent research shows that the prevalence of this disorder is higher and, depending on the type, is up to 6% [7]. The prevalence of mood disorders is not influenced by race or socioeconomic status, however, in the US, schizophrenia is more often diagnosed in the poor, and bipolar disorder in the wealthier strata. Bipolar disorder is more common in single and divorced people. In their case, it remains unclear whether it is a cause or a consequence of the disease, given that it most often occurs at the age when marital and emotional bonds are formed [8]. As part of their large study, Parlis et al. [9] examined the period of onset of the disease in the first 1,000 subjects, of whom the age could be determined for 983. 27.7% of respondents report the onset of the disease before the age of thirteen, and 37.6% of them between the ages of thirteen and eighteen (very early and early onset of the disease). The mean age of reporting was 17.37 years. Earlier presentation is associated with a more severe form of bipolar disorder, a greater chance of developing comorbidities (anxiety disorders, eating disorders, psychosis, addictions, dissociative disorders), a greater number of episodes and the number of days the patient spends depressed, as well as an increased risk of suicidal thoughts and behaviour [9]. A third of patients do not establish adequate work and social function due to cognitive disorders [10]. If we take into account the data that 10-15% of bipolar affective disorder sufferers commit, and 25-50% of them attempt suicide at least once in their life, we can see that it is one of the leading psychiatric disorders with regard to the risk of suicidality [11]. According to the World Health Organization, bipolar affective disorder is the second most common disease in terms of the number of days the patient was unable to work or function normally (days out-of-role) [4,12].

### Etiology of bipolar disorder

Bipolar affective disorder can be caused by various biological, psychosocial and neurocognitive factors [13]. Some of them are discussed below in this paper.

**Genetic predisposition.** An increased frequency of mood disorders has been observed in some families, so it is estimated that if both parents have bipolar disorder, the risk of a child developing a mood disorder is 50-70%; if only one of the parents is sick, the risk drops to 27%. It is also known that in 50% of

patients with bipolar disorder, at least one parent also suffers from some mood disorder, and most often it is depression [14].

**Neurotransmission disorder.** Changes in the metabolism of neurotransmitters (serotonin, noradrenaline, dopamine) and the sensitivity and number of their receptors are significant for mood disorders. In depressed patients, we find hypoactivity of those three systems with up-regulation, i.e. hypersensitivity of their receptors. Reduced concentration of serotonin in certain parts of the brain is associated with loss of pleasure and happiness, sleep disturbance and pessimism in depressed patients. A decrease in the concentration of noradrenaline in the hippocampus and hypothalamus leads to the development of physical symptoms that occur in depression (anorexia, loss of libido and energy), a drop in concentration and a decrease in the activity of the neurovegetative system; while the decrease in dopamine levels in the basal ganglia leads to psychomotor retardation. Dysfunction of the autonomic system is reflected in the up-regulation of  $\alpha$  and  $\beta$  receptors. Disorders in the action of Gamma-Aminobutyric Acid (GABA) and glutamate were also found. In manic patients, we find increased activity of catecholamines and endogenous opioids [15].

**Endocrinological theory.** People suffering from bipolar disorder often have an enlarged pituitary gland and adrenal gland with elevated levels of cortisol in plasma, urine and cerebrospinal fluid. Cortisol response to Adrenocorticotrophic Hormone (ACTH) is also emphasized, and secretion of Corticotropin-Releasing Hormone (CRH) is increased [16]. Cortisol concentration is additionally enhanced with increased glutamate transmission in stress states, which leads to apoptosis of neurons in the hippocampus and a decrease in its volume with a decrease in the secretion of Neurotrophic Brain Factor (BDNF). Its role is to prevent apoptosis, form new synapses and support neuroplasticity, so in its absence, they lead to deterioration of the brain [17].

**Neurodegenerative theory.** Magnetic resonance analysis images in the patients showed a reduction in the volume of the entire brain and the prefrontal lobe, along with increased lateral cerebral ventricles and globus pallidus. The severity of these changes depends on the age and duration of the disease itself [18]. Functional analyzes also show an increase in metabolic activity in the thalamus [19,20].

**Psychodynamic theory.** Freud relates depression to the unsatisfactorily processed grieving process that pursued the loss. The patient directs the negative feelings that arise due to the loss towards himself, instead of towards the lost object. Depression represents a regression to the oral phase of psychosexual development, in which the patient seeks tenderness and attention and is essentially a desperate request for love. Mania, according to this theory, occurs as a response to depression in the sense of the negation of dependence on the object. Underlying it is a mechanism of denial that allows a person to avoid responsibility and reduce depression [21].

**Behavioral theory.** This theory explains the development of depression in some individuals with a lack of social skills, due to which they do not develop interpersonal relationships and their behaviour causes a negative reaction from the environment, and as a result, further isolation and worsening of depression occur [22].

**Cognitive theory.** According to Beck, depression develops from negative thinking and conceptualization, a person perceives himself as sinful, abandoned, inadequate and develops

feelings of grief, sadness, loneliness and guilt. A characteristic cognitive triad occurs: negative thinking about oneself, the future and the world, which results in the development of depressive symptoms. However, Seligman explains the development of depression with the theory of learned helplessness, according to which a person feels helpless when exposed to unpleasant situations, and adopts this feeling to the extent that it begins to interfere with his functioning and leads to the development of depressive symptoms [23,24].

**Stressful event theory.** The connection between stressful events and the occurrence of the first depressive episode has been proven. This is also explained by the theory of life events, which explains that the disease develops in those individuals who fail to adapt to new life circumstances. The disease can develop immediately after the change or delayed [25].

### **Clinical picture of bipolar disorder**

Bipolar affective disorder is characterized by changes in depressive, hypomanic, manic and mixed episodes. Bipolar disorders include: bipolar disorder type I (depressive and manic episodes: this disorder can be diagnosed on the basis of one manic episode); bipolar disorder type II (depressive and hypomanic episodes); cyclothymic disorder (hypomanic and depressive symptoms that do not meet criteria for depressive episodes); and bipolar disorder not otherwise specified (depressive and hypomanic-like symptoms that do not meet the diagnostic criteria for any of the aforementioned disorders) [26].

#### **A manic episode**

This episode is characterized by a typical triad of symptoms: elevated mood, increased motor activity, and rapid speech. Over 90% of those who experience such an episode continue to have recurrent episodes of pathological mood throughout their lives [27]. The mood in mania is elevated (it can also be described as euphoric, high, noisy, expansive, etc.), often accompanied by laughter, puns, and posing; people who are normally reserved, in mania, also take on these characteristics, and in addition they can become vulgar, logorrheic and undistanced. The expansive mood is characterized by inappropriately expressed and uncritical enthusiasm for interactions with others [28]. Such a mood is not stable, the frustration threshold of these patients is low and can quickly turn into an irritable mood accompanied by belligerent behaviour and quarrelsomeness. If someone opposes them, they easily become hostile and irritable. The psychomotor skills of a manic patient are accelerated, they are restless and have difficulty staying in one place, and due to the subjective and uncritical general feeling of well-being, patients who have genuine complications with movement ignore them and thereby endanger their physical health. The external appearance is striking, the clothes that the patients choose are aggressive, bright colours, as well as the make-up [28]. The thinking is also accelerated, there is often a flight of ideas, so their associations are very difficult to follow; patients get involved in a series of activities, create numerous and unrealistic plans with great enthusiasm. They are preoccupied with unimportant details, logorrheic and usually very loud; they can give speeches, dance or sing to the point of exhaustion. In the content of the opinion, there are often grandiose delusions about oneself, stating that they have special physical or psychological abilities. Persecutory delusions are less common and are usually the product of the patient's self-importance. In more severe cases, these insanities can progress to psychosis. Their attention is hypotensive and hypervigilant, and they are hyperbolic, but they are usu-

ally unable to complete any activity [27,28]. As a rule, cognitive functions are preserved. The condition is also characterized by impulsive behaviour. Often, such patients are guided only by their instincts, ignoring moral principles and legal restrictions. They engage in various risky activities, are often promiscuous and enter into unsafe sexual relationships, engage in various inappropriate business ventures and other interpersonal interactions, spend overly on themselves or someone else; they assess social situations inadequately, so they can sing or dance in the street, behave without distance, etc. In short, it can be said that they are not critical of situations, other people or their own condition, which is why they can put themselves and others in danger. Because of all this, they can seem infantile, as if they are mildly mentally deficient [28]. As a rule, the urges of such people are heightened, especially those of a sexual nature. Their need for sleep is reduced so that, even after only a few hours of sleep, such a patient claims to be completely rested. Some do not sleep for several days at a time without slowing down their exaggerated activity. Given that they sleep less and are awake most of the night, they can engage in activities inappropriate for that time of day, e.g. vacuuming, phone calls, cooking, etc. Their appetite is not reduced per se, but they often forget to eat because they are preoccupied with other things. When taking into account their excessive activity and lack of sleep, it is not surprising that they often lose weight [27,28].

#### **A hypomanic episode**

Hypomania is a period of persistent, elevated or irritable mood lasting 4 days. It is characterized by psychomotor restlessness, grandiosity, logorrhea, hyposomnia, exaggeration in pleasant activities with painful consequences.

The symptoms are less pronounced than in mania and usually do not lead to great impairment in work and social life. Mood, activity and energy are slightly elevated, there is no insanity and there is no need for hospitalization [27].

#### **A depressive episode**

Bipolar disorder most often begins with depression in 75% of cases in women and 67% in men [29]. Depression is characterized by low mood, loss of interest and unreasonable feelings of inferiority, sadness, grief, hopelessness and despair. Anxiety, inner restlessness and panic attacks are also common [27]. The beginning of the depressive phase is easy to see: patients have a sad facial expression, often because of this they look older than they are, wrinkles on their face become more pronounced, they have limited movements; they leave the impression of someone suffering [28]. This phase is characterized by anhedonia, i.e. a reduction in the capacity for enjoyment, accompanied by a loss of interest in things in which the person previously found leisure or pleasure; it can go so far that the patient loses feelings for his loved ones, feels emotionally cut off from other people and experiences depersonalization and derealization [28]. Psychomotorically, such patients are slow, they have little spontaneous motor skills and facial expressions, and they sit or lie down most of the day. They have no vital energy, every movement or action is a problem for them, and they complain of fatigue that was not preceded by any objective effort. Their poor motor skills can, in extreme cases, progress to a stupor. Although slowness is more common, some patients may be psychomotorically agitated and agitated [27]. Thought and speech are slowed down, response latency is prolonged; speech is monotonous and quiet. In the patient, a slowing down of mental functions can be observed, which can be so severe

that the patient appears to be demented. The content contains ideas of guilt, helplessness, and worthlessness; the outlook on the world is pessimistic and the patient does not see the possibility of improving his condition, and thoughts of death and suicidal ideas are also frequent. As many as 15-20% of inadequately treated patients commit suicide [11]. These insanities can go to the extreme and be reflected in psychotic symptoms, and hallucinations and delusions are following the patient's mood [28]. The patient is hypobulic, hypovigilant and hypertensive for depressive content [27]. As a rule, the drives of depressed patient are lowered, they have no appetite or sexual needs, and the sleep cycle is also disturbed. Central or terminal insomnia usually occurs, so the patient either wakes up in the middle of the night and has difficulty falling asleep again, or wakes up too early and cannot fall asleep again [28].

### A mixed episode

The clinical picture is dominated by rapid alternation of manic, hypomanic and depressive symptoms or a mixed picture of the disorder. Anamnestically, there is information about at least one manic/hypomanic episode. Although typical forms of bipolar affective disorder consist of manic and depressive episodes alternating with periods of regular mood or remission in between, it is relatively rare for manic and depressive symptoms to alternate from day to day or even hour to hour. All the described symptoms of mania, hypomania and depression can also appear in such a mixed episode and have a wide range in intensity, frequency and quality [26].

### Course and prognosis of bipolar disorder

Bipolar disorder has a worse prognosis than the major depressive disorder. Patients with only manic episodes have a better prognosis than patients with depressive or mixed episodes. Psychotic symptoms do not automatically mean a worse prognosis [30].

The course of the disease is adversely affected by the following factors: [31,32]

- Positive family history,
- Pronounced comorbidity with other psychiatric disorders,
- Early onset of disease,
- Poor functioning in the premorbid period,
- Rapid changes of episodes, i.e. short inter-episode phases,
- Frequent hospitalizations,
- Mixed symptomatology of mania and depression,
- Absence of response to the applied therapy,
- Lack of patient cooperation in the treatment process.

The course of the disease is favorably influenced by:

- Negative family history (of bipolar disorder and other psychiatric disorders),
- Medical causes of illness,
- Sudden onset of illness after some stress,
- Good premorbid functioning,
- Good response to pharmacotherapy,

- Cooperation in the treatment process [31,32].

Untreated manic phases last 3-6 months with a high rate of recurrence (on average 10 repeated episodes), 80-90% experience a full depressive episode. The prognosis is favourable, 15% of patients recover, 50-60% partially recover with numerous relapses, and one-third have signs of chronic symptoms and social deterioration [32].

### Therapy of bipolar disorder

In the therapy of bipolar affective disorder, the following forms of treatment are applied: pharmacological, psychosocial and psychotherapeutic methods and electroconvulsive therapy [33].

Pharmacological treatment of bipolar affective disorder always begins with mood stabilizers. The most important representative of that group of drugs are lithium salts, and some anti-epileptics (carbamazepine, valproate, lamotrigine, topiramate, gabapentin) which are also used for this purpose [34]. If the patient is manic, therapy is usually started with lithium, to which antipsychotics and benzodiazepines can be added. When the acute phase passes, only lithium remains in treatment. Treatment can be carried out with antipsychotics alone (quetiapine, olanzapine, clozapine). One should strive to achieve a euthymic mood while making sure that the patient does not "shift" into a depressive phase [35,36]. Unlike unipolar, the treatment of depression in bipolar disorder is based on the use of a mood stabilizer to which an antidepressant is then added, while being careful not to use a drug that is known to "shift" patients into a manic phase (tricyclic antidepressants carry the highest risk for such an outcome, and it can also be caused by some selective serotonin reuptake inhibitors - SSRIs) [36]. It should also be borne in mind that these patients often have reduced cooperation when taking pharmacotherapy (interruption of taking or modification without consulting a doctor) and that they are more prone to abuse alcohol or psychoactive substances, all of which reduces the effectiveness of that method of treatment [32,37]. According to one study, only 30% of patients adhered to the agreed therapy regimen [38].

Psychotherapeutic and psychosocial procedures can be applied in the acute phase of the disease, to maintain remission and prevent a repeat episode. They are most often applied as an addition to pharmacotherapy, but they can also be implemented alone, in a situation where there is no indication for forced hospitalization, and the manic patient refuses to take medication. In mildly to moderately depressed patients, it can be used without the addition of antidepressants (thereby avoiding their side effects), thereby preventing the transition to mania and a rapid change of phases. These procedures include: psychoeducation, psychotherapy (cognitive-behavioural, psychodynamic and other methods applied by trained experts), social skills training and treatment coordination ("case management"). The goal of these therapeutic procedures is to preserve the quality of life, empower the patient (and his environment) and accelerate recovery. When developing a therapeutic plan, the psychological and psychosocial difficulties of that individual patient should be taken into account [39,40]. Psychotherapy is focused on exploring a person's inner world and relationships with others, while sociotherapeutic and psychosocial procedures emphasize learning new information, skills and behaviour [13]. Psychoeducation can be performed individually or in a group, it provides the patient with information related to the nature of the disease itself, prevents the development of self-

stigmatization and offers strategies to prevent discrimination and stigmatization by the environment. It also offers concrete advice for the patient's daily life. Work with the family can also be carried out individually or in a group to optimizing the capacity of family members to support the patient and to recognize their own need for external help. It can be based on cognitive, behavioural, systemic or psychoanalytic principles. Coordination of treatment is an alternative method to hospital treatment and is used in frequently hospitalized, poorly cooperative patients with markedly impaired functioning and increased risk of suicide. Cognitive-behavioral therapy involves working with dysfunctional thoughts and connecting them with concrete difficulties that the patient has; the goal of this therapy is to establish control over such thoughts and reduce their influence. Social skills training offers the patient tools to improve their functioning in the community. In the use of psychotherapy for the treatment of bipolar disorder, the relationship between supportive methods (which focus on strengthening defenses and suppressing the unconscious) and analytical approach (which aims to analyze defenses and translate the unconscious into the conscious) should be moderated. The extent of using these methods depends on the current stage of the disease and the ego strength of the patient. Namely, in the acute phase, it is more important to reduce the panic and fear that overwhelms the patient, and only after these symptoms have subsided can one move on to developing an understanding of the disease and connecting psychological factors with the development of the clinical picture [41].

Electroconvulsive therapy is reserved for the most severe patients who do not respond to previous treatment, for extremely suicidal patients or for stupor. Both bipolar and unipolar depression respond well to this treatment, as well as mania (in case of resistance or contraindications to the use of pharmacotherapy) [42,43].

Attempts to prevent bipolar disorder have focused on stress (such as childhood adversity or highly conflicted families) which, although not a diagnostically specific cause of bipolar disorder, puts genetically and biologically vulnerable individuals at risk of a more severe course of the disease. Longitudinal studies have shown that full manic stages are often preceded by various prodromal clinical features, providing support for the emergence of risk states of the disorder when early intervention can prevent its further development and/or improve its outcome [44,45].

### Conclusion

Bipolar affective disorder is a disease characterized by pathological mood changes that vary from mania to depression. Episodes tend to recur, so the disease often becomes chronic. Damage to emotions is dominant, from which damages to other psychological functions arise. The disease is endogenous with a pronounced hereditary factor [46].

Patients diagnosed with bipolar disorder are often not independent enough, they depend on their families, their work abilities and social functioning are impaired, and they are prone to suicidal behaviour. Contemporary neuropsychiatry aims to recover from illness and enable a person to lead a satisfying life with maximum functionality in the community. The means used for these purposes are pharmacotherapy, psychotherapy and various psychosocial methods that have shown their usefulness in a series of scientific studies. In the most severe patients, refractory to all other forms of treatment, the use of electroconvulsive therapy is justified. By combining these methods, it is

necessary to find the right "formula" that suits each patient and create an individual therapy plan.

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