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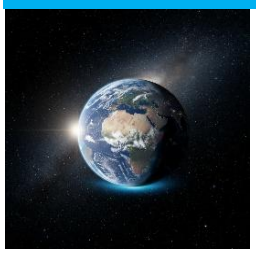

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Bipolar disorder - A review of current knowledge - from etiology and diagnosis to treatment

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Abstract
Introduction: Bipolar disorder is a chronic mental illness characterized by significant and often unpredictable changes in mood and energy levels. It is characterized by periods of mania or hypomania alternating with episodes of depression. Unfortunately, it often remains underdiagnosed and difficult to treat as it requires a comprehensive approach that combines pharmacological and non-pharmacological strategies tailored to the phase and severity of the illness.
Aim of the study: The aim of this review is to summarize the latest knowledge related to bipolar disorder, including epidemiology, pathophysiology, clinical types, and risk factors. In particular, it focuses on diagnostic difficulties and appropriate treatment.
Materials and methods: A comprehensive literature review was conducted using "PubMed", Google Scholar and other databases. The following keywords were used: "bipolar disorder", "mood stabilizers", "lithium", "antipsychotics", "electroconvulsive therapy"
Conclusions: Bipolar disorder is a severe but underdiagnosed mental illness that poses a therapeutic challenge. The etiology is multifactorial, and the incidence is the same in women and men. Treatment should include two main components: acute treatment of mood episodes and maintenance therapy. Current treatment strategies include mood stabilizers and antipsychotic medications. Nevertheless, lithium remains extremely important, as it is the only medication with proven anti-suicidal effects. Psychological interventions and electroconvulsive therapy may be valuable adjuncts. Further research is needed to optimize treatment and improve outcomes for patients with bipolar disorder.

Keywords: bipolar disorder; mood stabilizers; lithium; antipsychotics; quetiapine; lurasidone; asenapine

1. Introduction

Bipolar disorder (BD) is a frequent and serious mental condition characterized by significant and often unpredictable shifts in mood and energy levels[1]. BD , which affects roughly 1.5% of people, typically begins between ages 13 and 30 and often goes undiagnosed for many years . It involves periods of mania or hypomania marked by heightened activity, impulsive actions, and elevated mood, alternating with depressive episodes defined by a deep decline in motivation and interest [2]. BD was ranked as the disease with the second greatest impact on the number of days off work in the WHO World Mental Health surveys [3]. Bipolar disorder is a chronic, episodic condition with an unpredictable trajectory that frequently leads to difficulties in daily functioning, cognitive challenges, and a diminished quality of life [3,4,5]. The contemporary understanding of bipolar disorder stems from the concept, which emerged in the mid-20th century. It is primarily based on distinguishing between disorders characterized by episodes of mania or hypomania and depression, and those characterized by recurrent episodes of major depression [6]. During the 1970s, researchers identified a subset of individuals with bipolar disorder who experienced frequent episodes of major depression accompanied by hypomania, but without full manic episodes (BD-I). This presentation was classified as bipolar disorder type II (BD-II) [6,7]. Bipolar I disorder is defined by the presence of at least one fully developed manic episode during a person's lifetime, with depressive episodes frequently occurring as well. Bipolar II disorder, in contrast, is diagnosed when an individual has experienced at least one hypomanic episode along with at least one episode of major depression. It is no longer viewed as a less severe variant of bipolar I, as individuals with bipolar II often spend substantial periods in depression and experience significant functional difficulties related to mood instability [8,9]. A mixed-features bipolar disorder describes situations in which a manic or depressive episode is accompanied by meaningful but subthreshold symptoms of the opposite mood state, resulting in a particularly complex clinical picture [8]. Treatment of bipolar disorder begins with confirming whether the patient is in a manic, hypomanic, depressive, or stable phase, as each state requires a different therapeutic strategy. A wide range of factors can influence both medication choices and psychological interventions [3].

2. Epidemiology

BD is affecting over 5.7 million adults in the United States each year [10]. Two large community-based studies of the general population in the United States on the prevalence of bipolar disorder estimate that the disease affects 1.0% to 1.6% of adults and 1.2% of children and adolescents. Genetic studies suggest that type I bipolar disorder may be the more common clinical variant of the disorder. In the National Institute of Mental Health Epidemiologic Catchment Area (ECA) study, the percentage of people over 65 years of age diagnosed with bipolar disorder was estimated at 0.1% [11]. The prevalence of bipolar disorder is comparable between men and women. However, some studies indicate that women may have a higher likelihood of hospitalization during manic episodes and are more prone to experience rapid cycling than men [12]. Globally, bipolar disorder ranks as the sixth most common cause of medical disability in people aged 15–44, with an estimated annual cost to the United States of approximately $45 billion. The disorder causes significant limitations in social and occupational functioning for both patients and their families. It is estimated that up to 20% of those with the most severe illness commit suicide [13].

3. Risk factors

There is strong evidence that genetic factors substantially contribute to bipolar disorder. Relatives of people diagnosed with bipolar disorder have a higher risk of developing recurrent unipolar depression and schizoaffective disorder [14]. The heritability of bipolar I disorder is estimated at around 75%, mainly driven by common genetic variants. The disorder's expression arises from the interplay between genetic predisposition and environmental influences [15,16].

4. Overview and clinical types

Bipolar disorder, formerly known as manic-depressive illness, is a serious and chronic mood disorder that includes episodes of mania, hypomania, and alternating or mixed episodes of depression [3]. The fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders identifies four primary subtypes of bipolar disorder:

- Bipolar disorder type I – which involves episodes of depression and at least one full manic episode [3,17]
- Bipolar disorder type II- characterized by multiple prolonged depressive episodes and at least one hypomanic episode, but no full manic episodes [3,17]
- Cyclothymic disorder- marked by numerous periods of hypomanic and depressive symptoms that do not meet the criteria for full depressive episodes [17]
- Bipolar disorder not otherwise specified, which includes depressive and hypomanic-like symptoms that may alternate rapidly but do not fulfill the full diagnostic criteria for any of the subtypes [17]

5. Diagnosis

Bipolar disorder occurs frequently, yet it still often goes unrecognized in primary care. Up to one-third of patients presenting with depressive or anxiety symptoms may have bipolar disorder. The Mood Disorder Questionnaire (MDQ), which contains three questions, and the Composite International Diagnostic Interview 3.0 (CIDI 3.0) are useful in diagnosing bipolar disorder. Using these instruments with a clinical interview can strengthen diagnostic accuracy [2]. The diagnostic boundaries of bipolar disorder remain unclear. Both underdiagnosis and overdiagnosis carry significant risks. Underdiagnosis can delay the initiation of appropriate treatment, while overdiagnosis can lead to unnecessary exposure to medication [18]. Bipolar disorder often first appears as depression, leading to many initial episodes being misdiagnosed as major depressive disorder. A correct diagnosis is usually made only after manic symptoms appear, which causes significant delays in the implementation of appropriate treatment. Research indicates that the average delay between initial diagnosis of major depressive disorder and diagnosis of bipolar disorder is nearly 10 years, meaning that many patients do not receive optimal treatment for an extended period [19].

6. Pathophysiology

The exact pathophysiological mechanism of bipolar disorder has not yet been fully explained. Postmortem studies of patients with bipolar disorder have shown reduced numbers or density of glial cells, particularly astrocytes and oligodendrocytes, in specific layers of the prefrontal cortex and anterior cingulate cortex, while other areas of the brain appear unaffected. Activation, rather than loss, of microglia may also play a role [20]. Research indicates that the hippocampus also plays a role in the pathophysiology of BD, and postmortem studies show abnormal GABA and glutamate transmission [21]. It is believed that oxidative stress may

contribute to the development of bipolar disorder. Studies consistently show an increase in the concentration of lipid peroxidation products and changes in the concentration of antioxidant enzymes in patients with this disease. For example, postmortem analysis of the anterior cingulate cortex in individuals with bipolar disorder showed a 59% increase in 4-hydroxynonenal, a major lipid peroxidation product, compared with controls, indicating that oxidative damage could contribute to the disease process [22].

7. Treatment

7.1 Nonpharmacological treatment

7.1.1 Psychological interventions

It is extremely important in the treatment of bipolar disorder to provide assistance and convey necessary information related to bipolar disorder to the patient, as well as to offer support. Effective treatment of bipolar disorder involves pharmacotherapy combined with various forms of therapy: psychoeducation, family therapy, cognitive behavioral therapy, and interpersonal therapy [2]. Meta-analyses evaluating the effectiveness of cognitive behavioral therapy (CBT) in bipolar disorder indicate that its effects after completion of therapy are small to moderate and usually diminish over time. This applies to both depressive and manic symptoms. At the same time, there is few evidence that CBT alone, without parallel pharmacotherapy, is sufficiently effective in treating BD. Research indicates that cognitive behavioral therapy can effectively reduce the risk of recurrence of bipolar disorder compared to standard treatment [23]. Family-focused therapy (FFT) is a well-researched method that supports the treatment of adults and children with bipolar disorder, usually used in conjunction with pharmacotherapy after the end of an episode of the illness. Research conducted over more than 30 years shows that combining FFT with mood-stabilizing medications accelerates recovery, reduces the risk of relapse, and lowers symptom severity compared to shorter forms of psychoeducation and medication [24]. Interpersonal and social rhythms therapy (IPRST), originally developed by Klerman, aims to stabilize the patient's daily habits and improve the quality of their relationships and social functioning. As a result, the therapy not only improves the patient's current mood and functioning but also equips them with skills to protect against further episodes of the illness [25].

7.1.2 Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) was first introduced in 1938 and has undergone significant improvements since then. Current protocols differ mainly in terms of electrode placement (bipolar, unilateral right, or bilateral frontal), electrical pulse dose, and pulse width [26]. Electroconvulsive therapy has found wide therapeutic application in many neuropsychiatric disorders, including psychotic disorders, neurodegenerative diseases, and mood disorders. ECT is effective in depressive, manic, and mixed episodes. It is characterized by high response and remission rates, often exceeding the effectiveness of other available forms of therapy [27]. Patients with bipolar disorder frequently undergo electroconvulsive therapy (ECT) due to high symptom severity and poor response to standard treatments [28].

7.2 Pharmacological treatment

The treatment of bipolar disorder aims to quickly control acute episodes of mania or depression and maintain mood stability in the long term. This includes reducing relapses and decreasing the severity and frequency of symptoms. The choice of treatment for bipolar disorder should consider the phase of the illness, the type of symptoms, rapid cycling, polarization, comorbid disorders, and psychotic and cognitive symptoms. The potential side effects of medications are also important [29]. Treatment of bipolar disorder mainly involves mood stabilizers-lithium, valproate, and lamotrigine and selected antipsychotics- quetiapine, aripiprazole, asenapine, lurasidone, and cariprazine. The use of antidepressants alone is not recommended [30]. Lithium continues to be the preferred first-line option for long term

maintenance therapy in bipolar disorder [31]. When lithium is ineffective or poorly tolerated, alternatives include valproate, olanzapine, or quetiapine. First-line treatment options generally include monotherapy with lithium, lamotrigine, or quetiapine as well as combination therapies such as lithium with an SSRI or bupropion, or olanzapine with an SSRI other than paroxetine. Management of manic or hypomanic episodes involves several first-line treatments, including lithium, risperidone, paliperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, and asenapine. Although many guidelines do not distinguish between recommendations for BD-I and BD-II, quetiapine remains the only recommended first-line treatment option for depression in BD-II [32].

7.2.1 Mood stabilizers

LITHIUM

Lithium has been used since 1870 in the treatment of many conditions, such as gout, depression, and heart failure. Studies indicate that lithium reduces the release of norepinephrine and dopamine in synapses, while temporarily increasing serotonin release. This profile of action presumably contributes to its mood-stabilizing effect [33]. Lithium effectively stabilizes mood in people with bipolar disorder, but its effectiveness varies, and only about 20–30% of patients achieve a full therapeutic response [34]. The response to lithium treatment has a hereditary basis and appears to be genetically determined, being associated with variability in the gene encoding glutamate decarboxylase-like protein 1 (GADL1) [35]. Lithium has a very narrow therapeutic range. Symptoms of toxicity may appear even at plasma concentrations close to the upper limit of therapeutic values. Lithium poisoning can result from either deliberate overdose or unintentional treatment errors leading to gradual, chronic accumulation of the drug [33]. According to the Rybakowski J.K. (2024) review, lithium monotherapy has been shown to be more effective in preventing episodes than other mood stabilizers. This also applies to pediatric patients, as confirmed by randomized placebo-controlled trials. Lithium therapy has been shown to be associated with fewer suicide attempts, milder symptoms of depression and aggression, and better psychosocial functioning than treatment with other mood stabilizers [36]. The only drug with proven anti-suicidal efficacy is lithium [37]. In the systematic review by Airainer, Seifert (2024) of studies on lithium therapy indicates that lithium is more effective than aripiprazole, valproic acid, and quetiapine in alleviating manic symptoms and reducing the risk of relapse compared to valproic acid. Lithium is an effective and safe drug for children, but in some analyses risperidone and quetiapine performed better. Therefore, they may be a valuable therapeutic alternative [38].

VALPROATE

Valproate is one of the most commonly used drugs in the treatment of mania and was approved for the treatment of BD in 1995. According to the current guidelines of the International College of Neuro-psychopharmacology, it is a first-line treatment for acute mania, similar to atypical antipsychotics. The mechanism of action of valproate is not fully understood, but it is believed that the drug affects the dopamine and serotonin systems, inhibits NMDA receptors, increases GABA activity, and blocks voltage-dependent sodium channels [39]. Valproate appears to be particularly effective in the treatment of acute mania but is less effective in maintenance therapy. It may be preferred in patients with numerous previous episodes of the disease, frequent hospitalizations, and coexisting mental disorders [40]. The therapeutic concentration of valproate is in the range of 50-125 μg/ml, with a dosage of approximately 10-20 mg/kg per day. Side effects such as shaking, weight gain, and ataxia may occur when using this medication. The drug may also inhibit the activity of certain liver enzymes, which increases the levels of other substances, especially lamotrigine, while carbamazepine accelerates the metabolism of valproate [41]. An overview of systematic reviews with meta- analyses by Mari J. et al. (2024) found that in acute episodes of mania, the drug clearly outperformed placebo, and its effectiveness was similar to lithium. Valproate had a similar effect to quetiapine, while

the results of comparisons with olanzapine were inconclusive and its efficacy was slightly lower than that of risperidone. In bipolar depression, its efficacy was similar to combination therapies based on lithium, lurasidone, quetiapine, or a combination of olanzapine and fluoxetine, while it outperformed aripiprazole, ziprasidone, and agomelatine. In maintenance treatment, valproate significantly reduced the risk of mood disorder recurrence compared to placebo. However, no advantage over lithium, olanzapine, or lamotrigine was demonstrated [42].

LAMOTRIGINE

Lamotrigine is a drug used for maintenance treatment in adults with bipolar disorder and is recommended as a first-line drug in the treatment of bipolar depression. Lamotrigine is considered to be as effective as lithium [43]. It is an antiepileptic drug and works by stabilizing the presynaptic membrane of neurons, which leads to a reduction in the release of glutamate and aspartate into the postsynaptic part [44]. According to a systematic review and meta-analysis conducted by Haenen N. et al. (2024), lamotrigine is effective in the treatment of bipolar disorder, reducing depressive symptoms and lowering the risk of relapse during maintenance therapy [45]. Lamotrigine may affect the immune system, leading to rare but serious adverse reactions such as Stevens-Johnson syndrome, hemophagocytic lymphohistiocytosis, or drug reaction with eosinophilia and systemic symptoms. In such cases, it is necessary to immediately discontinue the drug and initiate immunosuppressive treatment [44].

7.2.2 Selected antipsychotics

QUETIAPINE

Quetiapine fumarate was developed in 1985 and is used in the treatment of schizophrenia and both manic and depressive episodes in bipolar disorder. It can be used in monotherapy as well as in combination with other drugs [46]. The mechanism of action of quetiapine is mainly due to the blocking of dopamine and serotonin 5-HT2 receptors. The drug also binds strongly to histamine H1 and adrenergic α1 receptors, and has a significant effect on 5-HT2, α2, and D2 receptors. Quetiapine has similar efficacy to lithium in the treatment of acute manic episodes and in the prevention of mania. However, in monotherapy, quetiapine may be more effective in preventing depressive episodes in bipolar disorder. Side effects such as drowsiness, dizziness, and hypotension are the most common, but weight gain, increased blood cholesterol levels, and hypertriglyceridemia may also occur [47]. A systematic review conducted by Maneeton B. et al. which included 3 randomized trials (a total of 251 participants) evaluated the efficacy and tolerability of quetiapine in the treatment of depression in the course of bipolar disorder in children and adolescents. The review found no evidence supporting quetiapine's effectiveness in this population, and therefore its use is not recommended for bipolar depression in youth. However, further research is needed [48].

LURASIDONE

Lurasidone works by blocking dopamine D2 and serotonin 5-hydroxytryptamine (5-HT2A) receptors, but it also affects other serotonergic and noradrenergic receptors [49]. Lurasidone, an atypical antipsychotic drug from the benzisothiazole group, is used in doses ranging from 20 to 120 mg to treat depression in bipolar disorder. The drug is rapidly absorbed, reaching peak serum concentrations within 1-3 hours. Lurasidone is effective in treating depression in patients with BD. It can reduce symptoms of depression when used as monotherapy, but also in combination with mood stabilizers [50].

ASENAPINE

Asenapine has been approved in Europe for the treatment of moderate to severe manic episodes in adults. Research indicates that asenapine effectively treats both acute and long-term manic and mixed episodes in bipolar disorder. It has a complex pharmacological profile and acts as an antagonist on serotonin receptors 5-HT2A, 5-HT2C, H1, α2 and various subtypes of 5-HT receptors (including 5-HT1A, 5-HT1B/D, 5-HT5, 5-HT7), and exhibits partial

antagonistic activity on 5-HT1A receptors [51]. Asenapine is available in the form of tablets administered sublingually twice daily 5 and 10 mg [52]. The rapid onset of action may be particularly beneficial in patients in the manic phase and also promotes better compliance with therapeutic recommendations [51]. Oral hypoesthesia is a recognized side effect of asenapine and is thought to stem from its local anesthetic action and this effect typically resolves within about one hour [52].

ARIPIPRAZOLE

Aripiprazole is approved in the United States for the treatment of schizophrenia and manic and mixed episodes in adults and adolescents aged 10-17 years with type I bipolar disorder. It can be used as monotherapy or in combination with lithium or valproate [53]. The most commonly observed adverse effects are akathisia and tremor, while other extrapyramidal symptoms, such as dystonia, pseudoparkinsonism, and tardive dyskinesia, are rare [54]. A systematic review and meta- analysis of randomized control trials conducted by Li D. et al. Included 20 randomized controlled trials investigating the efficacy and safety of aripiprazole in the treatment of bipolar disorder. The results indicate that aripiprazole is effective in alleviating the symptoms of acute mania and psychosis but has no significant effect on acute depressive episodes. In maintenance therapy, aripiprazole reduces the risk of mania recurrence compared to placebo, is associated with fewer treatment discontinuations, and has a beneficial effect on HDL levels. No significant differences in extrapyramidal symptoms were found in the maintenance phase compared to placebo, haloperidol, or lithium. The results suggest that aripiprazole is effective and safe in the treatment of mania in BD, although further studies are needed to evaluate its efficacy and tolerability compared to other drugs [55].

8. Conclusions

Bipolar disorder is a serious illness that presents challenges for patients, their families, and clinicians. It is characterized by unpredictability and increased energy levels, which leads to difficulties in daily functioning. Despite its prevalence, bipolar disorder often remains undiagnosed, especially when depression is the first symptom of the disease. This delays the therapeutic process, making early and accurate diagnosis crucial. The etiology of bipolar disorder includes both genetic and environmental factors, and the prevalence is comparable for women and men. The choice of treatment should be individualized, taking into account the episode of the disease and preventing recurrence. Currently, treatment strategies are primarily based on pharmacotherapy using mood stabilizers such as lithium, valproate, and lamotrigine, as well as antipsychotic drugs. These drugs are effective in different phases of the disease. The lithium used since 1870 is of great importance, as it effectively prevents episodes. In addition, it has proven anti-suicidal efficacy. Psychological interventions can be a valuable complement to pharmacological treatment. In severe and treatment-resistant cases, electroconvulsive therapy may be used. Further research is needed to improve early diagnosis and treatment effectiveness.

Disclossure:

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