

Review

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Posted Date: 2 September 2024

doi: 10.20944/preprints202408.2235.v1

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Review

Bipolar Disorder: A Comprehensive Review of Genetics, Causal Hypotheses, Clinical Signs, Evolution, Biomarkers, and Treatment Options

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Abstract: Bipolar disorder (BD) is a complex mental health condition characterized by alternating periods of mania and depression. This review provides a comprehensive overview of BD, focusing on its genetics, causal hypotheses, clinical signs and evolution, potential biomarkers with an emphasis on electroencephalography (EEG), and treatment options. Genetic studies have identified several susceptibility genes and polygenic risk scores, highlighting the heritable nature of BD. Various causal hypotheses, including monoamine dysregulation, kindling, circadian rhythm disruptions, and neuroinflammation, have been proposed to explain its pathophysiology. The clinical course of BD is characterized by recurrent episodes of mania/hypomania and depression, with significant heterogeneity among individuals. EEG and other biomarkers hold promise for improving diagnosis, predicting treatment response, and elucidating the neurobiological underpinnings of BD. Current treatment options include pharmacotherapy, psychotherapy, and neuromodulation techniques, which can be tailored to individual needs based on clinical presentation and response to treatment. Future research should focus on identifying more specific biomarkers, developing novel treatments, and optimizing existing therapies to improve outcomes for individuals with BD.

Keywords: biomarker; bipolar disorder; computational model; multi-layer perceptron

1. Introduction

1.1. History of Bipolar Disorder

Bipolar disorder (BD) has a rich and complex history, with its roots tracing back to ancient times. The recognition and understanding of the condition have evolved significantly over centuries, shaped by cultural, scientific, and medical advancements. This section provides an overview of the historical context of BD, from its earliest descriptions to modern conceptualizations and treatments.

The earliest descriptions of symptoms resembling BD can be found in ancient medical texts. In the second century AD, the Greek physician Aretaeus of Cappadocia provided detailed accounts of what he called "mania" and "melancholia." He described mania as a state of elevated mood, increased energy, and impulsive behavior, while melancholia was characterized by sadness, despair, and lethargy. Aretaeus noted that these states could alternate in the same individual, suggesting a cyclical nature of the disorder (Aretaeus, 1856).

In ancient Chinese medicine, the concept of "Yu Zheng" (depression) and "Kuang Zheng" (mania) was recognized. The Huangdi Neijing, an ancient Chinese medical text, described these states as imbalances in the body's energies, or "qi," and suggested treatments involving herbs, acupuncture, and lifestyle modifications (Unschuld, 2003).

During the Middle Ages, the understanding of mental illness was heavily influenced by religious and supernatural beliefs. Individuals with symptoms of BD were often seen as possessed by demons or cursed by divine punishment. Treatments during this period were largely ineffective and often harmful, including exorcisms, bloodletting, and confinement in asylums.

The Renaissance brought a renewed interest in scientific inquiry and a shift away from purely religious explanations of mental illness. Physicians such as Paracelsus and Thomas Sydenham began to describe mental disorders in more medical terms, although their understanding remained limited by the scientific knowledge of the time (Sydenham, 1848).

The 19th century marked a significant turning point in the history of BD. French psychiatrist Jean-Pierre Falret coined the term "folie circulaire" (circular insanity) in 1851 to describe a condition characterized by alternating periods of mania and depression. Falret's work highlighted the cyclical nature of the disorder and its hereditary component (Falret, 1851).

Around the same time, German psychiatrist Emil Kraepelin introduced the term "manic-depressive insanity" in his influential textbook on psychiatry. Kraepelin's classification system distinguished manic-depressive illness from dementia praecox (schizophrenia) and emphasized the recurrent and episodic nature of the disorder. Kraepelin's work laid the foundation for modern diagnostic criteria and influenced the development of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Kraepelin, 1921).

The 20th century saw significant advancements in the understanding and treatment of BD. In the early part of the century, psychoanalytic theories, such as those proposed by Sigmund Freud, dominated the field of psychiatry. Freud and his followers viewed manic-depressive illness as a result of unconscious conflicts and early life experiences (Freud, 1917).

The mid-20th century brought a shift towards biological explanations of mental illness. The discovery of lithium's mood-stabilizing properties by Australian psychiatrist John Cade in 1949 revolutionized the treatment of BD. Lithium became the first effective pharmacological treatment for the disorder, and its use led to significant improvements in patient outcomes (Cade, 1949).

The development of the DSM in the 1950s further standardized the diagnosis of BD. The DSM-I and DSM-II classified manic-depressive illness as a distinct category, although the criteria were broad and encompassed a wide range of mood disorders. The DSM-III, published in 1980, introduced more specific diagnostic criteria and the term "bipolar disorder," distinguishing it from unipolar depression (American Psychiatric Association, 1980).

The late 20th century and early 21st century have seen continued advancements in the understanding and treatment of BD. Genetic studies have identified several susceptibility genes and polygenic risk scores, highlighting the heritable nature of the disorder (McGuffin et al., 2003). Neuroimaging and electrophysiological studies have provided insights into the neurobiological underpinnings of BD, leading to the development of potential biomarkers (Strakowski et al., 2012; Andreazza et al., 2008).

New pharmacological treatments, such as atypical antipsychotics and anticonvulsants, have been introduced to manage acute episodes and prevent relapse (Yatham et al., 2018). Psychotherapeutic interventions, including cognitive-behavioral therapy (CBT), interpersonal and social rhythm therapy (IPSRT), and family-focused therapy (FFT), have been shown to improve outcomes when used in conjunction with pharmacotherapy (Miklowitz & Scott, 2009).

Neuromodulation techniques, such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS), have emerged as effective treatments for severe, treatment-resistant episodes of mania or depression (Loo et al., 2011; McGirr et al., 2016).

The history of BD is a testament to the evolving understanding of mental illness and the ongoing quest for effective treatments. From ancient descriptions of mania and melancholia to modern diagnostic criteria and therapeutic interventions, the progressive understanding of BD reflects the interplay of cultural, scientific, and medical advancements. As our knowledge of the disorder continues to grow, so too does our ability to improve the lives of those affected by BD.

1.2. Definitions

Bipolar disorder (BD) is a chronic, recurrent mental health condition characterized by alternating periods of mania and depression. It affects approximately 1-3% of the global population, with significant impacts on individuals, families, and society (Merikangas et al., 2011). BD is associated with substantial morbidity and mortality, including increased risk of suicide, comorbid medical conditions, and reduced life expectancy (Goodwin & Jamison, 2007). Despite its prevalence and impact, the underlying mechanisms of BD remain poorly understood, and effective treatments are limited.

The complexity of BD is reflected in its diverse clinical presentations, which range from mild hypomania to severe mania and depression. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) categorizes BD into several subtypes, including BD I, BD II, and cyclothymic disorder (American Psychiatric Association, 2013). Each subtype is characterized by specific patterns

of mood episodes, with varying degrees of severity and impairment. The course of BD is typically chronic and recurrent, with approximately 90% of individuals experiencing multiple episodes (Goodwin & Jamison, 2007). The average age of onset is around 25 years, with a higher prevalence in women for rapid cycling and mixed features (Kessler et al., 1997).

The etiology of BD is multifactorial, involving a complex synergism of genetic, environmental, and neurobiological factors. Genetic studies have identified several susceptibility genes and polygenic risk scores, highlighting the heritable nature of BD (McGuffin et al., 2003). Various causal hypotheses have been proposed to explain the pathophysiology of BD, including monoamine dysregulation, kindling, circadian rhythm disruptions, and neuroinflammation (Schildkraut, 1965; Post, 1992; McClung, 2007; Rosenblat & McIntyre, 2017). These hypotheses provide a framework for understanding the neurobiological mechanisms underlying BD and inform the development of targeted treatments.

2. Discussion

Despite advances in our understanding of BD, the diagnosis and treatment of this condition remain challenging. The lack of objective biomarkers for BD contributes to diagnostic uncertainty and delays in treatment initiation. Recent research has focused on identifying potential biomarkers, including neuroimaging, peripheral markers, and electrophysiological measures (Strakowski et al., 2012; Andreazza et al., 2008). Electroencephalography (EEG) is a non-invasive, cost-effective tool that measures electrical activity in the brain. Several EEG abnormalities have been identified in BD, including alterations in resting-state EEG, event-related potentials (ERPs), and sleep EEG (Clementz et al., 1994; Muñoz et al., 2011; Plante & Winkelman, 2008). These findings suggest that EEG may serve as a valuable biomarker for BD, aiding in diagnosis, predicting treatment response, and elucidating the neurobiological underpinnings of the disorder. For electrophysiological biomarkers for BD see Montgomery (Montgomery, 2024).

Current treatment options for BD include pharmacotherapy, psychotherapy, and neuromodulation techniques. Pharmacotherapy involves the use of mood stabilizers, antipsychotics, and antidepressants to manage acute episodes and prevent relapse (Yatham et al., 2018). Psychotherapeutic interventions, such as cognitive-behavioral therapy (CBT), interpersonal and social rhythm therapy (IPSRT), and family-focused therapy (FFT), have been shown to improve outcomes in BD when used in conjunction with pharmacotherapy (Miklowitz & Scott, 2009). Neuromodulation techniques, such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS), are used to treat severe, treatment-resistant episodes of mania or depression (Loo et al., 2011; McGirr et al., 2016). These treatments can be tailored to individual needs based on clinical presentation and response to treatment.

2.2. Genetics of Bipolar Disorder

BD is a highly heritable disorder, with heritability estimates ranging from 60% to 85% (McGuffin et al., 2003). Genetic studies, including linkage approximations, candidate gene association diversity, and genome-wide associations (GWAS), have identified several genetic variants associated with BD. Early linkage papers identified several chromosomal regions potentially harboring BD susceptibility genes, but results were inconsistent (Barnett & Smoller, 2009). These studies focused on genes involved in neurotransmission, neurodevelopment, and circadian rhythms. Notable candidates include COMT, BDNF, DISC1, and CLOCK (Barnett & Smoller, 2009).

GWAS have identified several single nucleotide polymorphisms (SNPs) associated with BD, including variants in CACNA1C, ODZ4, and NCAN (Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011).

Polygenic Risk Scores (PRS) analyses suggest that BD shares genetic overlap with other psychiatric disorders, such as schizophrenia and major depressive disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013).

2.3. Causal Hypotheses

Several hypotheses have been proposed to explain the pathophysiology of BD, including the Monoamine Hypothesis which posits that BD results from dysregulation in monoamine neurotransmission, particularly serotonin, dopamine, and norepinephrine (Schildkraut, 1965).

The Kindling Hypothesis suggests that recurrent affective episodes in BD lead to increased sensitivity to subsequent episodes, similar to the kindling phenomenon in epilepsy (Post, 1992). Circadian Rhythm Hypothesis proposes that disruptions in circadian rhythms contribute to the development and maintenance of BD (McClung, 2007). Neuroinflammation suggests that immune dysregulation and neuroinflammation play a role in BD pathophysiology (Rosenblat & McIntyre, 2017).

2.3. Clinical Signs and Evolution

BD is characterized by recurrent episodes of mania/hypomania and depression. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) categorizes BD into several subtypes, including BD I, BD II, and cyclothymic disorder (American Psychiatric Association, 2013).

Manic Episode: Symptoms include elevated or irritable mood, increased energy or activity, grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, and excessive involvement in risky activities.

Hypomanic Episode: Symptoms are similar to those of a manic episode but are less severe and do not cause significant impairment.

Major Depressive Episode: Symptoms include depressed mood, loss of interest or pleasure, changes in appetite or weight, sleep disturbances, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, cognitive impairment, and suicidal ideation.

Mixed Features: Symptoms of mania/hypomania and depression can occur simultaneously.

The course of BD is typically chronic and recurrent, with approximately 90% of individuals experiencing multiple episodes (Goodwin & Jamison, 2007). The average age of onset is around 25 years, with a higher prevalence in women for rapid cycling and mixed features (Kessler et al., 1997).

2.4. Biomarkers in Bipolar Disorder

Biomarkers are objective, quantifiable characteristics of biological processes. Several potential biomarkers have been investigated in BD, including neuroimaging, peripheral markers, and electrophysiological measures.

2.4.1. Electroencephalography (EEG) Biomarkers

EEG is a non-invasive, cost-effective tool that measures electrical activity in the brain. Several EEG abnormalities have been identified in BD, including:

Resting-State EEG: Individuals with BD exhibit increased delta and theta activity, as well as decreased alpha activity, during resting-state EEG (Clementz et al., 1994). **Event-Related Potentials (ERPs)** are averaged EEG responses time-locked to specific events or stimuli. In BD, alterations in ERP components, such as P300 and error-related negativity (ERN), have been observed, suggesting impairments in cognitive processes like attention, working memory, and error monitoring (Muñoz et al., 2011).

Sleep disturbances are common in BD. Sleep EEG studies have revealed reduced slow-wave sleep, increased rapid eye movement (REM) density, and shorter REM latency in individuals with BD (Plante & Winkelman, 2008).

Recent studies have employed qEEG and machine learning algorithms to identify potential EEG biomarkers in BD. For instance, one study found that a combination of EEG features and machine learning algorithms could accurately distinguish individuals with BD from healthy controls (Akdeniz et al., 2020), (Montgomery, 2024).

2.4.2. Other Biomarkers

Structural and functional neuroimaging studies have identified abnormalities in brain regions involved in emotion regulation, such as the prefrontal cortex, amygdala, and hippocampus (Strakowski et al., 2012). Alterations in inflammatory markers, neurotrophic factors, and oxidative stress markers have been observed in individuals with BD (Andreazza et al., 2008).

2.5. Treatment Options

The primary goals of BD treatment are to manage acute episodes, prevent relapse, and improve long-term functioning. Treatment options include pharmacotherapy, psychotherapy, and neuromodulation techniques.

2.5.1. Pharmacotherapy

Mood Stabilizers: Lithium is a first-line mood stabilizer for the treatment of acute mania and the prevention of recurrent episodes. Anticonvulsants, such as valproate and carbamazepine, are also used as mood stabilizers (Yatham et al., 2018). Atypical antipsychotics, such as quetiapine, olanzapine, and aripiprazole, are effective in treating acute mania and maintaining remission (Yatham et al., 2018). Antidepressants are used to treat depressive episodes in BD, although their use is controversial due to the risk of inducing mania or rapid cycling (Pacchiarotti et al., 2013).

2.5.2. Psychotherapy

Psychotherapeutic interventions, such as cognitive-behavioral therapy (CBT), interpersonal and social rhythm therapy (IPSRT), and family-focused therapy (FFT), have been shown to improve outcomes in BD when used in conjunction with pharmacotherapy (Miklowitz & Scott, 2009).

2.5.2. Neuromodulation Techniques

Electroconvulsive Therapy (ECT) is an effective treatment for severe, treatment-resistant episodes of mania or depression in BD (Loo et al., 2011).

Transcranial Magnetic Stimulation (TMS) or Repetitive TMS (rTMS) has shown promise in treating depressive episodes in BD, although more research is needed to establish its efficacy (McGirr et al., 2016).

3. Conclusions

BD is a complex, multifactorial mental health condition with a strong genetic component. Several causal hypotheses have been proposed, implicating monoamine dysregulation, kindling, circadian rhythm disruptions, and neuroinflammation in its pathophysiology. The clinical course of BD is characterized by recurrent episodes of mania/hypomania and depression, with significant heterogeneity among individuals. EEG and other biomarkers hold promise for improving diagnosis, predicting treatment response, and elucidating the neurobiological underpinnings of BD. Current treatment options include pharmacotherapy, psychotherapy, and neuromodulation techniques, which can be tailored to individual needs based on clinical presentation and response to treatment. Future research should focus on identifying more specific biomarkers, developing novel treatments, and optimizing existing therapies to improve outcomes for individuals with BD.

Conflicts of Interests: The Author claims no conflicts of interest.

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