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Comprehensive Review of Bipolar Disorder : Etiology, Diagnosis and Treatment

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Abstract: *Bipolar disorder is a predominantly intermittent and chronic psychiatric condition that diminishes life expectancy, induces functional impairment, and disrupts social, occupational, and familial aspects of life. Various forms of bipolar disorder are acknowledged, encompassing both bipolar I and bipolar II disorder. Bipolar I is characterized by recurring episodes of depression and mania, whereas bipolar II disorder involves recurrent episodes of depression and a milder form of mania known as hypomania. The definition of hypomania has been a subject of debate since at least the 1970s, with discussions centering on its minimal duration, underlying criteria, and the requisite number of symptoms for diagnosis. Achieving an accurate depiction of hypomania is a pivotal diagnostic challenge. Emerging evidence supports the existence of a broad spectrum of bipolar disorders, and there is growing data substantiating the clinical validity of adjusting certain criteria for hypomania. These disorders significantly diminish psychosocial functioning and are associated with a loss of approximately 10–20% of potential years of life. The mortality disparity between individuals with bipolar disorders and the general population primarily results from elevated deaths due to cardiovascular disease and suicide. Bipolar disorder exhibits a high heritability, approximately 70%, and shares genetic risk alleles with other mental and medical conditions.*

Keywords: manic episodes, depressive episodes, Lithium, Manic, Mood stabilizers

I. INTRODUCTION

Bipolar disorder stands as a severe and incapacitating psychiatric condition, encompassing a diverse array of illnesses. Global prevalence estimates across populations indicate the significant impact of this disorder. Bipolar I disorder is characterized by the occurrence of one or more manic episodes, often accompanied by one or more major depressive episodes. This distinguishes it from bipolar II disorder, where one or more major depressive episodes occur along with at least one hypomanic episode. Bipolar disorders constitute a category of persistent internal illnesses, including both bipolar I and bipolar II disorder.Bipolar I disorder is identified by the manifestation of a syndromal manic episode, with a global estimated prevalence ranging from 0.6% to 1.0%. On the other hand, bipolar II disorder is characterized by the presence of a syndromal hypomanic episode and a major depressive episode, with an estimated global prevalence ranging from 0.4% to 1.1%. The chronic nature of these disorders underscores the significance of understanding and addressing their impact on individuals and communities.(1) The preceding estimates have primarily been derived from studies conducted in high-income countries, leaving a notable gap in our understanding of the prevalence of bipolar disorders in low-income and middle-income countries. In these regions, the occurrence frequency of bipolar diseases has been underreported. For instance, the prevalence of bipolar disorders in Ethiopia and Nigeria is approximately 0.1% to 1.8%, while in South Africa, it ranges from 3.0% to 4.0%. These figures highlight the importance of conducting more extensive and region-specific research to capture the true scope of bipolar disorders on a global scale. Addressing the prevalence of these disorders in diverse socioeconomic contexts is crucial for developing effective and inclusive strategies for diagnosis, treatment, and support. (2) (3)While some individuals with bipolar I disorder may experience primarily manic or predominantly manic episodes, the majority of people with bipolar I disorder are variably affected by depressive symptoms and episodes. In other words, individuals with bipolar I disorder commonly face a range of

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mood episodes, including manic episodes characterized by elevated or irritable mood, as well as depressive episodes marked by persistent feelings of sadness, hopelessness, or a lack of interest in previously enjoyed activities. The fluctuation between these manic and depressive states contributes to the complexity of bipolar I disorder and underscores the need for a comprehensive understanding and management of both manic and depressive symptoms in affected individuals. (4)A widely replicated finding in studies of individuals with bipolar disorders is the early age of onset. More than 70% of individuals with bipolar disorders exhibit clinical characteristics of the illness before the age of 25. This early manifestation highlights the significance of recognizing and addressing bipolar disorders in young adulthood. Early detection and intervention can play a crucial role in managing the condition, improving outcomes, and enhancing the overall quality of life for individuals affected by bipolar disorders. (5) (6)Bipolar disorder is a serious and debilitating psychiatric condition that encompasses a broad spectrum of illnesses. Global prevalence estimates underscore the substantial impact of this disorder on populations worldwide. Bipolar I disorder is identified by the occurrence of one or more manic episodes, frequently accompanied by one or more major depressive episodes. This sets it apart from bipolar II disorder, where one or more major depressive episodes co-occur with at least one hypomanic episode. Bipolar disorders represent a category of enduring internal illnesses, encompassing both bipolar I and bipolar II disorder. The distinctive features of manic and depressive episodes contribute to the complexity and variability of the disorder, emphasizing the need for a nuanced understanding in diagnosis and treatment.

Types of Bipolar Disorder

There are three fundamental types of bipolar disorder, each characterized by distinct changes in mood, energy, and activity levels. These mood shifts encompass periods of intense elevation, elation, and heightened activity levels known as manic episodes, and contrasting periods of deep sadness, hopelessness, or decreased activity levels known as depressive episodes. Individuals with bipolar disorder may also experience normal (euthymic) moods alternating with depressive states. If someone experiences four or more episodes of mania or depression in a year, it is termed "rapid cycling."

- **Bipolar I Disorder:** This type is defined by manic episodes lasting at least seven days (most of the day, nearly every day) or when the manic symptoms are severe enough to require hospitalization. Typically, separate depressive episodes also occur, lasting at least two weeks. Additionally, episodes of mood disturbance with mixed features, involving both depressive and manic symptoms simultaneously, can occur.
- **Bipolar II Disorder:** This type is characterized by a pattern of depressive episodes and hypomanic episodes. Unlike full-blown manic episodes, hypomanic episodes are less severe but still involve an observable increase in energy and activity levels. Individuals with Bipolar II Disorder do not experience the extreme manic episodes seen in Bipolar I Disorder. (7)
- **Cyclothymic Disorder (Cyclothymia):**This disorder is characterized by persistent hypomanic and depressive symptoms that do not reach the intensity or duration required to qualify as full hypomanic or depressive episodes. In adults, these symptoms typically persist for at least two years, while in children and teenagers, they should last for at least one year. Cyclothymic Disorder represents a milder but chronic form of bipolar spectrum disorder.
- **Other Specified and Unspecified Bipolar and Related Disorders:** This category encompasses bipolar disorder symptoms that do not neatly fit into the defined criteria of the recognized bipolar disorder categories. It includes situations where individuals exhibit bipolar-like symptoms, but the specific characteristics do not align with Bipolar I, Bipolar II, or Cyclothymic Disorder. This category allows for the acknowledgment and diagnosis of individuals whose symptoms deviate from the typical presentations of established bipolar disorders. (8).

Varied clinical features

The genetic complexity of Bipolar Disorder (BD) is evident in its intricate and diverse clinical presentation. While the initial episode of major depression or mania typically emerges between the ages of 18 and 24, cases with earlier or later onset are not uncommon. The frequency of episodes can vary significantly, ranging from frequent occurrences to long

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intervals between episodes. Additionally, some individuals may experience rapid cycling, with mood shifts occurring within a matter of hours or days.

Comorbidities such as anxiety and substance abuse are frequently observed in individuals with bipolar disorder. Psychotic features often accompany mood episodes, particularly during manic phases. Interepisode periods can vary, with some individuals being entirely symptom-free, while others may grapple with chronic depressive or manic symptoms during these periods. It's worth noting that while most individuals with bipolar disorder experience both manic and depressive episodes, some may solely suffer from manic episodes, though this is relatively uncommon. The diverse and complex nature of bipolar disorder highlights the importance of tailored and comprehensive approaches to diagnosis and treatment.(9) Indeed, mixed states, where symptoms of both mania and depression coexist, are not uncommon in individuals with Bipolar Disorder. These states can present unique challenges in diagnosis and management, as they involve a complex interplay of elevated and depressive mood features simultaneously.Additionally, periods of prolonged and treatment-resistant depression are observed in some individuals with Bipolar Disorder. This can mean that depressive episodes persist for an extended duration and may not respond well to standard treatments. Managing these treatment-resistant cases often requires a careful and individualized approach, possibly involving a combination of psychotherapy, medication adjustments, and other therapeutic interventions.The varied and sometimes challenging clinical presentations in Bipolar Disorder highlight the importance of ongoing research and personalized treatment strategies to address the complexity of this psychiatric condition.(10)With such protean manifestations, it seems likely that what we now call BD may ultimately be resolvedinto dozens of biologically distinguishable disease entities.

The familiality of clinical features in Bipolar Disorder (BD) has been the subject of numerous studies, revealing specific patterns of heritability for different aspects of the disorder. Here's a breakdown of some key findings:

1. High Familiality:

- Age at Onset: The age at which individuals first experience major depressive or manic episodes in BD shows a high degree of familiality. This suggests a genetic influence on the timing of onset.
- Psychotic Symptoms:The presence of psychotic symptoms during mood episodes is highly familial, indicating a genetic predisposition for these features within families.
- Frequency of Manic and Depressive Episodes: The frequency of mood episodes, whether manic or depressive, is also strongly familial. This implies a genetic component influencing the recurrence and cycling patterns in individuals with BD.
- Polarity at Onset: Whether the first manifestation of BD is in the form of mania or depression (polarity at onset) is highly familial, suggesting a genetic influence on the initial presentation of the disorder.

2. Moderate Familiality:

- Comorbid Anxiety and Substance Abuse: While comorbidities such as anxiety and substance abuse show familial patterns, the degree of familiality is generally less pronounced compared to other clinical features.

3. Genetic Signals:

The identification of specific genetic signals may help explain the observed familial patterns in BD. Studies have focused on uncovering genetic variations associated with age at onset, psychotic symptoms, episode frequency, and polarity at onset.

Understanding the genetic underpinnings of these clinical features not only contributes to our comprehension of the disorder but may also have implications for the development of targeted treatments and interventions in the future.(11)

High risk of suicide

Indeed, numerous studies consistently highlight a significantly elevated risk of suicide in individuals with Bipolar Disorder (BD). This increased risk is a serious concern associated with the condition. Several factors contribute to the heightened vulnerability to suicidal behavior in individuals with BD:

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1. Mood Episodes: Both depressive and manic episodes in BD are associated with an increased risk of suicide. The intense emotional states experienced during these episodes can contribute to suicidal thoughts and behaviors.
2. Comorbidities: Individuals with BD often experience comorbid conditions such as anxiety disorders and substance abuse, which can further elevate the risk of suicide.
3. Impulsivity: Impulsivity is a common trait associated with BD, especially during manic episodes. Impulsive behavior can contribute to a higher likelihood of engaging in self-harming actions.
4. Psychosocial Factors: Issues related to interpersonal relationships, financial difficulties, and social isolation can contribute to the risk of suicide in individuals with BD.
5. Access to Lethal Means: Individuals with BD may have increased access to lethal means during periods of heightened risk, potentially increasing the likelihood of completed suicide.(12)(13) The statistic you mentioned, approximately 15% of individuals diagnosed with Bipolar Disorder (BD) dying by suicide, underscores the significant and persistent concern regarding suicide risk in this population. It's indeed a troubling figure that has remained relatively stable over the years.

Several ongoing areas of research aim to better understand the factors influencing suicide risk in BD:

1. **Genetic Studies:** Researchers are exploring the genetic basis of suicide risk within families affected by BD. Identifying specific genetic markers associated with increased suicide risk could contribute to improved risk assessment and intervention.
2. **Neurobiological Factors:** Investigations into the neurobiological aspects of BD and suicide risk are ongoing. This includes studying changes in brain structure and function that may contribute to suicidal ideation and behavior.
3. **Environmental Factors:** Research is examining environmental factors, such as childhood trauma, chronic stress, and access to lethal means, to better understand their role in suicide risk among individuals with BD.

II. GENETIC EPIDEMIOLOGY

Prior to the era of molecular genetics, much of our knowledge about the origins of Bipolar Disorder (BD) came from genetic epidemiology. Family studies revealed a clear familial tendency in BD, with a 10–15% risk of mood disorders among first-degree relatives. Twin studies suggested a substantial genetic contribution, estimating heritability between 70–90%. Adoption studies supported a primarily genetic cause for BD, as elevated risk was observed only in the biological parents of adoptees with the disorder. These early studies laid the foundation for understanding the significant role of genetics in BD, a notion further advanced by molecular genetics research.(15)While there is robust and consistent evidence supporting a genetic basis for Bipolar Disorder (BD), attempts using segregation analyses have not identified a clear Mendelian pattern of transmission. Instead, these analyses tend to lean towards more complex models of inheritance. The intricate nature of how genetic factors contribute to BD suggests a multifaceted and polygenic mode of inheritance, involving the interplay of multiple genes and possibly environmental factors. This complexity underscores the challenges in identifying a straightforward genetic pattern for BD transmission.(16)

Symptoms

Bipolar disorder is characterized by episodes of mania, hypomania, and major depression. Here are the symptoms associated with each:

Manic Episode:

- Abnormally upbeat, jumpy, or wired mood
- Increased activity, energy, or agitation
- Exaggerated sense of well-being and self-confidence (euphoria)
- Decreased need for sleep
- Unusual talkativeness
- Racing thoughts
- Distractibility
- Poor decision-making (e.g., reckless behavior, impulsive actions)

Mania may also lead to psychosis and may require hospitalization.

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Hypomanic Episode (similar to manic but less severe):
- Shared symptoms with manic episodes but to a lesser degree
- Generally does not result in severe impairment in daily functioning
- Individuals may not recognize the changes in their behavior

Major Depressive Episode:
- Depressed mood (feeling sad, empty, hopeless, or tearful)
- Loss of interest or pleasure in activities
- Changes in appetite or weight (either loss or gain)
- Sleep disturbances (insomnia or hypersomnia)
- Restlessness or slowed behavior
- Fatigue or loss of energy
- Feelings of worthlessness or excessive guilt
- Difficulty concentrating or making decisions
- Thoughts of death, suicide, or suicide attempts

Symptoms in children and teens can be challenging to identify, and they may experience distinct episodes of mania, hypomania, or major depression. Mood swings may be rapid, and some may have periods without mood symptoms between episodes. Severe mood swings that differ from their usual behavior may be indicative of bipolar disorder in children and teenagers. Identifying symptoms early and seeking professional help is crucial for appropriate management and support. (17)

SYMPTOMS OF A MANIC EPISODE	SYMPTOMS OF A DEPRESSIVE EPISODE
Feeling very up, high, elated, or extremely irritable or touchy	Feeling very down or sad, or anxious
Feeling jumpy or wired, more active than usual	Feeling slowed down or restless
Racing thoughts	Trouble concentrating or making decisions
Decreased need for sleep	Trouble falling asleep, waking up too early, or sleeping too much
Talking fast about a lot of different things ("flight of ideas")	Talking very slowly, feeling like you have nothing to say, or forgetting a lot
Excessive appetite for food, drinking, sex, or other pleasurable activities	Lack of interest in almost all activities
Thinking you can do a lot of things at once without getting tired	Unable to do even simple things
Feeling like you are unusually important, talented, or powerful	Feeling hopeless or worthless, or thinking about death or suicide

Diagnosis

To diagnose bipolar disorder, a doctor or healthcare provider typically follows a comprehensive process, including:

1.Full Physical Exam:
- Conducting a thorough physical examination to rule out other medical conditions that may contribute to the symptoms.

2.Medical Testing:
- Ordering medical tests to exclude other illnesses that might present with similar symptoms.

3.Psychiatric Evaluation:
- Referring the individual to a psychiatrist or mental health professional for a comprehensive evaluation.

The diagnosis of bipolar disorder is based on a combination of factors:
- Symptoms: The mental health professional assesses the presence and intensity of symptoms associated with bipolar disorder.
- Lifetime Course: Evaluating the individual's lifetime history, considering the pattern and duration of mood episodes.

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- Experiences: Considering the individual's personal experiences related to mood fluctuations.

It's not uncommon for individuals with bipolar disorder to go undiagnosed for an extended period. Several factors contribute to this delay:

- Overlapping Symptoms: Bipolar disorder shares symptoms with other mental health disorders, leading to misdiagnosis.
- Lack of Recognition: Family and friends may observe symptoms without recognizing their connection to a larger problem.
- Coexisting Health Conditions: The presence of other health conditions can complicate the diagnostic process.

Diagnostic methods may include:

-Physical Exam: Identifying any underlying medical issues contributing to symptoms.

-Psychiatric Assessment: Conducted by a psychiatrist, exploring thoughts, feelings, and behavior patterns. Family members or friends may also provide input.

-Mood Charting: Keeping a daily record of moods, sleep patterns, and other relevant factors.

-Criteria for Bipolar Disorder: Referring to the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published by the American Psychiatric Association.

The comprehensive evaluation aids in accurately diagnosing bipolar disorder and tailoring an appropriate treatment plan. (18)

Treatment

Acute Mania

Acute mania is considered a medical emergency due to the potential risks associated with the condition. If left untreated, individuals experiencing acute mania may engage in activities that jeopardize their marriage, job, and even their life. The unpredictable nature of acutely manic episodes, where individuals may appear rational at one moment and out of control the next, underscores the urgency of intervention.

For instance, a person in a manic state driving recklessly through the city may have just had a seemingly rational conversation with their family physician. Collateral information from relatives, friends, and coworkers becomes crucial to supplement the clinical interview. This additional information helps identify potential dangers and aids in making decisions about the need for involuntary hospitalization.

Effective treatments for acute mania are available, including neuroleptic (antipsychotic) drugs. These medications have demonstrated clear efficacy in managing symptoms associated with acute mania. Timely intervention and a comprehensive approach, including collateral information from those close to the individual, are essential in addressing the immediate risks associated with acute manic episodes. (19) The use of neuroleptic (antipsychotic) drugs in the long-term prophylaxis of bipolar disorder is not recommended due to the risk of tardive dyskinesia. Tardive dyskinesia is a condition characterized by involuntary, repetitive movements, often of the face.

However, in the acute management of manic episodes, these medications offer advantages such as readily available parenteral and oral forms, as well as a rapid onset of psychomotor inhibition. This can be particularly crucial in cases involving violent or psychotic patients, where prompt intervention may be life-saving.

Patients with milder forms of the disease often find these medications detestable, and compliance may be a challenge. On the other hand, individuals with severe mania may benefit from the rapid psychomotor inhibition these medications provide.

Newer, atypical antipsychotic drugs, which lack extrapyramidal side effects, have shown efficacy in compliant patients and may carry lower risks of inducing depression compared to classic neuroleptic drugs. Parenteral preparations of these atypical antipsychotic drugs are becoming available. However, it's important to note that these drugs may have adverse effects, including weight gain, changes in lipid levels, and abnormalities in glucose tolerance. The decision to use these medications should be based on a careful consideration of the individual's condition, potential benefits, and risks. (20)The statement suggests that if a patient has previously responded well to a classic neuroleptic in the treatment of manic episodes, it may be prudent to use the same drug if a recurrent manic episode occurs.

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Additionally, research studies indicate that lithium, valproate, and carbamazepine have demonstrated efficacy in the treatment of acute mania. They are considered effective as monotherapy for occasional episodes of mild mania, especially in unusually compliant patients. However, surveys of clinicians have suggested that these drugs may work too slowly for the majority of patients with acute mania.

This underscores the complexity of bipolar disorder treatment, with considerations for individual patient history, response to previous medications, and the need for a balance between efficacy and speed of action in managing acute manic episodes. Treatment decisions should be made based on a thorough assessment of the patient's specific condition and needs. (21) The recommended approach to treatment involves initiating therapy with either a typical or an atypical neuroleptic drug. Subsequently, a mood stabilizer like lithium, valproate, or carbamazepine is added to the treatment plan once compliance with oral therapy is assured. This combination aims to address acute symptoms effectively while providing longer-term stability and management of bipolar disorder.

The use of neuroleptic drugs helps in the rapid control of symptoms associated with acute manic episodes, while mood stabilizers play a crucial role in preventing relapses and maintaining a stable mood over time. The timing of introducing mood stabilizers is contingent on ensuring the patient's adherence to oral therapy, as these medications often require consistent and ongoing use for optimal effectiveness. The combined approach seeks to balance the immediate need for symptom control with the long-term goal of managing bipolar disorder in a sustainable manner. Individualized treatment plans are essential, taking into account the patient's specific presentation, history, and response to medications.

Bipolar depression

Bipolar depression, occurring within bipolar disorder, often responds to antidepressant medications such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs). However, caution is needed as the use of antidepressants in bipolar disorder requires careful monitoring due to the risk of inducing manic or hypomanic episodes. Treatment decisions are typically individualized, considering the overall clinical presentation and may involve a combination of mood stabilizers, antipsychotics, or other strategies. (22) The response time for treating bipolar depression is typically three to six weeks, similar to unipolar depression. However, caution is essential as antidepressants may trigger a switch from depression to mania in bipolar patients. Those with a history of risky manic episodes may not be suitable for antidepressant treatment. Yet, individuals with recurrent, debilitating depression following a moderate manic episode might benefit from antidepressants, with careful risk assessment. Newer antidepressants like selective serotonin reuptake inhibitors and bupropion are considered less likely to induce mania in bipolar depression, but treatment decisions should be personalized based on the individual's history and overall condition. (23) It's important to note that studies suggesting a lower risk of inducing mania with newer antidepressants, like selective serotonin reuptake inhibitors (SSRIs) and bupropion, have often focused on patients with mild mania, specifically bipolar II disorder. Extrapolating these findings to all patients with bipolar illness may not be appropriate, as the severity and nature of the disorder can vary widely across individuals. Treatment decisions should consider the specific characteristics and history of each patient, and caution should be exercised in applying research findings to the broader bipolar population. (24) (25) Preliminary studies have reported that omega-3 fatty acids, specifically n-3 fatty acids, show antidepressant effects and could potentially open up a new avenue for treating bipolar disorder. Additionally, inositol, another natural substance, has been studied in the context of bipolar depression. These exploratory findings suggest ongoing research into the potential benefits of these substances as part of bipolar disorder treatment strategies. (26) (27)

Drug	Side effects	Indication	Effectiveness
Classic oral neuro-leptics	Extrapyramidal syndrome, hypotension	Moderate-to-severe mania in patients with good compliance	Highly effective but poses risk of depression
Clozapine	Agranulocytosis	Inadequate responsiveness to other treatment	Highly effective
Atypical neuroleptics	Diabetes and weight gain (olanzapine),	Extrapyramidal side effects and risk of tardive dyskinesia with	Established for moderate mania, but not for severe

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	hyperprolactinemia (risperidone), prolonged QTc interval (ziprasidone)	typical neuroleptics	mania
Intramuscular neuroleptics	Extrapyramidal syn-drome, hypotension	Noncompliance with oral agents	Highly effective but poses risk of depression
Lithium	Polyuria, hypothyroidism, weight gain	Good compliance	Highly effective, slow onset, low risk of depression
Valproate	Rare hepatotoxic effects, tremor, weight gain	Good compliance	Highly effective, slow onset, low risk of depression
Carbamazepine	Rare hepatotoxic effects, rash	Good compliance	Few data available
Clonazepam and lorazepam	Excessive sedation	Anxiety, psychomotor tension, insomnia	Questionable for core syndrome,useful as adjunct

Table 2. Drug Treatments for Mania and Bipolar Disorder.

III. CONCLUSION

The definitions of hypomania, bipolar disorder, and subthreshold bipolar disorders are undergoing changes. There's a growing recognition that bipolar disorder might be more prevalent than previously thought, and further research is needed to determine its precise prevalence. Early identification of patients with a major depressive episode who may exhibit 'soft' criteria for bipolar disorder is crucial, as they are at risk of switching to hypomania when treated with antidepressants. A deeper understanding of bipolar disorder and subthreshold variants will significantly contribute to the development of more effective treatment strategies for bipolar depression.

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