Review Article

Bipolar Disorder

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ABSTRACT

Bipolar disorder (BD) is a complex and chronic psychiatric condition charac- terized by alternating episodes of mania, hypomania, and depression. This comprehensive review synthesizes current knowledge on BD, spanning its his- torical conceptualization, clinical features, epidemiology, etiology, neurobiology, treatment approaches, and future research directions. The historical perspective traces the evolution of BD from ancient descriptions to modern diagnostic criteria, highlighting pivotal shifts in understanding. Clin- ical features and diagnostic challenges are examined, emphasizing the nuanced presentations of BD subtypes and their differentiation from other mood disor- ders. Epidemiological data reveal a global lifetime prevalence of approximately 2%, with onset typically occurring in late adolescence or early adulthood. The review explores the multifaceted etiology of BD, including genetic predisposition, en- vironmental factors, and their complex interactions. Neurobiological investiga- tions, encompassing neuroimaging, neurochemical, and neuroendocrine studies, provide insights into the underlying pathophysiology of BD. Treatment approaches are critically evaluated, covering both established and emerging therapies. Pharmacological interventions, including mood stabilizers, antipsychotics, and antidepressants, are discussed alongside evidence-based psy- chosocial treatments such as cognitive-behavioral therapy and interpersonal and social rhythm therapy. The review also addresses the management of comor- bidities and special considerations for pediatric and geriatric populations. Current research trends and future directions are explored, highlighting promis- ing areas such as precision medicine, novel drug targets, and integrative treat- ment models. This comprehensive review aims to provide clinicians, researchers, and students with an up-to-date understanding of bipolar disorder, fostering im- proved patient care and guiding future investigative efforts in this critical area of mental health.

INTRODUCTION

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Bipolar disorder (BD) is a complex and chronic psychiatric condition that has captured the attention of clinicians, researchers, and the public alike due to its profound impact on individuals, families, and society. Characterized by alternating episodes of mania, hypomania, and depression, BD presents a unique challenge in both diagnosis and treatment. This comprehensive review aims to synthesize current knowledge on BD, providing an in-depth exploration of its various facets and the latest advancements in the field. The significance of BD in the landscape of mental health cannot be overstated. With a global lifetime prevalence of approximately 2%, BD affects. millions of individuals worldwide, often emerging during the critical years of late adoles- cence or early adulthood. The cyclical nature of mood episodes in BD can lead to significant disruptions in personal relationships, educational pursuits, and occupational functioning. Moreover, individuals with BD face an elevated risk of suicide, substance abuse, and other comorbid conditions, underscoring the critical need for effective management strategies. Over the past few decades, our understanding of BD has evolved dramatically. Advances in neuroscience, genetics, and neuroimaging have shed new light on the underlying mechanisms of the disorder. Concurrently, the development of new pharmacological agents and evidence-based psychosocial interventions has expanded the therapeutic arsenal available to clinicians.

However, despite these advancements, many individuals with BD continue to experience suboptimal outcomes, highlighting the need for continued research and innovation in this field.

This review seeks to provide a comprehensive overview of BD, addressing several key objectives: To trace the historical conceptualization of BD and its evolution into current diagnostic frameworks.

To examine the clinical features, epidemiology, and diagnostic challenges associated with BD.

To explore the current understanding of the etiology and neurobiology of BD, including genetic, environmental, and neurobiological factors. To critically evaluate existing treatment approaches, encompassing both pharmacological and psychosocial interventions. To discuss special considerations in the management of BD, including comorbidities and age-specific issues.

To highlight current research trends and future directions in BD, with a focus on emerging therapeutic strategies and personalized medicine approaches. By addressing these objectives, this review aims to provide clinicians, re- searchers, and students with a comprehensive and up-to-date understanding of bipolar disorder. It is our hope that this synthesis of knowledge will not only enhance clinical practice and patient care but also stimulate further research and innovation in this critical area of mental health.

Historical Background
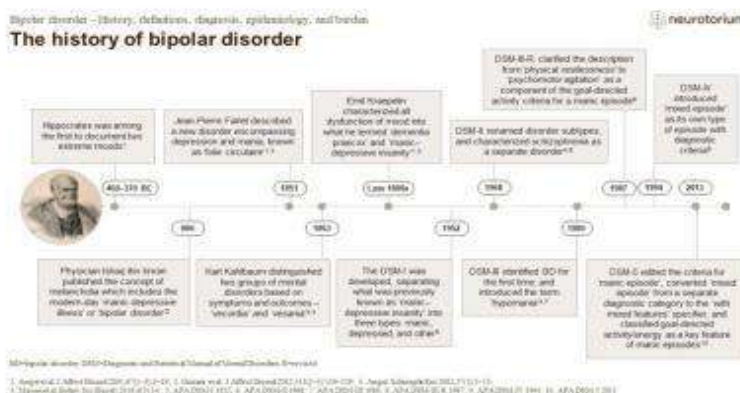
The conceptualization of bipolar disorder has a rich and complex history, span- ning millennia and crossing diverse cultures. This historical perspective is cru- cial for understanding the evolution of our current diagnostic criteria and treat-ment approaches.

Ancient Roots

The earliest known descriptions of mania and melancholia, the hallmark states of bipolar disorder, can be traced back to ancient civilizations. In the 5th cen- tury BCE, Hippocrates provided some of the first medical descriptions of thesemood states, attributing them to imbalances in four bodily fluids or "humors": blood, phlegm, yellow bile, and black bile. This humoralism theory persisted for centuries and influenced medical thought well into the Renaissance period.

Emergence of Modern Concepts

The modern conception of bipolar disorder began to take shape in the 19th century. In 1851, French psychiatrist Jean-Pierre Falret described "la folie cir- culaire" (circular insanity), noting a cycle of mania and depression with inter- vening periods of wellness. Shortly after, Jules Baillarger identified "la folie à double forme" (dual-form insanity), a similar concept emphasizing the cyclicalnature of the disorder.

Kraepelin's Contribution

Emil Kraepelin, often referred to as the father of modern psychiatry, made sig- nificant contributions to the understanding of bipolar disorder in the late 19th and early 20th centuries. In his 1899 textbook, Kraepelin distinguished between "dementia praecox" (later known as schizophrenia) and "manicdepressive in- sanity." This latter term encompassed both unipolar and bipolar presentations, emphasizing the episodic nature of the illness and the potential for full recovery between episodes.

Mid-20th Century Developments

The mid-20th century saw further refinement of bipolar disorder as a diagnos- tic entity. In 1957, Karl Leonhard proposed a distinctionbetween unipolar and bipolar disorders, a concept that gained. traction in the following decades. This period also saw the introduction of lithium as a treatment for mania by John Cade in 1949, marking a significant advancement in the pharmacological management of the disorder

Modern Classification

The publication of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) in 1980 marked a significant shift in the formal classi- fication of bipolar disorder. It introduced specific diagnostic criteria and distin- guished between Bipolar I and Bipolar II disorders. Subsequent editions of the DSM and the International Classification of Diseases (ICD) have further refined these criteria, reflecting ongoing research and clinical observations.

Contemporary Understanding

In recent decades, the conceptualization of bipolar disorder has continued to evolve. The recognition of a bipolar spectrum, encompassing a range of presen- tations from subsyndromal symptoms to full-blown mania, has gained increasing attention. Additionally, advances in genetics, neurobiology, and neuroimaging have deepened our understanding of the underlying mechanisms of the disorder. The historical journey of bipolar disorder from ancient observations to modern neuroscientific investigations underscores the complexity of this condition. It also highlights the ongoing nature of scientific inquiry, reminding us that our current understanding, while advanced, is part of a continuum of knowledge that will undoubtedly continue to evolve.

Clinical Features and Diagnosis

Bipolar disorder (BD) is characterized by distinct episodes of mania or hypoma- nia, often alternating with periods of depression. The accurate diagnosis and understanding of these

clinical features are crucial for effective management and treatment.

Manic Episodes

Manic episodes are the hallmark of Bipolar I Disorder. Key features include:

Elevated, expansive, or irritable mood

Increased energy and goal-directed activity

Decreased need for sleep

Grandiosity or inflated self-esteem

Pressured speech and flight of ideas

Distractibility

Increased involvement in risky or pleasurable activities To meet diagnostic criteria, these symptoms must persist for at least one week (or any duration if hospitalization is necessary) and cause significant impairment in social or occupational functioning.

Hypomanic Episodes

Hypomanic episodes, characteristic of Bipolar II Disorder, share similar symp- toms with manic episodes but are less severe and shorter in duration (at least 4 consecutive days). Unlike mania, hypomania does not cause marked impairment in social or occupational functioning and does not include psychotic features.

Depressive Episodes

Depressive episodes in BD are similar to those in major depressive disorder and include:

Depressed mood

Loss of interest or pleasure in activities

Significant weight loss or gain

Insomnia or hypersomnia

Psychomotor agitation or retardation

Fatigue or loss of energy

Feelings of worthlessness or excessive guilt

Mixed Episodes

Mixed episodes, where features of both mania and depression occur simultane- ously or in rapid alternation, are now recognized as a common presentation in BD. These episodes can be particularly challenging to manage and are associated with a higher risk of suicide.

Diagnostic Criteria

According to the DSM-5, the diagnostic criteria for the main types of bipolar disorder are as follows:

Bipolar I Disorder: At least one manic episode, which may be preceded or followed by hypomanic or major depressive episodes. Bipolar II Disorder: At least one hypomanic episode and one major depressive episode, but no manic episodes.

Cyclothymic Disorder: Numerous periods of hypomanic and depressive symptoms that do not meet full criteria for hypomanic or major depressive episodes, persisting for at least two years (one year in children and adolescents).

Other Specified and Unspecified Bipolar and Related Disorders: For pre-sentations with bipolar features that do not meet the criteria for the abovedisorders. Diagnostic Challenges

Diagnosing BD can be challenging due to several factors:

Overlap with other disorders: Symptoms of BD can overlap with those of other psychiatric conditions, such as major depressive disorder, schizophre- nia, and borderline personality disorder.

Variability in presentation: The clinical presentation of BD can vary sig- nificantly between individuals and even within the same individual over time.

Underreporting of hypomanic symptoms: Patients often do not report hypomanic episodes, as they may be perceived as positive experiences.

Diagnostic Tools
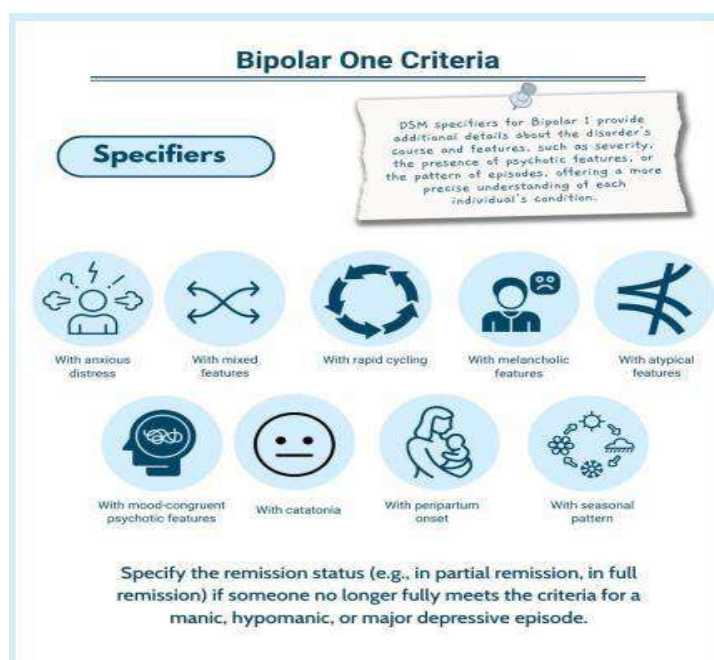
Several structured diagnostic interviews and rating scales are used to aid in thediagnosis and assessment of BD severity:

Structured Clinical Interview for DSM-5 (SCID-5)

Young Mania Rating Scale (YMRS)

Montgomery-Åsberg Depression Rating Scale (MADRS)

Mood Disorder Questionnaire (MDQ)

Bipolar Spectrum Diagnostic Scale (BSDS)

These tools, combined with a comprehensive clinical evaluation, family history, and longitudinal course of symptoms, are essential for accurate diagnosis and effective treatment planning in bipolar disorder.

Epidemiology

The epidemiology of bipolar disorder (BD) provides crucial insights into its prevalence, incidence, and distribution across various populations. Understand- ing these patterns is essential for public health planning, resource allocation, and identifying risk factors.

Prevalence.

The lifetime prevalence of bipolar disorder varies depending on the specific type and the population studied:

Bipolar I Disorder: The lifetime prevalence is estimated to be around 1%of the general population.

Bipolar II Disorder: Estimates range from 0.5% to 1.1% of the general population.

Subthreshold Bipolar Disorder: When including subthreshold forms of BD, the lifetime prevalence increases to approximately 24% of the general population.

It's important to note that these figures may underestimate the true prevalencedue to diagnostic challenges and potential underreporting.

Incidence

The incidence rate of bipolar disorder is estimated to be around 0.5-1 per 1,000 person-years. However, this can vary significantly depending on the populationstudied and the diagnostic criteria used.

Age of Onset

The age of onset for bipolar disorder typically falls within a broad range:
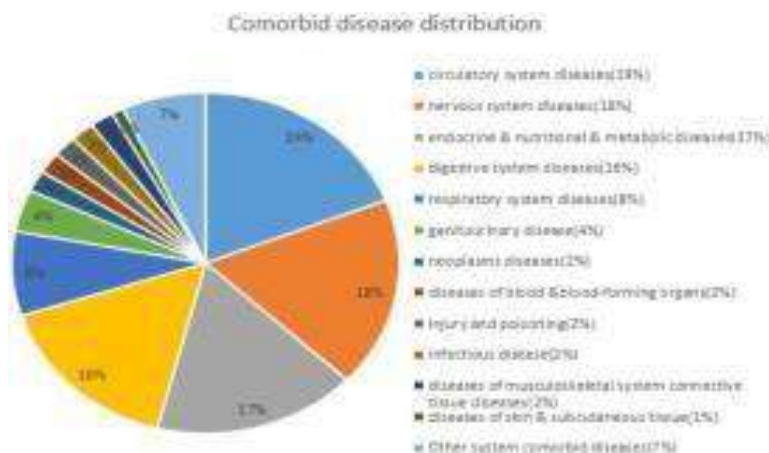
The median age of onset is around 25 years.

Approximately 28% of cases begin before age 13. About 65% of all cases begin before the age of 18. Late-onset cases (after age 50) are less common but do occur. Early-onset BD is often associated

with a more severe course of illness and poorer outcomes.

Comorbid disease distribution

- circulatory system diseases(19%)
- nervous system diseases(18%)
- endocrine & nutritional & metabolic diseases(17%)
- digestive system diseases(16%)
- respiratory system diseases(8%)
- genitourinary disease(4%)
- neoplasms diseases(2%)
- diseases of blood &blood-forming organs(2%)
- injury and poisoning(2%)
- infectious disease(2%)
- diseases of musculoskeletal system connective tissue diseases(2%)
- diseases of skin & subcutaneous tissue(1%)
- Other system comorbid diseases(7%)

Geographical and Ethnic Variations

While bipolar disorder occurs across all cultures and ethnicities, some variationshave been observed.

Higher rates have been reported in North America compared to Asia andEurope.

Some studies suggest higher rates among African American and Hispanic populations in the United States, though this may be influenced by diagnostic practices and access to healthcare.

Socioeconomic Factors

The relationship between socioeconomic status and bipolar disorder is complex: • Some studies suggest a higher prevalence in lower socioeconomic groups, potentially due to the disorder's impact on educational and occupationalfunctioning.

However, BD also occurs across all socioeconomic strata, and some forms (particularly Bipolar II) may be associated with highachieving individu- als.

Comorbidity

Bipolar disorder frequently co-occurs with other psychiatric and medical condi-tions:

Anxiety disorders: Up to 70% of individuals with BD also meet criteriafor an anxiety disorder.

Substance use disorders: Approximately 40-60% of individuals with BDhave a lifetime history of substance use disorders.

Attention-Deficit/Hyperactivity Disorder (ADHD): About 20% of adultswith BD also have ADHD.

Medical comorbidities: Increased rates of cardiovascular disease, diabetes, and obesity are observed in individuals with BD.

Etiology and Risk Factors

Bipolar disorder (BD) is a complex psychiatric condition with a multifactorial etiology. Understanding the various factors contributing to its development is crucial for improving diagnosis, treatment, and prevention strategies. 10.1 Genetic Factors

Bipolar disorder has a strong genetic component, with heritability estimates ranging from 60% to 85%. Family studies have consistently shown an increased risk of BD among first-degree relatives of affected individuals. Twin studies fur- ther support the genetic basis, with concordance rates of 40-70% in monozygotic twins compared to 5-10% in dizygotic twins.

Genome-wide association studies (GWAS) have identified several susceptibility loci associated with BD. Some of the most replicated genes include:

CACNA1C (calcium channel subunit)

ANK3 (ankyrin 3)

ODZ4 (teneurin transmembrane protein 4)

NCAN (neurocan)

These genes are involved in various neurobiological processes, including synaptic plasticity, neurotransmitter release, and neuronal development. 10.2 Environmental Influences

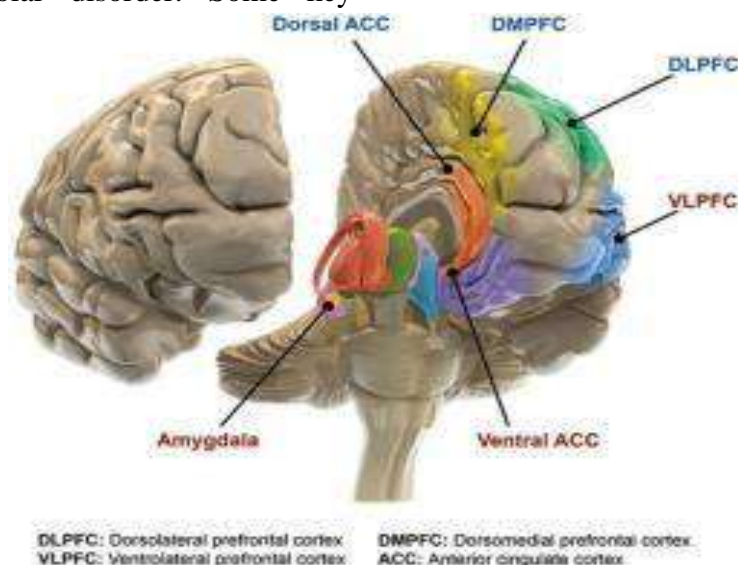While genetic factors play a significant role, environmental factors are also cru- cial in the development of bipolar disorder. Some key environmental influences include: 1. Childhood trauma and adversity.

Stressful life events

Substance abuse

Sleep disturbances Seasonal changes

Neurobiology

DLPFC: Dorsolateral prefrontal cortex
VLPFC: Ventrolateral prefrontal cortex
DMPFC: Dorsomedial prefrontal cortex.
ACC: Anterior cingulate cortex.

The neurobiology of bipolar disorder is complex and multifaceted, involving structural, functional, and neurochemical alterations in the brain. Recent ad- vances in neuroimaging and molecular biology have provided valuable insights into the underlying neural mechanisms of BD.

11.1 Structural Brain Changes

Neuroimaging studies have revealed several structural brain abnormalities in individuals with BD:

Reduced gray matter volume in prefrontal cortex regions, particularly theventrolateral and dorsolateral prefrontal cortex

Enlarged lateral ventricles

Reduced volume of the anterior cingulate cortex

Alterations in amygdala and hippocampus volumes (findings have been inconsistent, with some studies showing enlargement and others showing reduction)

White matter abnormalities, particularly in fronto-limbic circuits These structural changes may contribute to the emotional dysregulation and cognitive deficits observed in BD.

11.3 Neurotransmitter Systems.

Dysregulation of several neurotransmitter systems has been implicated in BD: 1. Dopamine: Increased dopaminergic activity is associated with manic symp-toms, while decreased activity may contribute to depressive episodes.

Serotonin: Alterations in serotonergic function may contribute to moodinstability and impulsivity.

Norepinephrine: Dysregulation of the noradrenergic system may play arole in both manic and depressive episodes.

Glutamate and GABA: Imbalances in excitatory (glutamate) and inhibitory (GABA) neurotransmission have been observed in BD.

11.4 Neuroendocrine Abnormalities

The hypothalamic-pituitary-adrenal (HPA) axis, which regulates the stress re-sponse, is often dysregulated in BD:

Elevated cortisol levels, particularly during depressive episodes

Altered cortisol awakening response

Abnormal dexamethasone suppression test results

These neuroendocrine abnormalities may contribute to the stress sensitivity ob-served in individuals with BD.

11.5 Circadian Rhythm Disruptions

Disruptions in circadian rhythms are common in BD and may play a role inmood episode onset and maintenance: 1. Altered sleep-wake cycles

Disrupted melatonin secretion patterns

Changes in body temperature regulation

Abnormalities in clock gene expression

12. Treatment Approaches

The management of bipolar disorder (BD) requires a comprehensive, multi- modal approach that addresses both acute symptoms and longterm mainte- nance. Treatment strategies typically involve a combination of pharmacological and psychosocial interventions, with ongoing research exploring novel therapies.

Global prevalence of bipolar spectrum disorders
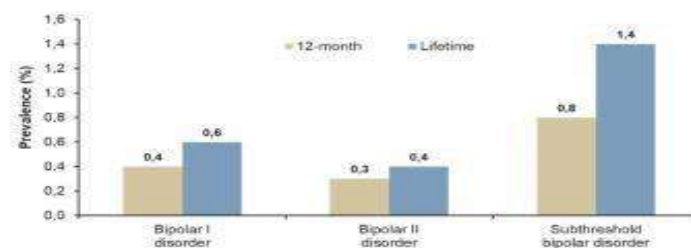
12.1 **Pharmacological Interventions**

Medication is the cornerstone of bipolar disorder treatment, aiming to stabilizemood, prevent recurrences, and manage acute episodes. 12.1.1 Mood Stabilizers Lithium:

Gold standard for BD treatment

Effective in reducing both manic and depressive episodes • Requires regular monitoring of serum levels and renal/thyroid func-tion

Potential side effects include tremor, weight gain, and cognitivedulling 2.

Valproic Acid:

Effective for manic episodes and rapid cycling

Requires liver function monitoring

Side effects may include

weight gain, hair loss, and gastrointestinaldisturbances Carbamazepine:

Used for manic episodes and maintenance

Requires monitoring of blood counts and liver function • Potential side effects include dizziness, drowsiness, and skin rashes Lamotrigine:

Particularly effective for bipolar depression and maintenance

Requires careful titration due to risk of severe skin reactions

Generally well-tolerated with fewer cognitive side effects

Pharmacotherapy for bipolar disorder
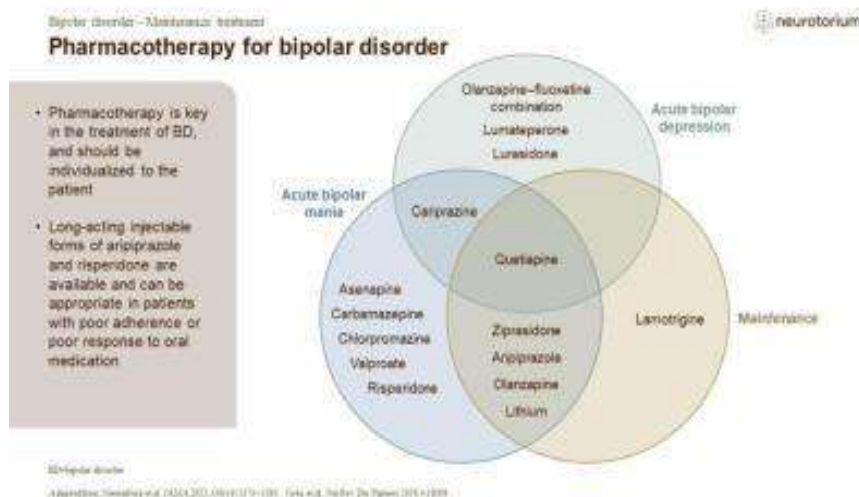
13. Psychosocial Aspects

Bipolar disorder (BD) has significant impacts on various aspects of an individ- ual's life, extending beyond the clinical symptoms to affect social functioning, relationships, and overall quality of life. 13.1 Impact on Relationships and Social Functioning • Mood instability can strain personal relationships, leading to conflicts andmisunderstandings

Impulsivity during manic episodes may damage relationships and socialstanding

Social withdrawal during depressive episodes can lead to isolation

Difficulty maintaining long-term friendships and romantic relationships • Challenges in parenting due to symptom fluctuations and treatment demands

13.2 Occupational and Educational Challenges

Higher rates of unemployment and underemployment compared to thegeneral population

Difficulty maintaining consistent job performance due to mood fluctua-tions Challenges in academic settings, including inconsistent attendance andperformance

Cognitive symptoms (e.g., attention deficits, memory problems) can im-pact work and study

Disclosure issues in workplace settings, balancing need for accommodations with privacy concerns

13.3 Stigma and Discrimination

Persistent societal stigma surrounding mental illness, particularly mooddisorders

Self-stigma leading to decreased self-esteem and reluctance to seek treatment

Discrimination in employment, housing, and social settings

Media portrayals often reinforce stereotypes about bipolar disorder• Efforts to combat stigma through education and awareness campaigns

13.4 Quality of Life Considerations

Overall reduced quality of life compared to the general population • Impacts on physical health due to both the disorder and side effects ofmedications.
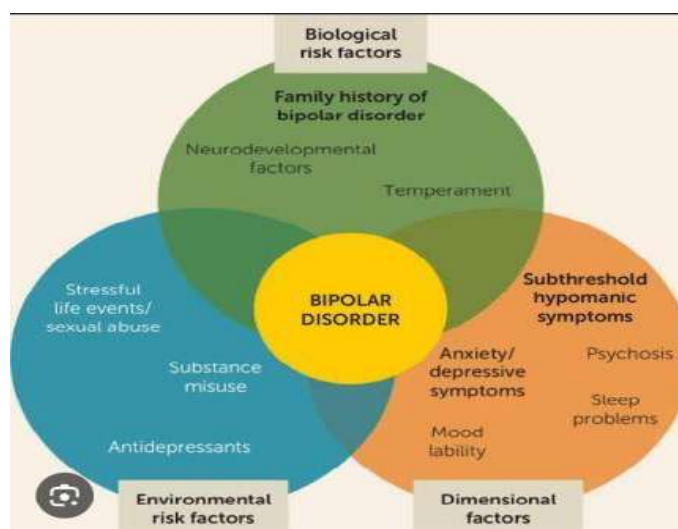
14. Comorbidities

Bipolar disorder frequently co-occurs with other psychiatric and medical condi-tions, complicating diagnosis and treatment.

14.1 Anxiety Disorders

High comorbidity rates, with up to 50% of BD patients experiencing acomorbid anxiety disorder Common comorbid conditions include generalized anxiety disorder, socialanxiety disorder, and panic disorder

Presence of anxiety can worsen BD outcomes and increase suicide risk • Treatment challenges, including potential for antidepressants to inducemania

14.2 Substance Use Disorders

Prevalence rates of 40-60% for lifetime substance use disorders in BD • Bidirectional relationship: substance use can trigger mood episodes, andmood symptoms can lead to self-medication • Alcohol and cannabis are most commonly abused substances • Integrated treatment approaches addressing both BD and substance useare crucial

14.3 Attention-Deficit/Hyperactivity Disorder (ADHD)

Significant overlap in symptoms, particularly during manic/hypomanicepisodes

Challenges in differential diagnosis, especially in youth

Presence of ADHD can complicate BD treatment and worsen functional outcomes

Special Populations

Pediatric Bipolar Disorder

Diagnostic Challenges in Youth

Debate over the validity and reliability of BD diagnosis in very young children Overlap with other disorders (e.g., ADHD, oppositional defiant disorder)complicating diagnosis

Need for developmentally appropriate diagnostic criteria and assessment tools Developmental Considerations Differences in symptom presentation compared to adults (e.g., more irri-tability, rapid cycling)

Impact on social, emotional, and cognitive development

Importance of early intervention to improve long-term outcomes

16. Current Research and Future Directions

The field of bipolar disorder research is rapidly evolving, with new insights and technologies paving the way for improved understanding, diagnosis, and treatment of this complex condition. 16.1 Biomarker Discovery and Personalized Medicine

Ongoing search for reliable biomarkers to aid in diagnosis and treatment selection

Exploration of genetic markers, neuroimaging patterns, and peripheral biomarkers (e.g., inflammatory markers) Development of pharmacogenomic tests to predict medication response and side effects

Potential for machine learning algorithms to integrate multiple biomarkers for improved diagnostic accuracy

16.2 Neuroimaging Advances

Use of advanced neuroimaging techniques (e.g., fMRI, DTI, PET) to better understand neural circuits involved in BD

Longitudinal neuroimaging studies to track brain changes over the course of illness

Integration of neuroimaging data with genetic and clinical

Trends in Neurosciences
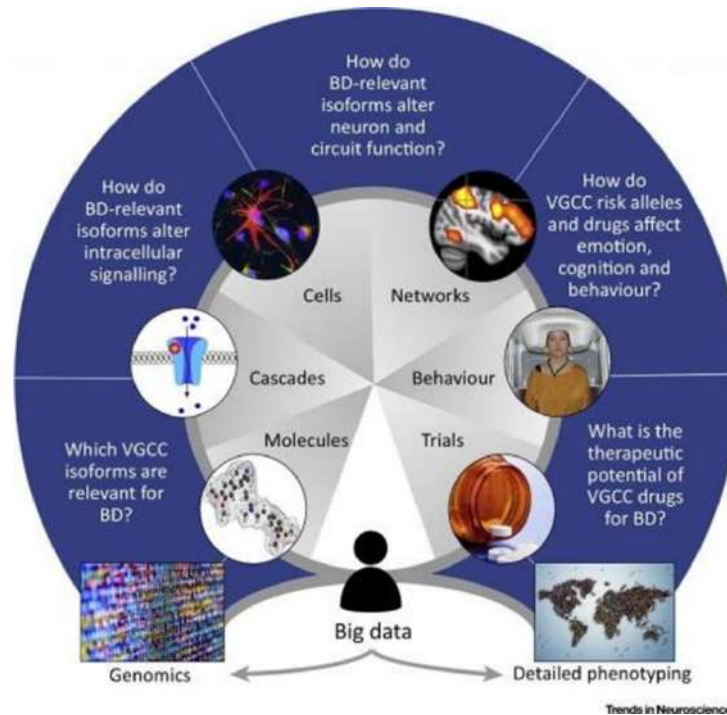
information fora more comprehensive understanding of BD neurobiology Exploration of neuroimaging as a tool for monitoring treatment responseand predicting outcomes

16.3 Genetic and Epigenetic Studies

Large-scale genome-wide association studies (GWAS) to identify addi-tional risk loci

Investigation of rare genetic variants and copy number variations in BD • Epigenetic studies examining the role of environmental factors on geneexpression

Exploration of gene-environment interactions in BD onset and progression

16.4 Novel Treatment Targets

Investigation of glutamatergic agents for rapid antidepressant effects • Exploration of anti-

inflammatory approaches based on the neuroinflammation hypothesis

CONCLUSION

Bipolar disorder remains a complex and challenging psychiatric condition, with significant impacts on individuals, families, and society as a whole. This compre- hensive review has highlighted the multifaceted nature of

BD, from its historical context and clinical features to the latest advances in understanding its etiologyand treatment.

Key points to emphasize include:

The importance of accurate diagnosis, particularly in differentiating BD from other mood disorders and addressing the challenges of diagnosis in special populations such as youth and older adults.

The critical role of both pharmacological and psychosocial interventions in managing BD, with an emphasis on personalized treatment approaches that address the unique needs of each patient.

The significant impact of BD on psychosocial functioning, including rela- tionships, occupation, and overall quality of life, highlighting the need for comprehensive care that extends beyond symptom management.

The high prevalence of comorbid conditions in BD, necessitating integrated treatment approaches that address both bipolar symptoms and associated disorders.

The rapid advances in research, particularly in the areas of neurobiology, genetics, and novel treatment approaches, offering hope for improved out- comes in the future.

Despite these advances, significant challenges remain in the field of bipolar dis-order. Unmet needs include:

The development of more effective treatments for bipolar depression, whichremains difficult to manage with current therapies.

Improved strategies for early identification and intervention, potentially altering the course of the illness. Better management of cognitive symptoms and functional impairments associated with BD. Reduction of stigma and discrimination faced by individuals with BD in various aspects of life. Enhanced understanding of the underlying neurobiology to facilitate the development of targeted, mechanism-based treatments.

Looking to the future, the field of bipolar disorder research and treatment is poised for significant advancements. The integration of big data approaches, precision medicine, and digital health technologies offers the potential for more personalized and effective management strategies. Continued research into the genetic and neurobiological underpinnings of BD may lead to novel treatment targets and improved diagnostic tools.

Ultimately, the goal remains to improve the lives of individuals affected by bipo- lar disorder, reducing the burden of illness and enhancing overall functioning and quality of life. This will require ongoing collaboration between researchers, clinicians, patients, and families, as well as continued support for mental health research and services at a societal level.

As our understanding of bipolar disorder continues to evolve, so too will our ability to provide hope and effective care for those affected by this challenging but manageable condition.

REFERENCES

1. American Psychiatric Association. (2013). Diagnostic and statistical man- ual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.
2. Goodwin, F. K., & Jamison, K. R. (2007). Manic-depressive illness: Bipo- lar disorders and recurrent depression (2nd ed.).
3. New York: Oxford Uni-versity Press.
4. Grande, I., Berk, M., Birmaher, B., & Vieta, E. (2016). Bipolar disorder. The Lancet, 387(10027), 1561-1572.
5. Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey,
6. B. N., … & Berk, M. (2018). Canadian
7. Network for Mood and Anxiety Treatments (CANMAT) and
8. International Society for Bipolar Disorders (ISBD) 2018 guidelines
9. for the management of patients with bipolar disorder. Bipolar disorders, 20(2), 97-170.
10. Geddes, J. R., & Miklowitz, D. J. (2013). Treatment of bipolar disorder. The Lancet, 381(9878), 1672-1682.
11. Phillips, M. L., & Swartz, H. A. (2014). A critical appraisal of neuroimag- ing studies of bipolar disorder: toward a new conceptualization of underly- ing neural circuitry and a road map for future research.

American Journalof Psychiatry, 171(8), 829-843.

12. Craddock, N., & Sklar, P. (2013). Genetics of bipolar disorder. The Lancet, 381(9878), 1654-1662.

13. Kupka, R. W., Altshuler, L. L., Nolen, W. A., Suppes, T., Luckenbaugh, D. A., Leverich, G. S., … & Post, R. M. (2007). Three times more days de- pressed than manic or hypomanic in both bipolar I and bipolar II disorder. Bipolar disorders, 9(5), 531-535.

14. Judd, L. L., Akiskal, H. S., Schettler, P. J., Endicott, J., Maser, J., Solomon, D. A., … & Keller, M. B. (2002). The long-term natural his- tory of the weekly symptomatic status of bipolar I disorder. Archives of general psychiatry, 59(6), 530-537. 10. Berk, M., Kapczinski, F., Andreazza, A. C., Dean, O. M., Giorlando, F., Maes, M., … & Malhi, G. S. (2011). Pathways underlying neuropro- gression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neuroscience& Biobehavioral Reviews, 35(3), 804- 817.

15. 11. Miklowitz, D. J., & Chung, B. (2016). Family-focused therapy for bipolar disorder: reflections on 30 years of research. Family process, 55(3), 483- 499..