Bipolar disorder

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The hallmark of bipolar disorder is hypomania or mania, and the predominant phase of illness is depression. Affecting approximately 40 million individuals worldwide, bipolar disorder is associated with a substantial psychosocial, medical, and financial burden and increased mortality from suicide and other causes. Diagnosis can be challenging due to symptom overlap with attention-deficit hyperactivity disorder, major depressive disorder, psychotic spectrum disorders, and personality disorders, which often leads to a delay in diagnosis. Recent advancements in understanding disease risk and pathophysiology have identified multigene risk and possible infectious and mitochondrial causes. Treatment approaches include pharmacotherapy, psychotherapy, and lifestyle modifications, which should always be patient-centred and aligned with individual goals and priorities. Future directions for bipolar disorder care include increasing the availability of psychosocial interventions aimed at self-management, addressing treatment-resistant bipolar depression, deepening the understanding of pathophysiology, and exploring novel interventions, such as ketamine, esketamine, other rapid-acting antidepressants, and various neuromodulation approaches.

Lancet 2025; 406: 963–78

Published Online July 22, 2025 https://doi.org/10.1016/S0140-6736(25)01140-7

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See Online for appendix

Introduction

Bipolar disorder is a chronic illness marked by episodes of hypomania or mania, depression, mixed states, and functionally impairing subsyndromal symptoms.[1,2] Bipolar disorder often co-occurs with multiple psychiatric and somatic comorbidities, making it a challenging condition to manage. The disorder has substantial heritability, early age of onset, and high comorbidity rates with anxiety and substance use disorders that lead to substantial psychosocial impairment and a negative impact on overall quality of life.[3]

Bipolar disorder is one of the costliest mental health conditions,[4] and its economic burden is substantial.[5–8] In the USA, the economic burden of bipolar disorder exceeds US$195 billion annually, with 25% of this cost attributed to medical expenses.[6] In the UK, the annual burden was estimated to be £6·4 billion for 2018–19.[7] Individuals with bipolar disorder, and particularly those with moderate-to-severe depression, require more health-care services, have more frequent hospitalisations, and incur higher direct health-care costs compared with the general population.[8]

Epidemiology

According to the WHO World Mental Health Survey Initiative, the 12-month prevalence for bipolar spectrum disorder was 1·5%, with bipolar I disorder at 0·4%, bipolar II disorder at 0·3%, and subthreshold bipolar disorder (ie, meeting at least one hypomania or mania symptom but not meeting full hypomania or mania criteria) at 0·8%.[9] The prevalence rates are similar in male individuals and female individuals[10] and vary among countries.[2] Individuals aged 10–19 years have the highest incidence of new cases of bipolar disorder,[2] and individuals aged 20–44 years contribute the most bipolar disorder-related disability-adjusted life-years (DALYs).[11] The overall age-standardised rate of DALYs was lowest in east Asia and highest in tropical Latin America.[11]

The age of onset for bipolar disorder differs across various regions, with an increasing incidence of childhood-onset bipolar disorder in the USA compared with Europe, possibly due to increased familial loading and higher stress.[12] In low-income and middle-income countries, inadequate health-care access, economic constraints, and high medication costs restrict bipolar disorder treatment. Socioeconomic factors such as poverty, low education, and poor care continuity hinder adherence, increasing discontinuation rates and worsening outcomes.[13] Furthermore, individuals with bipolar disorder have a reduced life expectancy, with a weighted average of 12·9 years of potential life lost.[14] A comparison of geographical regions shows the lowest life expectancy among people with bipolar disorder in Africa (54·1 years), followed by North America (65·6 years), Europe (67·3 years), and Asia (68·0 years).

Natural causes, such as general somatic illnesses, are common contributors to reduced life expectancy in individuals with bipolar disorder.[15] Bipolar disorder is highly comorbid with anxiety and substance use disorders,[3] and individuals with bipolar disorder have a high burden of cardiovascular diseases, stroke, and metabolic syndrome.[10] In addition, bipolar disorder is an independent risk factor for major adverse cardiac events, even after accounting for cardiovascular disease.[16]

Search strategy and selection criteria

We searched PubMed for relevant articles, studies, and meta-analyses in English between Jan 1, 2017, and July 22, 2024, using the term "bipolar disorder" along with "depression", "mania", "mixed features", "rapid cycling", "guidelines", "management", and "clinical treatment" (appendix p 2). We prioritised articles using meta-analytic methodologies. We also reviewed guidelines from leading psychiatric associations and studies on epidemiology, treatment outcomes, and patient-reported experiences. The inclusion of people with lived experience is recognised as important, and one of the seminar authors has lived experience of bipolar disorder.

Unnatural causes (ie, suicide and accidents) are another major contributor to mortality for people with bipolar disorder. The risk of suicide among people with bipolar disorder is more than 20–30 times higher than that of the general population.[17] Suicide rates in bipolar disorder range from 5% to 20%,[10,17] with similar rates for both bipolar I and bipolar II disorder.[18] In a 2023 systematic review in south Asian individuals with psychosis or bipolar disorder, the pooled prevalence rate of suicide attempts was 22% (95% CI 17–27) and the pooled prevalence rate of suicidal ideation was 38% (95% CI 27–51).[19] Prominent risk factors for suicide among those with bipolar disorder include being male, White, single, divorced, childless, younger than 35 years or older than 75 years, or unemployed, and having suicidal ideation, a history of suicide attempts, a depressive or mixed mood state, a rapid-cycling pattern, an early age of illness onset, a family history of attempting or dying by suicide, and depressive-predominant polarity.[17,20,21] Women are more likely to attempt suicide overall, whereas men have a higher risk of dying by suicide. Furthermore, individuals with bipolar disorder have an increased risk of accidents, road injuries, and accidental poisoning.[22]

Diagnosis

Bipolar disorder is categorised into two primary subtypes in both the ICD-11 and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, text revision (DSM-5-TR): bipolar I disorder and bipolar II disorder. A single manic episode is sufficient for a diagnosis of bipolar I disorder, whereas bipolar II disorder requires at least one major depressive episode and one hypomanic episode. A hypomanic or manic episode is marked by a distinct period of elevated, expansive, or irritable mood with increased activity or energy. The diagnosis of hypomania or mania requires at least three symptoms (or four with irritability; table 1). An episode must last at least 7 days or lead to hospitalisation to be considered a manic episode, or last at least 4 days to be considered a

	DSM-5-TR (bipolar and related disorders)	ICD-11 (bipolar or related disorders 6A60–6A6Z)
Types	Bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance-induced or medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder	Bipolar type I disorder (6A60), bipolar type II disorder (6A61), cyclothymic disorder (6A62), other specified bipolar or related disorders (6A6Y), and bipolar or related disorders, unspecified (6A6Z)
Hypomania and mania symptoms	Flight of ideas, pressured speech, talkativeness, grandiosity, distractibility, reduced need for sleep, impulsivity, increase in goal-directed activities or agitation, and excessive involvement in activities with high potential for painful consequences	Flight of ideas, pressured speech, talkativeness, grandiosity, distractibility, reduced need for sleep, impulsivity, increase in goal-directed activities or agitation, and excessive involvement in activities with high potential for painful consequences
Psychotic features	Present only in mania, not hypomania	Present only in mania, not hypomania
Bipolar I disorder	At least one manic episode, with or without depression	At least one manic episode, with or without depression
Bipolar II disorder	At least one hypomanic and one depressive episode	At least one hypomanic and one depressive episode
Cyclothymic disorder	Persistent mood instability with hypomanic and depressive symptoms for at least 2 years, without ever fully meeting criteria for a hypomanic or a major depressive episode; symptoms are present ≥50% of the time without remitting for ≥2 months	Fluctuating hypomanic and depressive symptoms for at least 2 years, never fully meeting criteria for hypomanic or major depressive episodes; symptoms are present ≥50% of the time, without remitting for ≥2 months at a time
Mixed features or episodes	Mixed features as a specifier require at least three symptoms from the opposite pole; when mania or hypomania predominates, depressive symptoms include dysphoria, anhedonia, psychomotor changes, fatigue, inappropriate guilt or worthlessness, and suicidal ideation; when depressive symptoms predominate, manic or hypomanic symptoms include elevated mood, grandiosity, racing thoughts, increased talkativeness, increased energy, decreased need for sleep, and excessive involvement in high-risk activities	A mixed episode is defined as prominent manic and depressive symptoms occurring most days for ≥2 weeks, either simultaneously or alternating rapidly; when hypomanic or manic symptoms predominate, depressive symptoms include dysphoric mood, worthlessness, hopelessness, and suicidal ideation; when depressive symptoms predominate, manic symptoms include irritability, racing thoughts, increased talkativeness, and increased activity
Rapid cycling	≥4 mood episodes in 12 months	≥4 mood episodes in 12 months
Other specified bipolar and related disorder	Used when bipolar symptoms predominate but do not meet full criteria for bipolar disorder I, bipolar disorder II, or cyclothymia; a clinician specifies why a presentation does not meet criteria for any specific bipolar disorder; examples include short-duration hypomanic episodes (2–3 days) and major depressive episodes, hypomanic episodes with insufficient symptoms and major depressive episodes, a hypomanic episode without a previous major depressive episode, short-duration cyclothymia (less than 24 months), and a manic episode superimposed on schizophrenia or other psychotic disorders	Presentation includes manic or hypomanic symptoms (with or without depression) but does not meet full criteria for bipolar I disorder, bipolar II disorder, or cyclothymia
Unspecified bipolar and related disorder	This category applies when symptoms do not fully meet criteria for bipolar and related disorders, often due to insufficient information, such as in emergency settings	Bipolar or related disorder, unspecified

DSM-5-TR=Diagnostic and Statistical Manual of Mental Disorders, 5th edition, text revision.

Table 1: **Bipolar and related disorder diagnoses based on DSM-5-TR and ICD-11**

hypomanic episode. Duration for either mania or hypomania has no upper limit for diagnosis. As diagnosing hypomania can be particularly challenging when relying solely on patient history, caution is essential for clinicians when assessing bipolar II disorder. Corroborative history can be helpful in diagnosis.

A dominance of mania over depressive episodes during the illness history of someone with bipolar disorder can be associated with several factors, such as young age, male sex, a diagnosis of bipolar I disorder, psychotic features, earlier onset, and manic onset of the disorder. By contrast, depressive-predominant polarity is associated with depressive onset, a higher number of mood episodes (compared with manic-predominant or hypomanic-predominant polarity), a history of suicide attempts, and being in a relationship.[23] Unipolar mania accounts for 5% of bipolar disorder cases, predominantly type I, and is more prevalent in men.[24] People with unipolar mania receive earlier clinical interventions, have more psychotic features, have higher morbidity and more frequent clinic visits, and show fewer depressive symptoms compared with people with bipolar disorder; they also frequently use mood stabilisers and rarely use antidepressants.

Cyclothymic disorder involves frequent hypomanic or depressive symptoms that fall short of full hypomanic or depressive episodes, lasting most of the time for at least 2 years without remission lasting more than 2 months. Approximately 35–53% of people with cyclothymic disorder have the potential to develop full manic or hypomanic and depressive episodes. 7–11% of people with cyclothymic disorder progress to bipolar I disorder and 28–42% progress to bipolar II.[25]

Additionally, mixed states, during which both hypomanic or manic and depressive symptoms co-occur—referred to as mixed episodes in ICD-11 and with mixed features as a specifier in DSM-5-TR—should be identified due to their effect on treatment selection and potential safety risks. Anxiety, agitation, and irritability are three symptoms commonly observed during mixed states that substantially contribute to misdiagnosis and increase the risk of suicide,[26] which has important clinical implications. Avoiding prescribing antidepressants during mixed episodes or features is recommended.

Rapid cycling, as a specifier in DSM-5-TR, is characterised by at least four mood episodes of mania, hypomania, or depression within a 12-month period, which can involve episodes of the same or opposite polarity. Rapid cycling is associated with female sex, childhood maltreatment, mixed features, metabolic disturbances, antidepressant exposure, and hypothyroidism.[27]

People with bipolar disorder are often misdiagnosed with unipolar depression, which necessitates a re-evaluation of their diagnosis and attention to their history. The delay between diagnosing unipolar depression and bipolar disorder can be up to 10 years, with nearly a quarter of people with major depressive disorder having their diagnosis changed to bipolar disorder, mostly within the first 5 years after initial diagnosis.[28] The misunderstanding and delayed diagnosis of bipolar disorder are partly due to its association with classic mania. People who have fewer classic features, predominantly depressive symptoms, or mixed presentation might be misdiagnosed. Furthermore, the median duration of untreated bipolar disorder is 6 years and is linked to female sex, early onset, and non-bipolar I disorder diagnosis.[29] This delay leads to incorrect treatment, treatment resistance, and poor outcomes. Predictors of bipolar depression include a family history of bipolar disorder, early onset of depression, and psychotic symptoms (appendix p 4).[28]

More than half of individuals with bipolar I disorder have psychotic symptoms, which necessitates careful evaluation for other psychotic disorders, such as schizophrenia.[30] Many individuals with bipolar disorder, particularly bipolar II disorder and subthreshold bipolar disorder, risk misdiagnosis as their symptoms might be overlooked or misattributed to personality features.[31] Ruling out bipolar disorder secondary to general medical conditions is crucial,[32] especially in people with atypical or late-onset cases (figure 1). Ruling out substance-induced mania or depression is also important, especially in populations with high rates of substance use disorder.[3] As steroids and other medications can trigger bipolar-like symptoms, recognising these potential causes is crucial for accurate diagnosis.

Distinguishing bipolar disorder from attention-deficit hyperactivity disorder (ADHD) or borderline personality disorder can be particularly challenging, as behavioural features such as hyperactivity, impulsivity, emotional instability, and disruptive behaviours overlap between diagnoses (table 2). The clinical presentation of bipolar disorder can be complicated by comorbid conditions, including anxiety disorders, substance use disorders, ADHD, obsessive-compulsive disorder, post-traumatic stress disorder, eating disorders, and personality disorders. Assessing whether these behaviours occur exclusively during mood episodes or are persistent features of the person's condition is crucial. Such comorbidities frequently contribute to treatment resistance in bipolar disorder and underscore the need for comprehensive assessment in clinical decision making.

Importantly, the ICD-11 and DSM-5-TR diagnoses represent only one aspect of a thorough case formulation. Beyond diagnosis, a careful evaluation of the biological, psychological, and social dimensions of the individual's condition is necessary to fully understand their clinical picture and to develop a multidimensional treatment plan.

Pathophysiology

Bipolar disorder is characterised by multifactorial pathophysiology that encompasses genetic, inflammatory,

and mitochondrial processes and neurostructural alterations. Bipolar disorder is highly heritable (60–80%),[33] with genome-wide association studies (GWAS) suggesting a polygenic architecture. The largest GWAS by the Psychiatric Genomics Consortium identified 298 risk loci for bipolar disorder.[34] Post-GWAS analyses suggest enrichment in genes associated with synaptic functions, dopamine and calcium signalling, and GABAergic interneuron development.[34] Genetic correlations between bipolar disorder and conditions or behaviours such as schizophrenia (genetic correlation 0·54–0·70), major depression (genetic correlation 0·36–0·52), substance use, and self-harm suggest overlapping pathophysiological mechanisms rather than discrete entities.[34] Environmental factors, including childhood adversity,[35] cardiometabolic disorders,[36] and lifestyle factors,[37] interact with genetic risk to shape clinical manifestations.[38]

Mitochondrial dysfunction is implicated in bipolar disorder pathophysiology. Magnetic resonance spectroscopy studies reveal atypical brain energy metabolism in people with bipolar disorder, and animal models of mitochondrial DNA mutations replicate depressive and manic states.[39] Post-mortem studies show reduced electron transport chain activity, particularly complex I subunits, that contributes to oxidative stress.[40,41] Regional mitochondrial DNA depletion,[42] increased mitochondrial DNA copy number (seemingly modulated by lithium),[43] and mitochondrial tRNA heteroplasmy[44] underscore

Secondary causes of mania

Neurological	Systemic and metabolic disorders	Infectious and autoimmune causes	Medications and substance use
• Brain tumours (temporal, frontal, and basitemporal) • Complex partial seizures • Delirium • Dementia • Diencephalic and third ventricle tumours • Huntington's disease • Multiple sclerosis • Right-sided cerebrovascular disease • Stroke • Traumatic brain injury	• Cushing's syndrome • Hypercalcaemia or hypocalcaemia of any cause • Thyrotoxicosis • Uraemia • Vitamin B12 deficiency • Carcinoid syndrome • Premenstrual psychosis • Puerperal psychosis	• Autoimmune encephalitis • HIV and AIDS • Lupus • Meningitis • Neurosyphilis • Viral infection (eg, SARS-CoV-2, influenza, and herpes simplex) • Prion disease	• Adrenal steroids (eg, corticosteroids) • Alcohol • Anabolic steroids • Cannabis • Cocaine • Dopamine agonists • Hallucinogens • Levodopa • Monoamine oxidase inhibitors • Stimulants (eg, amphetamines) • TNF inhibitors • Tricyclic antidepressants

Figure 1: **Secondary causes of bipolar disorders**

	Bipolar disorder	Borderline personality disorder	ADHD
Onset	Episodes of syndromal depression or activated mood, energy, or cognition that represent a clear departure from baseline; first episode usually occurs before age 25 years	Chronic (often long-term) depression and poor self-image, often emerging in the context of abuse, neglect, or insecure attachments	Onset during childhood in most cases, consistent, and not episodic
Activation *vs* lability	Activation affecting mood or affect, cognition, psychomotor function, and energy that lasts for days or weeks	Lability reflecting rapid changes in emotional reactivity, typically lasting from minutes to a few hours	Mood changes are usually situational
Core symptoms	Euphoria, irritability stemming from euphoria, manic or hypomanic expansiveness, and excess energy	Irritability, rage, or anxiety stemming from interpersonal setbacks, abandonment fears, intolerance of aloneness, self-loathing; elation is rarely present	Inattention, distractibility, difficulty relaxing, hyperactivity, impulsivity, or a combination of these traits; low frustration tolerance; and irritability
Impulsivity	Motivated by manic or hypomanic expansiveness or excess energy; confined to activated mood states	Trait-like, often self-destructive impulsivity (eg, reactive suicidality or self-injury) that is often cue-dependent (eg, interpersonal events, perceived abandonment, etc)	Impulsivity is mostly chronic, especially if untreated; can present as being fidgety, on the go, talking excessively, or difficulty waiting turn
Thoughts racing	Usually motivated by manic or hypomanic expansiveness and confined to activated mood states	Cued to external stressors, often driven by feelings of anxiety or anger, in absence of grandiosity or enhanced self-esteem	Cued to external stressors, often with coexisting anxiety
Sleep	Sleep deficits and preserved or even enhanced energy and goal-directed activity (sleep-deprived energy enhancement), and confined to episodes (decreased need for sleep; ask about nocturnal and daytime activity)	Chronic or stress-related sleep deficits and nightmares are common with history of trauma; sleep deficits usually lead to worse functioning and emotional dysregulation	Sleep deficits are situational, usually lead to worse functioning, and respond well to pharmacotherapy
Management	Mood stabilisers and psychotherapy are often helpful	Mood stabilisation using mood stabilisers and antidepressants (in some cases) can be helpful, but psychotherapy is typically the first-line treatment	Stimulants, noradrenergic medications, and α2-adrenergic agonists have the most evidence; psychotherapy can be helpful as well

ADHD=attention-deficit hyperactivity disorder.

Table 2: **Features of bipolar disorder, borderline personality disorder, and ADHD**

mitochondrial involvement. Nevertheless, the implication of mitochondrial alterations in bipolar disorder remains uncertain; for instance, mitochondrial modulators cannot be recommended to date due to the heterogeneity of study designs and the preliminary nature of many findings.[45]

Circadian rhythm dysregulation is another putative causal factor. Abnormalities in circadian gene expression have been implicated in animal models of bipolar disorder with disturbances in circadian periodicity characterising bipolar disorder psychopathology at both the cellular and behavioural levels.[46]

Inflammatory mechanisms are also implicated in bipolar disorder and are driven by genetic predisposition, hypothalamic–pituitary–adrenal axis dysregulation, and infections. Elevated antibodies to cytomegalovirus[47,48] and herpes simplex virus type 2 are reported,[48] alongside increased leukocytes, neutrophils,[49] and T-cell dysfunction.[50] Pro-inflammatory mediators, such as C-reactive protein, IL-6, and tumour necrosis factor, are elevated during euthymic states, with fluctuations across mood episodes.[40,51] Chronic inflammation can induce microglial activation, excitotoxicity, and oxidative stress, disrupting cognition and mood regulation circuits. High cardiometabolic comorbidities in bipolar disorder[52] probably exacerbate these inflammatory changes.[53]

Structural brain alterations in bipolar disorder are well documented. Enhancing Neuro Imaging Genetics Through Meta-Analysis Consortium meta-analyses highlight cortical thinning in frontal, parietal, and temporal areas that worsens with manic episodes.[54] Lithium treatment, however, is associated with increased cortical thickness and brain volume.[54,55] White matter disruptions, notably reduced fractional anisotropy in the corpus callosum and cingulum, reflect broad microstructural abnormalities. Higher fractional anisotropy is observed in cases with shorter illness duration, later onset, and lithium use.[56]

Functional MRI studies show frontolimbic network dysfunction in people with bipolar disorder. Amygdala and hippocampal hyperactivation and frontal hypoactivation during emotion processing and dorsolateral prefrontal cortex hypoactivation during emotion regulation and executive function[57,58] scale with behavioural impairment in emotion regulation and global cognition, respectively.[59] This dysfunction is seen in individuals at risk of bipolar disorder and varies by mood state.[60,61] Frontolimbic, cognitive, and neurotransmitter-related networks, particularly elevated dopamine synthesis capacity[62] and serotonin systems, are consistently implicated.[63] Advanced machine learning and artificial intelligence-driven approaches could prove useful in improving both our biological understanding and clinical management of heterogeneity in bipolar disorder, but these approaches are beyond the scope of this Seminar.[64,65]

Management

Pharmacotherapy and psychotherapy are the most extensively studied treatment options for bipolar disorder. Moreover, chronotherapy and lifestyle interventions play a crucial role in a comprehensive management plan for long-term recovery. Treatment approaches are individualised to meet each person's needs. For female individuals with bipolar disorder, planning for pregnancy and postpartum periods and addressing important issues, such as medication adjustments, childcare, sleep management, and breastfeeding, are important.

Pharmacotherapy

Pharmacological treatments (figure 2) are central to managing bipolar disorder.[5] The International College of Neuropsychopharmacology issued treatment guidelines in 2017, and the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) published their treatment guidelines in 2018 and updated them in 2023.[66] Treatment approaches vary by region due to insurance and government formularies. In North America and Europe, second-generation antipsychotics are common, whereas in Asia, mood stabilisers or first-generation antipsychotics are frequently used to treat bipolar disorder.[3,67]

For acute mania, first-line monotherapy options include lithium, quetiapine, valproate semisodium, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine (ordered per the CANMAT guideline).[66] First-line combination therapies involve lithium or valproate semisodium paired with quetiapine, aripiprazole, risperidone, or asenapine. Combination therapy using antipsychotics with lithium or valproate semisodium is frequently more effective than monotherapy for managing acute mania.[68] Second-line treatments for acute mania include olanzapine, carbamazepine, olanzapine–lithium, olanzapine–valproate, lithium–valproate semisodium, ziprasidone, haloperidol, and electroconvulsive therapy.[66] Third-line options for acute mania comprise carbamazepine or oxcarbazepine in combination with lithium or valproate semisodium, chlorpromazine, clozapine, haloperidol in combination with lithium or divalproex, repetitive transcranial magnetic stimulation (TMS), tamoxifen, and tamoxifen combined with lithium or valproate semisodium. Randomised controlled trials (RCTs) published in 2022 and 2024 showed the efficacy of iloperidone and olanzapine–samidorphan, which offers the advantage of lower weight gain compared with olanzapine in treating bipolar mania.[69,70]

For bipolar depression, olanzapine–fluoxetine, quetiapine, olanzapine, lurasidone, lumateperone, cariprazine, and lamotrigine (ordered on the basis of efficacy in reducing depressive symptoms) have shown statistically significant efficacy in reducing depressive symptoms.[71] Lithium reduces suicidality, prevents mood episode recurrence, and decreases depression-related hospitalisation.[72] Second-line options for bipolar depression

include valproate semisodium, adjunctive selective serotonin reuptake inhibitors (SSRIs), adjunctive bupropion, and electroconvulsive therapy.[66] Despite the low efficacy of antidepressants and the associated risk of mania, antidepressants continue to be prescribed frequently for people with bipolar disorder.[3] Although some evidence supports the safety and effectiveness of SSRIs and venlafaxine monotherapy for treating bipolar II disorder,[73] if an antidepressant is pursued for someone with bipolar I disorder, it should be prescribed alongside a mood stabiliser or second-generation antipsychotic. Treatments with little supporting data and considered third-line in the CANMAT guidelines are carbamazepine and adjunctive treatments including aripiprazole, armodafinil, modafinil, asenapine, ketamine, levothyroxine, light therapy, acetylcysteine, dopamine agonists such as pramipexole, TMS, and serotonin-norepinephrine reuptake inhibitors or monoamine oxidase inhibitors.[66]

For maintenance relapse prevention, lithium, quetiapine with or without valproate semisodium or lithium, valproate semisodium, lamotrigine, asenapine, and aripiprazole with or without valproate semisodium or lithium are first-line options.[66] Olanzapine, risperidone long-acting injectable, carbamazepine, paliperidone, lurasidone with adjunctive lithium or valproate semisodium, and ziprasidone with adjunctive lithium or valproate semisodium are considered second-line treatments. Little long-term data that compare long-acting injectables to oral second-generation antipsychotics in bipolar disorder are available. Comparative effectiveness studies of valproate semisodium that examined serum concentrations suggest that a valproate serum concentration between 50 µg/mL and 74 µg/mL is optimal for reducing or preventing mood episodes during maintenance treatment.[74]

In mixed states, treatment options include mood stabilisers and second-generation antipsychotics, whereas lithium might not be as effective and antidepressants are avoided.[26,66] Treatment options include aripiprazole, asenapine, carbamazepine, cariprazine, valproate semisodium, iloperidone, lumateperone, olanzapine, olanzapine–samidorphan, quetiapine, adjunct risperidone, and ziprasidone. Lurasidone is considered a second-line option for depression with mixed states.[26] Antidepressants or stimulants require dose reduction or discontinuation, whereas mood stabilisers need optimisation. Electroconvulsive therapy is a key option for people with severe mixed states.

Often, the decision to choose between a mood stabiliser and a second-generation antipsychotic depends on the side-effect profile and patient preference. Lithium requires regular monitoring due to thyroid and kidney risks, whereas second-generation antipsychotics can cause metabolic syndrome, diabetes, and movement disorders. Valproate semisodium is associated with teratogenicity, intellectual disability, and behavioural disorders in the offspring of mothers taking this medication, as well as risks of sexual dysfunction, infertility in male individuals, and neurodevelopmental issues in the offspring of male individuals taking this medication. The UK's Medicines and Healthcare products Regulatory Agency recommends avoiding initiating valproic acid in individuals younger than 55 years unless the condition is treatment-refractory and documented by two specialists.[75] A network meta-analysis evaluating the metabolic effects of mood stabilisers and second-generation antipsychotics found that risperidone ranked first in terms of increasing fasting serum glucose and serum insulin, whereas olanzapine ranked first in elevating serum total cholesterol, triglycerides, and low-density lipoprotein.[76] Lumateperone, olanzapine, and quetiapine were associated with higher odds of sedation compared with placebo. Another network meta-analysis comparing US Food and Drug Administration-approved medications for bipolar depression found that, compared with placebo, lurasidone, olanzapine, quetiapine, and cariprazine, lumateperone is associated with a significantly lower risk of clinically significant weight gain (≥7%). Notably, lurasidone did not differ significantly from placebo.[77]

Psychosocial interventions

Psychotherapy is a crucial component of bipolar disorder treatment. Consensus guidelines[78,79] recommend

Mania	Mixed	Depression	Maintenance
• Aripiprazole • Asenapine ± lithium or valproate • Carbamazepine • Cariprazine • Chlorpromazine • Divalproex • Haloperidol • Lithium • Olanzapine ± lithium or valproate • Olanzapine–samidorphan • Quetiapine ± lithium or valproate • Risperidone • Ziprasidone	• Aripiprazole • Asenapine • Carbamazepine • Cariprazine • Divalproex • Olanzapine • Olanzapine–samidorphan • Quetiapine • Risperidone ± lithium or valproate • Ziprasidone	• Cariprazine • Lamotrigine • Lithium • Lumateperone • Lurasidone ± lithium or valproate • Olanzapine–fluoxetine • Quetiapine • SSRI or bupropion*	• Aripiprazole ± lithium or valproate • Asenapine • Lamotrigine • Lithium • Olanzapine • Olanzapine–samidorphan • Quetiapine ± lithium or valproate • Risperidone long-acting injectable • Valproate • Ziprasidone ± lithium or valproate

Figure 2: **Pharmacotherapeutic treatments for bipolar disorder**
Dexmedetomidine (sublingual) and loxapine (inhaled) are used for the rapid treatment of agitation. SSRI=selective serotonin reuptake inhibitor. *Used as an adjunct with a mood stabiliser (second-line agent).

four evidence-based (ie, supported by meta-analyses or a replicated double-blind RCT that includes a placebo or active control comparison with ≥30 participants in each group) psychosocial interventions for bipolar disorder, administered adjunctive to pharmacotherapy: psychoeducation, cognitive behavioural therapy (CBT), family-focused therapy (FFT), and interpersonal and social rhythm therapy (IPSRT; figure 3). Psychoeducation helps individuals to self-manage, better understand bipolar disorder, and adhere to pharmacotherapy. CBT encourages patients to challenge negative thought patterns and develop more adaptive behaviours. IPSRT addresses disturbances in relationships and circadian rhythms by encouraging individuals to improve interpersonal communication and develop more regular daily routines. FFT, administered conjointly with family members or partners, uses a skills-based approach to help families communicate more effectively and acquire better tools for managing bipolar disorder.

CBT, IPSRT, and FFT are considered evidence-supported treatments for acute depression; CBT, IPSRT, FFT, and psychoeducation are indicated for maintenance treatment.[79] Effect sizes, as estimated by a meta-analysis, are modest and range from 0·2 (for depression symptom reduction) to 0·7 (for risk of relapse).[80] Thus, psychotherapy is most effective in terms of prevention of recurrences, contributing to an approximately 50% reduction in relapse risk.[81] Psychoeducation, CBT, IPSRT, and FFT are all indicated for use in euthymic patients to prevent future episodes, whereas CBT, IPSRT, and FFT (but not psychoeducation) can be used for individuals with syndromal depression to hasten recovery from depressive episodes, or in euthymic patients to prevent relapse and recurrence. No studies show superiority of one modality over another. Other therapeutic modalities (eg, short-term psychodynamic therapy, peer support, mindfulness-based cognitive therapy, dialectal behaviour therapy, and cognitive remediation) have been explored as treatments for bipolar disorder but do not have adequate empirical support to recommend them unequivocally at present.[78,79] Nevertheless, these modalities can be considered emerging treatments that merit more study.

As very few studies have compared specific psychotherapies to each other, recommending one modality over another is not feasible. Systematic reviews suggest considerable overlap in treatment approaches across therapies.[82] A network meta-analysis published in 2021 evaluated active ingredients (ie, components) of bipolar-specific psychotherapies and found that cognitive restructuring, regulating daily rhythms, and communication training were most effective for reducing depression severity. Delivery of therapy in a family format and encouraging patients to monitor prodromal symptoms were associated with lower recurrence rates compared with delivery via other formats (eg, individual therapy) and other treatment strategies.[81] Figure 3 summarises types of strategies used in each psychotherapy.

Despite its benefits, many people are unable to access bipolar-specific psychotherapy. In this situation, the Japanese Society of Mood Disorders guidelines recommend receiving psychoeducation focusing on the so-called minimal essentials, which are the common factors of bipolar-specific psychotherapies.[83] Technology-enabled interventions can help expand the reach of bipolar-specific psychotherapy by facilitating self-management strategies. Early studies have identified several facilitators, such as focused interventions addressing patient needs, simple digital interfaces, and support from humans, and have also noted barriers such as the complexity of interventions and discomfort with self-reflection.[84] Overcoming these barriers should facilitate more research. Digital self-management strategies are used by more than 40% of individuals diagnosed with bipolar disorder.[85] Commonly used self-management strategies include mood monitoring, psychoeducation about bipolar disorder, regulating routines (including sleep schedules), developing plans for maintaining wellness

Strategies	Evidence-supported psychotherapies				Self-management
	Cognitive behavioural therapy	Psychoeducation	Family-focused therapy	Interpersonal and social rhythm therapy	
Cognitive restructuring	×				
Daily rhythms regulation				×	×
Communication training			×	×	
Mood monitoring	×	×	×	×	×
Relapse prevention planning	×	×	×	×	×
Sleep–wake cycle regulation	×	×		×	×
Illness psychoeducation	×	×	×	×	×
Medication adherence support	×	×	×	×	
Instilling hope					×

Figure 3: **Bipolar-specific therapeutic strategies**

and crisis intervention, and maintaining hope.[86] Despite little evidence from RCTs, these approaches are widely used and perceived as helpful by many living with bipolar disorder (figure 3).

Chronotherapy and lifestyle interventions

Chronotherapy plays a crucial role in bipolar disorder, particularly in managing bipolar depression. Bright light therapy, which typically delivers 7000–10 000 lux in the morning, is a promising treatment approach for bipolar depression.[87] A 2018 RCT showed the efficacy of adjunctive midday bright light therapy using a lightbox with 7000 lux intensity between noon and 1430 h for 45–60 min daily, without increasing the risk of treatment-emergent affective switching.[88] Data from 2023 provide preliminary evidence for the use of light therapy in managing irritability in bipolar depression.[89] Partial wake therapy combined with light therapy has shown effectiveness in people with bipolar depression;[90] however, it poses a risk of affective switching and necessitates careful monitoring to ensure safety. Preliminary evidence suggests that blue-spectrum-light-blocking glasses used in the evening might serve as an adjunctive treatment for acute mania.[91]

From a lifestyle intervention standpoint, a 2023 meta-analysis found that combined diet and physical activity interventions (consisting of a CBT-based approach focusing on nutrition psychoeducation and improving food choices, promoting moderate-intensity exercise [5 days per week, 30 min per day], and enhancing problem-solving skills) and sleep interventions (eg, modified CBT for insomnia) led to statistically significant improvements in depressive symptoms.[92] Regulating sleep–wake cycles, limiting stimulants, and managing disruptions such as shift work are crucial for mood stability in people with bipolar disorder. Seasonal mood changes are common and frequently include depression in autumn and winter and hypomania and mania in spring and summer. Maintaining circadian rhythm and good sleep hygiene supports wellbeing. Social rhythm therapy, a component of IPSRT focused on helping individuals develop regular daily routines, has evidence of efficacy[93] and has been used as a self-help intervention.[94]

Neuromodulation (electroconvulsive treatment and transcranial magnetic stimulation)

Electroconvulsive therapy is highly effective for treatment-resistant bipolar depression and severe mixed states, but its use is infrequent due to stigma from both patients and clinicians.[95] Electroconvulsive therapy is typically considered after pharmacotherapy does not work or in cases of catatonia unresponsive to benzodiazepines. An RCT that compared right unilateral electroconvulsive therapy with pharmacological treatment in participants with treatment-resistant bipolar depression (n=73) showed that the electroconvulsive therapy was significantly more effective, with a response rate of 73·9% versus 35·0% for pharmacotherapy (p=0·01).[96] A 2021 meta-analysis of 12 studies from Asia (n=863) found that electroconvulsive therapy combined with medication outperformed medication alone for acute mania after just 3–5 electroconvulsive therapy sessions, with a standardised mean difference of −3·5 (95% CI −4·6 to −2·4; p<0·0001).[97] Large Swedish registry studies have shown response rates of 80·2% for bipolar depression (n=1251) and 84% for mania (n=571).[98,99] The ISBD guidelines recommend electroconvulsive therapy as a second-line treatment for mania and depression.[79] In unipolar depression, increased treatment resistance was found to be a poor predictor for response, suggesting that electroconvulsive therapy should be offered sooner rather than as a last-resort option.[100]

Regarding repetitive TMS, a meta-analysis studying mania (n=102) and a systematic review studying bipolar depression (of 24 studies with mean sample size of 22) showed that available findings were non-significant or from very small samples.[101,102] Although TMS response rates are variable, a meta-analysis of 19 studies (n=181) found no significant difference in the risk of affective switching between active TMS and placebo (0·9% *vs* 1·3%) in participants with acute bipolar depression.[103] More adequately powered placebo-controlled studies are required to verify the efficacy of TMS.

Special issues

Suicide

For people with bipolar disorder, the highest cause-specific elevated risk of premature mortality is seen for death by suicide.[104] Comprehensive suicide prevention is a complex endeavour that requires widespread interventions across society and health-care ecosystems.[105] This endeavour might seem daunting clinically; however, key new approaches provide more options for clinicians and patients in terms of suicide prevention. Although strong risk factors, such as a history of suicide attempts and depressive or mixed mood state, have been identified, knowledge of suicide prediction is still insufficient to more effectively prevent suicide.[106] Many people with bipolar disorder who die by suicide are not considered to be at high risk at the time of their last clinical encounter.[107] These findings support the importance of emphasising suicide prevention efforts for all people with bipolar disorder, irrespective of perceived risk status.[108]

What is considered to be an anti-suicide intervention in bipolar disorder is also shifting. Historically, much of the emphasis was placed on the role that lithium can play, especially due to putative suicide-preventive effects independent of mood stabilisation.[109] Although lithium remains a first-line mood stabiliser and can be foundational for suicide prevention, more general approaches should also be considered[110] in addition to the delivery of the usual evidence-based pharmacological and psychotherapeutic approaches. These approaches include structured universal screening for suicidal

thoughts and behaviours,[111] conducting a safety planning intervention,[112] delivering caring contacts (ie, messages sent to patients following discharge from acute care settings, which express support, provide reminders of coping strategies, link to resources, and invite returning to hospital if needed) after acute care interactions,[113] ensuring access to care during high-risk transitions,[114] and limiting access to means of suicide.[115] Because of the nature of these interventions, all interprofessional care providers can and should play a role, and the need to implement systems of care that incorporate anti-suicide interventions for all people with bipolar disorder across varied care settings should be emphasised.

Female populations

Female individuals with bipolar disorder have an increased likelihood of having depressive episodes and developing thyroid disorders compared with male individuals with bipolar disorder, and can be affected by interactions between psychotropic drugs and oral contraceptives, which necessitates careful monitoring. In female individuals with bipolar disorder, some phases of life, such as menarche, peripartum, postpartum, perimenopause, and postmenopause, carry a higher risk of mood instability. Data from 2024 indicate that perimenopause is a high-risk period for the first episode of mania, with rates of first-onset mania returning to premenopause rates during the postmenopause phase.[116] Understanding of the role of hormone replacement therapy in bipolar disorder is still evolving. Interest in understanding bipolar disorder during the menopausal transition is growing, but despite clear evidence of clinical worsening during this life stage, effective symptom management remains poorly understood.[117]

Additionally, the postpartum period is another high-risk phase. In female individuals with bipolar disorder, the risk of postpartum relapse (hypomania or mania, depression, or mixed states) is 39% (95% CI 29–49).[118] Relapse rates are more than double in studies without medication use, with 58·1% relapse in those without medication compared with 25·9% in those with medication use ($p=0·04$).[118] Female individuals with bipolar disorder are often advised to continue taking mood stabilisers during pregnancy and postpartum, except for valproic acid due to it leading to a high risk of birth defects.[119] Lithium is usually recommended despite a slight increase in fetal cardiac abnormality risk during the first trimester.[119] Clinicians should monitor mood during pregnancy and the peripartum period, involve a perinatal psychiatrist, educate their patients about relapse risks, and discuss breastfeeding and sleep management. Shared decision making is essential during peripartum and postpartum care.

Cognition

Cognitive dysfunction affects 50–70% of people with bipolar disorder and impacts psychosocial functioning and quality of life, making it an important treatment target independent of affective symptomology.[120,121] Cognitive functioning is heterogeneous in people with bipolar disorder, with substantial evidence pointing to the idea that three subgroups of these individuals exist: a subgroup of people with typical or even above-average cognition, a subgroup with mild-to-moderate impairments, and another subgroup with more substantial deficits.[122,123] In addition to deficits across traditional cognitive measures, performance of tasks of emotional and social cognition, especially tasks of facial emotion recognition and implicit emotion regulation, is impaired in many people with bipolar disorder.[124] Impaired reward processing and affective decision making (non-emotional cognition) are more closely associated with affective episodes, whereas trait-related impairments include facial expression recognition and implicit emotion regulation (emotional cognition).[124]

Factors that contribute to cognitive impairment in bipolar disorder include sleep problems,[125] comorbid substance use disorder,[126] cardiovascular burden, sedative use, use of high dose antipsychotics, anticholinergic medication burden, and frequent episodic recurrence. In terms of brain circuitry, cognitive impairment in bipolar disorder is accompanied by hypoactivity in the frontoparietal cognitive control network and hyperactivity in the default mode network.[57] Inflammation might play a key role in cognitive impairment in bipolar disorder. The neuroprogression model suggests that recurrence of episodes, especially acute mania, affects brain structure and function.[127] Studies show elevations in inflammation markers such as C-reactive protein and TNF[128] and decreases in neurotrophic factors such as brain-derived neurotrophic factor during severe episodes. Early in the disorder, these biomarkers stabilise during remission, but later-stage bipolar disorder shows chronic inflammation even during euthymia. This finding suggests that inflammation correlates with cognitive changes in bipolar disorder, making it a promising target for prevention and intervention efforts.[129]

Strategies to mitigate cognitive impairment are to optimise physical health, treat somatic comorbidities, avoid high doses of antipsychotics, minimise sedative use, reduce anticholinergic burden, address comorbid substance use disorder, focus on sleep management, and encourage physical activity. Although cognitive remediation strategies have proven effective in treating cognition in bipolar disorder, their effect on improving psychosocial functioning is uncertain;[130] however, data from 2024 suggest that cognitive reserve might protect against cognitive decline if targeted early in the disorder.[131]

Ageing

Older-age bipolar disorder (OABD) is used for individuals aged 50 years and older who have been diagnosed with bipolar disorder. Despite the increasing prevalence of

OABD, research in this area remains scarce, which hinders the development of evidence-based guidelines tailored to the specific needs of this population.[132] OABD is characterised by cognitive deficits[133], an increased risk of dementia,[134] impaired psychosocial functioning,[135] frequent physical comorbidities,[136,137] and premature mortality.[138,139] Several factors associated with ageing additionally negatively influence outcomes in OABD, including shrinking social networks, loss of support from friends and family, lifestyle choices, reduced mobility, and other age-related challenges.

The Global Aging & Geriatric Experiments in Bipolar Disorder project showed that people with OABD have more physical morbidities compared with matched control participants,[140,141] with women bearing a statistically significantly higher health burden.[142] Additionally, lower functioning in OABD was linked more closely to a higher number of depressive and manic symptoms than to the elevated somatic burden.[143] These findings highlight the urgent need for integrated care approaches in the management of bipolar disorder.

Cognitive impairment in OABD is particularly pronounced in the domains of verbal learning and delayed memory[144] and occurs more frequently than in major depressive disorder or in healthy control participants.[145] The severity of bipolar disorder and medication use are key determinants of cognitive dysfunction.[146] Follow-up studies have identified three distinct cognitive trajectories in bipolar disorder that need conformation in OABD: typical ageing (32–38%), selective impairment (28–45%), and a progressive course leading to dementia (18–40%).[147,148]

For individuals with bipolar disorder, the presence of somatic and cognitive comorbidities impedes daily functioning and limits treatment options. Whether these comorbidities are intrinsic to bipolar disorder or are a consequence of lifestyle choices and medication use remains unclear. Future longitudinal studies comparing people with bipolar disorder with neurotypical peers or people with bipolar disorder who are not on maintenance medication are necessary to provide more insight.

Substance use disorder

Epidemiological studies report a 30–60% lifetime prevalence of developing any substance use disorder for people bipolar disorder;[3] alcohol use disorder is the most prevalent.[149] A meta-analysis showed that among people with bipolar disorder, the alcohol use disorder rate is 42% and the rate of cannabis use disorder is 20%. Other disorders include those relating to use of cocaine (seen in ~12·5% of people with bipolar disorder), amphetamine (~6%), and opiates (~6%).[150] High rates of alcohol use disorder (70%) and cannabis use disorder (39%) are reported in people with bipolar disorder seeking treatment.[151] Co-occurring substance use disorder has multiple potential causes, including shared neurobiological factors, such as impaired cognitive control[152,153] and reward processing.[154] The self-medication hypothesis suggests substances might be used to reduce symptoms or enhance mood, but evidence is scarce.[155,156]

Co-occurring substance use disorder has been linked to a worse symptom trajectory (earlier age of onset, more depressive episodes, decreased recovery time, rapid cycling, greater inter-episodic affective instability, and higher rates of suicide attempts) and worse psychosocial functioning compared with bipolar disorder without substance use disorder.[157] In addition, new research suggests that alcohol use increases the risk of future depressive and hypomanic or manic symptoms,[155] highlighting the need for ongoing monitoring of and attention to alcohol use in bipolar disorder treatment regardless of substance use disorder diagnostic status.

Treating co-occurring substance use disorders is challenging and requires integrated treatments. Few RCTs on this topic exist, but the CANMAT taskforce published recommendations for managing alcohol, cannabis, and cocaine abuse and dependence in bipolar disorder.[158] Naltrexone 50 mg daily can reduce alcohol use and cravings.[158] Mood stabilisers such as valproate semisodium, carbamazepine, and gabapentin can help with alcohol withdrawal.[158] Adding valproic acid to lithium has been shown to reduce heavy drinking days and delay relapse in bipolar I disorder and alcohol use disorder.[159] Evidence for valproic acid or lithium in cannabis use disorder and stimulant use disorder is weak.[158] Integrated group therapy, consisting of 12 sessions, addresses dual diagnosis, promoting abstinence, medication adherence, symptom recognition, skill development, and relapse prevention.[158] More RCTs are urgently needed for individuals with co-occurring substance use disorder.

Experts by experience

Clinicians often prioritise eliminating symptoms in bipolar disorder treatment, whereas people with lived experience of bipolar disorder emphasise building a meaningful life despite their symptoms.[160] Treatment plans should align with each individual's self-identified goals. The experience of personal recovery in bipolar disorder from the perspective of people with lived experience was summarised in the following framework: Purpose and Meaning, Optimism and Hope, Empowerment, Tensions, Identity, Connectedness.[161] Tensions refers to the conflicts inherent in living with bipolar disorder, such as balancing acceptance with ambition, opposing goals surrounding disclosure, and ambivalence about hypomania. A range of self-management strategies, including sleep regulation, mood monitoring, and peer support, can enhance an individual's ability to live well with bipolar disorder.[162,163] Resources for these strategies are available through organisations such as the Depression and Bipolar Support Alliance, Bipolar UK, and The German Society for Bipolar Disorders; clinicians should encourage use of these and similar resources. Stigma and self-stigma negatively affect people

with bipolar disorder[164] and correlate with poorer functioning,[165] worse depressive symptoms,[166] and diminished quality of life compared with people without bipolar disorder.[167] Development of anti-stigma initiatives and interventions should be a priority. In the past 10 years or so, research initiatives around the globe have been shifting towards coproduction with people with lived experience and stakeholder involvement at every step, from identifying research questions in priority-setting partnerships (such as the James Lind Alliance) to selecting patient-reported outcome measures and disseminating results within the lived experience community. These efforts should be continued and expanded.

Challenges and future developments

Little funding and insufficient understanding about pathophysiology have substantially restricted research on treatment options for bipolar depression. Recognising hypomania and mixed states, improving diagnosis, and reducing treatment delays are key clinical challenges. In addition, individuals with bipolar disorder often face high treatment non-adherence, suboptimal care, and major barriers such as non-specialist care and lack of continuity. Although ongoing maintenance treatment for individuals with bipolar disorder is recommended by all current treatment guidelines, some investigators have begun to wonder whether indefinite treatment is needed for all individuals. Well designed longitudinal studies are needed to evaluate this intriguing (if preliminary) concept. To improve treatment outcomes and maintain continuity, a collaborative care approach is essential. Integrating lifestyle interventions and self-management is key.[83,94]

Pro-cognitive treatments for the 50–70% of people with bipolar disorder who have persistent cognitive impairment are urgently needed. Advancing cognition-targeted therapies is essential for enhancing daily functioning and improving the quality of life for these individuals. Treatment resistance or refractoriness is commonly observed in bipolar disorder, with many people with the disorder struggling with subsyndromal symptoms that contribute to functional impairment.[95] Although a universally accepted definition is unavailable, an international panel of bipolar disorder experts defined treatment-resistant bipolar depression as not reaching sustained remission after at least two adequate treatment trials, each lasting a minimum of 8 weeks at therapeutic doses with acceptable adherence.[95] These adequately dosed pharmacological treatments should involve monotherapy with quetiapine, lurasidone, lamotrigine, or the olanzapine–fluoxetine combination, or one of these as monotherapy and another in combination with valproate semisodium, lamotrigine, or lithium.[168]

Neuromodulation is a novel therapeutic approach that warrants more investigation, especially for difficult-to-treat depression or treatment-resistant bipolar depression.[169] Most studies have used repetitive TMS targeting the left dorsolateral prefrontal cortex in bipolar depression.[170] Recent studies[171,172] have been exploring accelerated TMS combined with neuronavigation, which allows precise targeting and multiple treatment sessions per day. This innovation reduces the overall treatment duration and is hypothesised to result in faster response rates. Pilot studies have shown promising results without increasing the rates of treatment-emergent affective switching.[171,172]

With advancements in understanding of glutamatergic and GABAergic neurotransmitter systems, interest in rapid-acting antidepressants has been growing. The N-methyl-D-aspartate receptor antagonists, such as ketamine, esketamine, and dextromethorphan–bupropion, have shown promising results. Racemic intravenous ketamine and intranasal esketamine have been used off-label to treat bipolar depression.[173] Non-randomised studies indicate that single and serial intravenous ketamine infusions might offer promising short-term benefits, with response rates of 53% and remission rates of 38% reported during the acute phase of one clinical trial.[173] Treatment-emergent affective switching has been reported in 2·4% of cases,[173] although long-term data on switching rates with ketamine and esketamine in bipolar disorders remain scarce. RCTs exploring the efficacy of serial ketamine treatments and longitudinal studies assessing long-term outcomes and dose escalation are needed in treatment-resistant bipolar depression research.[174]

Interest in psilocybin and other psychedelics for treating depression has been renewed. A 2024 open-label trial with a small sample size of 15 participants with bipolar-II depression reported significant reductions in depressive symptoms after administering 25 mg of psilocybin alongside psychological support;[175] however, concerns regarding unmasking, lack of placebo, and risk of affective switching with psilocybin use in bipolar disorder highlight the need for cautious optimism and more rigorous investigation.[176]

Conclusion

Bipolar disorder is a chronic illness with a genetic basis that is associated with high rates of comorbid anxiety, substance use disorders, and cognitive and psychosocial impairment. Cardiovascular comorbidities and overall mortality rates are notably higher than in the general population, highlighting the need for thorough assessment and early intervention to improve long-term outcomes. Suicide rates are elevated among people with bipolar disorder, but new approaches to suicide prevention in this population emphasise the importance of not only evidence-based treatments, but also safety planning, ensuring access to care during high-risk periods, and means restriction.

Mood stabilisers and second-generation antipsychotics are effective treatments for bipolar disorder, with lithium remaining the cornerstone therapy despite the increasing use of second-generation antipsychotics. Psycho-therapeutic interventions are crucial for improving outcomes, with sleep regulation, mood monitoring, and

stigma reduction playing key roles in enhancing the quality of life for individuals with bipolar disorder. Developing anti-stigma initiatives, fostering meaningful collaboration with individuals with lived experience, and engaging these individuals in every step of the process is essential.

Emerging therapies and therapies with renewed interest, including rapid-acting antidepressants such as ketamine and esketamine, accelerated TMS with neuronavigation, GABAergic modulators, and psilocybin, are promising interventions. These novel treatments bring cautious optimism, as their mechanisms and therapeutic roles are fundamentally different from conventional treatments; however, this difference underscores the importance of large-scale investigations that focus on mechanisms and biomarker development to facilitate advancing treatment options and improving patient outcomes with an evidence-based medicine approach.

An integrated, patient-centred approach to treatment fosters collaboration and empowers individuals with bipolar disorder to self-manage their symptoms while optimising their physical and mental health. As individuals often prioritise building a meaningful life even in the presence of symptoms, treatment plans should be tailored to align with each individual's self-identified goals and priorities.

Contributors

BS: conceptualisation, investigation, methodology, project administration, validation of data, preparation of figures and data presentation, writing of the original draft, and review and editing of the manuscript. MAF: conceptualisation, investigation, methodology, project administration, writing of the original draft, and review and editing of the manuscript. HAS: investigation, methodology, project administration, validation, visualisation, writing of the original draft, and review and editing of the manuscript. ABC-B, AS, TK, AD, SHS, ABV, and KEB: investigation, methodology, project administration, validation, writing of the original draft, and review and editing of the manuscript. All authors have read and approved the final submitted manuscript and agree to be accountable for the work.

Declaration of interests

BS has received research grant support from Mayo Clinic, the National Network of Depression Centers, Breakthrough Discoveries for Thriving with Bipolar Disorder (BD2), and the National Institutes of Health. He is a KL2 Mentored Career Development Program scholar, supported by Clinical and Translational Science Award Grant Number KL2TR002379 from the National Center for Advancing Translational Science. He has received honoraria (to the Mayo Clinic) from Elsevier for editing a clinical overview on treatment-resistant depression. HAS has received honoraria from or consulted for Intracellular Therapies, Physician Postgraduate Press, Medscape and WebMD, Mediflix, and Clinical Education Alliance. AS has received support from an Academic Scholars Award, Sunnybrook Health Sciences Centre, and the University of Toronto, and has received honoraria from AbbVie, Lundbeck, and Otsuka. KEB has received honoraria from BD2 and as a scientific advisory board member for Merck, Alto Neuroscience, and Suven Life Sciences. MAF has received grant support from Assurex Health, the Mayo Foundation, and BD2, has received CME travel support and honoraria from Carnot Laboratories and American Physician Institute, and financial interest in, stock ownership in, or royalties from Chymia. All other authors declare no competing interests.

Acknowledgments

This publication was supported by Clinical and Translational Science Award Grant Number KL2 TR002379 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. We would like to sincerely thank Larry J Prokop for conducting a comprehensive literature search for the Seminar. We would like to thank Trisha Suppes for her help and support with the Seminar. During the preparation of this work, the authors used open AI ChatGPT 3.5/4 to edit and condense text. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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