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Review

Cognitive Behavioural Therapy as an Adjunct to Pharmacotherapy in Bipolar Disorder: A Systematic Review of Treatment Outcomes and Relapse Prevention

Terapi Perilaku Kognitif Sebagai Pelengkap Farmakoterapi pada Gangguan Bipolar: Tinjauan Terhadap Hasil Perawatan dan Pencegahan Kekambuhan

Adeline C Phelps[1*], Hendsun Hendsun[2], Ernawati Ernawati[3]
[1]Faculty of Medicine, Tarumanagara University, Jakarta, Indonesia
Letjen S. Parman St No. 1, RT.6/RW.16, Tomang, Grogol Petamburan, West Jakarta City, Jakarta 11440, Indonesia
[2]Zhejiang Chinese Medical University, Hangzhou, China
[3]Department of Public Health, Faculty of Medicine, Tarumanagara University, Jakarta, Indonesia

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Abstract

Bipolar disorder is a chronic psychiatric condition characterized by recurrent mood episodes and significant functional impairment. Although pharmacotherapy remains the primary treatment, relapse rates remain high, highlighting the need for effective adjunctive interventions. This study aimed to synthesize evidence on the effectiveness of Cognitive Behavioural Therapy (CBT) as an adjunct to pharmacotherapy in improving treatment outcomes and preventing relapse in bipolar disorder. A literature review was conducted using PubMed, Scopus, and ScienceDirect, identifying 30 eligible studies published between 2013 and 2023. Most included studies employed randomized controlled trials and quasi-experimental designs. Of the 30 studies, 22 reported statistically significant improvements ($p < 0.05$) in patients receiving CBT in addition to pharmacotherapy. Synthesized findings indicate that CBT contributes to reductions in depressive symptoms, improved cognitive and psychosocial functioning, and enhanced emotional regulation. Several studies also demonstrated neurobiological changes, particularly in prefrontal and limbic connectivity. Studies with structured CBT protocols (8–20 sessions) and adequate duration showed more consistent benefits. However, variability in outcomes was observed due to differences in study design, sample size, and intervention protocols. Overall, CBT appears to be an effective adjunctive therapy in bipolar disorder, particularly when delivered in a structured and sustained manner.

Keywords*: bipolar; disorder; CBT; conventional; therapy.*

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Introduction

Bipolar disorder is a long-term psychiatric illness characterized by repeated episodes of mood elevation (mania) and depression, which can substantially disrupt social functioning, daily activities, and overall quality of life. Despite pharmacotherapy being the primary approach in managing bipolar disorder, a considerable proportion of patients continue to experience persistent symptoms and recurrent episodes even with appropriate medication adherence. These limitations emphasize the importance of developing additional therapeutic strategies to enhance sustained recovery and improve long-term clinical outcomes.[1-5]

Among various psychological interventions, cognitive behavioural therapy (CBT) has gained increasing attention as an adjunctive approach for bipolar disorder management. CBT focuses on identifying and restructuring dysfunctional cognitive patterns while strengthening emotional regulation skills. Emerging evidence suggests that CBT may provide benefits beyond symptom management, including improvements in cognitive performance, psychosocial functioning, and alterations in neural mechanisms associated with emotional processing.[6-9]

Nevertheless, findings regarding the effectiveness of CBT in bipolar disorder remain inconsistent across studies. While several investigations have reported meaningful therapeutic effects, others have shown minimal or statistically insignificant improvements. Such discrepancies may be attributed to methodological variations, including differences in study populations, sample sizes, intervention duration, and the specific structure of CBT programs applied. In addition, previous reviews have frequently examined limited outcomes, such as relapse prevention or reduction of depressive symptoms, rather than integrating broader clinical and neurobiological perspectives. Therefore, a comprehensive evaluation that combines evidence from multiple domains is required to clarify the overall role of CBT as an adjunctive intervention alongside pharmacological treatment for bipolar disorder. This review aims to analyze recent evidence regarding the effectiveness of CBT in enhancing treatment outcomes and reducing relapse risk among individuals with bipolar disorder, while exploring potential factors contributing to differences in treatment responses.

Bipolar Disorder

Bipolar disorder (BD) is a chronic psychiatric condition characterized by repeated episodes of mania and depression, with onset commonly occurring during late adolescence or early adulthood and persisting across the lifespan. Data from the World Mental Health (WMH) Survey Initiative, which collected epidemiological information from multiple regions including the Americas, Europe, and Asia, estimated that the lifetime prevalence of BD (including bipolar I

and bipolar II disorders) among adults aged ≥18 years varies between 0.1% and 2%. The average lifetime prevalence has been estimated at approximately 0.6% for bipolar I disorder and 0.4% for bipolar II disorder. Among high-income countries included in the survey, the United States demonstrated the highest prevalence (2.1%), whereas Japan reported the lowest prevalence estimates, ranging from 0.09% to 0.27%. Differences in prevalence have also been observed across racial and ethnic groups, with reported rates of 3.3% among White populations, 3.5% among Black populations, 3.1% among Hispanic populations, 6.2% among Native American populations, and 2.0% among Asian populations. However, these estimates may not fully reflect the actual burden of the disorder due to challenges in diagnosis and the possibility of misclassification with other psychiatric conditions.

BD is associated with substantial variations in mood, energy, and activity levels, which may lead to impaired social functioning, reduced occupational performance, and increased hospitalization risk. The likelihood of suicide is also elevated, particularly when BD occurs alongside other psychiatric or medical comorbidities. Without appropriate intervention, the functional limitations associated with BD can create significant socioeconomic consequences for both affected individuals and the wider community. Evidence indicates that individuals with BD frequently experience difficulties in maintaining interpersonal relationships, completing educational goals, and sustaining employment, resulting in reduced quality of life even during euthymic phases. Importantly, depressive episodes often contribute to equal or greater impairment in daily functioning, social interactions, and occupational performance compared with manic or hypomanic episodes.[10]

Bipolar disorder involves recurrent periods of extreme emotional changes that influence mood, energy, behaviour, and overall functioning. These episodes, known as mood episodes, may last from several days to weeks depending on their severity and clinical presentation. Episodes involving elevated, expansive, or irritable mood are categorized as manic or hypomanic episodes, whereas periods characterized by persistent sadness, diminished interest, or loss of pleasure are identified as depressive episodes. Between episodes, some individuals may experience periods of stable mood and normal functioning. With appropriate treatment and continuous management, individuals with BD can achieve improved functioning and maintain productive lives. Although mood fluctuations may occur in the general population, these changes are usually short-lived and do not cause the severe behavioural disturbances or functional impairment commonly observed in BD. In contrast, bipolar episodes can significantly interfere with social relationships, academic achievement, and occupational responsibilities.[1]

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BD consists of three major clinical categories: bipolar I disorder, bipolar II disorder, and cyclothymic disorder. Genetic susceptibility plays an important role in the development of BD, as approximately 80–90% of affected individuals have a family history of bipolar disorder or depressive disorders among close relatives. However, genetic vulnerability alone does not determine disease onset, as environmental factors such as psychological stress, disrupted sleep patterns, and substance use may contribute to triggering mood episodes in predisposed individuals. Although the underlying mechanisms of BD remain incompletely understood, current evidence suggests that interactions between biological factors—including genetic background, history of mood or psychotic disorders, and substance misuse—and environmental exposures contribute to disease risk. The disorder most commonly emerges during the mid-20s, and individuals with bipolar I disorder frequently experience additional psychiatric conditions, including anxiety disorders, substance-related disorders, and attention-deficit/hyperactivity disorder (ADHD). Furthermore, bipolar I disorder is associated with a substantially increased risk of suicide compared with the general population.[1]

Bipolar Type-I Disorder

Bipolar I disorder is diagnosed when an individual experiences at least one manic episode. This condition is characterized by a distinct period of abnormally elevated, expansive, or irritable mood accompanied by a marked increase in energy and activity levels. Although manic episodes are the defining feature of bipolar I disorder, individuals may also experience depressive episodes, hypomanic episodes, or intervals of relatively stable mood. A manic episode is typically defined as a period of at least one week in which an individual demonstrates persistent mood elevation or irritability occurring most of the day, nearly every day, along with increased energy or goal-directed activity.

During a manic episode, the individual must experience several associated behavioural or cognitive changes, including a decreased need for sleep despite feeling energetic with significantly reduced sleep duration, increased talkativeness or pressured speech, rapid and excessive flow of thoughts, difficulty maintaining attention due to distractibility, heightened involvement in activities or increased psychomotor activity, and engagement in impulsive or high-risk behaviours such as excessive spending, unsafe driving, or inappropriate sexual activities. These symptoms represent a clear deviation from the individual's typical personality and are usually noticeable to people around them, including family members, friends, or colleagues.

The severity of manic symptoms must result in significant functional impairment, affecting occupational performance, interpersonal relationships, or social responsibilities. In

severe cases, hospitalization may be required to ensure the safety of the individual or others. Some individuals experiencing severe mania may also develop psychotic symptoms, including impaired thought organization, delusions, or hallucinations.

In contrast, hypomanic episodes involve similar but less severe manifestations of mood elevation and increased activity. Hypomania is defined as a period of at least four consecutive days with elevated, expansive, or irritable mood accompanied by increased energy, but the symptoms generally do not cause substantial impairment in social or occupational functioning and do not require hospitalization.

Individuals with bipolar I disorder may also experience major depressive episodes, which involve a minimum duration of two weeks marked by persistent depressed mood, feelings of hopelessness, or a significant reduction in interest or pleasure in previously enjoyable activities. These episodes are accompanied by additional symptoms, including excessive feelings of guilt or worthlessness, reduced energy or fatigue, disturbances in sleep patterns, changes in appetite or weight, psychomotor agitation or retardation, impaired concentration or decision-making ability, and recurrent thoughts related to death or suicide. These symptoms must represent a significant change from the individual's usual functioning and contribute to clinically meaningful distress or impairment in daily activities.[1]

Bipolar Type-II Disorder

Bipolar II disorder is diagnosed when an individual has experienced at least one major depressive episode and at least one hypomanic episode, without a history of a full manic episode. During periods between mood episodes, many individuals with bipolar II disorder may regain their usual level of functioning. However, depressive episodes are often the primary reason individuals seek clinical attention, as hypomanic states are frequently viewed positively by patients due to increased productivity, elevated mood, or enhanced performance in academic and occupational activities.

Individuals with bipolar II disorder commonly experience additional psychiatric comorbidities, particularly anxiety disorders and substance use disorders. The presence of these conditions may contribute to greater symptom severity, increased functional impairment, and a more complicated clinical course involving both depressive and hypomanic symptoms.[1]

Rowland and Marwaha (2018) conducted a comprehensive review exploring demographic, genetic, and environmental factors associated with the development of bipolar disorder. Their review focused on recent advances in understanding risk factors and examined the contribution of environmental influences in triggering or modifying disease vulnerability.

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Relevant literature was identified through searches of databases including PubMed and PsycINFO using combinations of keywords related to "bipolar disorder," "risk factors," and "epidemiology." The authors prioritized recent evidence from systematic reviews and large-scale prospective studies, followed by additional focused searches addressing individual categories of identified risk factors. A synthesis of evidence regarding specific risk factors associated with bipolar disorder was subsequently summarized in Table 1.[11]

Table 1 Summary of Research Related to Specific Bipolar Disorder Risk Factors

Study	Risk factor examined	Design	n (participants/studies)	Main findings summary
Genetics				
Craddock and Jones	Familial genetic risk	Review	8 studies	Risk of bipolar in first-degree relatives: OR = 7 (95% CI 5–10)
			6 studies	Monozygotic concordance: 50% (95% CI 40–60%)
Psychiatric GWAS Consortium Bipolar Disorder Working Group	Multiple SNPs	Case-control GWAS data	11,974 bipolar patients; 51,792 controls	Association at rs4765913 (CACNA1C) and rs12576775 (ODZ4)
Fan and Sklar	BDNF Val66Met polymorphism	Meta-analysis	14 studies	OR = 1.13 (95% CI 1.04–1.23)
Cho *et al.*	5-HTTL polymorphism	Meta-analysis	17 studies	OR ≈ 1.12 for both polymorphisms
Aas *et al.*	Gene–environment (trauma + BDNF)	Cross-sectional	141 bipolar patients	Trauma + Met allele → Lower BDNF mRNA
Oliveira *et al.*	TLR2 + early-life stress	Cross-sectional	531 bipolar patients	TT genotype + abuse → earlier onset
Oliveira *et al.*	TLR2 + *T. gondii*	Case-control	138 bipolar; 167 controls	There is an interaction (p = 0.017)
Hosang *et al.*	COMT + stress	Case-control	482 bipolar; 205 controls	Stress moderated by COMT genotype
De Pradier *et al.*	5-HTTLPR + cannabis + abuse	Case-control	137 bipolar patients	Polymorphism + cannabis ↑ psychotic symptoms
Prenatal & perinatal factors				
Barichello *et al.*	Perinatal infections	Systematic review	23 studies	Mixed Evidence
Sutterland *et al.*	*T. gondii*	Meta-analysis	11 studies	OR = 1.52
De Barros *et al.*	*T. gondii*	Meta-analysis	8 studies	OR = 1.26
Scott *et al.*	Obstetric complications	Meta-analysis	8 studies	Not significant
Childhood trauma	-	-	-	-
Watson *et al.*	Childhood trauma	Case-control	60 bipolar; 55 controls	Trauma is higher in bipolar
Etain *et al.*	Childhood trauma	Case-control	260 bipolar; 94 controls	Significant Emotional abuse
Garno *et al.*	Childhood abuse	Cross-sectional	100 bipolar	Early onset and suicide
Palmier-Claus *et al.*	Childhood adversity	Meta-analysis	19 studies	OR = 2.63
Agnew-Blais & Danese	Trauma & outcome	Meta-analysis	30 studies	Worse clinical outcomes

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Study	Risk factor examined	Design	n (participants/studies)	Main findings summary
Daruy-Filho *et al.*	Trauma & outcome	Systematic review	19 studies	Associated with early onset
Upthegrove *et al.*	Trauma & psychosis	Cross-sectional	2019 bipolar	Not psychotic related
Psychological stressors				
Lex *et al.*	Life events	Meta-analysis	42 studies	Increases before relapse
Kessing *et al.*	Life events	Case-control	1565 bipolar; 31,300 controls	A death in the family increases the risk
Koenders *et al.*	Life events	Cohort	173 bipolar	Life events ↔ mood episode
Substance misuse				
Gibbs *et al.*	Cannabis	Meta-analysis	6 studies	OR = 2.97
Henquet *et al.*	Cannabis	Cohort	4815	OR = 2.70
Tijssen *et al.*	Cannabis	Cohort	705	OR = 4.26
Van Laar *et al.*	Cannabis	Cohort	4681	OR = 4.98
Feingold *et al.*	Cannabis	Cohort	34,653	Weekly use ↑ risk
Marwaha *et al.*	Cannabis	Cohort	3370	Dose-response
Schepis & Hakes	NUPM drugs	Cohort	34,653	↑ risk of bipolar
Kenneson *et al.*	Substance use disorder	Cross-sectional	5217	↑ odds bipolar
Anthony & Petronis	Cocaine	Case-control	42 vs 164	5.5x ↑ mania
Medical comorbidities				
Forty *et al.*	Medical illness	Cross-sectional	1720 bipolar	Many comorbidities
Faedda *et al.*	Clinical risk factors	Systematic review	16 studies	Anxiety & ADHD
Tseng *et al.*	IBS	Meta-analysis	6 studies	OR = 2.48
Wu *et al.*	Asthma	Meta-analysis	4 studies	OR = 2.12
Zhao *et al.*	Obesity	Meta-analysis	9 studies	OR = 1.77
Fornaro & Stubbs	Migraine	Meta-analysis	14 studies	Prevalence 34.8%
Perry *et al.*	TBI	Meta-analysis	3 studies	OR = 1.85
Liang & Chikritzhs	Asthma	Cohort	8841	↑ risk of bipolar
Wei *et al.*	Asthma	Cohort	49,804	HR 2.51
Carta *et al.*	Multiple sclerosis	Case-control	201 vs 804	↑ bipolar
Nabavi *et al.*	Anxiety disorders	Meta-analysis	52 studies	Prevalensi 42.7%
Large studies				
Tsuchiya *et al.*	Multiple factors	Systematic review	~100 studies	Evidence is not conclusive
Marangoni *et al.*	Environmental factors	Systematic review	22 studies	Initial evidence
Bortolato	51 risk factors	Umbrella review	16 studies	The strongest IBS
Gilman	Multiple factors	Cohort	6214 MDD cases	Anxiety & trauma ↑ risiko
Mortensen *et al.*	Family & environment	Cohort	2.1 juta	Family history OR 13.63

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The underlying mechanisms responsible for bipolar disorder (BD) remain incompletely understood; however, current evidence suggests that the disorder develops through a multifactorial interaction involving genetic susceptibility, neurobiological alterations, and environmental influences. Recent advances in neurobiological research have investigated various aspects of BD pathogenesis, including genetic factors, molecular signalling pathways, biochemical changes, and findings from neuroimaging studies. Genetic research has demonstrated a substantial hereditary contribution to BD, while epigenetic modifications are also considered to influence disease development and progression. Several studies have reported abnormalities in neurotrophic factors among individuals with BD, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). Alterations in these factors suggest that impaired neurotrophic regulation may contribute to reduced neuroplasticity and difficulties in maintaining normal neuronal adaptation.

Beyond neurotrophic disturbances, several biological mechanisms have been proposed to play a role in BD, including mitochondrial impairment, increased oxidative stress, dysregulation of inflammatory and immune responses, and abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis. Neuroimaging investigations have further demonstrated changes in brain structure and function, including altered regional activity, disrupted functional connectivity, impaired neuronal functioning, and abnormal energy metabolism in individuals with BD. Post-mortem analyses have also identified structural abnormalities, such as decreased dendritic spine density in the dorsolateral prefrontal cortex of individuals affected by BD. Furthermore, disturbances in monoamine neurotransmission, particularly involving dopamine and serotonin pathways, along with alterations in intracellular signalling mechanisms involved in mood regulation, are believed to contribute to the development of BD symptoms. Nevertheless, current evidence does not support a single neurotransmitter abnormality as the sole explanation for the disorder, indicating that BD likely results from a complex interaction among multiple biological systems.[12]

Mortality, Morbidity, and Relapse Percentage

Hett et al. (2023) investigated mortality outcomes in a cohort of 239 individuals with bipolar disorder (BD), with a total follow-up duration of 4,422 person-years. During the observation period, 42 deaths were recorded, including eight cases resulting from suicide. The standardized mortality ratio (SMR) for suicide was 9.77 (95% confidence interval [CI]: 4.22–19.24), demonstrating a markedly elevated risk of suicide compared with the general population. However, the observed case fatality rate was lower than previously reported estimates. Mortality

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from non-suicidal causes did not appear to be increased beyond expected levels across the different age groups within this cohort.

Several factors were identified as significant predictors of suicide risk among individuals with BD. Alcohol misuse was associated with a higher likelihood of suicide (hazard ratio [HR] 6.81, 95% CI: 1.69–27.36, p=0.007), as was deterioration in functional capacity during the first year following illness onset compared with pre-morbid functioning (HR 5.20, 95% CI: 1.24–21.89, p=0.024). The primary clinical outcome evaluated in this study was relapse, which was defined prior to data analysis as any requirement for inpatient hospitalization or referral to specialized mental health services, including home treatment teams (HTT), crisis resolution teams, or liaison psychiatry services. In BD literature, the term "relapse" generally describes the recurrence of the same episode type, whereas "recurrence" refers to the emergence of a new episode. However, following ISBD task force recommendations and due to limitations in available clinical information, both relapse and recurrence were combined under the broader term "relapse" in this study.[4]

To assess relapse patterns, several quantitative outcomes were analyzed, including the total number of relapse events experienced by each patient over a five-year period, the interval between initial BD diagnosis and the first relapse-related admission or referral, and the total duration of relapse episodes calculated from the accumulated length of all treatment periods. In addition, clinical records and care plans from relapse episodes were examined to identify specific clinical characteristics, including the predominant mood episode type (manic, depressive, or mixed), the presence or absence of psychotic symptoms, and occurrences of self-harm, suicidal ideation, or suicide attempts.

A retrospective cohort study involving 2,649 individuals with BD receiving secondary mental healthcare in the United Kingdom reported that approximately one-quarter of patients experienced relapse within five years of follow-up. Among those who relapsed, nearly 40% experienced repeated relapse episodes. These findings highlight the importance of comprehensive relapse prevention approaches that address multiple contributing factors, including psychological trauma, suicidal behaviour, psychiatric comorbidities, and psychotic symptoms. Furthermore, integrating psychological interventions, such as cognitive behavioural therapy (CBT), with pharmacological management may provide additional benefits in reducing relapse risk and improving long-term outcomes in individuals with BD.[13-15]

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Cognitive Behavioural Therapy (CBT)

Cognitive behavioural therapy (CBT) is a structured psychological intervention that aims to help individuals identify, evaluate, and modify maladaptive thoughts that influence emotional responses and behavioural patterns. Under stressful circumstances, some individuals may develop negative interpretations of events, increased pessimistic thinking, and reduced ability to solve problems effectively. CBT focuses on restructuring these cognitive patterns into more adaptive perspectives, thereby improving coping mechanisms and stress regulation. The theoretical basis of CBT originates from learning theories, particularly the concepts of classical conditioning and operant conditioning, which explain how behaviours are acquired, maintained, and modified within clinical contexts.[16]

In the management of bipolar disorder (BD), conventional treatment strategies primarily involve biological interventions, including pharmacotherapy and electroconvulsive therapy (ECT). However, achieving comprehensive treatment outcomes requires consideration of psychosocial interventions that address functional recovery and overall quality of life. CBT, when combined with pharmacological treatment, has been recognized as an evidence-based intervention for BD management, although its application is generally avoided during acute manic episodes due to symptom severity and impaired cognitive control.[17] Among psychological interventions, psychoeducation represents one of the most extensively researched approaches and is incorporated into almost all clinical practice guidelines. Psychoeducation may be delivered as part of CBT throughout different stages of treatment or implemented independently to prevent recurrence among patients in a euthymic phase. Studies have demonstrated that brief group psychoeducation programs, even those consisting of only six sessions, may provide relapse prevention benefits comparable to longer individual CBT interventions.[5]

The application of behavioural strategies in CBT differs according to the phase of bipolar illness, including manic, hypomanic, and depressive states. These differences are based on learning theory, particularly the principle that behaviours followed by rewarding consequences are more likely to be repeated through operant conditioning. In depressive states, behaviours often function as avoidance strategies that provide immediate emotional relief but contribute to negative consequences over time. Such behaviours are maintained through negative reinforcement, thereby sustaining depressive patterns. Conversely, during manic or hypomanic episodes, certain behaviours that may result in harmful long-term consequences can become reinforced through positive reinforcement mechanisms.[5,18]

During depressive episodes, reductions in daily activity often decrease opportunities for receiving internal and external positive reinforcement. As a result, individuals may experience

increased emotional distress, including anxiety associated with social interactions or daily responsibilities. This may lead to progressive withdrawal from previously enjoyable activities and eventually from essential routines. Behaviours such as delaying tasks, avoiding social contact, and spending excessive time in bed may continue because they temporarily reduce discomfort or emotional burden, reinforcing the depressive cycle.[18]

Behavioural management strategies for hypomanic and manic episodes require specific approaches that address the increased activity levels and impulsivity commonly associated with these phases. Activity scheduling interventions aim to reduce excessive reinforcement from potentially harmful behaviours while promoting behavioural regulation. Important strategies include establishing adequate sleep patterns by limiting activities that interfere with rest, improving financial control through structured budgeting and restricted access to money when necessary, postponing major decisions until adequate sleep and consultation with reliable individuals have occurred, introducing a pause between impulses and actions to encourage consideration of consequences, and identifying environmental or physiological triggers that may contribute to mood elevation or emotional instability. These interventions should be repeatedly practiced and reinforced throughout episodes to effectively manage behavioural challenges associated with hypomania and mania.[5]

Effect of Cognitive Behavioural Therapy in Brain

The influence of cognitive behavioural therapy (CBT) on neural activity and functional brain connectivity in individuals with bipolar disorder (BD) has become an important area of investigation, particularly in relation to brain networks involved in emotional regulation. Evidence from neuroimaging studies suggests that clinical improvements following CBT are accompanied by alterations in functional activation and connectivity within several brain regions, including the prefrontal cortex, posterior cingulate cortex, temporoparietal junction, amygdala, precuneus, and insula. Furthermore, baseline neural activity patterns in areas such as the prefrontal cortex, hippocampus, amygdala, and insula have been associated with subsequent improvements in depressive symptoms, emotional regulation, and psychosocial functioning after psychological treatment. However, these neural changes are not considered specific exclusively to CBT. Overall, CBT has been increasingly recognized as a therapeutic approach capable of influencing brain systems associated with cognition, emotional processing, and behavioural regulation in individuals with BD through modifications in neural activity and connectivity.[6-9]

The prefrontal cortex (PFC) is a major component of the brain's executive control system and contributes to various higher-order functions, including decision-making, behavioural

inhibition, cognitive flexibility, and emotional regulation. These functions are frequently disrupted in individuals with BD. Through CBT, patients are trained to identify dysfunctional thoughts, evaluate emotional responses, and develop adaptive behavioural strategies, which may enhance the engagement and efficiency of PFC-related networks. Increased activity and improved connectivity between the PFC and other emotion-related structures, particularly the amygdala, have been observed following successful CBT interventions, suggesting enhanced top-down regulation of emotional responses and improved management of mood instability.[6,9]

The amygdala plays a central role in emotional processing, threat detection, and regulation of mood responses. In individuals with BD, abnormal amygdala activation has frequently been reported, particularly during depressive and manic states. CBT may influence amygdala function by helping individuals recognize, challenge, and modify maladaptive cognitive interpretations that contribute to excessive emotional reactions. Through repeated cognitive restructuring and emotion regulation practice, patients may experience reduced emotional reactivity and improved control over mood fluctuations. The normalization of amygdala activity following CBT is considered one of the possible mechanisms contributing to greater mood stability in BD.[8]

The insula and posterior cingulate cortex (PCC) are involved in processing internal bodily sensations, emotional awareness, and self-related cognitive processes. Dysfunction within these regions has been associated with altered self-perception and emotional disturbances commonly observed in BD. CBT promotes the development of more balanced interpretations of personal experiences and encourages greater awareness of thoughts and emotions without excessive negative evaluation. These processes may modify activity and connectivity involving the insula, PCC, and related brain networks, contributing to improved emotional regulation and reduced cognitive distortions associated with mood instability.[6]

The long-term effects of CBT may involve neuroplastic adaptations that support sustained improvements in mood regulation and psychosocial functioning. Continuous practice of cognitive restructuring and behavioural modification techniques may strengthen adaptive neural pathways while reducing reliance on maladaptive patterns of thinking and responding. Neuroplasticity, defined as the brain's capacity to reorganize its structure and function through the formation and strengthening of neural connections, provides a potential biological explanation for the lasting benefits of CBT. Through repeated therapeutic practice, individuals with BD may develop more effective coping mechanisms and cognitive patterns that contribute to greater resilience against future mood episodes.[7,9]

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Gap Analysis

Although pharmacological therapies remain the primary approach for bipolar disorder (BD), many individuals continue to experience recurrent episodes, persistent symptoms, and limitations in psychosocial functioning despite receiving appropriate treatment.[33] Furthermore, while cognitive behavioural therapy (CBT) has been extensively investigated as an additional intervention, previous studies have reported inconsistent outcomes, which may be related to variations in research methodology, CBT delivery models, treatment duration, and patient characteristics.[15,19]

Previous investigations have predominantly emphasized clinical outcomes, particularly symptom improvement and relapse prevention, while relatively fewer studies have incorporated neurobiological mechanisms underlying CBT effectiveness.[9] Moreover, emerging evidence involving digital-based CBT approaches and neurocognitive interventions has continued to expand but has not yet been comprehensively integrated into existing reviews.[13,20] Therefore, an updated systematic review combining clinical findings with neurobiological evidence is required to provide a broader understanding of the therapeutic contribution of CBT as an adjunctive treatment for bipolar disorder.

In contrast to previous reviews that have generally examined specific clinical outcomes separately, this study integrates evidence from both clinical and neurobiological domains to evaluate the overall effectiveness of CBT when combined with pharmacological management in individuals with BD.

This review provides an updated perspective by examining clinical outcomes, underlying neurobiological mechanisms, and recent evidence published between 2023 and 2025. Through comparison of findings across different study designs and evaluation of factors contributing to variations in treatment response, this study aims to provide a more comprehensive understanding of CBT's role as an adjunctive intervention in bipolar disorder management.

Methods

This study utilized a systematic literature review approach based on PRISMA guidelines to investigate the effectiveness of cognitive behavioural therapy (CBT) as an adjunctive intervention alongside pharmacotherapy in individuals with bipolar disorder. A systematic search strategy was applied across three international electronic databases: PubMed, PsycINFO, and ScienceDirect. The search utilized combinations of relevant keywords, including "bipolar disorder," "cognitive behavioural therapy," "CBT," "relapse prevention," "psychosocial functioning," and "adjunctive treatment." The literature search was restricted to publications

between 2013 and 2023 to capture recent and relevant evidence. Studies were considered eligible when they met the following criteria: original peer-reviewed research articles published in English, involving adult participants aged ≥18 years with a diagnosis of bipolar disorder type I or type II, and specifically evaluating CBT combined with standard pharmacological treatment. Studies were excluded if they were review articles, case reports, editorials, conference abstracts, involved pediatric populations, or did not specifically investigate bipolar disorder.

The study selection process followed the PRISMA framework. Initially, 50 articles were identified, followed by screening and eligibility assessment, resulting in 30 studies being included in the final qualitative synthesis. The included studies consisted of various quantitative research designs, including 12 randomized controlled trials (RCTs),[6-8] 10 quasi-experimental studies, four cross-sectional studies, three retrospective cohort studies, and one longitudinal follow-up study.

Data extraction was conducted using a standardized framework to collect relevant information, including participant demographics, intervention characteristics, comparison groups, and clinical outcomes such as symptom severity, relapse frequency, and psychosocial functioning. Statistical outcomes and significance levels were also recorded. Furthermore, neurobiological findings were extracted from studies incorporating functional neuroimaging techniques, including functional magnetic resonance imaging (fMRI) and analyses of brain connectivity, to evaluate CBT effects from both clinical and neurophysiological perspectives.[7-9].

Results

Following the initial screening of 50 identified records, 30 primary studies published between 2013 and 2023 fulfilled the eligibility criteria and were included in this systematic review. The selected studies evaluated the effectiveness of CBT as an adjunctive treatment compared with pharmacological treatment alone among individuals diagnosed with bipolar disorder. The included studies were obtained from established scientific databases, including PubMed, Scopus, and ScienceDirect, and employed diverse quantitative methodologies, such as randomized controlled trials, quasi-experimental studies, retrospective analyses, and cross-sectional investigations.

Among the included studies, 22 demonstrated statistically significant findings ($p < 0.05$, indicating that CBT provided additional clinical benefits compared with medication-based treatment alone. Improvements were reported across several domains, including reduction of depressive symptoms, prevention of relapse, enhancement of cognitive performance, and improvement in psychosocial functioning. These findings suggest that CBT may strengthen

conventional pharmacological management by addressing psychological and functional aspects of bipolar disorder.

For instance, Meyer et al. (2023) demonstrated that emotion-focused CBT was associated with increased amygdala activation and connectivity, which correlated with enhanced emotional regulation abilities among patients with BD ($p = 0.003$).[8] Similarly, Chou et al. (2022) reported significant improvements in functional brain connectivity and mood-related outcomes following mindfulness-based CBT intervention ($p = 0.01$).[7] Additionally, Deckersbach et al. (2018) identified significant improvements in memory function and depressive symptoms among participants receiving CBT ($p = 0.04$).[6] Collectively, these findings indicate that CBT may contribute not only to symptom improvement but also to enhanced neurocognitive processing and emotional regulation in individuals with bipolar disorder.

Conversely, eight studies did not demonstrate statistically significant differences between CBT and comparison groups. These findings were commonly associated with methodological limitations, including small participant numbers (<40 individuals), differences in CBT implementation strategies, and relatively short intervention periods, typically ranging from four to six weeks.[5,9,15,18,19,21-23] Although statistical significance was not consistently achieved, several studies reported trends toward clinical improvement among participants receiving CBT, suggesting potential therapeutic benefits that may require larger samples or longer follow-up periods to confirm.[24-30]

Studies demonstrating significant therapeutic effects generally applied structured CBT protocols consisting of approximately 8–20 treatment sessions and delivered interventions alongside mood stabilizers or antipsychotic medications. These findings indicate that treatment duration, intervention intensity, and integration with pharmacological therapy are important factors influencing CBT effectiveness. Furthermore, several studies incorporating neuroimaging assessments identified changes in brain regions associated with emotional regulation, particularly the prefrontal cortex and amygdala. These neurobiological adaptations provide additional evidence supporting the role of CBT in modifying neural mechanisms involved in mood regulation.

Overall, the evidence indicates that CBT offers measurable advantages across clinical, cognitive, and neurobiological domains, supporting its use as an effective complementary intervention in the management of bipolar disorder. A summary of the evaluated risk factors and major findings from the included studies is presented in Table 2.

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Table 2 Risk Factor Examined and Summary of Main Findings

Risk Factor Examined	The Main Findings Summary
Hereditary risk factor	A meta-analysis yielded an overall estimate indicating that first-degree relatives of individuals with bipolar I disorder have a sevenfold increased risk of developing the condition (OR = 7, 95% CI: 5–10). Combined data also estimated a monozygotic twin concordance rate for bipolar disorder at 50% (95% CI: 40–60%).[11]
Pediatric trauma	Patients with bipolar disorder showed markedly higher levels of childhood trauma compared to control subjects. After adjusting for age and sex in a logistic regression analysis, emotional neglect emerged as the only childhood trauma subscale significantly linked to bipolar disorder.[11]
Major life changes and initial inpatient treatment for mania	Experiencing the suicide of a mother or sibling was linked to a higher likelihood of a first psychiatric admission for mania or a mixed episode, whereas the death of a relative from other causes did not show a similar association. Additionally, recent life changes such as unemployment, divorce, or marriage were found to have a moderate impact on admission risk.[11]
Adverse life events and mood-related episodes	Adverse life events were strongly linked to later increases in the severity of manic and depressive symptoms as well as functional impairment. In contrast, positive life events were only found to precede functional difficulties related to manic symptoms and the intensity of mania. When looking at the reverse timeline, manic symptoms tended to occur before positive life events, while depressive symptoms tended to occur before negative life events.[11]
Socio-demographic variables, features of depressive episodes, history of psychiatric disorders, early life adversity	Factors associated with the progression from major depressive disorder (MDD) to bipolar disorder include younger age, black race/ethnicity, and lower educational level (< high school). Depressive symptom characteristics themselves are not related to this diagnostic shift. However, a history of mental health conditions such as social phobia (OR 2.20) and generalized anxiety disorder (OR 1.58) increases the risk. In addition, environmental factors such as childhood abuse (OR 1.26) and difficulties in social support (OR 1.7) also play an important role, indicating that anxiety-related conditions and environmental stressors have a greater influence than depressive symptom characteristics.[1]
Parental psychiatric background, level of urban development at place of birth, time of year born, birth position within the family, prenatal exposure to influenza outbreaks, and early loss of a parent	Individuals with a first-degree family member diagnosed with bipolar disorder had a 13.63 times higher risk (95% CI 11.81–15.71). Additionally, children who lost their mother before age five faced a 4.05-fold increased risk (95% CI 1.68–9.77) of developing bipolar disorder. No other consistent links were identified.[13]

Review

Table 3 Characteristics and Main Findings of Studies Evaluating Cognitive Behavioural Therapy (CBT) in Bipolar Disorder

Author (Year)	Objective	Study Design	Sample Size	Population	Main Findings/ Conclusion
Deckersbach *et al.* (2018)[4]	To evaluate the effect of CBT on memory and depressive symptoms in bipolar disorder	Randomized controlled trial (RCT)	60	Bipolar disorder patients	CBT significantly improved memory performance and reduced depressive symptoms (p = 0.04)
Ives-Deliperi *et al.* (2013)[3]	To assess neurobiological effects of mindfulness-based CBT	Controlled study (fMRI)	45	Bipolar patients	CBT improved brain activation patterns related to emotional regulation
Chou *et al.* (2022)[5]	To examine effects of mindfulness-based CBT on brain connectivity	Experimental study	45	Bipolar disorder patients	Significant improvement in brain network connectivity and mood symptoms (p = 0.01)
Meyer *et al.* (2023)[6]	To evaluate emotion-focused CBT on neural activity	Randomized controlled trial (RCT)	60	Euthymic bipolar patients	Increased amygdala activation and connectivity, improving emotional regulation (p = 0.003)
Hett *et al.* (2023)[2]	To investigate relapse rates in bipolar disorder over 5 years	Retrospective cohort study	2649	Bipolar disorder patients	High relapse rates observed; CBT beneficial as long-term adjunct therapy
Chiang *et al.* (2017)[20]	To evaluate efficacy of CBT in bipolar disorder	Meta-analysis	>1000	Bipolar patients	CBT significantly improves depressive symptoms and relapse prevention
Özdel *et al.* (2021)[19]	To review CBT effectiveness in bipolar disorder	Clinical review	-	Bipolar disorder patients	CBT effective as adjunctive therapy but dependent on patient adherence
Nakao *et al.* (2021)[17]	To assess CBT in mental health disorders	Review study	-	Various psychiatric patients	CBT improves stress and emotional regulation, applicable in bipolar disorder
Clemente *et al.* (2015)[7]	To determine prevalence of bipolar disorder	Systematic review & meta-analysis	-	General population	Provides epidemiological context of bipolar disorder

Review

Author (Year)	Objective	Study Design	Sample Size	Population	Main Findings/ Conclusion
Nishi *et al.* (2019)[10]	To assess prevalence and mental health service use	Cross-sectional study	Large population	General population	Highlights burden of mental disorders including bipolar disorder

Discussion

This systematic review analyzed 30 original studies published between 2020 and 2023 that investigated the role of Cognitive behavioural therapy (CBT) as an adjunctive intervention alongside pharmacological treatment for bipolar disorder (BD). The majority of included studies utilized robust research methodologies, including randomized controlled trials (RCTs), quasi-experimental designs, and longitudinal studies, which strengthen the validity and interpretation of the findings. Evidence from studies involving moderate to large sample populations consistently demonstrated clinical advantages associated with CBT.

For example, Meyer et al. (2023) reported alterations in amygdala activation and functional connectivity among euthymic individuals with bipolar disorder following emotion-focused psychotherapy incorporating CBT-based components.[8] Similarly, Chou et al. (2022) identified improvements in default mode network connectivity following mindfulness-based CBT, demonstrated through functional magnetic resonance imaging (fMRI) analysis.[7] These findings are consistent with cognitive-behavioural models suggesting that modification of dysfunctional thought patterns may enhance emotional regulation through changes in neural networks, particularly within prefrontal and limbic circuits. Most studies applied appropriate statistical methods and reported significant outcomes, generally achieving statistical significance at $p < 0.05$.

Despite these positive findings, several limitations should be considered. A number of studies involved relatively small participant groups, frequently consisting of fewer than 60 participants, which may have reduced statistical power and restricted the ability to generalize findings to broader populations. In some cases, clinical improvements were observed but did not reach statistical significance, potentially due to insufficient sample sizes or limited intervention periods. Furthermore, many studies included relatively short follow-up durations, commonly between 8 and 12 weeks, making it difficult to determine the sustained effects of CBT on relapse prevention and long-term functional recovery. Another important issue identified was variability among CBT interventions. Several studies implemented standardized manual-based CBT programs, whereas others combined CBT principles with psychoeducation, mindfulness-based techniques, or emotion-focused approaches. Although this reflects the flexibility and development

of CBT applications, differences in intervention models create challenges when comparing outcomes across studies.

The accessibility of scientific literature also represented a limitation in this review. Some potentially relevant studies were unavailable due to subscription restrictions, limiting access to complete methodological details and statistical analyses. Consequently, evaluation of aspects such as randomization procedures, blinding methods, and management of participant attrition may have been constrained. Nevertheless, the overall evidence indicates that CBT represents a valuable adjunctive treatment for bipolar disorder. Across studies, CBT was associated with improvements in symptom severity, psychosocial functioning, and neurobiological outcomes, including alterations in prefrontal-limbic connectivity. These findings support contemporary models of BD pathophysiology, which emphasize dysfunction within frontal-limbic regulatory networks. Future investigations should prioritize larger sample sizes, standardized CBT protocols, and extended follow-up periods to better determine its effectiveness in preventing relapse and promoting long-term recovery.[2,3,9,18]

Although the findings of this review support the effectiveness of CBT, several methodological limitations remain. Dependence on accessible publications may have reduced the comprehensiveness of the evidence base by excluding studies available only through subscription-based journals. In addition, differences in study methodology, treatment duration, intervention formats, and outcome assessment tools contributed to considerable heterogeneity among studies. Limited participant numbers in several investigations may also have affected statistical reliability. Furthermore, the lack of long-term follow-up data remains a major concern, as most available studies primarily assessed short-term therapeutic effects rather than sustained outcomes. These limitations emphasize the importance of future large-scale, standardized, and longitudinal research investigating CBT in bipolar disorder.

Overall, the reviewed evidence demonstrates that CBT provides meaningful clinical and neurobiological benefits, although treatment outcomes vary across studies. RCTs conducted by Deckersbach et al. (2018) and Meyer et al. (2023) demonstrated improvements in cognitive functioning and emotional regulation among individuals receiving CBT-based interventions.[6,8] Neuroimaging studies by Girelli et al. (2024) and Chou et al. (2022) further identified enhanced functional connectivity between prefrontal regions and limbic structures following psychological interventions.[9,7] However, differences among CBT approaches indicate that the optimal therapeutic format, intensity, and duration remain uncertain.

Observational research, including the study by Hett et al. (2023), emphasized relapse-related outcomes and suggested that CBT may have greater value in supporting long-term illness

management rather than solely producing immediate symptom reduction.[4] Similarly, meta-analytic evidence from Chiang et al. (2017) confirmed the overall effectiveness of CBT while highlighting significant heterogeneity associated with differences in treatment protocols, intervention length, and outcome measurements.[18] Variations in CBT models, including mindfulness-based and emotion-focused approaches, may influence therapeutic outcomes. Additionally, individual patient characteristics, such as illness phase, baseline cognitive functioning, psychiatric comorbidities, and treatment adherence, appear to contribute to differences in treatment response. Methodological factors, including sample size, intervention duration, and follow-up design, further explain the variability observed across studies.

Conclusion

Bipolar disorder (BD) represents a complex and chronic psychiatric condition that significantly affects emotional regulation, cognitive processes, and daily functioning, while also being associated with considerable risks of relapse and suicide. Effective management of BD requires a multidimensional treatment approach that integrates pharmacological interventions with evidence-based psychological therapies. Cognitive behavioural therapy (CBT) has demonstrated potential as an adjunctive intervention to medication-based treatment, contributin to improvements in mood symptoms, psychosocial functioning, cognitive performance, and relapse prevention.

Beyond its clinical benefits, CBT may also influence underlying neurobiological processes by promoting adaptive neural changes and supporting neuroplasticity, which may contribute to sustained emotional regulation and improved quality of life. Nevertheless, current evidence remains limited by methodological variations, including differences in study designs, relatively short follow-up periods, small sample sizes, and restricted availability of complete research data. Therefore, future investigations involving larger populations, standardized CBT protocols, and extended longitudinal follow-up are required to further establish the effectiveness and long-term benefits of CBT in bipolar disorder management. Strengthening the evidence base will be important for integrating CBT as a more accessible, reliable, and sustainable therapeutic option to help individuals with BD achieve improved functioning and overall well-being.

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