Med. Psychol. Health Res. J. **(2026),** Volume 2, Issue 6, 438-451

Medicinal, Psychological, and Health Research Journal

Journal homepage: https://www.mphrj.com/

DOI: 10.22034/mphrj.2026.591046.1108

The Efficacy of Cognitive Behavioral Therapy (CBT) in Treating Treatment-Resistant Depression: Mechanisms and Long-Term Outcomes

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Article info
Received: 01.05.2026
Accepted: 10.07.2026
Available Online: 11.07.2026
Checked for Plagiarism: Yes

Keywords:
Treatment-Resistant Depression, Cognitive Behavioral Therapy, Augmentation Strategy, Psychological Flexibility, Long-Term Outcomes

A B S T R A C T

Background: Treatment-resistant depression (TRD) represents a significant clinical challenge, affecting approximately 30% of individuals with major depressive disorder who fail to respond to conventional antidepressant pharmacotherapy. Cognitive Behavioral Therapy (CBT) has emerged as a promising intervention for this population, yet the specific mechanisms and long-term efficacy remain incompletely understood.

Objective: This study systematically examines the efficacy of CBT in treating TRD, investigating psychological and neurobiological mechanisms of change and evaluating long-term outcomes.

Methods: A comprehensive review was conducted of randomized controlled trials, meta-analyses, and key observational studies published between 2000 and 2025, identified from PubMed, PsycINFO, and Cochrane Library databases. Special attention was given to studies examining CBT as an augmentation strategy, sudden gains in treatment response, and neural correlates of therapeutic change.

Results: Robust evidence supports CBT as an effective augmentation strategy for TRD, with effect sizes comparable to pharmacological augmentation approaches (ES=1.58, 95% CI:1.09-2.07). Psychological flexibility emerged as a key mechanism predicting long-term outcomes at 12-month follow-up. Neuroimaging findings reveal both treatment-responsive prefrontal and parietal regions and treatment-resistant cerebellar regions, suggesting that CBT may not uniformly normalize all neural abnormalities. Long-term relapse rates among TRD patients receiving CBT augmentation range from 25-50% at 12 months, with the greatest durability observed in those who achieve sudden therapeutic gains early in treatment.

Conclusion: CBT constitutes an essential component of the TRD treatment arsenal, offering durable benefits beyond pharmacotherapy alone. Future research must prioritize standardized TRD definitions, biomarker-driven personalization, and scalable delivery models to optimize clinical implementation.

Introduction

Major depressive disorder (MDD) represents one of the most prevalent and debilitating psychiatric conditions worldwide, with an estimated lifetime prevalence of approximately 12% and ranking as the leading cause of disability globally. Despite the availability of numerous pharmacological and psychological interventions, a substantial proportion of patients do not achieve adequate response to first-line treatments [1].

Response rates to initial antidepressant medication or cognitive behavioral therapy are estimated at approximately 50%, and up to 30% of patients fail to respond to available treatment modalities [2]. This phenomenon, broadly termed treatment-resistant depression (TRD), constitutes one of the most significant challenges in contemporary psychiatric practice, associated with severe

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functional impairment, elevated healthcare utilization, and increased risk of mortality [3].

The definition of TRD remains a subject of ongoing debate, though the most frequently employed criterion is the failure to respond to at least two adequate trials of antidepressant pharmacotherapy of sufficient dose and duration within the current depressive episode. This definition, operationalized in staging models such as the These and Rush model, has been instrumental in identifying patients who may benefit from more intensive or alternative treatment approaches [4]. More contemporary perspectives suggest that treatment resistance should be conceptualized more broadly, encompassing non-response to psychological therapies as well as pharmacological agents, and recognizing that the construct represents a spectrum rather than a categorical entity. This expanded conceptualization has significant implications for treatment planning, particularly in light of evidence suggesting that non-response to one treatment modality predicts increased risk of non-response to subsequent interventions [5].

Cognitive Behavioral Therapy (CBT) has long occupied a central position in the evidence-based treatment of depression, with extensive research supporting its efficacy as both monotherapy and in combination with pharmacotherapy. However, its specific application to TRD populations warrants careful examination, as these patients often present with more entrenched cognitive patterns, greater chronicity, and reduced responsiveness to standard treatment protocols. The theoretical rationale for CBT in TRD is compelling: the therapy directly targets the persistent negative cognitive schemas, maladaptive information processing biases, and behavioral avoidance that characterize depressive episodes and may be less responsive to pharmacological intervention alone. By teaching patients to identify, challenge, and modify automatic negative thoughts and core beliefs, CBT aims to produce durable changes in cognitive patterns that confer lasting resilience against relapse [6].

The neurobiological underpinnings of CBT's efficacy have garnered increasing research attention, with advances in neuroimaging techniques enabling investigators to examine treatment-induced neural changes. Theoretical models propose that CBT exerts its effects through modulation of prefrontal cortical structures implicated in cognitive control and emotion regulation. These models suggest that CBT enhances top-down regulatory capacity, enabling patients to exert greater control over subcortical limbic regions involved in emotional reactivity [7]. The prefrontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC) and medial prefrontal regions, has been identified as a key locus of treatment response, consistent with the cognitive demands of therapeutic exercises that require sustained attention, reappraisal, and cognitive restructuring. However, the neural mechanisms of CBT in TRD may differ from those observed in treatment-responsive populations, as the presence of treatment resistance may indicate more fundamental neurobiological abnormalities that are less amenable to modification [8-10].

Beyond neurobiological mechanisms, psychological processes of change in CBT for TRD have been the subject of considerable investigation. Emerging research has identified psychological flexibility the capacity to remain in contact with the present moment and act in accordance with valued goals despite difficult internal experiences as a particularly important mechanism. This construct, central to Acceptance and Commitment Therapy (ACT) but also relevant to traditional CBT approaches, appears to facilitate therapeutic change by enabling patients to disengage from rigid, maladaptive cognitive patterns and pursue meaningful behavioral engagement. Related mechanisms include reductions in rumination, decreased avoidance behaviors, and enhanced emotional processing capacity. Understanding which mechanisms are most predictive of favorable outcomes in TRD populations has important implications for treatment optimization and personalization [11].

The question of long-term outcomes in TRD patients receiving CBT is of paramount clinical importance. While acute treatment gains are consistently documented, the durability of these effects and the factors that predict sustained improvement versus relapse are less well understood. TRD patients are at elevated risk for recurrent and chronic depression, making relapse prevention a critical treatment goal. The sequential treatment model, which proposes that acute-phase interventions should be followed by continuation or maintenance strategies to consolidate gains and prevent relapse, has particular relevance for this population. Recent research has examined the potential of CBT to sustain antidepressant effects of rapid-acting interventions such as ketamine, suggesting that CBT may play a crucial role in extending the duration of response beyond the acute treatment period [12].

The current review seeks to systematically examine the evidence base for CBT in TRD, with particular attention to: (1) the efficacy of CBT as both monotherapy and augmentation strategy, (2) the psychological and neurobiological mechanisms that mediate therapeutic change, (3) predictors of treatment response and non-response, (4) long-term outcomes and maintenance strategies, and (5) emerging approaches to enhance treatment delivery and personalization. By synthesizing findings from randomized controlled trials, meta-analyses, and mechanistic studies, this review aims to provide a comprehensive overview of the current state of knowledge and identify priorities for future research. The clinical significance of this endeavor

is underscored by the substantial burden of TRD and the potential for optimized CBT protocols to improve outcomes for this challenging patient population [13].

Literature Review

Historical Development and Theoretical Foundations

The application of CBT to TRD represents a logical extension of cognitive theory and its evolution over several decades. Beck's cognitive model, first articulated in the 1960s, proposed that depression arises from the activation of negative cognitive schemas—stable, latent structures that bias information processing toward negative interpretations of self, world, and future. These schemas, often formed through early adverse experiences, become particularly accessible during periods of stress, giving rise to the automatic negative thoughts that characterize depressive episodes. The cognitive theory of depression posits that these patterns are not merely symptoms of the disorder but rather causal mechanisms that maintain and perpetuate depressive states. This formulation provides a clear rationale for psychological intervention: by modifying the content and structure of negative schemas, therapy can produce lasting change in vulnerability to depression [14].

The application of cognitive theory to TRD raises important questions about the nature of treatment resistance. If negative cognitive patterns maintain depression, why would some patients fail to respond to therapy that directly targets these patterns? Several possibilities have been proposed. First, TRD patients may present with more entrenched or severe cognitive distortions that require more intensive or prolonged intervention. Second, the presence of neurobiological abnormalities such as impaired prefrontal cortical function or dysregulated limbic reactivity may limit the capacity for cognitive change, even when patients engage fully in therapeutic exercises. Third, TRD patients may exhibit reduced cognitive flexibility, limiting their ability to generate and implement alternative perspectives. Fourth, the chronicity and severity of TRD may be associated with greater behavioral avoidance, reducing opportunities for the behavioral experiments that are essential to cognitive change. These possibilities highlight the need for a more nuanced understanding of the mechanisms that mediate treatment response in this population [15].

The theoretical foundations of CBT for TRD have been enriched by the integration of findings from affective neuroscience, which have illuminated the neural circuitry underlying emotion regulation and its dysfunction in depression. The cortico-limbic model, one of the most influential neurobiological frameworks for understanding depression, proposes that the disorder involves a disturbance in the balance between prefrontal cortical regions that subserve cognitive control and limbic regions that generate emotional responses. According to this model, depression is characterized by reduced top-down regulation of limbic reactivity, resulting in excessive and sustained negative emotional responses to stressors. The dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and anterior cingulate cortex (ACC) have been identified as key nodes in the cognitive control network, while the amygdala, hippocampus, and subgenual ACC are implicated in emotional processing and reactivity [16].

The cortico-limbic model has important implications for understanding CBT's mechanisms of action. According to this framework, CBT may exert its therapeutic effects by strengthening prefrontal cognitive control, enabling patients to more effectively regulate emotional responses. This is consistent with the nature of CBT exercises, which require patients to repeatedly practice identifying, evaluating, and modifying negative thoughts a process that places substantial demands on prefrontal executive functions. Over time, this repeated practice may strengthen neural pathways supporting cognitive control, producing lasting changes in emotion regulation capacity. However, recent neuroimaging findings have revealed a more complex picture, suggesting that CBT may also affect limbic regions directly, possibly through the prefrontal modulation of amygdala reactivity. The extent to which these mechanisms operate similarly in TRD and treatment-responsive populations remains an open question, though preliminary evidence suggests that TRD patients may show more limited prefrontal engagement during cognitive tasks, potentially constraining the effectiveness of CBT [17].

Efficacy of CBT for TRD: Evidence from Clinical Trials

The evidence base for CBT in TRD has grown substantially over the past two decades, with a particular focus on its role as an augmentation strategy to pharmacotherapy. One of the most influential studies in this area was the CoBalT trial, which examined the clinical effectiveness and cost-effectiveness of CBT as an adjunct to usual care for patients with TRD in primary care settings. The trial demonstrated that augmentation with CBT significantly reduced depressive symptoms compared to usual care alone, with effects maintained over 12 months of follow-up. The economic evaluation indicated that this approach was cost-effective, supporting the recommendation that primary care physicians should refer non-responsive patients for CBT. These findings provided robust evidence that CBT can produce meaningful clinical benefit in a population that had previously been considered particularly difficult to treat [18].

Subsequent meta-analyses have further substantiated these findings. A comprehensive systematic review and meta-analysis of augmentation and combination treatments for early-stage TRD identified CBT as having the highest effect size among all augmentation strategies examined (ES=1.58, 95% CI:1.09-2.07), exceeding even pharmacological augmentation approaches such as ketamine and atypical antipsychotics. This finding is particularly striking given that the meta-analysis included 115 trials investigating 48 different treatments, providing a robust basis for comparison. The high effect size observed for CBT suggests that psychological interventions may be particularly well-suited to addressing the residual cognitive and behavioral symptoms that persist despite pharmacotherapy [19].

Specialized CBT protocols have been developed specifically for chronic and treatment-resistant depression. The Cognitive Behavioral Analysis System of Psychotherapy (CBASP), developed by James McCullough, represents one such adaptation. CBASP is unique among CBT approaches in its explicit focus on interpersonal consequences and the therapist-patient relationship, conceptualizing chronic depression as stemming from early developmental experiences that interfere with the ability to perceive and respond to interpersonal consequences. A randomized controlled trial comparing CBASP to Behavioral Activation (BA) in persistently depressed treatment-resistant inpatients is currently underway, with results expected to provide important insights into the differential efficacy of these approaches. The trial includes a substantial sample size of 396 patients and will examine both short-term and long-term outcomes, as well as moderators and mediators of treatment response. The inclusion of a 48-week follow-up period will provide valuable data on the durability of treatment effects [20].

The phenomenon of sudden gains large, rapid improvements that occur between therapy sessions—has been identified as a particularly important process in CBT for TRD. Research has shown that both sudden gains and having a defined trajectory of symptom change predict lower depression severity at 6- and 12-month follow-up, even when controlling for baseline depression symptoms, early slopes of change, and symptom variability. This finding suggests that the manner in which patients improve during treatment may be as important as the overall degree of improvement. Sudden gains may represent opportunities for accelerated cognitive change, during which patients are particularly receptive to therapeutic interventions and able to consolidate new learning. Understanding the factors that facilitate sudden gains could provide a basis for enhancing treatment protocols and optimizing the timing of specific therapeutic interventions.

Mechanisms of Change in CBT for TRD

The identification of mechanisms that mediate therapeutic change in CBT for TRD has been a focus of considerable research attention. Psychological flexibility has emerged as one of the most robust predictors of long-term outcomes. In a study examining processes of change in CBT for TRD, psychological flexibility during the pre-sudden gain period predicted less depression at 12-month follow-up, beyond baseline symptoms and other co-occurring processes. This finding suggests that the capacity to remain flexibly engaged with the present moment and to act in accordance with valued goals, even when experiencing difficult emotions, may be a key mechanism that enables patients to maintain therapeutic gains over time.

The interaction between psychological flexibility and other therapeutic processes has been examined in detail. Interaction analyses revealed that when flexibility was low during the post-spike period, avoidance and rumination predicted higher depressive symptoms, whereas emotional processing predicted lower symptoms at the 12-month follow-up. Conversely, when flexibility was high, none of these variables were associated with outcome. These findings suggest that psychological flexibility may serve as a protective factor that buffers the negative effects of maladaptive processes such as avoidance and rumination. When patients are able to maintain flexible engagement with their internal experiences, they may be less vulnerable to being derailed by negative thoughts and feelings, allowing them to continue making progress toward their therapeutic goals.

Rumination and avoidance have been identified as particularly important targets in CBT for TRD. Rumination the repetitive, passive focus on one's symptoms, their causes, and their consequences has been consistently implicated in the maintenance of depressive episodes and has been shown to predict poorer treatment outcomes. CBT protocols often include interventions specifically designed to reduce rumination, such as thought stopping, distraction techniques, and the cultivation of metacognitive awareness. Similarly, avoidance behaviors actions taken to avoid or escape negative internal experiences have been identified as a key mechanism maintaining depression. Behavioral activation, which is often integrated into CBT protocols, directly targets avoidance by encouraging patients to engage in rewarding activities despite their depression, thereby breaking the cycle of withdrawal and negative reinforcement.

Emotional processing the capacity to experience, tolerate, and make meaning of emotional experiences has also been identified as an important mechanism in CBT for TRD. Patients with chronic depression often display difficulties in emotional processing, including emotional numbing, suppression, or avoidance. The therapeutic

relationship in CBT may provide a safe context in which patients can begin to experience and explore emotions that they have previously avoided. This process may be particularly important for patients with TRD, who often have long histories of emotional suffering and may have developed highly routinized patterns of emotional avoidance. Research suggests that emotional processing during critical periods of treatment may predict long-term outcomes, particularly when combined with high psychological flexibility.

Neuroimaging Findings in CBT for TRD

Advances in neuroimaging have provided unprecedented opportunities to examine the neural correlates of CBT response in depression. A recent study using functional magnetic resonance imaging (fMRI) examined neural response and non-response to cognitive therapy in patients with MDD, comparing them to never-depressed controls. The study utilized conjunction analyses to identify brain regions that showed both differences between patients and controls at baseline and either response or non-response to treatment. The findings revealed a complex pattern: non-response was observed in a cerebellar region, while response was observed in prefrontal and parietal regions. This pattern is consistent with prior theoretical models of CBT's direct effect on cortical regulatory processes but expands on them with the identification of additional regions of response and non-response.

The finding of non-response in a cerebellar region is particularly intriguing. The cerebellum has historically been viewed primarily as a motor control structure, but accumulating evidence suggests that it also plays important roles in emotion regulation and cognitive processing. The cerebellum has extensive reciprocal connections with prefrontal and limbic regions and has been implicated in the generation of predictive models that guide behavior. The persistence of cerebellar abnormalities despite CBT may help to explain why even after successful treatment, patients with a history of depression remain vulnerable to recurrence. This finding suggests that the cerebellum may represent a treatment-resistant neural process that could be a target for future interventions, potentially including neuromodulation approaches.

The response observed in prefrontal and parietal regions is consistent with the cognitive control model of CBT's mechanisms. These regions are implicated in executive functions such as attention, working memory, and cognitive reappraisal processes that are centrally involved in CBT. The finding that these regions show functional changes following CBT suggests that the therapy may indeed strengthen prefrontal regulatory capacity, enabling patients to more effectively modulate emotional responses. However, the identification of treatment-resistant neural processes underscores the limitation of current interventions and highlights the need for strategies that target neural circuits that may be less accessible to psychological intervention. The combination of CBT with neuromodulation or pharmacological agents that enhance neuroplasticity may offer one approach to addressing these treatment-resistant processes.

Long-Term Outcomes and Maintenance Strategies

The durability of treatment effects is of particular importance in TRD, given the elevated risk of relapse and recurrence in this population. Long-term follow-up studies have provided valuable insights into the trajectories of response following CBT. Among ketamine responders who received concurrent CBT, the relapse rate at the end of the CBT course (8 weeks following the last ketamine exposure) was 25%, and the median time to relapse was 12 weeks. This compares favorably to the results of similar open-label protocols, where relapse rates at 4 weeks or earlier following 6 infusions range from 55-89%. These findings suggest that CBT may play an important role in extending the duration of response to rapid-acting antidepressant interventions.

However, the long-term prognosis for TRD patients remains sobering. Even among those who achieve initial response, a substantial proportion eventually relapse, with most relapses occurring following the conclusion of active treatment. This pattern suggests that TRD patients may require longer or more intensive maintenance treatment to sustain their gains. A longer course of CBT may be more effective at modifying negative core beliefs and producing a longer relapse-free period. Additionally, the integration of CBT with other treatment modalities, such as repetitive transcranial magnetic stimulation (rTMS), has shown promise in extending treatment effects. A current randomized controlled trial is evaluating the efficacy of smartphone-based CBT for preventing relapse in TRD patients who have achieved response or remission with rTMS therapy, offering a potentially scalable approach to maintenance treatment.

The identification of predictors of long-term outcome is a priority for future research. Baseline characteristics such as the severity of depression, the presence of comorbid conditions, and history of childhood maltreatment have been associated with poorer outcomes, though findings have been inconsistent across studies. Neurobiological markers, including patterns of brain activation and structural connectivity, may offer more predictive utility. The integration of clinical and biological predictors could enable more personalized treatment planning, helping to identify patients who may require more intensive or alternative approaches. Moderator analyses, examining whether the differential efficacy of treatments can be explained

by treatment-specific changes in interpersonal problems or activity levels, are currently underway in several large-scale trials.

Method

Search Strategy and Study Selection

This study employed a narrative review methodology to synthesize the existing evidence on the efficacy of CBT in treating TRD. A systematic search was conducted across PubMed, PsycINFO, and Cochrane Library databases to identify randomized controlled trials (RCTs), meta-analyses, and key observational studies published between January 2000 and October 2025. Search terms included: "treatment-resistant depression," "cognitive behavioral therapy," "CBT," "augmentation," "long-term outcomes," "mechanisms of change," "psychological flexibility," and "neuroimaging." Additional studies were identified through screening reference lists of included articles and relevant review papers. The search was restricted to English-language publications involving adult populations (age ≥ 18 years) with a primary diagnosis of major depressive disorder (MDD) or persistent depressive disorder (PDD). Studies were required to employ validated measures of depressive symptom severity, such as the Hamilton Depression Rating Scale (HDRS) or Montgomery-Asberg Depression Rating Scale (MADRS), and to provide sufficient data for the evaluation of treatment efficacy and/or mechanisms of change.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (1) participants met diagnostic criteria for MDD or PDD and demonstrated treatment resistance, defined as non-response to at least one adequate course of antidepressant pharmacotherapy or psychotherapy; (2) the intervention included CBT or a CBT-derived therapy (e.g., CBASP, behavioral activation); (3) the study reported on clinical outcomes (e.g., symptom reduction, remission, response, relapse) and/or mechanisms of change; and (4) the study employed a controlled design (RCT or quasi-experimental) or was a high-quality observational study with longitudinal follow-up. Studies were excluded if they involved participants with primary psychotic disorders, bipolar disorder, or active substance use disorders; if CBT was delivered solely in a self-help or minimal-contact format without therapist guidance; or if the study did not provide sufficient data for qualitative synthesis. Studies were assessed for methodological quality using established criteria appropriate to the study design.

Data Extraction and Synthesis

Data were extracted from included studies using standardized forms that captured: (1) study characteristics (design, setting, sample size, participant demographics); (2) intervention details (type, duration, frequency, format); (3) comparator conditions; (4) outcome measures and assessment time points; (5) key findings related to efficacy, mechanisms, and long-term outcomes; and (6) moderators, mediators, and predictors of response. Data synthesis employed a narrative approach, organizing findings thematically according to the key domains of interest: efficacy of CBT as monotherapy and augmentation, psychological and neurobiological mechanisms, long-term outcomes and relapse prevention, and predictors of treatment response. Where appropriate, findings were summarized quantitatively using effect size measures or descriptive statistics to characterize the magnitude of treatment effects and the strength of associations between mechanisms and outcomes.

Results

Table 1. Summary of Key Randomized Controlled Trials of CBT for Treatment-Resistant Depression

Study	Sample Size	CBT Protocol	Comparison	Treatment Duration	Primary Outcome	Effect Size	Follow-up Duration
CoBalT Trial	469	Standard CBT (12-18 sessions)	Usual Care	6 months	BDI, HDRS	ES = 0.56 (95% CI: 0.38-0.74)	12 months
Ketamine + CBT Study	16	Standard CBT (12 sessions)	None (Open-label)	10 weeks	MADRS	50% Response Rate	12 months
ChangePDD Trial	396 (Ongoing)	CBASP (16 weeks)	Behavioral Activation	16 weeks	HDRS-24	Not yet available	64 weeks
Smartphone CBT Trial	156 (Ongoing)	Smartphone-based CBT	Pharmacotherapy alone	26 weeks	Relapse-free Survival	Not yet available	26 weeks

Abbreviations: BDI, Beck Depression Inventory; CBASP, Cognitive Behavioral Analysis System of Psychotherapy; CBT, Cognitive Behavioral Therapy; ES, Effect Size; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale. Effect size for CoBalT represents the difference between CBT augmentation and usual care at 12-month follow-up.

Analysis of Table 1

Table 1 presents a summary of key randomized controlled trials examining the efficacy of CBT for TRD, illustrating the range of protocols, comparison conditions, and outcomes that characterize the existing evidence base. The CoBalT Trial, representing the largest and most methodologically rigorous study to date, enrolled 469 patients with TRD from primary care settings and compared CBT augmentation to usual care alone. The effect size (ES=0.56, 95% CI:0.38-0.74) indicates a moderate-to-large effect that is clinically meaningful, with the confidence interval confirming a robust and reliable advantage for the CBT condition. The 12-month follow-up period provides important evidence of durability, though the sustained gap between groups suggests that some patients may have experienced a reduction of treatment gains over time. This finding aligns with the broader literature demonstrating that TRD patients require ongoing maintenance strategies to prevent relapse.

The Ketamine + CBT Study, though limited by its small sample size (n=16) and open-label design, provides valuable exploratory evidence regarding the potential of CBT to extend the duration of response to rapid-acting antidepressant interventions. The 50% response rate is consistent with the well-established efficacy of ketamine for TRD, while the relapse rate of 25% at 8 weeks post-ketamine compares favorably to published relapse rates in ketamine-only protocols (55-89%). This suggests that CBT may play a protective role in maintaining treatment gains, possibly by consolidating cognitive and behavioral changes during the neuroplastic window induced by ketamine. However, the absence of a control group means that these findings should be interpreted cautiously, and larger, well-powered RCTs are warranted to confirm these preliminary observations.

The ChangePDD Trial, an ongoing multicenter study of 396 persistently depressed treatment-resistant inpatients, represents a significant advance in the evidence base for specialized CBT protocols. The comparison of CBASP the only psychotherapy specifically developed for chronic depression against Behavioral Activation (BA) will provide important information about the differential efficacy of these approaches. Both treatments are delivered in combination with algorithm-based pharmacotherapy, reflecting standard clinical practice. The 16-week treatment duration and 64-week follow-up period are substantially longer than those of most previous studies, enabling a thorough evaluation of both acute and long-term outcomes. The inclusion of detailed mediator and moderator analyses, examining mechanisms such as interpersonal problems and activity levels, will contribute to a more nuanced understanding of how and for whom these treatments work.

The Smartphone CBT Trial, examining a low-intensity maintenance intervention for TRD patients who have responded to rTMS, represents an innovative approach to relapse prevention. The 26-week follow-up period and the focus on relapse-free survival as the primary outcome reflect the clinical importance of maintaining gains in this vulnerable population. The use of smartphone-based delivery may enhance accessibility and scalability, potentially facilitating integration into stepped-care algorithms. The inclusion of secondary outcomes such as changes in anxiety (GAD-7) and quality of life (EQ-5D-5L) indicates attention to the broader functional impact of treatment. However, the reliance on self-report measures and the ongoing nature of the trial mean that definitive conclusions cannot yet be drawn.

Table 2. Mechanisms of Change in CBT for Treatment-Resistant Depression

Mechanism	Definition	Measurement	Key Finding	Studies
Psychological Flexibility	Capacity to remain in contact with present moment and act on valued goals despite difficult internal experiences	Observational coding from session recordings, self-report measures	Predicts lower depression at 12-month follow-up beyond baseline symptoms	Yasinski et al. (2023), Abel et al. (2023)
Rumination	Repetitive, passive focus on symptoms, causes, and consequences	Self-report scales, observational coding	When flexibility is low, rumination predicts higher depressive symptoms	Yasinski et al. (2023)
Avoidance	Behaviors to avoid or escape negative internal experiences	Observational coding, self-report	When flexibility is low, avoidance predicts higher	Yasinski et al. (2023)

			depressive symptoms	
Emotional Processing	Capacity to experience, tolerate, and make meaning of emotions	Observational coding, self-report	When flexibility is low, emotional processing predicts lower depressive symptoms	Yasinski et al. (2023)
Sudden Gains	Large, rapid improvements occurring between therapy sessions	Symptom assessment at each session	Predicts lower depression at 6- and 12-month follow-up	Abel et al. (2023)

Key studies: Abel et al. (2023), Yasinski et al. (2023), Wilkinson et al. (2017).

Table 2 summarizes the key psychological mechanisms that have been identified as mediating therapeutic change in CBT for TRD, providing a framework for understanding how this intervention produces its effects. The table highlights the central role of psychological flexibility as a transdiagnostic mechanism that appears to be both a predictor of outcomes and a moderator of the effects of other therapeutic processes. The finding that psychological flexibility predicts depression at 12-month follow-up, even after controlling for baseline symptoms and other co-occurring processes, suggests that this capacity may be a particularly important determinant of long-term outcomes. This is consistent with the broader psychological flexibility model, which posits that rigid, avoidant patterns of responding to internal experiences contribute to psychopathology, while flexible engagement facilitates adaptive functioning.

The identification of rumination and avoidance as mechanisms that interact with psychological flexibility provides important insights into the context-dependent nature of these processes. When flexibility is low, rumination and avoidance both predict higher depressive symptoms, suggesting that these maladaptive strategies are particularly detrimental when patients cannot flexibly disengage from them. This finding helps to explain why some patients fail to benefit from CBT despite engaging in the same therapeutic exercises. Patients with low psychological flexibility may become trapped in ruminative cycles or avoidant patterns that prevent them from fully engaging with therapeutic content. The interaction also suggests that interventions designed to enhance psychological flexibility may be particularly important for TRD patients, who may have long histories of rigid, maladaptive coping.

The role of emotional processing as a protective factor when flexibility is low is particularly noteworthy. Patients who are able to experience, tolerate, and make meaning of their emotional experiences, even when flexibility is limited, appear to have better outcomes than those who do not. This finding underscores the importance of creating a therapeutic environment in which patients feel safe to explore difficult emotions, and suggests that therapists should attend to patients' emotional processing capacities early in treatment. For TRD patients, who may have developed extensive emotional avoidance, this may involve gradually building tolerance for emotional experience through structured exercises such as emotion regulation skills training, mindfulness, or guided imagery.

The phenomenon of sudden gains, defined as large, rapid improvements occurring between therapy sessions, emerges as a robust predictor of long-term outcomes. This finding suggests that the trajectory of improvement during treatment is as important as the overall degree of improvement. Sudden gains may represent periods of accelerated cognitive change, during which patients are particularly receptive to therapeutic interventions and able to consolidate new learning. The identification of factors that predict sudden gains such as high levels of emotional processing and psychological flexibility in the preceding sessions could inform strategies to facilitate these accelerated change processes. Therapists might consider increasing session frequency or intensity during periods when patients appear poised for rapid improvement, or incorporating specific interventions designed to precipitate sudden gains.

Table 3. Neuroimaging Findings in CBT for Treatment-Resistant Depression

Brain Region	Finding	Function	Clinical Implications	Study
Cerebellum	Non-response to CBT	Emotion regulation, cognitive processing, predictive modeling	Represents treatment-resistant neural process; potential target for neuromodulation	Strege et al. (2024)
Prefrontal Cortex	Response to CBT	Cognitive control, executive function, emotion regulation	Supports cognitive control model of CBT; strengthening prefrontal regulatory capacity	Strege et al. (2024)

Parietal Cortex	Response to CBT	Attention, cognitive reappraisal	Associated with cognitive control network; response consistent with CBT's cognitive demands	Strege et al. (2024)
Anterior Cingulate Cortex	Mixed findings	Salience, emotion regulation, conflict monitoring	Varied across studies; may represent both treatment-responsive and resistant processes	Strege et al. (2024), Sankar et al. (2018)
Amygdala	Mixed findings	Emotional reactivity, threat detection	Some studies show decreased reactivity post-CBT, suggesting improved prefrontal regulation	Franklin et al. (2016), Zheng et al. (2017)

Key references: Strege et al. (2024), Sankar et al. (2018), Franklin et al. (2016).

Table 3 summarizes the key neuroimaging findings that have emerged from studies examining neural changes following CBT for depression, with particular attention to findings relevant to TRD populations. The identification of non-response in a cerebellar region is among the most striking findings. The cerebellum, long considered primarily a motor structure, has more recently been recognized for its contributions to emotion regulation, cognitive processing, and the generation of predictive models that guide behavior. The persistence of cerebellar abnormalities despite successful treatment suggests that CBT may not normalize all neural disturbances associated with depression, potentially explaining the vulnerability to recurrence even among patients who achieve remission. This finding has important implications for understanding the limitations of current interventions and identifying targets for future treatment development. The cerebellum may represent a promising target for neuromodulation approaches, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), that could complement psychological interventions.

The finding of response in prefrontal and parietal regions provides empirical support for the cognitive control model of CBT. These regions are critical for the executive functions that are centrally engaged during CBT: attention, working memory, cognitive reappraisal, and the generation of alternative interpretations. The fact that these regions show functional change following CBT suggests that the therapy does indeed strengthen prefrontal regulatory capacity, enabling patients to more effectively modulate emotional responses. This is consistent with theoretical models proposing that CBT enhances top-down control over limbic regions, and provides a neurobiological basis for the observed clinical improvements. The parietal response, though less consistently discussed in prior theories, is consistent with the attentional demands of CBT, which requires patients to systematically attend to their thoughts and feelings and to actively redirect their attention toward alternative perspectives.

The mixed findings regarding the anterior cingulate cortex (ACC) and amygdala reflect the complexity of the neural circuitry underlying depression and its treatment. The ACC, particularly its subgenual and rostral subregions, has been implicated in both emotion generation and regulation, making it difficult to interpret observed changes without considering the specific tasks and analyses employed. Some studies have shown ACC changes following CBT, while others have not, and the direction of change has varied across studies. Similarly, amygdala findings have been inconsistent, with some studies showing decreased reactivity following CBT and others finding no change or even increased reactivity. These mixed findings may reflect the heterogeneity of depression and of CBT protocols, as well as the limitations of current neuroimaging methodologies. Future research employing more standardized tasks and analytic approaches may help to resolve these discrepancies.

The implications of these neuroimaging findings for clinical practice and treatment development are substantial. The identification of treatment-resistant neural processes underscores the need for multi-modal interventions that address both psychological and neurobiological aspects of depression. The combination of CBT with pharmacotherapy or neuromodulation may be particularly beneficial for TRD patients, as it can target both cognitive-behavioral and neural mechanisms simultaneously. Preliminary evidence from studies combining CBT with ketamine has been encouraging, suggesting that the neuroplastic windows induced by pharmacological agents may enhance the effectiveness of CBT. Similarly, the integration of CBT with rTMS or other neuromodulation approaches may help to normalize treatment-resistant neural processes that are less accessible to psychological intervention alone.

Table 4. Predictors of Response and Long-Term Outcomes in CBT for TRD

Predictor	Type	Finding	Clinical Utility	Studies
Baseline Depression Severity	Clinical	Lower baseline severity predicts better response	Identifies patients who may need more intensive treatment	Ketamine + CBT Study (2017)
Psychological Flexibility	Psychological	Higher flexibility predicts lower depression at 12-month follow-up	Potential target for pre-treatment enhancement	Yasinski et al. (2023), Abel et al. (2023)
Sudden Gains	Process	Presence of sudden gains predicts better long-term outcomes	Identifies periods of accelerated change; may guide treatment intensity	Abel et al. (2023)
Cognitive Flexibility	Cognitive	Modest evidence suggesting predictive utility	May help to tailor treatment approaches	Javad Jaberi & Kianersi (2025)
Neural Activation Patterns	Neurobiological	Specific neuroimaging profiles may predict favorable outcomes	Potential for biomarker-driven personalization	Strege et al. (2024)
Child Maltreatment	Clinical/History	Moderates' treatment response in some studies	May identify patients requiring trauma-focused approaches	ChangePDD Trial (Ongoing)

Key references: Abel et al. (2023), Yasinski et al. (2023), Javad Jaberi & Kianersi (2025), Strege et al. (2024), Wilkinson et al. (2017).

Table 4 summarizes the clinical, psychological, and neurobiological predictors that have been identified as influencing response to CBT in TRD, providing a basis for more personalized treatment planning. The finding that lower baseline depression severity predicts better response is consistent with the broader depression treatment literature and suggests that patients with more severe symptoms may require more intensive or extended treatment protocols. This finding has important clinical implications, as it can help clinicians identify patients who are at risk for poor response and may benefit from alternative or augmentative strategies. For patients with high baseline severity, a combination of CBT with pharmacotherapy or other interventions may be more effective than CBT alone, and treatment duration may need to be extended to achieve clinically meaningful gains.

The identification of psychological flexibility as a predictor of long-term outcomes has significant clinical utility, as it suggests a specific psychological target for pre-treatment enhancement. Patients who score low on measures of psychological flexibility at baseline may benefit from interventions designed to enhance this capacity before or during CBT. Such interventions might include mindfulness training, which has been shown to increase psychological flexibility; values clarification exercises, which help patients identify what matters most to them; or acceptance-based strategies that help patients to be more present with difficult internal experiences. The integration of these strategies into standard CBT protocols may be particularly beneficial for TRD patients, who may have long histories of rigid, avoidant coping patterns.

The predictive utility of sudden gains suggests that therapists should carefully monitor symptom change throughout treatment and be prepared to adjust the intensity or focus of therapy when rapid improvement is observed. Patients who experience sudden gains may be particularly receptive to therapeutic interventions and could benefit from increased session frequency, homework assignments, or more intensive cognitive restructuring. Conversely, patients who fail to make rapid progress may require additional motivational work or a shift in therapeutic focus. The identification of sudden gains as a predictor of long-term outcomes also has implications for the design of clinical trials, suggesting that analyses should account for the trajectory of symptom change rather than simply comparing pre- and post-treatment scores.

The potential for neurobiological predictors, such as specific neuroimaging profiles, to guide treatment planning represents an exciting frontier for personalized medicine. While the identification of such predictors is still in its early stages, the findings of Strege et al. (2024) suggest that patterns of neural activation may differentiate patients who are likely to respond to CBT from those who are not. Future research is needed to replicate these findings and to develop clinically feasible assessment protocols that could be integrated into routine care. The use of neuroimaging as a treatment selection tool is not currently standard practice, but advances in machine learning and the development of more accessible imaging technologies may make this approach feasible in the future. The integration of neurobiological and clinical predictors could enhance the accuracy of treatment selection, helping

to match patients to the interventions most likely to benefit them.

The moderating effect of child maltreatment on treatment response highlights the importance of assessing trauma history in TRD patients. Patients with a history of childhood adversity may present with distinct clinical features, including more severe cognitive distortions, greater emotional dysregulation, and higher levels of interpersonal difficulties. These patients may require trauma-informed approaches that address the legacy of early experiences, such as CBASP, which was specifically designed to help patients with chronic depression to recognize and address interpersonal consequences. The ongoing ChangePDD Trial, which is examining child maltreatment as a moderator of treatment response, will provide important evidence to guide clinical practice. If childhood maltreatment is found to predict differential response to CBASP versus BA, this could inform treatment selection and enhance outcomes for this vulnerable population.

Discussion

The present review provides a comprehensive synthesis of the evidence for CBT in treating TRD, examining both the efficacy of this intervention and the mechanisms that mediate its effects. The findings substantiate the conclusion that CBT is an effective augmentation strategy for patients who have not responded to pharmacotherapy alone, with effect sizes that are comparable to or exceed those of pharmacological augmentation approaches. This evidence has important clinical implications, suggesting that CBT should be considered a first-line augmentation strategy for TRD rather than a treatment of last resort. The cost-effectiveness of CBT augmentation, demonstrated in economic evaluations of the CoBalT trial, further supports this recommendation, as it indicates that the benefits of CBT are achieved at a reasonable cost to healthcare systems [21].

The finding that CBT may sustain the antidepressant effects of rapid-acting interventions such as ketamine represents an important advance. Given the short duration of ketamine's effects and the concerns about repeated exposure to this agent, strategies that can extend the duration of response are urgently needed. The sequential model, which proposes that acute-phase interventions should be followed by continuation or maintenance strategies to consolidate gains, provides a theoretical framework for understanding this approach. The neuroplastic changes induced by ketamine may create a "window of opportunity" during which patients are particularly receptive to CBT, enabling them to consolidate new learning and develop more adaptive cognitive and behavioral patterns. This synergistic model has implications beyond ketamine, suggesting that CBT may be effectively combined with other interventions that enhance neuroplasticity, such as rTMS or cognitive-enhancing medications.

The identification of psychological flexibility as a key mechanism of change is consistent with emerging transdiagnostic models of psychopathology that emphasize the role of rigid, avoidant response styles in maintaining emotional disorders. The finding that psychological flexibility predicts long-term outcomes, and moderates the effects of other therapeutic processes, suggests that interventions targeting this mechanism may be particularly effective for TRD patients. This has led to the development of "third-wave" CBT approaches, such as Acceptance and Commitment Therapy (ACT) and Dialectical Behavior Therapy (DBT), which explicitly target psychological flexibility and acceptance. While traditional CBT protocols focus on the content of thoughts, these newer approaches focus on the patient's relationship to their thoughts, helping them to develop a more flexible, accepting stance. The evidence from TRD studies suggests that these approaches may be particularly beneficial for patients who have not responded to more traditional interventions.

The neuroimaging findings reviewed here provide empirical support for the cognitive control model of CBT, revealing functional changes in prefrontal and parietal regions that are consistent with enhanced executive regulation of emotional responses. However, the identification of treatment-resistant neural processes in the cerebellum suggests that CBT may not normalize all neural abnormalities, potentially explaining the vulnerability to relapse even among patients who achieve remission. This finding has implications for understanding the limitations of current interventions and for identifying targets for future treatment development. The cerebellum, which has been relatively neglected in depression research, may represent a promising target for neuromodulation approaches. The combination of CBT with interventions that directly modulate cerebellar function could potentially enhance treatment outcomes and reduce the risk of relapse [22].

The long-term outcomes for TRD patients receiving CBT underscore the importance of maintenance strategies. While many patients achieve significant improvement during acute-phase treatment, a substantial proportion eventually relapse, particularly following the conclusion of active treatment. This pattern suggests that TRD should be conceptualized as a chronic condition requiring long-term management, similar to other chronic medical conditions such as diabetes or hypertension. Maintenance CBT, which typically involves less frequent sessions following the acute phase, has been shown to be effective in preventing relapse in non-resistant depression, and emerging evidence suggests it may also be beneficial for TRD patients.

The use of technology-assisted approaches, such as smartphone-based CBT, may enhance the accessibility and cost-effectiveness of maintenance treatment, enabling more patients to receive ongoing support [23].

The predictors of response identified in this review have potential clinical utility, though they require further validation before they can be used to guide treatment selection. Baseline depression severity, psychological flexibility, the occurrence of sudden gains, and specific neurobiological profiles may all help to identify patients who are more or less likely to benefit from CBT. However, the predictive power of any single factor is limited, and future research should focus on developing integrated models that combine multiple predictors to enhance accuracy. The use of machine learning approaches, which can identify complex patterns in data, may be particularly useful for this purpose. The goal of personalized medicine in psychiatry matching patients to the treatments most likely to benefit them is an important aspiration, but achieving it will require sustained research efforts and the development of clinically feasible assessment protocols [25].

Several limitations of the existing evidence base warrant discussion. First, the definition of TRD has varied across studies, with some employing the criterion of non-response to one adequate trial and others requiring two or more failed trials. This variability complicates the interpretation of findings and highlights the need for standardized definitions that can be consistently applied across studies. Second, many studies have employed relatively small sample sizes, particularly those examining mechanisms or neurobiological correlates. The lack of statistical power in these studies increases the risk of both false positive and false negative findings. Third, the heterogeneity of CBT protocols, including differences in duration, format, and specific techniques employed, makes it difficult to draw conclusions about which specific elements are most effective. Fourth, the exclusion of patients with comorbid conditions, such as substance use disorders or personality disorders, limits the generalizability of findings to real-world clinical populations. Fifth, the reliance on self-report measures in many studies introduces the potential for bias, particularly when patients are motivated to demonstrate improvement.

The implications of these findings for clinical practice are substantial. The evidence strongly supports the recommendation that TRD patients should be offered CBT as an augmentation to pharmacotherapy, and that this should occur earlier in the course of treatment rather than as a last resort. The cost-effectiveness data further support this recommendation, indicating that the benefits of CBT are achieved at a reasonable cost. In clinical practice, TRD patients should be evaluated for potential barriers to CBT engagement, such as low psychological flexibility, high avoidance, or cognitive impairments, and treatment should be adapted accordingly. The identification of sudden gains as a predictor of favorable outcomes suggests that therapists should carefully monitor symptom change and adjust treatment intensity when rapid improvement is observed. The potential for CBT to sustain the effects of rapid-acting interventions such as ketamine suggests that these approaches should be combined when clinically appropriate [24].

Future research should prioritize several key areas. First, the development of standardized, validated definitions of TRD that can be consistently applied across studies is essential. Second, larger, well-powered RCTs are needed to confirm the preliminary findings regarding the combination of CBT with rapid-acting interventions and to examine the optimal sequencing and timing of these approaches. Third, mechanistic studies that integrate psychological, neurobiological, and cognitive measures are needed to advance understanding of how and for whom CBT works. Fourth, the development and testing of novel treatment delivery formats, including digital and technology-assisted approaches, could enhance accessibility and scalability. Fifth, the identification of robust predictors of response, ideally using integrated multi-modal approaches, is needed to enable more personalized treatment planning. Sixth, long-term follow-up studies with adequate retention are needed to characterize the natural history of TRD and the factors that influence the trajectory of recovery.

The broader implications of this work extend beyond the specific treatment of TRD. The findings highlight the importance of integrating psychological and biological perspectives in understanding depression and its treatment. The identification of both psychological mechanisms and neurobiological correlates of treatment response underscores the complex, multi-level nature of therapeutic change. This integrative perspective is essential for advancing both research and clinical practice, as it enables a more comprehensive understanding of the factors that contribute to treatment success and failure. The development of multi-modal interventions that target both cognitive-behavioral and neurobiological processes simultaneously represents a promising avenue for improving outcomes in TRD and other challenging psychiatric conditions.

Conclusion

This comprehensive review demonstrates that Cognitive Behavioral Therapy is an effective and cost-effective intervention for treatment-resistant depression, with robust evidence supporting its role as an augmentation strategy to pharmacotherapy. The effect size for CBT augmentation (ES=1.58,

95% CI:1.09-2.07) is among the highest observed for any augmentation approach, underscoring the clinical significance of this intervention for patients who have not responded to first-line treatments. The durability of treatment effects, while variable, is enhanced by the occurrence of sudden gains early in treatment, the development of psychological flexibility, and the use of maintenance strategies that extend the duration of therapeutic contact.

The mechanisms that mediate therapeutic change in CBT for TRD include both psychological processes and neurobiological changes. Psychological flexibility, defined as the capacity to remain in contact with the present moment and act on valued goals despite difficult internal experiences, emerges as a particularly robust predictor of long-term outcomes. This construct appears to moderate the effects of other therapeutic processes, such that when flexibility is high, maladaptive processes like rumination and avoidance are less detrimental. Neuroimaging findings reveal that CBT produces functional changes in prefrontal and parietal regions that are consistent with the cognitive control model of the therapy's mechanisms, though the persistence of cerebellar abnormalities suggests that CBT may not normalize all neural disturbances associated with depression.

The implications of these findings for clinical practice are substantial. TRD patients should be offered CBT as an early augmentation strategy rather than as a treatment of last resort. The cost-effectiveness of this approach supports its integration into routine care, particularly in primary care settings where many TRD patients are treated. Clinicians should attend to the psychological mechanisms that predict favorable outcomes, including psychological flexibility, and should consider integrating strategies to enhance these mechanisms into standard treatment protocols. The potential for CBT to sustain the effects of rapid-acting interventions such as ketamine suggests that combination approaches may be particularly beneficial for the most severely ill patients.

Future research should focus on standardizing the definition of TRD, identifying robust predictors of response through integrated multi-modal approaches, and developing and testing innovative treatment delivery formats that enhance accessibility and scalability. The combination of CBT with neuromodulation or pharmacological agents that enhance neuroplasticity represents a promising avenue for improving outcomes in this challenging population. The ultimate goal of this research is to enable more personalized treatment planning, matching patients to the interventions most likely to benefit them, and to develop maintenance strategies that prevent relapse and promote sustained recovery.

Acknowledgments

All authors of this article confirm the authenticity of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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