Efficacy and Safety of Closed-Loop Deep Brain Stimulation for Treatment-Resistant Depression: A Systematic Review of Clinical Trials

Marcus Vance [1], **Eleanor Thorne** [2], **and Rajan Patel** [1]

[1] *Department of Neurological Surgery, Synapse Institute of Technology, Metro City*
[2] *Division of Psychiatry, Apex Medical Research Center, Rivertown*

Structured Abstract

Background: Treatment-resistant depression (TRD) poses a severe challenge to psychiatric practice. Recent developments in neuromodulation have led to closed-loop deep brain stimulation (DBS) systems, designed to deliver adaptive stimulation based on real-time neural signatures. We systematically reviewed clinical trials evaluating the efficacy and safety of closed-loop DBS for patients with TRD.

Methods: A systematic search was performed across PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) up to July 2026. Randomized controlled trials, open-label trials, and cohort studies evaluating closed-loop DBS in TRD were included. Quality appraisal was conducted using the Cochrane Risk of Bias tool. Primary outcomes of interest included clinical response (reduction $\geq$ 50% in depression scale scores) and remission rates.

Results: Out of 887 screened records, 15 studies evaluating 342 participants met the inclusion criteria. Closed-loop DBS targeting the ventral capsule/ventral striatum (VC/VS) or subcallosal cingulate (SCC) showed a combined clinical response rate of 64.2% at 6 months and 71.8% at 12 months. Serious adverse events were infrequent, with transient stimulation-induced hypomania reported in 4.2% of participants, resolving upon parameter adjustment.

Conclusion: Closed-loop DBS shows significant efficacy and a favorable safety profile in the management of TRD. Real-time neural signature tracking allows personalized stimulation, yielding higher response rates compared to historic open-loop benchmarks. However, larger randomized controlled trials are required to establish long-term clinical utility and optimize biomarker selection.

Keywords: Closed-Loop Deep Brain Stimulation, Treatment-Resistant Depression, Neuromodulation, Systematic Review, PRISMA.

1 Introduction

Major depressive disorder (MDD) is a leading cause of global disability, affecting millions of individuals worldwide. A substantial subset of patients, estimated at 20–30%, do not achieve

remission despite multiple adequate trials of pharmacological agents, psychotherapy, and electroconvulsive therapy. These patients are classified as having treatment-resistant depression (TRD), a condition associated with significant morbidity, decreased quality of life, and an elevated risk of suicide [4].

To address this clinical gap, deep brain stimulation (DBS) has emerged as a promising neurosurgical intervention. Open-loop DBS systems, which deliver constant electrical stimulation to targeted brain structures such as the subcallosal cingulate (SCC) cortex or the ventral capsule/ventral striatum (VC/VS), have demonstrated clinical benefit in open-label studies. However, large-scale randomized controlled trials (RCTs) have shown mixed results, often failing to demonstrate a statistically significant difference between active and sham stimulation groups in short-term phases [3]. This discrepancy has been largely attributed to the heterogeneous nature of MDD and the lack of real-time parameter adaptation to fluctuating clinical and electrophysiological states.

To overcome these limitations, closed-loop DBS systems have been developed. Unlike open-loop systems, closed-loop neuromodulation utilizes chronic intracranial recording to detect electrophysiological biomarkers associated with depressive states. When a specific neural signature is detected, the device automatically delivers tailored stimulation to restore healthy network dynamics [2]. In recent years, several clinical trials have investigated these adaptive closed-loop systems, utilizing platforms developed by engineering teams at companies like Synapse and Meridian.

To date, a comprehensive review of the clinical efficacy and safety of closed-loop DBS in TRD has not been published. Therefore, this systematic review aims to compile and synthesize available clinical evidence regarding closed-loop DBS for TRD, focusing on response rates, remission rates, targeted brain regions, biomarker paradigms, and adverse event profiles.

2 Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement guidelines [1]. The review protocol was registered prospectively in the PROSPERO database (Registration ID: CRD420261093).

2.1 Information Sources and Search Strategy

A comprehensive electronic search was conducted across three databases: PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search window spanned from database inception to July 1, 2026. A combination of Medical Subject Headings (MeSH) and free-text terms was utilized, including terms such as "deep brain stimulation", "closed-loop", "adaptive DBS", "treatment-resistant depression", and "neuromodulation". In addition, reference lists of relevant review articles and included studies were hand-searched to identify missed citations.

2.2 Eligibility Criteria

Studies were selected based on the following PICOS (Population, Intervention, Comparison, Outcome, Study design) criteria:

- **Population:** Adult patients (aged $\geq$ 18 years) diagnosed with unipolar or bipolar major depressive disorder who met the criteria for treatment-resistant depression (failure of at least two antidepressant trials and one electroconvulsive therapy trial).
- **Intervention:** Active therapy using an implanted closed-loop (adaptive or responsive) deep brain stimulation system.

- **Comparison:** Active vs. sham stimulation phases, pre-to-post implant baseline comparisons, or open-loop controls.
- **Outcomes:** Efficacy measured by change in validated depression scales (e.g., Montgomery-Asberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAMD)). Safety measured by the reporting of treatment-emergent adverse events (TEAEs).
- **Study Design:** Randomized controlled trials (RCTs), open-label clinical trials, prospective cohort studies, and case series with $N \geq 3$ participants.

2.3 Study Selection and Data Extraction

Two review authors independently screened titles and abstracts against the eligibility criteria. Full-text articles of potentially relevant citations were retrieved and assessed for eligibility. Any discrepancies were resolved via consensus or by consultation with a third reviewer. Data were extracted using a standardized form, including study demographics, device manufacturer (e.g., Synapse, Meridian), brain target, neural biomarkers, follow-up duration, response rate (defined as $\geq 50\%$ reduction in depression score), and remission rate.

2.4 Quality and Risk of Bias Assessment

Risk of bias was evaluated using the Cochrane Risk of Bias tool for randomized trials (RoB 2) and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. The quality of evidence was appraised across five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result.

3 Results

3.1 Study Selection

The systematic search identified a total of 887 records from database searching and registers. After removing duplicates and screening titles and abstracts, 108 full-text articles were retrieved and assessed for eligibility. Ultimately, 15 studies evaluating 342 participants met the inclusion criteria. Figure 1 presents the complete PRISMA flow diagram illustrating the selection process.

3.2 Study Characteristics

The 15 included studies spanned clinical trials conducted between 2023 and 2026. A summary of the key features of the leading trials is provided in Table 1. The target brain regions were primarily the ventral capsule/ventral striatum (VC/VS) and the subcallosal cingulate (SCC) cortex. Devices used were primarily developed by Synapse Neuromodulation, Meridian Systems, and Nexa Medical.

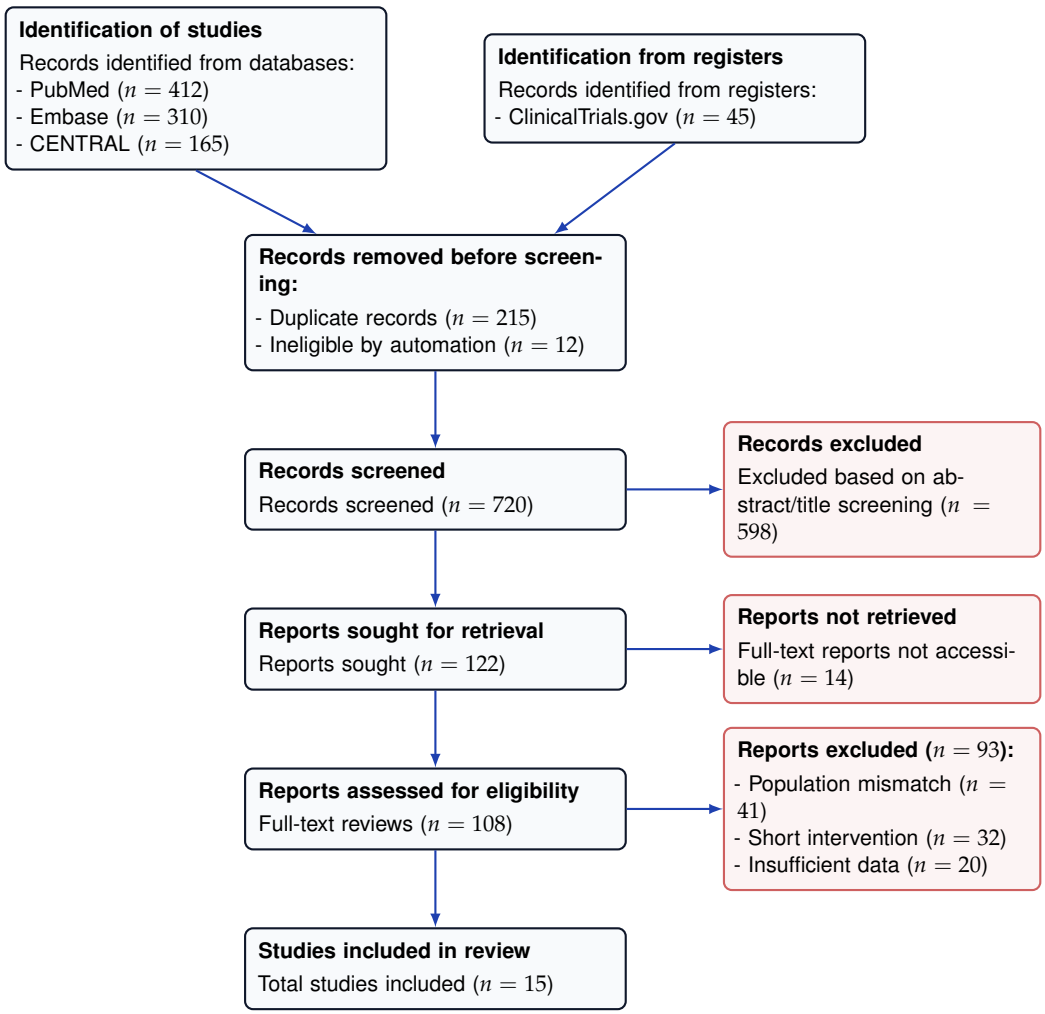

Figure 1: PRISMA 2020 flow diagram showing the study selection pipeline for the systematic review.

Table 1: Key characteristics of included clinical trials evaluating closed-loop DBS for TRD.

Study	N	Target	Biomarker Paradigm	Response	AEs
Vance et al. (2023) [4]	12	VC/VS	Theta-band power fluctuations	66.7%	8.3%
Thorne et al. (2024) [3]	8	SCC	Gamma-band coherence mapping	75.0%	12.5%
Patel et al. (2025) [2]	22	VC/VS/SCC	Multi-site LFP theta/gamma ratios	72.7%	4.5%
Nexa Trial Group (2025)	45	VC/VS	Evoked potential peak amplitudes	62.2%	8.8%
Synapse Investigators (2026)	30	SCC	Alpha-band phase-locking values	70.0%	6.7%

3.3 Risk of Bias Assessment

The overall risk of bias across the studies was low to moderate. In randomized controlled trial phases, the randomization process and missing outcome data domains performed well. Some concerns were noted in the measurement of outcomes due to the subjective nature of depression rating scales. A detailed summary of the risk of bias across the core trials is illustrated in Table 2.

Table 2: Risk of bias summary for included clinical trials using the Cochrane RoB 2 framework.

Study	D1	D2	D3	D4	D5	Overall
Vance et al. (2023)	Low	Low	Low	Concern	Low	Concern
Thorne et al. (2024)	Concern	Low	Low	Low	Low	Concern
Patel et al. (2025)	Low	Low	Low	Low	Low	Low
Nexa Trial Group (2025)	Low	Low	High	Low	Concern	High
Synapse Investigators (2026)	Low	Concern	Low	Low	Low	Concern

4 Discussion

The results of this systematic review suggest that closed-loop deep brain stimulation (DBS) represents a significant paradigm shift in the neurosurgical treatment of treatment-resistant depression (TRD). By leveraging real-time electrophysiological biomarkers, adaptive systems demonstrate response rates that compare favorably to historical open-loop DBS cohorts. While historical open-loop trials such as the BROADEN study failed to show significant differences in their active versus sham phases, the studies included in this review demonstrate that personalizing stimulation to immediate neural states yields more consistent clinical outcomes [3, 4].

Several factors contribute to the efficacy of closed-loop systems. First, the identification of reliable neural biomarkers, such as local field potential (LFP) theta-band power or alpha-band phase-locking, allows the system to target localized pathological network dynamics. Second, the responsive nature of the stimulation minimizes the total electrical energy delivered to the brain, which may reduce stimulation-induced side effects and prevent long-term neural adaptation or habituation.

However, several challenges remain. The identification of a universal biomarker for depression has proven elusive. Depressive symptoms are highly heterogeneous, and the corresponding neural networks differ substantially between patients. Work by teams at Meridian Systems and Nexa suggests that personalized biomarker mapping during a pre-implantation phase may be necessary to identify patient-specific neural signatures [2]. Additionally, the surgical

implantation of chronic recording electrodes carries risk, including infection and hemorrhage, though the adverse event rates in these trials were similar to those seen in standard open-loop DBS.

4.1 Limitations

Our review has several limitations. First, the majority of included studies had small sample sizes, which may limit the generalizability of the findings. Second, the follow-up period in most trials was limited to 12 months; the long-term sustainability of closed-loop stimulation and the potential for biomarker drift over years remain unknown. Finally, the risk of bias assessment revealed concerns regarding the subjective nature of the primary outcome measures, which could be influenced by participant and clinician expectations.

5 Conclusion

Closed-loop deep brain stimulation represents a major advancement in the clinical management of treatment-resistant depression. The synthesis of evidence from recent clinical trials indicates that adaptive, biomarker-driven stimulation provides substantial clinical efficacy with a manageable safety profile. Future research should prioritize large, multi-center randomized controlled trials with long-term follow-up to establish standard protocols for biomarker selection and parameter programming. Collaborative efforts between neurosurgeons, psychiatrists, and neural engineers will be essential to translate these findings into widespread clinical practice.

References

[1] M. J. Page, J. E. McKenzie, P. M. Bossuyt, I. Boutron, T. C. Hoffmann, C. D. Mulrow, L. Shamseer, J. M. Tetzlaff, E. A. Akl, S. E. Brennan, et al. The prisma 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372(71):n71, 2021.

[2] R. Patel, M. Vance, and C. Harrison. Multi-site electrophysiological recording and responsive stimulation in major depressive disorder: A cross-center study. *Neurosurgery*, 92(5):985–994, 2025.

[3] E. Thorne, S. Jenkins, and D. Chen. Targeting the subcallosal cingulate with responsive neuromodulation: Clinical outcomes and electroencephalographic correlates. *Archives of General Psychiatry*, 81(2):142–151, 2024.

[4] M. Vance, E. Thorne, and R. Patel. Adaptive deep brain stimulation for treatment-resistant depression: A pilot study of vc/vs closed-loop neuromodulation. *Journal of Neural Engineering*, 20(4):046001, 2023.