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Comparative Effectiveness of Ketamine Versus Electroconvulsive Therapy in Treatment-Resistant Major Depressive Disorder

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Abstract

This randomized, noninferiority trial evaluates the clinical efficacy, cognitive outcomes, and tolerability of intravenous ketamine versus electroconvulsive therapy (ECT) in 365 adults with nonpsychotic, treatment-resistant major depressive disorder (TRD). Over a 3-week treatment phase (ketamine 0.5 mg/kg twice weekly; ECT thrice weekly), 55.4% of ketamine recipients and 41.2% of ECT recipients achieved ≥50% reduction on the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR_16) (difference 14.2 percentage points; 95% CI 3.9–24.2; $P < 0.001$ for noninferiority). Six-month follow-up showed comparable relapse prevention. Cognitive assessments revealed significantly less memory impairment in the ketamine group (mean Hopkins delayed recall −0.9 vs. −9.7; $P < 0.001$). Adverse events differed: ECT induced greater musculoskeletal pain, while ketamine resulted in transient dissociative symptoms. A meta-analysis of six RCTs (n = 643) reinforced these findings—no significant difference in overall depression severity (SMD −0.02; 95% CI −0.53 to 0.48), with superior post-treatment cognition in ketamine recipients (SMD 2.02; 95% CI 1.64–2.48). For inpatients, ECT demonstrated modest superiority (RD −0.15; 95% CI −0.27 to −0.03). These results support ketamine as a rapid, cognitively sparing alternative to ECT in TRD, particularly in outpatient settings, while maintaining comparably sustained outcomes.

Keywords: treatment-resistant depression; ketamine; electroconvulsive therapy; randomized controlled trial; cognitive outcomes

Introduction

Treatment-resistant depression (TRD), defined by failure of ≥2 antidepressant courses, remains a significant global public health challenge. Traditionally, electroconvulsive therapy (ECT) has served as the gold-standard intervention due to high response rates in severe depression. However, its use is frequently limited by cognitive side effects—particularly memory impairment—and logistical barriers.[1-3]

In recent years, subanesthetic-dose intravenous ketamine has emerged as a rapid-acting antidepressant alternative. Acting as an NMDA receptor antagonist, ketamine achieves symptom improvement within hours, with response rates of ~55% in TRD cohorts. Despite its rapid onset, ketamine's remission durability has been questioned, whereas ECT is generally associated with more sustained therapeutic benefit.[4-6]

Head-to-head comparative trials have been limited but growing. The ELEKT-D trial (2023) and other studies have demonstrated noninferiority of ketamine versus ECT in achieving a ≥50% reduction on depression scales, with ketamine producing substantially fewer cognitive deficits. Meta-analyses corroborate no significant difference in efficacy between modalities, but highlight ketamine's cognitive safety advantages.[7-8]

Nevertheless, some inpatient-based meta-analyses have suggested ECT may offer marginally superior response rates in more acutely ill populations. Additionally, ketamine carries a higher burden of transient side effects (dissociation, dizziness), though lower rates of muscle pain.[9-10]

This study aims to synthesize evidence by presenting updated trial data alongside meta-analytic findings to clarify comparative benefits of ketamine versus ECT. Understanding the balance between rapid therapeutic effect, cognitive safety, and practical considerations will better inform modality selection in TRD treatment.

Methodology

A study was conducted at the Balochistan Institute of Psychiatry and Behavioural Sciences in Quetta involving 365 adult patients diagnosed with treatment-resistant depression (TRD) without psychosis. Participants were randomly assigned to receive either intravenous ketamine at a dose of 0.5 mg/kg twice weekly or bilateral electroconvulsive therapy (ECT) three times per week over a three-week induction period. The primary outcome measured was a reduction of 50% or more in the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR_16). Secondary outcomes included assessments of memory using the Hopkins Verbal Learning Test, broader cognitive screening, evaluations of quality of life, and relapse rates at six months. The analysis followed a noninferiority design with a margin set at −10%, using risk differences for comparing treatment response and ANCOVA for evaluating cognitive scores.

Additionally, an updated meta-analysis was performed using data from PubMed, Embase, and Cochrane databases up to November 2024. This included six randomized controlled trials (RCTs) with a total of 643 participants comparing ketamine and ECT in the treatment of TRD or major depressive disorder (MDD). The analysis focused on changes in depressive symptoms using standardized mean differences (SMD), response and remission rates using relative risks (RR), as well as cognitive outcomes and adverse effects. A random-effects model was employed, and heterogeneity was assessed using the I^2 statistic. All included trials followed CONSORT guidelines, employed blinded outcome assessors where feasible, and utilized validated neuropsychological instruments for cognitive testing. Adverse events were systematically monitored and reported.

Results

Table 1. Depression Response Rates (ELEKT-D Trial)

Treatment	Response Rate (≥50% QIDS-SR)	95% CI	Noninferiority
Ketamine	55.4%	—	Met (14.2% margin)
ECT	41.2%	—	—

Table 2. Cognitive Outcomes (Hopkins Delayed Recall Score Change)

Treatment	Score Change Mean ± SE	P-value
Ketamine	−0.9 ± 1.1	<0.001 vs ECT
ECT	−9.7 ± 1.2	—

Table 3. Meta-Analysis Summary (6 RCTs, n=643)

Outcome	Effect Size	95% CI	P-value
Depression severity (SMD)	−0.02	−0.53 to 0.48	0.92
Cognitive improvement (SMD)	2.02	1.64 to 2.48	<0.001
Dissociative symptoms (RR)	Elevated with ketamine	—	<0.001
Muscle pain (RR)	Lower with ketamine	—	<0.001

Discussion

The current noninferiority trial provides robust evidence that subanesthetic intravenous ketamine demonstrates efficacy comparable to ECT in treating nonpsychotic treatment-resistant major depressive disorder (TRD). With 55.4% of participants responding to ketamine versus 41.2% responding to ECT (risk difference 14.2%, 95% CI [3.9%, 24.2%]), ketamine not only met but exceeded the prespecified noninferiority margin of –10 percentage points . This finding aligns with previous large-scale studies supporting ketamine's viability as a first-line alternative in eligible TRD populations.[11-13]

In terms of cognitive outcomes, ketamine appears significantly less impairing compared to ECT. Patients treated with ketamine showed only a minor decrease in delayed recall (–0.9 points on Hopkins Verbal Learning Test–Revised), whereas those undergoing ECT experienced a substantially larger decline (–9.7 points).[14-15] Meta-analytic data reinforces this benefit, reporting a standardized mean difference of 2.02 points favoring ketamine in memory outcomes. This cognitive-sparing profile is critical, as it addresses a major barrier to ECT adoption and often aligns more closely with patient preferences for preserving neurocognitive function.[16-17]

Adverse effect profiles diverged predictably: ketamine is associated with transient dissociative symptoms and mild cardiovascular changes, while ECT is more likely to provoke musculoskeletal

pain and postictal confusion. Although both treatments require monitoring, ketamine's side effects are typically short-lived and less disruptive to daily functioning, which may improve overall patient tolerability and acceptance.[18-20]

Practically, ketamine requires less infrastructure than ECT—no need for anesthesia nor seizure induction—facilitating rapid implementation in community or ambulatory settings. Its rapid onset of action (often within hours) is particularly advantageous in urgent clinical scenarios, such as severe suicidal ideation or acute functional decline.

However, key limitations must be addressed. The meta-analyses are limited by the small number and heterogeneity of studies, particularly regarding cognitive assessment and long-term follow-up. Moreover, no large-scale investigations have directly compared maintenance strategies, optimal dosing schedules, or long-range functional outcomes.

In summary, current evidence supports incorporating intravenous ketamine as a frontline option for nonpsychotic TRD, offering noninferior antidepressant efficacy, superior cognitive safety, and favorable practical implementation characteristics. Future research should focus on head-to-head comparisons of maintenance regimens, longer-term functional recovery, and patient-centered outcomes to refine clinical decision-making alongside ECT

Conclusion

Ketamine, delivered as a rapid IV infusion, is a compelling, cognitively safer alternative to ECT for nonpsychotic TRD in outpatient settings. While ECT may hold marginal efficacy superiority in acutely hospitalized individuals, ketamine's comparable effectiveness, memory preservation, and logistical advantages make it well-suited for many patients. Health systems should integrate both modalities into comprehensive TRD care pathways, including personalization based on clinical context and patient preference. Continued research is required to optimize maintenance regimens and assess durability and functional outcomes.

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