ROUND THE CORNER

Ketamine for unipolar major depression: critical examination of antidepressant effects†

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SUMMARY

This critical appraisal of a Cochrane Review assesses the efficacy of ketamine for treating unipolar major depressive disorder. The review included 31 randomised controlled trials involving ketamine. Results indicate that intravenous (i.v.) ketamine significantly improves antidepressant response compared with i.v. saline and, to a lesser extent, i.v. midazolam within 24–72 h. However, the evidence is constrained by performance bias owing to masking ('blinding') concerns and study heterogeneity, necessitating further robust research to confirm ketamine's clinical potential.

KEYWORDS

Electroconvulsive therapy; depressive disorders; antidepressants; systematic review; general adult psychiatry.

Depression, specifically unipolar major depressive disorder (MDD), is a prevalent and debilitating mental health condition commonly characterised by anhedonia, persistent low mood and psychomotor impairment. The primary antidepressant treatments available in the UK are selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs), alongside forms of cognitive–behavioural therapy (CBT) – both often requiring weeks to achieve therapeutic effect and not universally effective (National Institute for Health and Care Excellence 2024). In the case of a severe depressive episode requiring a rapid response, electroconvulsive therapy (ECT) may be considered; however, this necessitates general anaesthesia to allow an electrical current to be delivered to the brain to induce swift mood relief (UK ECT Review Group 2003).

Ketamine has emerged as a novel rapid-acting agent for unipolar depression. Originally manufactured in the 1960s for its anaesthetic and analgesic properties, ketamine's role has expanded owing to its unique mechanism of action on the brain's glutaminergic system. Unlike traditional antidepressants that primarily modulate monoamine neurotransmitters, ketamine acts as an *N*-methyl-D-aspartate (NMDA) receptor antagonist, influencing transmission of glutamate, which is a crucial excitatory neurotransmitter in the central nervous system (Hirota 2018). The serendipitous discovery of using sub-anaesthetic doses of ketamine for rapid antidepressant effects offers a promising therapeutic option in urgent clinical situations.

Clinical research investigating ketamine's antidepressant effect and clinical potential generally offers evidence for the drug's efficacy in reducing depressive symptoms, usually within hours to days (Fond 2014; Romeo 2015; Corriger 2019). However, rigorous scrutiny must be applied to the findings to investigate whether they are without bias and whether there is scope for clinical translatability. Furthermore, given its increasing off-label recreational use, questions about ketamine's long-term safety profile must also be investigated (Kalsi 2011). This Round the Corner critical appraisal aims to shine a light on the findings of a Cochrane Review of ketamine and other glutamate receptor modulators for depression (Dean 2021). Owing to the limits of this appraisal and the limited evidence for the other glutamatergic agents assessed in the review, I focus here solely on ketamine.

What was investigated in the Cochrane Review?

Dean et al's (2021) database search (up to July 2020) identified 31 eligible studies involving ketamine. Their review assessed the effects and tolerability (both primary outcomes) of ketamine (intervention), in comparison with a saline placebo, other psychotropic drugs or ECT (comparison), in alleviating the acute symptoms of depression in adults with major unipolar depression (population).

Inclusion and exclusion criteria

The review makes a well-justified choice in including studies in which at least 80% of participants (aged ≥18 years) had only unipolar MDD (thus, less than 20% of participants had bipolar depression).

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Other concurrent comorbidities, such as generalised anxiety disorder, were not considered exclusion criteria, unless a study's participants all had a concurrent primary diagnosis of another psychiatric disorder. By broadening the population criteria to permit diseases that often present alongside major depression, it increases the generalisability (Box 1) of the findings, allowing them to be applied to the general clinical population. However, this does come at a cost to the specificity of the findings for people with unipolar depression. To mitigate this the authors undertook a pre-planned sensitivity analysis which excluded studies in which any participants had bipolar disorder, as this facilitates assessment of congruency between the results to see whether inclusion of bipolar depression skewed results. A pre-planned sensitivity analysis was also undertaken to exclude participants with treatment-resistant depression (TRD), as people with TRD may have different baseline characteristics and treatment responses compared with the general population with unipolar MDD (Nemeroff 2007).

Administration regimens

Ketamine as an intervention presented challenges to the reviewers as there is no general consensus on the most efficacious administration regimen. Consequently, the review includes studies with differing intervention protocols: ketamine in intravenous (i.v.) solution (the majority of studies), oral tablet (Arabzadeh 2018) or nasal spray (Lapidus 2014; Gálvez 2018); one-off doses versus multiple doses; and ketamine dose calculations from 0.2 to 0.5 mg/kg.

Single-dose ketamine was employed in eight studies in the saline comparison, typically demonstrating peak antidepressant effect within 24 h, with diminishing but significant effects lasting up to 7 days post-administration, followed by symptom relapse after 7 days. In contrast, repeated ketamine infusions, as explored in studies that dosed participants twice weekly (Anderson 2017; Ionescu 2019) or thrice weekly (Loo 2012; Chen 2017), demonstrated more sustained antidepressant responses. A randomised controlled trial by Phillips et al (2019) (a study not included in the review) also supports ketamine's ability to maintain antidepressant effects through additional infusions administered once weekly.

The heterogeneity in ketamine dosing across the studies complicates the interpretation of results and limits the ability to draw definitive conclusions about the optimal administration protocol. Additionally, the use of concomitant therapies, such as ECT or other antidepressants, although increasing the generalisability of findings, introduces additional variables to consider when interpreting ketamine's effects.

Comparator interventions

To observe ketamine's effect it was compared with another intervention. All comparator interventions matched the administration method of ketamine, aside from ECT. Only one study directly compared the efficacy and safety of ketamine with ECT (Ghasemi 2013) and nine compared it with other pharmacologically active agents (aside from midazolam) for treating unipolar MDD. This scarcity of comparative data makes it challenging to draw meaningful conclusions; therefore, this appraisal will not explore findings from these comparisons.

Using i.v. saline as a placebo comparator is common but has limitations. Although it accounts for the physical aspect of receiving an i.v. infusion, it does not mimic the unique dissociative and psychoactive effects of ketamine (Hirota 2018), thus weakening the integrity of the masking ('blind') and introducing performance bias (Box 2). As a result, i.v. saline may not fully capture the placebo effect's impact, potentially overestimating ketamine's relative efficacy. To mitigate this, the reviewers also assessed studies using an active placebo (Box 3) in the form of i.v. midazolam; i.v. midazolam has similar pharmacokinetic properties

BOX 1 Generalisability

Generalisability refers to the extent to which the findings of a study can be applied to broader, real-world settings beyond the specific conditions of the research. For instance, if a clinical trial shows that ketamine effectively reduces depressive symptoms in a highly controlled environment, generalisability examines whether these results would hold true in typical clinical practice.

Factors that suggest generalisability include diverse participant samples that represent the general population and intervention protocols that can be adjusted to real-world settings.

BOX 2 Performance bias

Performance bias describes the difference in results that arises from the knowledge of intervention allocation. In clinical trials, this often results from participants or observers being aware of which treatment the participants are receiving, potentially influencing their behaviour or outcomes. For example, in trials comparing ketamine with a saline placebo, if participants know they are receiving ketamine (owing to its distinctive effects), their perception of its effectiveness may be enhanced, thereby skewing results.

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BOX 3 Active placebo

An active placebo is a substance used in clinical trials that mimics some of the side-effects of the treatment being tested but does not have therapeutic effects on the condition. It is designed to make participants and clinicians believe that the treatment is real, thereby enhancing the masking ('blinding') process. However, it can be challenging to match the side-effect profile of the treatment closely enough to maintain effective masking without introducing confounding therapeutic effects.

to i.v. ketamine, alongside a degree of dissociative and sedative effects. Wilkinson et al (2019) describe patients being unable to distinguish between the two, supporting their finding of a smaller antidepressant effect size in single-infusion ketamine studies when i.v. midazolam was used as the comparator in comparison with i.v. saline. However, ketamine studies using i.v. midazolam in the review that tested masking found the masking to be ineffective (Fava 2020; Shiroma 2020).

Primary outcomes

The primary outcomes were response rate (50% reduction on a standardised rating scale) and adverse events. Efficacy was assessed at the following time points: 24 h, 72 h, 1 week, 2 weeks and 4 weeks. Although these short-term efficacy assessments are crucial, the absence of data beyond 4 weeks is a significant limitation. Depression often requires long-term management, and without data on the sustainability of ketamine's effects and long-term adverse effects, it is difficult to evaluate its full clinical utility for chronic symptom management.

Methods used to address the question

The studies included were randomised controlled trials (RCTs), with a minimum of a single-blind. Where cross-over trial data were used, only the first-phase data were assessed to mitigate concern of carry-over effects. The comprehensive search strategy yielded 22 new RCTs assessing ketamine in this 2021 update and the reviewers must be commended for their commitment to maintaining the relevance and accuracy of the evidence base. Despite identifying 64 studies in their full search (on ketamine and other glutamate receptor modulators), only 54 could be included in the meta-analysis owing to the unavailability of data, even after attempts to contact the authors (it is not immediately clear how many of the ketamine studies fell into this category, but this can be calculated from the review's reference list). This exclusion raises concerns about publication bias and selective reporting bias, as these missing studies may have contained unfavourable or null results that could alter the overall conclusions.

Results were based on odds ratios (OR) for dichotomous outcomes, and for continuous data the mean difference (m.d.) or standardised mean difference (s.m.d.) were used, all with corresponding 95% confidence intervals (95% CI). By employing a combination of intention-to-treat (ITT) analysis (assuming those who dropped out to be non-responders), contacting original authors and using validated imputation methods, the review attempts to mitigate the impact of missing data (Box 4) on its conclusions. The planned sensitivity analyses in the review are methodologically sound and appropriate for testing the robustness of the findings. These analyses aimed to isolate the effect of methodological quality, participant characteristics, dose comparisons, drop-out rates and data imputation on the primary outcomes. Subgroup analysis was conducted based on depression severity, treatment settings and participants' age (excluding participants >65 years).

Risk of bias was assessed using the Cochrane risk-of-bias tool RoB 2, and certainty of the evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Atkins 2004). The decision to rate masking bias based on the attempt to mask, rather than the actual effectiveness of the masking, does not adequately

BOX 4 Missing data and intention-to-treat analysis

Missing data refers to the absence of data points in a study, which can occur for various reasons, such as participants dropping out, incomplete responses or errors in data collection. In clinical research, missing data can significantly affect the validity of findings and their applicability to real-life settings. For instance, if many participants in a trial on ketamine for depression drop out because of side-effects and their data are not included, the results may not accurately reflect the treatment's effectiveness or safety for the general population.

Intention-to-treat (ITT) analysis is a strategy in clinical trials where all participants are analysed in the groups to which they were originally assigned, regardless of whether they completed the treatment per protocol. In this review, even if some participants discontinued ketamine because of side-effects, the ITT analysis still included their data in the final analysis.

An ITT approach maintains the benefits of randomisation and provides a more realistic estimate of a treatment's effectiveness in routine practice, reflecting real-world scenarios where patients may not always adhere to the prescribed regimen.

reflect the true risk of bias. We would recommend assigning 'unclear' risk to all studies that did not test their masking, given the uncertainty of achieving effective masking with the current placebo standards.

The findings of the review

For a comprehensive breakdown of efficacy, adverse effects and sensitivity analysis results we refer readers to the Cochrane Review. Here we highlight some key findings.

Response rates

The results suggest that ketamine provides a rapid antidepressant effect, significantly outperforming both saline placebo and midazolam in the short term, particularly within the first 72 h to 1 week after administration.

The OR for response rate at 72 h for ketamine versus saline was 15.84 (95% CI 3.68–68.12; $P = 0.0002$), with no heterogeneity ($I^2 = 0\%$) across 4 studies involving 83 participants. This suggests a consistent strong response across the studies. However, the evidence for these findings is rated as of very low certainty. This low certainty implies that the true effect may differ substantially from the observed effect, likely owing to factors such as performance bias.

At 24 h, the OR for ketamine versus midazolam was 2.48 (95% CI 1.00–6.18; $P = 0.05$), based on 4 studies with 296 participants, with moderate heterogeneity ($I^2 = 58\%$). This indicates a modest but significant advantage for ketamine over midazolam but the evidence is rated as of very low certainty. At 1 week the OR for ketamine versus midazolam was 3.11 (95% CI 1.38–7.04; $P = 0.006$), derived from 2 studies with 126 participants, with no heterogeneity ($I^2 = 0\%$).

Wide confidence intervals and moderate heterogeneity observed at 24 h (ketamine versus midazolam) and 72 h (ketamine versus saline) indicate imprecise results with an uncertain effect. The effect at 1 week (ketamine versus midazolam) should also be interpreted with caution as only two studies contributed to the results.

Suicidality

Although not a primary outcome, ketamine's potential to reduce suicidal ideation warrants further investigation in the review, particularly given the drug's rapid onset and accessibility, which may be relevant in acute suicidal crises. Two studies compared ketamine with the saline placebo for suicidal ideation, finding no significant differences up to 2 weeks post-administration (Chen 2017; Ionescu 2019). However, in one study, ketamine was more effective than midazolam at reducing suicidal ideation (m.d. = −1.32, 95% CI −2.52 to −0.12; $P = 0.03$) (Murrough 2013). These findings remain inconclusive, underscoring the need for additional research on ketamine's anti-suicidal effects, particularly in individuals with varying severities and acuity of suicidal ideation.

Tolerability, side-effects and long-term safety

One of the key concerns regarding the use of ketamine is its tolerability and side-effect profile. The review indicates that ketamine was associated with a higher incidence of adverse effects compared with both saline and midazolam. These effects were commonly observed in the hours immediately following administration, often peaking within the first 24 h. For instance, nausea and vomiting were more likely to occur on the day of infusion with ketamine compared with midazolam (OR = 3.62, 95% CI 1.13–11.58; $P = 0.03$), but this difference diminished over time and was not statistically significant at 1 week (OR = 2.57, 95% CI 0.78–8.52; $P = 0.12$). Dissociative symptoms in particular were significantly more prevalent in patients treated with ketamine compared with those receiving the saline placebo (OR = 7.72, 95% CI 1.31–45.51; $P = 0.02$). This raises concerns about patient acceptability and the practicality of using ketamine outside a controlled clinical environment. Although transient, these effects may limit the drug's use, particularly for individuals with a history of psychosis or those vulnerable to adverse psychiatric reactions.

Moreover, long-term safety concerns such as ketamine-induced bladder toxicity (ketamine cystitis), addiction potential and cognitive impairments, which have been observed in recreational and chronic users (Sassano-Higgins 2016), remain underexplored in the clinical studies included in the review. The lack of long-term follow-up data in the reviewed studies makes it difficult to fully assess the risk of developing such complications after repeated doses or prolonged use. Furthermore, the review lacks a comprehensive breakdown of adverse effects at all time points. This is crucial in a clinical context, as patients can be monitored and safety-netted according to occurrence of side-effects.

Cognition, quality of life and cost to healthcare services

The review's limited focus on cognition and quality of life is a notable shortcoming. Only one study assessed the impact of ketamine on cognitive function (Chen 2017), finding unexpected improvements in memory (immediate-term, short-term and long-term) compared with the saline placebo. However, basing such conclusions on a single study is

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insufficient to provide confident, generalisable insights into ketamine's cognitive effects. Similarly, quality of life was measured (using the 3-level version of EuroQol's EQ-5D) in only one study (Anderson 2017), which found no significant difference between ketamine and saline – an important finding if supported by other studies. The absence of any data on cognition and quality of life in the ketamine versus midazolam comparison further limits the depth of the review. Additionally, key outcomes such as cost to healthcare services remain unexplored, which reduces the review's relevance in terms of the feasibility of implementation. Addressing these gaps in future research would provide a fuller context to ketamine's clinical potential, ensuring a balanced assessment of its antidepressant efficacy alongside its side-effect profile.

Is the evidence convincing for ketamine implementation?

The reviewers aimed to collate evidence regarding ketamine's efficacy, with a view to guide clinical implementation. The results, as discussed, statistically show superior response to ketamine, in comparison with both saline and midazolam. Despite the promising findings, the evidence quality is rated as very low certainty according to the GRADE criteria. Several factors contribute to this low certainty, such as underpowered studies that have on average fewer than 100 participants. The moderate to high levels of heterogeneity observed in some comparisons, particularly at 24 and 72 h, indicate variability in the treatment effects. This could be owing to the variation in ketamine treatment regimens across the studies, as demonstrated in reviews by Andrade (2017) and Xu et al (2016). Additionally, potential biases from masking procedures further undermines the reliability of the finding.

A strength of Dean et al's review is the appropriate population choice across the studies, which enables generalisability of the findings to the clinical population. In addition, detailed analysis of response rates at various short-term time points allows for a nuanced understanding of ketamine's therapeutic window. Although short-term adverse effects were explored, the review lacked data on long-term adverse effects, an important consideration given the concerns over ketamine's potential impact on bladder function and its misuse liability (Sassano-Higgins 2016).

In light of several recent comparative trials between ketamine and ECT (Rhee 2022) the review may no longer be fully up to date. Specifically, the two large non-inferiority trials ELEKT-D (Anand 2023) and KetECT (Ekstrand 2022) have explored the comparative efficacy of ketamine versus ECT. The ELEKT-D trial demonstrated that ketamine was non-inferior to ECT in terms of treatment response, with fewer memory-related side-effects, suggesting that ketamine could be a safer alternative for some patients. Conversely, the KetECT trial found that ECT was superior in achieving remission, although ketamine still led to significant reductions in depressive symptoms and had fewer long-term adverse effects. Although more high-quality data are needed to firmly establish ketamine's role as an alternative to ECT, these trial data are promising. Updating the review to incorporate this newer evidence would significantly enhance its clinical relevance.

The final verdict

Dean et al's (2021) review highlights ketamine's potential for rapid symptom relief in acute depressive episodes; however, in the presence of bias and low-quality evidence, the results should be interpreted with caution. The review authors' thorough search strategy and critical consideration of bias are commendable, but achieving greater confidence in the results requires studies with more stringent methodological standards. Replicating these findings from high-quality studies that thoroughly address long-term adverse effects and compare ketamine's efficacy against established treatments such as ECT could better support ketamine's role as an option for rapid antidepressant intervention in clinical practice.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

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Declaration of interest

None.

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