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Ketamine for depression – a critical perspective

PERSPECTIVES

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Ketamine is described as a promising agent with rapid antidepressant effects. However, the evidence is more limited than many believe and has significant methodological weaknesses.

For several years, ketamine has been given to patients with depression at private clinics and some hospital departments in Norway, and recently the decision was made to offer intravenous ketamine for treatment-resistant depression in the specialist health service. This decision was based on a health technology assessment by the Norwegian Medical Products Agency (1). Some clinical communities claim that ketamine has a rapid and robust antidepressant effect, and that it appears to be a safe and effective treatment option for treatment-resistant depression (2). This article discusses challenges related to the evidence base for intravenous ketamine in the treatment of depression, with a focus on efficacy and safety. There is little evidence to suggest a sustained effect, and the risks associated with long-term use are insufficiently studied.

Ketamine

Ketamine has been used as an anaesthetic for several decades. It has dissociative and hallucinogenic effects and is also misused as a recreational substance. Any potential mechanism underlying its antidepressant effects remains unknown (3). Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist. NMDA receptors play a fundamental role in processes involving neuroplasticity, including memory, learning and the regulation of neuronal cell death versus survival. Ketamine is also an opioid receptor agonist (4). Mechanisms involving neuroplasticity are thought to be relevant (3), and phrases such as 'ketamine opens a window for neuroplasticity' are often used. This should be interpreted in the context that neuroplasticity is a normal physiological process.

Studies of ketamine in the treatment of depression

Numerous studies, literature reviews and meta-analyses have been published on intravenous ketamine for major depressive disorder. Following a broad review, we selected 22 controlled studies for closer evaluation (see Appendix). The patients mostly had treatment-resistant depression, although a couple of studies did not explicitly use this term. In most studies, doses of 0.5 mg/kg

were administered as an infusion. Many ketamine studies have considerable shortcomings in terms of methodology and reporting. Nearly half of the studies (10/22) were single-dose studies focusing on immediate effects. On average, the studies included 30 patients receiving ketamine, with a follow-up period of 14 days. Several were effectively pilot studies, exploring different doses in a small patient group.

When administered intravenously, ketamine produced a rapid effect in most studies, as reflected by improvements on depression rating scales such as the Montgomery–Åsberg Depression Rating Scale (MADRS) (5–7). In several studies, the effect waned over the course of days. It is not surprising that administration of a substance such as ketamine produces observable effects. This is a substance with marked psychoactive properties. The question is whether this immediate effect can truly be used to assess ketamine's benefit or role in the treatment of a chronic condition such as depression. The acute antidepressant effect of ketamine was substantially reduced when the opioid antagonist naltrexone was administered prior to ketamine infusion in patients with depression (4, 8). Many psychoactive substances are used as self-medication in psychiatric disorders, with well-known harmful effects over time.

There appears to be a general consensus that ketamine treatment must be repeated over time, but few studies had multiple dosing and follow-up beyond a couple of weeks after treatment cessation. We identified four studies that used multiple dosing (2–3 doses per week for 1–4 weeks), included at least 50 patients, and had a minimum follow-up of four weeks (9–12).

In one study, repeated ketamine infusions over two weeks were compared with midazolam infusions followed by a single ketamine infusion (n = 54) in outpatient veterans (9). The authors found no difference in response between the groups when measured 24 hours after infusion of the final dose. During a 12-week follow-up phase among responders, there was a substantial relapse rate within a few weeks in both groups. In the recently published KARMA-Dep 2 study, 65 hospitalised patients were randomised to up to eight ketamine or midazolam infusions, with six months of follow-up (12). Repeated ketamine infusions were not more effective than midazolam in reducing depressive symptoms during the treatment phase. Results from the follow-up phase are difficult to interpret because of attrition.

> ***«Ketamine studies are characterised by significant bias. Many are designed as randomised, controlled double-blind trials, but blinding is very difficult due to the acute hallucinogenic effects of ketamine»***

Two large-scale studies compared repeated ketamine infusions with electroconvulsive therapy (ECT) (10, 11). ELEKT-D was a pragmatic three-week study that included outpatients with no psychotic symptoms (10). The study found that ketamine (n = 195) was non-inferior to ECT (n = 170). Ketamine was 'the new treatment', and the drop-out rate in the ECT group was high (approximately 20 %) before treatment started, primarily because patients

wanted ketamine. The study included a six-month follow-up of responders, but the results are difficult to interpret due to the high drop-out rate and because many participants received ketamine during the follow-up period.

The KetECT study included inpatients referred for ECT (n = 186) (11). The authors found a lower remission rate with ketamine compared with ECT (46 % versus 63 %). Little information is given about the one-year follow-up phase, but relapse was observed in 64–70 % of patients, with a median remission duration of just less than a couple of months. Differences in results between KetECT and ELEKT-D have been discussed in terms of patient population differences, expectation bias, and the unusually low remission rate with ECT in ELEKT-D (22 %) compared with what was expected (13).

Based on both studies, ketamine does not appear to be more effective than ECT in treatment-resistant depression. The Norwegian health technology assessment only included the ELEKT-D study (1), not KetECT, and therefore does not provide a representative picture of the evidence base.

In the studies with long-term follow-up, there was substantial relapse within weeks to a few months (9–11), and the development of tolerance has been discussed (4).

Methodological challenges

Ketamine studies are characterised by significant bias. Many are designed as randomised, controlled double-blind trials, but blinding is very difficult due to the acute hallucinogenic effects of ketamine (9, 12, 14). This introduces a high risk of expectation bias, in addition to nocebo effects. In many studies, this is reflected by a very high drop-out rate in the control group (10, 15). Nevertheless, an interesting study with actual blinding has been conducted (14). In this study, 40 patients with major depressive disorder scheduled for routine surgery were randomised to receive a single ketamine infusion (0.5 mg/kg) or saline infusion under anaesthesia. The response rate was comparable to other single-dose studies, but ketamine did not demonstrate a greater antidepressant effect than the placebo.

> ***«It is often claimed that ketamine is a well-known, long-established drug, but this applies to its use in anaesthesia, and anaesthetic agents are rarely administered repeatedly over time»***

Safety

The safety of ketamine for depression is not well documented and is mainly based on studies with few doses and short follow-up periods. It is often claimed that ketamine is a well-known, long-established drug, but this applies to its use in anaesthesia, and anaesthetic agents are rarely administered repeatedly over time. Ketamine is also known to be used recreationally.

Somatic adverse effects have been reported, such as major increases in heart rate and blood pressure during ketamine infusion (7, 11, 16). This is of particular concern in older patients, who have a higher prevalence of cardiovascular disease. Cystitis and urinary tract injury can occur with prolonged use.

Ketamine affects NMDA receptors and can therefore potentially impact on fundamental processes such as memory and cognitive function (3). Neurotoxic effects have been observed in animal models, particularly during development, but these effects have not been adequately studied in humans receiving clinically relevant doses or repeated administration (17). This suggests a need for caution. Dissociative experiences, which can be highly distressing, have generally received little attention, despite being a common reason for study drop-out (11, 15, 18). Panic attacks during ketamine infusion have been reported (11). There is reason to question whether such negative experiences may trigger anxiety disorders and lead to clinical deterioration. The development of psychosis has been observed with ketamine use. In many studies, patients continued their usual treatment, including antipsychotic medication (12, 18), which may have masked psychotic symptoms. Suicidal ideation and suicide attempts have been reported in both ketamine and control groups (5, 10, 11, 16). The individual studies are, however, too small to draw conclusions in a high-risk population.

> ***«Neurotoxic effects have been observed in animal models, particularly during development, but these effects have not been adequately studied in humans receiving clinically relevant doses or repeated administration»***

The potential for misuse associated with ketamine in the treatment of depression remains unclear (19). If repeated use is required to maintain therapeutic effects, this risk must be taken seriously. Short-term studies provide little information on long-term risk, but the increase in customs seizures constitutes a clear warning signal. There are obvious challenges associated with treating psychiatric disorders using medications with the potential for misuse.

What now?

If a profound experience with ketamine can induce lasting changes in severely ill patients, this would be of considerable interest. Anecdotally, some patients report substantial improvement following ketamine treatment; however, this has not been clearly demonstrated at the group level. To date, ketamine has predominantly been studied over short periods, and the evidence base does not indicate that treatment administered over a limited time frame results in sustained improvement. If ketamine is to be administered over longer periods

as symptomatic treatment, it is essential to investigate the consequences for mental health and cognitive function in order to assess the benefit–risk balance.

Pre-existing expectations of efficacy can make it challenging to randomise patients. Such expectations also entail a risk of dose escalation and 'indication creep'. Studies have mainly included patients with treatment-resistant depression and therefore do not provide a basis for use in less severe cases.

At present, the use of intravenous ketamine for depression is experimental, even though the drug is well known and is used off-label. Widespread use in the absence of sufficient knowledge of dosing regimens or potential long-term neurotoxic effects represents a significant risk.

REFERENCES

1. Ohm IK, Flatby AV, Stoinska-Schneider A et al. Intravenous ketamine for treatment-resistant depression: a health technology assessment. Oslo: Norwegian Medical Products Agency, 2025. https://www.nyemetoder.no/49eba4/contentassets/3d24ef749d894a71a1022bfd90de6751/id2022_018-intravenos-ketamin-ved-behandlingsresistent-depresjon_kun-offentlig-versjon.pdf Accessed 6.1.2026.

2. Berthold-Losleben M, Autran I, Folstad RLS et al. Ketaminbehandling ved terapiresistent depresjon. Tidsskr Nor Legeforen 2025; 145. doi: 10.4045/tidsskr.25.0045. [PubMed][CrossRef]

3. Krystal JH, Kavalali ET, Monteggia LM. Ketamine and rapid antidepressant action: new treatments and novel synaptic signaling mechanisms. Neuropsychopharmacology 2024; 49: 41–50. [PubMed][CrossRef]

4. Williams NR, Heifets BD, Blasey C et al. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. Am J Psychiatry 2018; 175: 1205–15. [PubMed][CrossRef]

5. Fava M, Freeman MP, Flynn M et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol Psychiatry 2020; 25: 1592–603. [PubMed][CrossRef]

6. Zarate CA, Singh JB, Carlson PJ et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006; 63: 856–64. [PubMed][CrossRef]

7. Phillips JL, Norris S, Talbot J et al. Single, repeated, and maintenance ketamine infusions for treatment-resistant depression: a randomized controlled trial. Am J Psychiatry 2019; 176: 401–9. [PubMed][CrossRef]

8. Jelen LA, Lythgoe DJ, Stone JM et al. Effect of naltrexone pretreatment on ketamine-induced glutamatergic activity and symptoms of depression: a

randomized crossover study. Nat Med 2025; 31: 2958–66. [PubMed] [CrossRef]

9. Shiroma PR, Thuras P, Wels J et al. A randomized, double-blind, active placebo-controlled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. Transl Psychiatry 2020; 10: 206. [PubMed][CrossRef]

10. Anand A, Mathew SJ, Sanacora G et al. Ketamine versus ECT for nonpsychotic treatment-resistant major depression. N Engl J Med 2023; 388: 2315–25. [PubMed][CrossRef]

11. Ekstrand J, Fattah C, Persson M et al. Racemic ketamine as an alternative to electroconvulsive therapy for unipolar depression: A randomized, open-label, non-inferiority trial (KetECT). Int J Neuropsychopharmacol 2022; 25: 339–49. [PubMed][CrossRef]

12. Jelovac A, McCaffrey C, Terao M et al. Serial ketamine infusions as adjunctive therapy to inpatient care for depression: The KARMA-Dep 2 randomized clinical trial. JAMA Psychiatry 2025; 82: 1216–24. [PubMed] [CrossRef]

13. Ekstrand J, Takamiya A, Nordenskjold A et al. Ketamine or ECT? What have we learned from the KetECT and ELEKT-D Trials? Int J Neuropsychopharmacol 2024; 27. doi: 10.1093/ijnp/pyad065. [PubMed] [CrossRef]

14. Lii TR, Smith AE, Flohr JR et al. Randomized trial of ketamine masked by surgical anesthesia in patients with depression. Nat Ment Health 2023; 1: 876–86. [PubMed][CrossRef]

15. Ionescu DF, Bentley KH, Eikermann M et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: A randomized, double blind, placebo controlled trial. J Affect Disord 2019; 243: 516–24. [PubMed][CrossRef]

16. Murrough JW, Iosifescu DV, Chang LC et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 2013; 170: 1134–42. [PubMed][CrossRef]

17. Li SW, Kumpf KT, Urrutia J et al. Ketamine for depression, but at what cost? A review of ketamine's neurotoxic effects from preclinical and human studies. Am J Psychiatry 2025; 182: 903–12. [PubMed][CrossRef]

18. Wilkinson ST, Katz RB, Toprak M et al. Acute and longer-term outcomes using ketamine as a clinical treatment at the Yale Psychiatric Hospital. J Clin Psychiatry 2018; 79. doi: 10.4088/JCP.17m11731. [PubMed][CrossRef]

19. Freedman R. Ketamine and ECT in Depression - Risks and Rewards. N Engl J Med 2023; 388: 2389–90. [PubMed][CrossRef]

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