NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS · Nicolaus Copernicus University in Toruń

Cite as: SZULETA, Urszula, ZAWADA, Wiktoria, KACZMAREK, Krystian, LESZCZYŃSKA, Zofia Jadwiga, ROMANIUK, Vladyslav, BENECKA, Agnieszka, PIETROŃCZYK, Jakub, BENECKA, Alicja, WIECZOREK, Zuzanna, TARTAS, Iga and PRANKIEWICZ, Natalia. Ketamine and Esketamine in Depression: Current Evidence on Mechanisms, Efficacy, Safety and Clinical Use – A Review. Journal of Education, Health and Sport. 2026;93:72419. https://doi.org/10.12775/JEHS.2026.93.72419

ARTICLE TIMELINE
Received: 22.05.2026 **Revised:** 20.06.2026
Accepted: 20.06.2026 **Published:** 22.06.2026

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 201159
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Ketamine and Esketamine in Depression: Current Evidence on Mechanisms, Efficacy, Safety and Clinical Use – A Review

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ABSTRACT

Introduction and purpose.

Major depressive disorder is a serious clinical problem. Current treatments are often unsuccessful, and many patients do not achieve full remission. In a reanalysis of the STAR*D study, the cumulative remission rate after up to four treatment steps was about 41%, which highlights the limitations of currently available antidepressant strategies[1]. In recent years, growing attention has been paid to novel agents with potential rapid antidepressant effects. Among them, ketamine and its derivatives have become the subject of numerous studies evaluating their role in depressive disorders, particularly in treatment-resistant depression [2]. The aim of this review is to summarize current evidence regarding the efficacy, safety, and clinical use of ketamine and its derivatives in depression, with particular emphasis on treatment-resistant depression.

A brief description of the state of knowledge.

This review presents current evidence on novel therapeutic agents that may be useful in the treatment of severe depression. It discusses the concept of severe depression and its broader clinical and social consequences. Particular attention is given to the mechanisms of action of ketamine and its derivatives, the available evidence on their efficacy, their adverse effects, and their potential impact on suicidal ideation. The review also emphasises the limitations of existing data and the need for further research.

Summary (conclusions).

Current data indicate that ketamine is a promising option for the treatment of drug-resistant and severe depression because of its rapid onset of action. Some evidence suggests that it may reduce suicidal ideation in high-risk patients, however further large-scale, long-term studies are needed to clarify the durability of benefit and long-term safety. [2,3,4].

Key words:

Ketamine; Esketamine; Depressive Disorder; Treatment-Resistant Depression

INTRODUCTION AND PURPOSE

Depression is a common and serious mental disorder and, in its most severe form, it may lead to suicide. It is a multifactorial condition influenced by biological, psychological, and social factors [5]. According to the World Health Organization (WHO), about 5% of adults worldwide experience depression, and earlier WHO estimates indicated that the number of people living with depression increased by 18% between 2005 and 2015 [6]. A depressive episode is characterized by low mood or loss of interest or pleasure and may be accompanied by a wide range of other symptoms, including anhedonia, impaired concentration, indecisiveness, feeling of worthlessness or excessive guilt, recurrent thoughts of death, suicidal ideation, sleep disturbance, changes in appetite or weight, psychomotor agitation or retardation, low energy, and hopelessness about the future [7, 8]. In general, these symptoms should persist for at least 2 weeks [9]. There are two major classification systems used in psychiatry: ICD-10 (or the newer ICD-11) and DSM-5. Both are used to standardize diagnoses and are helpful in recognizing and describing mental disorders. In DSM-5, a major depressive episode is diagnosed when at least five symptoms are present for at least 2 weeks, including either depressed mood or diminished interest or pleasure [11]. In ICD-11, a depressive episode is characterized by depressed mood or reduced interest or pleasure present most of the day, nearly every day, for at least two weeks, together with other symptoms such as poor concentration, excessive guilt or low self-worth, hopelessness, thoughts of death or suicide, sleep disturbance, changes in appetite or weight, and low energy [12, 13]. Therefore, DSM-5 and ICD-11 describe depression in similar clinical terms, although they use somewhat different diagnostic frameworks [10, 11, 12, 13]. There are many questionnaires and rating scales used to assess depression: HAM-D (Hamilton Rating Scale for Depression), MADRS (Montgomery-Asberg Depression Rating Scale), BDI (Beck Depression Inventory), SDQ (Symptoms of Depression Questionnaire), QIDS (Quick Inventory of Depressive Symptoms), and CES-D (Center for Epidemiologic Studies Depression Scale). To sum up: major depressive disorder (MDD) is a diagnostic category, whereas severe depression refers to the intensity of a depressive episode [10, 11]. A large epidemiological study published in 2018 found that among adults with lifetime DSM-5 major depressive disorder, the worst depressive episode was classified as severe in 49.5% of cases and as moderate in 39.7% [14]. In the United States, an estimated 21.0 million adults had at least one major depressive episode in 2021, and 14.5 milion had an episode associated with severe impairment [15]. Another report published in 2023 found that 14.9% of adults in the United States had mild depressive symptoms and 7.2% had moderate to severe depressive symptoms [16].

Depression is also an important public health problem because of its high prevalence, its negative effect on daily functioning, and its association with disability, suicide, and premature mortality [6, 17, 18]. The limitations of current treatment are also reflected in clinical outcomes. In a reanalysis of the STAR*D study, the cumulative remission rate after up to four sequential treatment steps was approximately 41% [1]. Standard pharmacological treatment for depression is mainly based on the modulation of monoaminergic neurotransmission. However, although early neurochemical changes occur quickly, the clinical effect is usually delayed, probably because neuroadaptation and changes in neuronal plasticity require time [19]. Most definitions of treatment-resistant depression (TRD) describe it as lack of significant improvement after at least two adequate treatment trials [20]. Depending on the definition used and the population studied, TRD may affect about 10% to 50% of patients with depression [21, 22]. In addition, lack of early improvement has been associated with a higher risk of later treatment resistance [23].

In recent years, increasing attention has been paid not only to serotonin and other monoamines, but also to the glutamatergic system and to disturbances in synaptic plasticity in depression [24, 25, 26, 27]. For this reason, ketamine has attracted interest as an NMDA receptor antagonist with rapid antidepressant effects and possible effects on synaptic plasticity [28]. Ketamine is a widely used anesthetic and now is being increasingly studied in psychiatry, especially in treatment-resistant depression [2, 29]. Most clinical studies have used subanesthetic doses [30, 31]. The aim of this review is to summarize current knowledge on the use of ketamine in depression, with particular emphasis on treatment-resistant depression and severe depressive states. Special attention is given to the mechanism of action of ketamine and esketamine, their clinical efficacy, their possible effect on suicidal ideation, and their safety profile. The review also discusses the limitations of the current evidence and possible future directions for ketamine-based therapies in psychiatry.

This manuscript was prepared as a narrative review based on peer-reviewed publications and official regulatory documents addressing ketamine and esketamine in depressive disorders. Relevant sources published up to April 2026 were identified using PubMed, Google Scholar, FDA, EMA, and DARWIN EU materials. Greater emphasis was placed on systematic reviews, meta-analyses, randomized controlled trials, real-world utilization studies, and regulatory documents, whereas landmark early studies were included to provide historical context for the development of ketamine-based therapies.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Mechanisms of action of ketamine and esketamine.

Ketamine is an acrylcyclohexylamine that is commonly administreted as a racemic mixture of two enantiomers, whereas esketamine is the S-enantiomer of ketamine [32]. Originally developed and widely used as a dissociative anesthetic, ketamine exerts its principal pharmacological effects through non-competitive antagonism of the N-methyl-D-aspartate (NMDA) receptor [2, 32]. However, its antidepressant action is now understood as more complex than NMDA receptor blockade alone. One of the leading hypotheses suggests that ketamine preferentially inhibits NMDA receptors located on GABAergic interneurons. As a result, the inhibitory control over pyramidal neurons is reduced. This leads to a short-lasting increase in glutamatergic activity in brain regions involved in mood regulation, especially in the prefrontal cortex. This increase in glutamate signaling may then promote AMPA receptor activation and trigger downstream processes related to synaptic plasticity. Another important element of this process appears to be the modulation of brain-derived neurotrophic factor (BDNF) signaling [33, 34]. BDNF is involved in neuronal growth, synapse formation, and functional neuronal connectivity in the central nervous system. Therefore, the antidepressant effects of ketamine are best understood as the result of several interacting mechanisms, including NMDA receptor antagonism, increased glutamatergic signaling, AMPA receptor activation, and neuroplasticity-related pathways [2, 33, 34].

Clinical trials: early clinical evidence

The first clinical study describing the antidepressant effects of ketamine was published in 2000; ketamine was administered intravenously as a 40-minute infusion at a subanesthetic dose of 0.5mg/kg. It was a very small, early clinical study, but historically important because the authors presented it as the first randomized, double-blinded, placebo-controlled trial evaluating a single dose of an NMDA receptor antagonist in patients with depression. Nine individuals with a depressive episode were enrolled, of whom seven completed both arms of the study. Most had recurrent unipolar depression, and one had depression in the course of bipolar disorder. The patients had been free of antidepressant medications for at least two weeks before the study. All participants met the DSM-IV criteria for major depressive episodes[35,36].

Clinical trials: evidence from meta-analyses

This study initiated a series of subsequent research projects that carefully evaluated the potential of ketamine in the treatment of depression. In 2023 a large meta-analysis by Nikolin et al. was published including 49 randomized controlled trials (RCTs) and 3299 participants, which examined both racemic ketamine and esketamine, compared different doses, assessed the effect after the first administration and also evaluated outcomes during follow-up after the end of treatment. The following conclusions were: after the first single dose, all analyzed interventions showed a moderate to large antidepressant effect but the largest effect observed for high dose racemic ketamine (standardised mean difference – SMD -0.73; 95% CI -0.91 to -0.56).In repeated treatment the advantage over control was greatest for racemic ketamine (high dose: SMD -0.61; 95% CI -1.02 to -0.20; low dose: SMD -0.55; 95% CI -1.09 to 0.00). During post-treatment follow-up a sustained effect remained significant for racemic ketamine (SMD -0.65; 95% CI -1.23 to -0.07), but not for esketamine – the effect in this analysis was not statistically significant (high dose: SMD -0.22; 95% CI -0.54 to 0.10; low dose: SMD -0.15; 95% CI -0.49 to 0.19). The authors concluded that racemic ketamine performed numerically better than esketamine and that higher doses were more effective than lower ones. The dropout rate was similar in the active-treatment and control groups. However, the meta-analysis examined ketamine treatment in adults with major depression, including both unipolar and bipolar depression. Although treatment-resistant depression was an important subgroup within the included literature, the review was not designed exclusively around TRD populations. Similarly, the included studies were not confined to one predefined severity level, such as moderate or severe depression, but rather reflected a broader population of patients with major depressive episodes [36]. There were also studies in which repeated ketamine infusions showed greater antidepressant efficacy than midazolam used as an active placebo after a series of infusions [37]. Some studies have also shown that ketamine is effective in reducing suicidal ideation in high-risk patients [38]. Because studies showed that esketamine, the S-enantiomer of ketamine, has a higher affinity for NMDA receptors, the scientific community became interested in this substance in the hope of developing a drug with a better safety profile and simpler production. Esketamine also raised hopes for the development of a non-intravenous treatment [39]. Naudet et al. (2025) conducted a registered report systematic review with an individual patient data meta-analysis of randomized, double-blinded, placebo-controlled trials evaluating intranasal esketamine in treatment-resistant depression. Methodologically, this study is particularly valuable because the protocol was prospectively registered, study selection and risk-of-bias assessment were performed independently by two reviewers, and the analysis was based on raw patient-level data rather than on published summaries alone. The authors included 7 trials with 1505 participants and assessed efficacy primarily by change in MADRS score at 4 weeks. In the five initiation trials,

esketamine combined with an oral antidepressant was associated with a statistically significant but small benefit over placebo (mean difference -2.94 points; 95% CI -5.39 to -0.48), which did not reach the prespecified 6.5 point threshold used as a benchmark for clear clinical relevance. Esketamine also reduced relapse risk in the continuation trial (HR 0.38; 95% CI 0.26-0.57), but increased sedation, dissociation, and the overall frequency of adverse events. Overall, the authors concluded that esketamine shows antidepressant efficacy, although its clinical relevance remains uncertain and should be interpreted in light of adverse effects and methodological limitations [40].

Adverse effects

Ketamine treatment is associated with frequent adverse effects, but in most studies these effects are transient and usually resolve shortly after administration. The most commonly reported adverse effects include dissociation, dizziness, nausea, blurred vision, somnolence, sedation, transient psychotomimetic symptoms, and short-term increases in blood pressure and heart rate [36, 39]. In most cases, these events are described as mild to moderate in severity and are most prominent during or shortly after dosing [39]. Current evidence does not suggest that serious adverse events are common [34]. This distinction is important: ketamine and esketamine are often associated with noticeable short-term side effects, but these are not the same as severe medical complications.

At the same time, the available literature is much less certain about long-term safety. Some authors have emphasized that more data are needed on repeated exposure, pos

sible cognitive effects, and the addictive potential of ketamine-based therapies, especially when treatment is continued over a longer period. For these reason, the current safety profile of ketamine and esketamine appears more reassuring for short-term use than for long-term maintenance treatment [41].

Comparisons between ketamine and esketamine are still not fully consistent across studies. Some indirect comparative analyses suggest that esketamine may have a short-term tolerability advantage, whereas other data suggest mainly different patterns of adverse events rather than a clear overall superiority of one drug over the other [3]. Pharmacovigilance data also indicate that adverse-event signals may differ between ketamine and esketamine, but such findings should be interpreted with caution because they do not replace direct head-to-head clinical trials [42]. Therefore, although both agents appear to be relatively safe in the short term when used under medical supervision, more direct comparative studies are needed to determine their relative tolerability more precisely [42, 43].

Regulatory approval, clinical indications and prescribing trends of ketamine and esketamine in the United States and Europe.

Intranasal esketamine became the first ketamine-derived product formally approved for depressive disorders in both the United States and Europe, whereas racemic ketamine, although long approved as an anesthetic, remains off-label for depressive disorders. In the United States, current FDA labeling indicates esketamine for adults with treatment-resistant depression, either as monotherapy or in conjunction with an oral antidepressants, and for depressive symptoms in adults with major depressive disorder with acute suicidal ideation or behavior, in conjuction with an oral antidepressant. In the European Union, current EMA labeling indicates esketamine, in combination with an SSRI or SNRI, for adults with treatment-resistant major depressive disorder who have not responded to at least two different antidepressant treatments in the current moderate to severe major depressive episode considered a psychiatric emergency. Despite these approvals, the use of esketamine is subject to strict safety conditions. In the United States, the FDA requires administration under the supervision of a healthcare provider and monitoring for at least 2 hours after each treatment session because of the risk of sedation, dissociation, and respiratory depression; the product is also available only through the SPRAVATO REMS program. In Europe, the EMA similarly requires administration under healthcare professional supervision, with post-dose observation until the patient is clinically stable and ready to leave, together with blood pressure reassessment at approximately 40 minutes after dosing. These requirements highlight that esketamine is not a routine outpatient self-administered therapy, but rather a treatment that must be delivered in a controlled medical setting [44, 45].

Real-world prescribing data suggest that, although ketamine and esketamine are increasingly used in practice, their uptake remains limited and highly heterogeneous. In Europe, the DARWIN EU drug-utilisation report, based on 6 databases from 6 countries between 2014 and 2023, found generally low ketamine use, some increase in hospital-based prescribing from around 2021 onwards, and persistently rare esketamine use in most settings, with clearer uptake only in selected databases, particularly in Finland. A similar pattern was observed in the United States. Aguilar et al. showed that esketamine prescriptions in Medicaid increased from 12.668 in 2019 to 28.037 in 2020, while Medicaid spending on esketamine reached 25.3 million USD in 2020, indicating growing but still uneven access across states. Overall, these findings suggest that the real-world use of ketamine-based therapies remains constrained by regulatory, organizational, and healthcare-system factors [46,47].

Limitations of the current data

Despite the rapidly growing number of reports on the efficacy of ketamine and esketamine, there are also studies showing that the results remain inconclusive and often depend on the formulation, dose, stage of treatment, timing of assessment, and selected endpoint. An important limitation of a large meta-analysis by Nikolin et al. was the substantial heterogeneity of the included studies. Overall heterogeneity, expressed as I^2, ranged from 5.7% to 87.6%, indicating that the consistency of results varied markedly across analyses. In some models, heterogeneity was low, whereas in others it was considerable or very high, suggesting substantial differences between trials. This variability most likely reflected differences in ketamine formulations, dose, route of administration, treatment schedule, and the clinical characteristics of the studied populations. Therefore, although the meta-analysis supported the antidepressant efficacy of ketamine-based interventions, its findings should be interpreted with caution because of the considerable heterogeneity of the available evidence [36].

Even in the registration trials of esketamine, the results were inconclusive [40]. Some authors suggest that the clinical benefit reported in these studies may be interpreted differently [48]. Currently published studies are characterised by considerable methodological heterogeneity, including differences in doses, routes of administration, and racemic forms of ketamine. Moreover, these studies do not clearly determine the long-term durability of the antidepressant effects of ketamine and its derivatives [36].

Some studies have also reported no superiority of ketamine over midazolam as an active placebo – Shiroma et al. performed a randomized, double blind, active placebo-controlled study in patients with treatment-resistant depression. The study compared repeated ketamine infusions with a control regimen based on midazolam and a single final ketamine infusion. The results showed that repeated ketamine was not significantly better in the main outcome measured 24 hours after the last infusion. However, better response and remission rates were observed earlier during treatment, especially after the fourth and fifth infusions. The results should be interpreted with caution because of the small study group [37].

SUMMARY

Current data indicate that ketamine appears to be a promising option for the treatment of severe and treatment-resistant depression because of its rapid antidepressant effect and its potential to reduce suicidal thoughts in high-risk patients [2]. Racemic ketamine may show greater efficacy than esketamine, especially in the early phase of treatment and during its continuation. Although ketamine is

associated with frequent but usually transient side effects, short-term use does not appear to significantly increase the risk of serious adverse effects [3,4]. Still, the available data are limited because of the high heterogeneity of study methodologies, and there is a lack of sufficient long-term research. Further large-scale, long-term studies are needed to determine the durability of treatment effects and the safety of use [2].

Disclosure:

Author's contribution:

Conceptualization, Urszula Szuleta and Wiktoria Zawada; resources, Krystian Kaczmarek and Zofia Jadwiga Leszczyńska; writing—original draft preparation, Vladyslav Romaniuk and Agnieszka Benecka; writing—review and editing, Jakub Pietrończyk and Zuzanna Wieczorek; visualization, Natalia Prankiewicz; supervision, Iga Tartas.
All authors have read and agreed to the published version of the manuscript.

Funding Statement: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: Not applicable.

Acknowledgements: Not applicable.

Declaration of the use of generative AI and AI-assisted technologies in the writing process.
In preparing this work, the authors used ChatGPT for the purpose of enhancing language clarity, improve readability and basic data analysis. After using this tool/service, the authors have

reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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