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A review of the therapeutic and neuroprotective properties of ketamine

Abstract

Relevance. Depression is one of the leading causes of disability worldwide, and a significant proportion of patients suffer from treatment-resistant forms of the disorder. An innovative approach involves the use of ketamine and esketamine, which are capable of inducing a "window of neuroplasticity" – a period of enhanced synaptogenesis and the formation of new neural connections. Theoretically, this increased neuroplasticity may contribute to the improvement of not only mental but also motor and sensorimotor functions, which is critically important for neurological rehabilitation following brain injuries, strokes, and other CNS lesions.

Aim. To conduct a systematic review of the available scientific literature on the effects of ketamine and esketamine on neuroplasticity and neurological functions, with a particular focus on assessing their potential for use in neurological rehabilitation following various CNS injuries.

Materials and methods. A systematic search of the scientific literature was conducted in leading databases (PubMed, Cochrane Library, NICE, APA PsycInfo, CANMAT, UpToDate), focusing on studies from the past 20 years. The review included clinical trials, experimental animal studies (modelling acute CNS injuries), as well as systematic reviews and meta-analyses. The collected data were synthesised using a descriptive method.

Results. The systematic review did not identify any clinical studies that directly evaluated the use of ketamine or esketamine to enhance the effectiveness of human neurological rehabilitation programmes specifically due to their neuroplastic effects. On the other hand, preclinical data in animal models (traumatic brain injury and ischemic stroke) convincingly demonstrate that these drugs reduce neuroinflammation, excitotoxicity, and oxidative stress. Furthermore, they support structural neuroplasticity and positively correlate with improvements in sensorimotor and behavioural outcomes.

Conclusions. Ketamine and esketamine are promising candidates for use as adjunctive agents in neurological rehabilitation programmes. However, there is currently insufficient clinical evidence to formulate official recommendations. Well-designed randomised controlled trials with long-term follow-up and standardised assessment of functional outcomes are needed to confirm their efficacy and safety.

Keywords: neurorehabilitation; depression; neuroinflammation; neuroprotection; ketamine-assisted therapy.

INTRODUCTION

According to the most comprehensive study to date, the Global Burden of Disease (GBD) 2021, there were approximately 332 million cases of depressive disorders worldwide in 2021 [1]. Childhood depression is also a problem: between August 2021 and August 2023, the prevalence of depression among adolescents and

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adults (aged 12 and older) was 13.1%. A clear correlation has been observed: the prevalence is higher among adolescents (ages 12-19) and individuals with lower household incomes [2]. An estimated 4% of the population experience depression, including 5.7% of adults (4.6% among men and 6.9% among women), and 5.9% of adults aged 70 years and older. Depression is about 1.5 times more common among women than among men. Worldwide, more than 10% of pregnant women and women who have just given birth experience depression. In 2021, an estimated 727 000 people lost their lives to suicide. Suicide is the third leading cause of death in 15-29-year-olds [3]. Despite the availability of a wide range of antidepressants, a significant proportion of patients have treatment-resistant depressive disorders, creating a need to search for new, more effective therapeutic strategies. One such innovative approach is the use of ketamine. Esketamine (the S-enantiomer of ketamine), known under the brand name Spravato, was officially approved by the FDA in March 2019 for the treatment of treatment-resistant depression as an adjunct to antidepressants [4], and subsequently as monotherapy [5]. At the same time, racemic ketamine is actively used off-label by specialised clinics as part of ketamine-assisted therapy (KAT) for the treatment of treatment-resistant depression, post-traumatic stress disorder (PTSD), anxiety, and other mental disorders. A number of studies have demonstrated the rapid antidepressant effect of ketamine, particularly in patients with suicidal thoughts, making it an important tool in modern psychopharmacotherapy [6-7].

A key neurophysiological effect of ketamine, considered one of the possible mechanisms of its antidepressant action, is the induction of the so-called "window of neuroplasticity" – a temporary period following drug administration, during which there is an enhancement of gene expression, neurotrophy, synaptogenesis, and the formation of new neural connections [8-10]. In a psychotherapeutic context, this "window" is viewed as an opportunity to enhance the effectiveness of psychotherapeutic treatment and foster deeper and more lasting changes. At the same time, increased neuroplasticity is theoretically a prerequisite for improving not only mental but also motor and sensorimotor functions, which is critically important for neurological rehabilitation processes following traumatic brain injuries, strokes, concussions, brain contusions, and other lesions of the central nervous system (CNS). Theoretically, it can be assumed that the ketamine-induced "window of neuroplasticity" can be used not only to improve the quality of psychotherapy but also to enhance the effectiveness of physical and cognitive rehabilitation by intensifying the neurophysiological component of recovery processes. However, the degree of empirical support for this hypothesis remains unclear. The aim of this study was to conduct a systematic narrative review of the available scientific literature on the effects of ketamine and esketamine on neuroplasticity and neurological functions, summarising current preclinical and clinical data on their neuroprotective and neuroplastic effects.

MATERIALS AND METHODS

To achieve the aim of the study, a systematic narrative review of the scientific literature was conducted to identify studies evaluating the effects of ketamine and esketamine on neuroplasticity, neuroprotection, and the restoration of neurological functions. The search was conducted in leading medical and scientific databases: PubMed, Cochrane Library, NICE, APA PsycInfo, CANMAT, UpToDate, as well as in open catalogues of clinical guidelines and clinical trial registries (ClinicalTrials.gov, EU Clinical Trials Register). There was no time limit, but the focus was on studies published in the last 20 years, given the active development of ketamine research in psychiatry and neurology. The search utilised combinations of the following keywords and their synonyms in English: "ketamine", "esketamine", "NMDA antagonist", "neuroplasticity", "synaptogenesis", "BDNF", "mTOR", "AMPAR", "neuroprotection", "traumatic brain injury", "TBI", "stroke", "ischemic stroke", "spinal cord injury", "neurorehabilitation", "motor recovery", "cognitive recovery".

The review included:

- original clinical studies (randomised controlled trials, open-label, and pilot studies) that evaluated: the effect of ketamine/esketamine on neurological functions in humans (motor, cognitive, sensory) or changes in neuroplasticity biomarkers (BDNF, measures of synaptic function, neuroimaging markers of structural/functional plasticity);
- experimental studies in animal models (rats, mice, and others) in which: acute CNS injuries were modelled (traumatic brain injury, ischemic stroke, etc.); the effects of ketamine/esketamine on behavioural, neuro-morphological, and molecular indicators related to neuroplasticity and neuroprotection were studied;
- systematic reviews and meta-analyses that synthesised data on the neuroplastic and neuroprotective effects of ketamine.

The following were excluded from the review:

- narrative reviews without a clearly described methodology;
- case reports and case series without an objective assessment of neurological or neuroplastic outcomes;
- studies focusing exclusively on psychiatric symptoms (depression, anxiety, PTSD) without analysis of neurological or neuroplastic indicators;
- publications in which ketamine was used exclusively as an anesthetic without assessment of long-term neurofunctional outcomes.

The data obtained were synthesised descriptively, with a focus on identifying common trends, mechanisms, and gaps in current knowledge. Detailed a search strategy based on PRISMA 2020 protocol is shown in Figure 1.

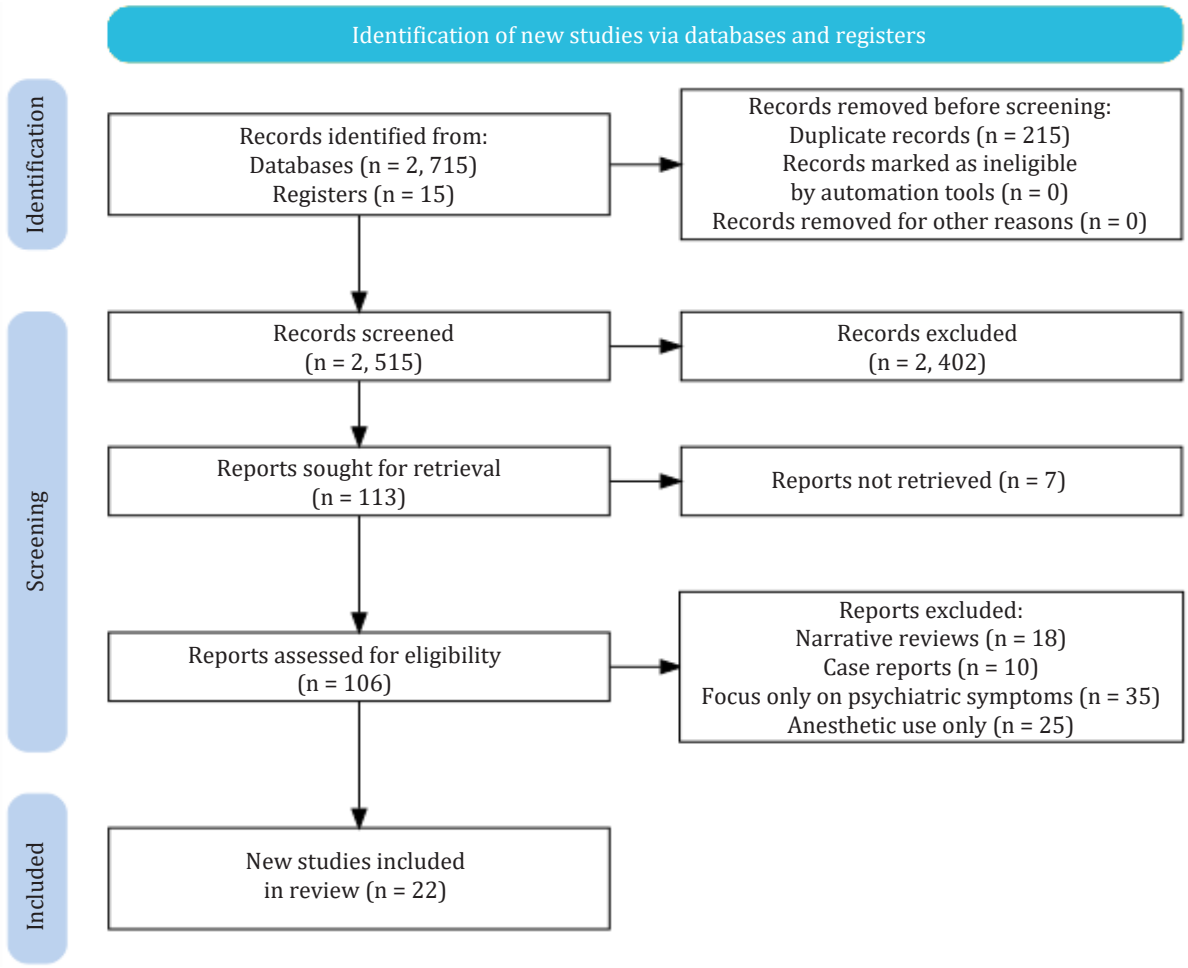

Figure 1. Detailed search strategy and workflow by PRISMA 2020 protocol
Source: compiled by the authors based on [11]

RESULTS

A systematic review did not identify any clinical studies whose primary objective was to evaluate the effect of ketamine on the restoration of human neurological functions specifically through its neuroplastic effects in the context of rehabilitation following CNS injuries. Instead, a large number of studies on depression and PTSD were found, which describe in detail the effects of ketamine on neuroplasticity, synaptic function, and related clinical changes. These studies demonstrate that ketamine, through activation of the BDNF-mTOR pathway, enhancement of AMPA receptor transmission, and stimulation of synaptogenesis, is capable of remodelling pathological neural networks and improving patients' functional status [12-14]. In contrast to the clinical setting, several experimental studies in animal models have been identified that directly demonstrate the positive effect of ketamine on neurological processes associated with functional recovery. In a mouse model of traumatic brain injury (TBI), repeated administration of sub-anaesthetic doses of ketamine (10 mg/kg for 7 days) led to a reduction in neuroinflammation, preservation of dendritic branches and synaptic spines, as well as improvements in memory and behavioural performance [15]. This indicates a neuroprotective effect associated with ketamine-induced neuroplasticity.

For esketamine, in a mouse model of TBI, a reduction in brain edema, neuronal death, and oxidative stress was demonstrated via activation of the AMPK/mTOR–TFEB pathway, accompanied by improvements in neurological parameters [16]. In a model of mild closed-head TBI in rats, intravenous ketamine increased synaptic density in the medial prefrontal cortex, although it did not restore synaptic loss in the hippocampal CA1; the functional (behavioural) consequences of these changes were not yet analysed in detail in this study [17]. This example indicates the regional specificity of ketamine's neuroplastic effects. Similarly, in a model of ischemic stroke (middle cerebral artery occlusion in rats), ketamine promoted improved sensorimotor function, reduced infarct volume, and increased BDNF levels and AMPA/GRIA1 expression, alongside enhanced dendritic branching [18].

Thus, available preclinical data convincingly demonstrate that ketamine and esketamine:

- reduce neuroinflammation, excitotoxicity, and oxidative stress;
- support structural neuroplasticity (dendrites, synaptic spines, synaptic density);
- modulate key molecular pathways (BDNF-mTOR, AMPAR, AMPK/mTOR-TFEB) associated with the restoration of neural networks (shown schematically in Figure 2);
- correlate with improvements in behavioural and sensorimotor parameters in animal models of TBI and ischemic stroke.

Ketamine indirectly leads to the activation of AMPA receptors, which in turn triggers two cascades with downstream effects: the AMPA-BDNF cascade (left) and the AMPA-AMPK cascade (right). The AMPAR-BDNF cascade (left) ultimately activates the mTORC1 complex, which stimulates protein synthesis, thereby enhancing synaptogenesis and synaptic plasticity. The AMPAR-AMPK cascade (right) inhibits the mTORC1 complex, leading to increased autophagy and the degradation of damaged cellular components, which in turn reduces neuroinflammation and apoptosis.

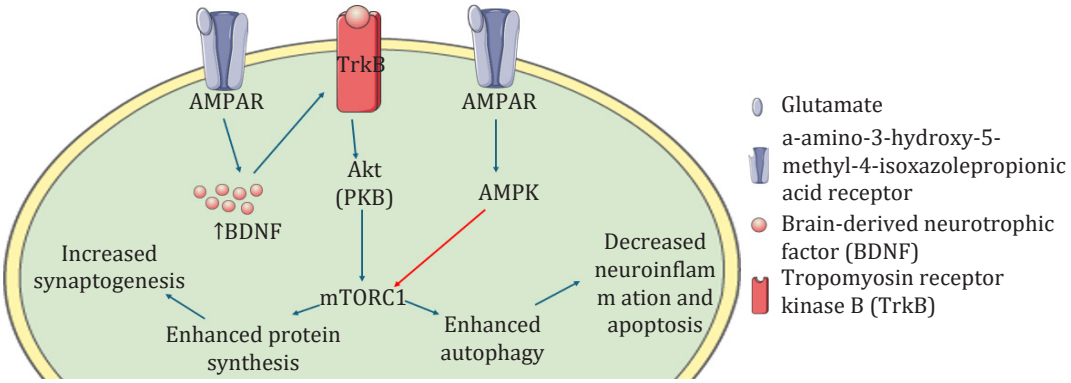

Figure 2. The main mechanisms of action of ketamine that underlie its neuroprotective and therapeutic effects
Source: compiled by the authors

The findings from psychiatric models are consistent with the theoretical concept regarding the central role of BDNF-AMPA-dependent pathways in the formation of the ketamine-induced "window of neuroplasticity". A number of review articles have also described the anti-inflammatory and neuroprotective properties of ketamine: reduction of excitotoxicity, levels of pro-inflammatory cytokines, suppression of excessive microglial activation, and reduction of oxidative stress [19]. Theoretically, these mechanisms may contribute to better neurological outcomes in acute brain injuries.

Despite strong preclinical evidence, clinical data on the use of ketamine as a neuroprotective agent in trauma or stroke, concussion, or contusion-related brain injury remain limited and insufficient for definitive conclusions. In the clinical setting, there are currently no well-designed studies that directly evaluate the use of ketamine to enhance the effectiveness of neurological rehabilitation in humans, particularly through the targeted integration of rehabilitation interventions during the "window of neuroplasticity". This creates a significant research gap and highlights the need for further clinical trials aimed at testing ketamine's potential as an adjunctive agent in recovery programmes following CNS injuries. However, it should be noted that some studies suggest the possibility of transient inhibition of neurogenesis or changes in the glial cell ratio in the hippocampus following TBI [20-21], which requires further analysis. Table 1 summarises the current state of the literature and outlines the discrepancy between preclinical successes and clinical research gaps.

Table 1. Summary of the literature on ketamine effects on neuroprotection and neurorehabilitation

Research focus	Key findings and implications	Mechanisms and characteristics	Sources
Clinical studies (neurological rehabilitation)	A systematic review did not identify any clinical studies that directly evaluated the use of ketamine/esketamine to enhance neurological rehabilitation specifically through their neuroplastic effects. Clinical data on the use of ketamine as a neuroprotective agent in cases of trauma or stroke remain limited.	Currently, there are no well-designed studies on the targeted integration of rehabilitation interventions during the "window of neuroplasticity", creating a significant gap in the research.	–

Table 1. *Continued*

Research focus	Key findings and implications	Mechanisms and characteristics	Sources
Clinical studies (psychiatry)	Studies on depression and PTSD demonstrate that ketamine is capable of remodelling pathological neural networks and improving patients' functional status.	These effects involve BDNF-mTOR activation, enhanced AMPA signalling, and synaptogenesis, along with reduced excitotoxicity, pro-inflammatory cytokines, and oxidative stress.	[12-14, 22-23]
Preclinical studies (traumatic brain injury models)	Reduced neuroinflammation, preserved dendrites and synaptic spines, and improved memory and behaviour in mice. Esketamine also reduced brain edema, neuronal death, and oxidative stress.	The action of esketamine is mediated by activation of the AMPK/mTOR-TFEB pathway. Regional specificity was observed: in rats, ketamine increased synaptic density in the prefrontal cortex but did not restore synaptic loss in the hippocampus.	[15-17, 19]
Preclinical studies (ischemic stroke)	Improvement in sensorimotor functions and reduction in infarct volume in rats.	These effects correlated with increased BDNF levels, AMPA/GRIA1 expression, and enhanced dendritic branching.	[18]
Potential risks (preclinical data)	Some studies suggest the possibility of transient suppression of neurogenesis following traumatic brain injury.	Possible changes in the glial cell ratio in the hippocampus were noted, which requires further analysis.	[20-21]

Source: compiled by the authors

As analysed in Table 1, while studies in psychiatry and preclinical models of TBI and stroke provide robust evidence of neuroplastic and neuroprotective mechanisms (such as BDNF-mTOR activation and reduced neuroinflammation), there is a complete absence of clinical trials evaluating these effects for neurological rehabilitation. This highlights the most critical promising direction for future research: bridging the gap between established preclinical models and human clinical applications.

DISCUSSION

A review of the current scientific literature reveals significant interest in the neuroprotective and neuroplastic properties of ketamine. Studies in animal models by L.R Aleksandrova & A.G. Phillips [22], Y. Gao *et al*. [24] and Y. Liu *et al*. [25], convincingly show that both racemic ketamine and its S-enantiomer (esketamine) are capable of reducing the extent of brain damage, improving sensorimotor functions, reducing inflammation and oxidative stress, and stimulate synaptogenesis and neuronal network remodelling. Furthermore, Y. Gao *et al*. [24] and Y. Liu *et al*. [25] demonstrated that the mechanisms of action include activation of BDNF/TrkB-, AMPAR-, mTOR-, and Nrf2-dependent pathways, as well as modulation of the immune response through polarisation of microglia into the M2 phenotype.

Clinical studies on the use of ketamine in TBI, ischemic stroke, or other acute and chronic neurological conditions remain extremely limited. Some studies, such as those by A.P. Carlson *et al*. [26], M.C.T. Gregers *et al*. [27], and M. Sameer & D.A. Abbas [28], demonstrate a positive effect on reducing the frequency of cortical depolarisations (SD), stabilising intracranial pressure, and improving cerebral perfusion. However, systematic reviews by M.C.T. Gregers *et al*. [27], M. Sameer & D.A. Abbas [28], and T.H. Andreasen *et al*. [29] highlight the low level of evidence for clinical effects: results regarding functional recovery are inconsistent, and the risk of bias remains high. At the same time, M.C.T. Gregers *et al*. [27], S. Himmelseher & M. Durieux [30], and C. Zanza *et al*. [31] note that no significant adverse effects of ketamine on the course of acute TBI or stroke have been identified under controlled ventilation and appropriate monitoring.

In experimental animal models of cerebral ischemia and TBI, ketamine promotes neuronal survival, reduces apoptosis, and supports plasticity through its effects on antioxidant systems (Nrf2), autophagy (AMPK/mTOR/TFEB), and regulation of the cytokine profile, as supported by N.I. Martínez-Torres *et al*. [18], G.N. Silva *et al*. [19], and Y. Liu *et al*. [25]. Esketamine additionally demonstrates the ability to modulate glial responses and metabolism via STAT3- and AKT-dependent pathways [24-25]. However, it is crucial to consider potential risks. M. Boese *et al*. [20], A. Peters *et al*. [21] and J. Liang *et al.* [32] suggest the possibility of transient inhibition of neurogenesis or changes in the glial cell ratio in the hippocampus following TBI, which requires further analysis. Overall, preclinical data support ketamine's potential as an agent for stimulating neuroplasticity and recovery from neurological injuries. However, clinical efficacy remains insufficiently proven due to the limited number of high-quality randomised trials with long-term follow-up and standardised endpoints, a limitation repeatedly emphasised by M.C.T. Gregers *et al*. [27], M. Sameer & D.A. Abbas [28] and T.H. Andreasen *et al*. [29]. It is necessary to consider the dose-dependence of effects, the difference between ketamine enantiomers, and the possible influence of concomitant therapy.

CONCLUSIONS

1. A systematic review of the existing literature has shown that, to date, there are no clinical studies that directly evaluate the use of ketamine or esketamine to enhance the effectiveness of human neurological rehabilitation

through their neuroplastic effects. Instead, there is a compelling body of data from psychiatry demonstrating ketamine's ability to induce a "window of neuroplasticity" through the activation of BDNF-mTOR and AMPAR-dependent pathways, stimulation of synaptogenesis, remodelling of neural networks, and anti-inflammatory effects.

2. Experimental animal models of traumatic brain injury and ischemic stroke indicate that ketamine and esketamine can reduce neuroinflammation, excitotoxicity, and oxidative stress, preserve dendritic architecture and synaptic density, modulate autophagy and glial responses, accompanied by improvements in sensorimotor and cognitive parameters. These data are consistent with the concept of a ketamine-induced "window of neuroplasticity" and suggest the potential for its use in supporting recovery processes following CNS injuries.

3. At the same time, existing clinical studies of ketamine in acute neurological conditions (traumatic brain injury, stroke) are largely focused on safety parameters, control of intracranial pressure, and cortical depolarisations, rather than on the targeted integration of rehabilitation interventions during the period of heightened neuroplasticity. The level of evidence for clinical effects regarding long-term functional recovery remains low, and the results are heterogeneous. Furthermore, some experimental data point to potential risks associated with dosage, administration regimen, and effects on neurogenesis and glial ratios, which requires cautious interpretation.

4. Thus, ketamine and esketamine may be considered promising candidates for use as adjunctive agents in neurological rehabilitation programmes; however, the available evidence is insufficient to formulate clinical recommendations.

5. To translate the concept of the ketamine-induced "window of neuroplasticity" from the theoretical level and preclinical models into the practical realm of evidence-based neurological rehabilitation, future research must focus on: well-designed randomised controlled trials with long-term follow-up;

standardised assessment of motor, cognitive, and functional endpoints; investigating optimal doses, administration regimens, and time windows for combination with physical and cognitive rehabilitation; analysing differences between racemic ketamine and esketamine, as well as the impact of concomitant pharmacological and rehabilitation therapy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Огляд терапевтичних та нейропротективних властивостей кетаміну

Анотація

Актуальність. Депресія є однією з головних причин інвалідності у світі, і значна частина пацієнтів страждає на резистентні до лікування форми розладу. Інноваційним підходом є використання кетаміну та ескетаміну, здатних індукувати «вікно нейропластичності» – період посиленого синаптогенезу та формування нових нейронних зв'язків. Теоретично, ця підвищена нейропластичність може сприяти покращенню не лише психічних, але й моторних та сенсомоторних функцій, що є критично важливим для неврологічної реабілітації після травм головного мозку, інсультів та інших уражень ЦНС.

Матеріали. Провести систематичний огляд доступної наукової літератури щодо впливу кетаміну та ескетаміну на нейропластичність і неврологічні функції, зосередивши особливу увагу на оцінці їх потенціалу для використання в неврологічній реабілітації після різних уражень ЦНС.

Матеріали та методи. Було проведено систематичний пошук наукової літератури у провідних базах даних (PubMed, Cochrane Library, NICE, APA PsycInfo, CANMAT, UpToDate) з фокусом на дослідження за останні 20 років. До огляду включалися клінічні дослідження, експериментальні дослідження на тваринах (з моделюванням гострих травм ЦНС), а також систематичні огляди та мета-аналізи. Зібрані дані синтезувалися описовим методом.

Результати. Систематичний огляд не виявив клінічних досліджень, які б безпосередньо оцінювали використання кетаміну або ескетаміну для підвищення ефективності програм неврологічної реабілітації людини саме завдяки їх нейропластичним ефектам. З іншого боку, доклінічні дані на тваринних моделях (черепно-мозкові травми та ішемічний інсульт) переконливо демонструють, що ці препарати зменшують нейрозапалення, екситотоксичність та окислювальний стрес. Крім того, вони підтримують структурну нейропластичність та позитивно корелюють із покращенням сенсомоторних і поведінкових показників.

Висновки. Кетамін та ескетамін є перспективними кандидатами на роль допоміжних засобів у програмах неврологічної реабілітації. Проте наразі клінічних доказів недостатньо для формування офіційних рекомендацій. Для підтвердження їх ефективності та безпеки необхідні добре сплановані рандомізовані контрольовані дослідження з тривалим періодом спостереження та стандартизованою оцінкою функціональних результатів.

Ключові слова: нейрореабілітація; депресія; нейрозапалення; нейропротекція; кетамін-асистована терапія.