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Effects of Ketamine and Esketamine on Cognitive Functions in Treatment-Resistant Depression

Ketamin ve Esketaminin Tedaviye Dirençli Depresyonda Bilişsel İşlevler Üzerindeki Etkileri

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ABSTRACT

Major depressive disorder is a public health issue that negatively impacts quality of life and leads to cognitive impairments, causing significant disruptions in work, education, and social life. Treatment-resistant depression is defined as the failure to achieve improvement in depressive symptoms despite the use of at least two different antidepressant medications at adequate doses and durations. Current pharmacological approaches are inadequate for about half of treatment-resistant depression patients, and the effects of these medications on cognitive impairments are limited. Therefore, there is a need for new and effective treatment methods. This review aims to evaluate the effects of ketamine and esketamine on cognitive functions in the treatment of treatment-resistant depression patients. Relevant literature has been reviewed and recent studies have been evaluated. The results of randomized controlled trials indicate that ketamine is effective in treating treatment-resistant depression and can improve specific cognitive domains. Significant improvements in cognitive functions such as visual memory, processing speed, working memory, and attention have been recorded in patients responding to 0.5 mg/kg ketamine infusion. However, long-term use of ketamine may have negative effects on spatial working memory. Esketamine, an NMDA receptor antagonist, has shown rapid and effective antidepressant outcomes, providing stability or improvement in cognitive functions. Additionally, its intranasal administration offers practical advantages. However, findings suggest that high doses of esketamine may have neurotoxic effects and negatively impact cognitive functions. The effects of both drugs on depressive symptoms and cognitive functions vary depending on dose, duration of use, and frequency of administration. In conclusion, while ketamine and esketamine show significant potential in the treatment of treatment-resistant depression and improvement of cognitive symptoms, further research is needed regarding their long-term effects and safety.
Keywords: Treatment-resistant depression, ketamine, esketamine, cognitive functions

ÖZ

Majör depresif bozukluk, yaşam kalitesini olumsuz etkileyen ve bilişsel bozulmalara yol açarak iş, eğitim ve sosyal yaşamda ciddi aksaklıklara neden olan bir halk sağlığı sorunudur. Tedaviye dirençli depresyon, en az iki farklı antidepresan ilacın yeterli süre ve dozda kullanımına rağmen depresyon belirtilerinde iyileşme sağlanamaması durumudur. Mevcut farmakolojik yaklaşımlar, tedaviye dirençli depresyon hastalarının yarısında yetersiz kalmakta ve bu ilaçların bilişsel bozulmalar üzerindeki etkileri sınırlı kalmaktadır. Dolayısıyla, yeni ve etkili tedavi yöntemlerine ihtiyaç duyulmaktadır. Bu derlemenin amacı, tedaviye dirençli depresyon hastalarının tedavisinde kullanılan ketamin ve esketaminin bilişsel fonksiyonlar üzerindeki etkilerini değerlendirmektir. Bu bağlamda gerekli alan yazın incelenmiş ve güncel çalışmalar değerlendirilmiştir. Randomize kontrollü çalışmaların sonuçları, ketaminin tedaviye dirençli depresyon tedavisinde etkili olduğunu ve belirli bilişsel alanlarda iyileşme sağlayabileceğini göstermektedir. Özellikle 0.5 mg/kg ketamin infüzyonuna yanıt veren hastalarda görsel bellek, işleme hızı, çalışma belleği ve dikkat gibi bilişsel işlevlerde anlamlı iyileşmeler kaydedilmiştir. Ancak, uzun süreli ketamin kullanımının mekânsal işlem belleği üzerinde olumsuz etkileri olabileceği belirtilmiştir. Esketamin ise NMDA reseptör antagonisti olarak hızlı ve etkili antidepresan sonuçlar elde etmiş, bilişsel işlevlerde stabilite veya iyileşme sağlamıştır. Ayrıca, intranazal uygulanabilirliği de pratik bir avantaj sunmaktadır. Ancak, yüksek dozda esketamin kullanımının nörotoksik etkiler ve bilişsel işlevler üzerinde olumsuz etkiler yaratabileceğine dair bulgular vardır. Her iki ilacın da depresyon semptomları ve bilişsel işlevler üzerindeki etkileri doz, kullanım süresi ve uygulama sıklığına bağlı olarak değişiklik göstermektedir. Sonuç olarak, ketamin ve esketaminin tedaviye dirençli depresyon tedavisinde ve bilişsel semptomların düzelmesinde önemli bir potansiyele sahip olduğu görülmekle birlikte, uzun vadeli etkiler ve güvenilirlik konusunda daha fazla araştırma gerekmektedir.
Anahtar sözcükler: Tedaviye dirençli depresyon, ketamin, esketamin, bilişsel fonksiyonlar

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Introduction

Major depressive disorder (MDD) is a serious health concern affecting approximately 300 million individuals worldwide (Sadock et al. 2017). Individuals diagnosed with MDD report significantly reduced quality of life, which negatively impacts public health. MDD is associated with high mortality rates and can trigger severe health issues such as cardiovascular diseases, stroke, Alzheimer's disease, epilepsy, diabetes, and cancer (Catalina-Romero et al. 2017, Chan et al. 2020). Additionally, MDD adversely affects cognitive functions. Cognitive impairments associated with MDD are observed in 40% of patients, disrupting attention, memory, thinking, and decision-making processes, thereby causing significant challenges in work, education, and social life (Bortolato et al. 2014, Bortolato et al. 2015). Although these impairments may be linked to structural changes in the prefrontal cortex and hippocampus, the exact nature of these alterations remains unclear (Dale et al. 2015, Phillips et al. 2015). MDD is also associated with neurodegenerative and cerebrovascular disorders, and abnormalities in the limbic-thalamo-cortical circuits significantly contribute to the manifestation of MDD symptoms (Kaltenboeck and Harmer 2018, Wen et al. 2022). The roles of the striatum and pallidum in reward-punishment systems lead to loss of motivation and changes in emotional responses (Zhukovsky et al. 2021). Furthermore, thalamic dysfunctions alter information transmission and processing (Gong and He 2015). Understanding these structural and functional changes in the brain will not only provide a deeper insight into the pathophysiology of MDD but also facilitate the development of more targeted and effective treatment strategies.

One of the greatest challenges in the treatment of depression is the condition known as treatment-resistant depression (TRD). TRD is defined as the failure to achieve improvement in depressive symptoms despite the use of at least two different antidepressant medications at adequate doses and durations (Rush et al. 2006). It is observed in approximately 30% of patients with major depressive disorder, presenting a significant obstacle in depression treatment and severely impacting patients' quality of life (Al-Harbi 2012). Fava (2003) emphasized the importance of alternative strategies in the management of TRD, including pharmacological adjustments, psychotherapeutic interventions, and neuromodulation techniques. Therefore, understanding the pathophysiology of major depressive disorder and treatment approaches for TRD is critical for developing more effective and targeted therapeutic strategies.

Current pharmacological approaches in the treatment of MDD and TRD face significant challenges. Only half of the patients diagnosed with TRD respond favorably to monoaminergic antidepressants. The increased risk of relapses, hospitalization, and suicide associated with TRD further underscores the severity of the condition (Keefe et al. 2014, Conway et al. 2017, Prado et al. 2018, McIntyre et al. 2023). Common classes of medications include serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs), which exert their effects by increasing serotonin and norepinephrine levels. However, these medications often cause undesirable side effects such as headaches, nausea, anticholinergic effects, cardiac complications, and weight gain (Bschor and Adli 2008, Olfson et al. 2014). Additionally, despite their positive impact on mood, antidepressants generally exhibit limited and mild effects on cognitive functions (Biringer et al. 2009). In conclusion, the limitations of current antidepressants in the treatment of MDD and TRD underscore the need for novel and effective therapeutic approaches (Peltoniemi et al. 2016, Zanos et al. 2018).

Ketamine was first introduced as an anesthetic in the 1960s and later considered an alternative treatment option for psychiatric disorders such as depression (Perry et al. 2007). Its ability to rapidly alleviate depressive symptoms is attributed to changes in neurotransmitter systems, inhibition of glycogen synthase kinase-3 (GSK-3) activity, and enhanced communication and plasticity between neurons (Mion and Villevieille 2013). Additionally, ketamine reduces brain inflammation, exerts regulatory effects on the immune system, and influences kynurenine metabolism (Zanos et al. 2018). Its effects on enhancing synaptic plasticity occur through several molecular mechanisms, including the increase in brain-derived neurotrophic factor (BDNF) levels, activation of the mTOR signaling pathway, and upregulation of synaptic protein synthesis (Li et al. 2010, Autry and Monteggia 2012, Hashimoto 2019).

The effects of ketamine also arise through the antagonism of N-methyl-D-aspartate (NMDA) receptors. Inhibition of NMDA receptors increases glutamate release, which, in turn, activates α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, leading to the strengthening of synaptic connections and activation of the mTOR signaling pathway (Zanos and Gould 2018). Activation of AMPA receptors enhances synaptic plasticity, contributing to long-term structural changes in the brain (Lepow et al. 2021). By increasing

the levels of synaptic proteins, ketamine elevates synapse density, thereby strengthening neuroplasticity (Kang et al. 2022).

Despite ketamine's neuroplasticity-enhancing effects, there are several potential side effects that warrant caution during treatment. Notably, its psychotomimetic properties and addiction potential necessitate careful management of its use. Long-term administration of ketamine has been shown to cause neurotoxicity and impair cognitive functions (Wilkinson et al. 2017). For example, studies in animal models have revealed that repeated high doses of ketamine exert toxic effects on hippocampal neurons, negatively impacting learning and memory functions (Zhou and Duan 2024). Similarly, human studies have indicated that chronic ketamine use leads to lasting adverse effects on attention, executive functions, and working memory (Strous et al. 2022). Furthermore, prolonged ketamine use has been reported to increase dissociative symptoms in some individuals, potentially exacerbating psychiatric disorders such as anxiety and depression (Van Amsterdam and Van Den Brink 2022).

Esketamine, the (S)-ketamine isomer, affects neurotransmission by blocking NMDA receptors. Additionally, it modulates other neurotransmitter systems, including serotonin, dopamine, and norepinephrine (Swainson et al. 2019, Perez-Ruixo et al. 2021, Wei et al. 2022). Administered intranasally, intravenously, or orally, esketamine is rapidly absorbed, reaching plasma levels within 10-20 minutes and producing a rapid effect (Jonkman et al. 2017). Approved by the United States Food and Drug Administration (FDA) in 2019, esketamine is considered an effective option for TRD. Its potential to quickly alleviate symptoms and enhance neuroplasticity in patients unresponsive to traditional antidepressants suggests that it may improve long-term treatment outcomes (Gastaldon et al. 2020, Huang et al. 2023).

Esketamine stands out as a significant agent in depression treatment by rapidly enhancing synaptic plasticity through NMDA receptor antagonism and AMPA receptor activation (Wajs et al. 2020). Inhibition of NMDA receptors increase glutamate release, which activates AMPA receptors, this process strengthens synaptic connections and triggers the release of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF) (Autry et al. 2011, Zanos and Gould 2018). Esketamine's rapid mechanism of action activates the mTOR signaling pathway, increasing synaptic protein synthesis and synapse density, thereby contributing to the restoration of disrupted synaptic networks in depression (Duman and Aghajanian 2012). In cases of TRD, esketamine's clinical advantages are evident, and studies have confirmed its rapid and robust effects (Fedgchin et al. 2019). However, due to its psychotomimetic effects and addiction potential, careful management of treatment is required (Wilkinson et al. 2017).

However, the use of esketamine requires careful management due to potential side effects and the risk of misuse. The primary side effects include dissociative symptoms, dizziness, and drowsiness, which may cause feelings of detachment from reality and affect motor skills following treatment (Matveychuk et al. 2020). Additionally, esketamine can lead to cardiovascular issues such as hypertension, making blood pressure monitoring during treatment essential (Ceban et al. 2021). In patients with a history of psychotic symptoms or mania, esketamine may be risky due to the potential exacerbation of psychotic symptoms or triggering of manic episodes (Gautam et al. 2020). Moreover, due to its potential for addiction and misuse, treatment must be carefully managed (Jawad et al. 2022).

The aim of this study is to evaluate the effects of ketamine and esketamine on cognitive functions in patients diagnosed with TRD. The effectiveness of ketamine and esketamine in the treatment of TRD and their impact on neurocognitive functions have been examined based on the results of randomized controlled trials. This review looks to elucidate the mechanisms and effects of these drugs in the treatment of depression. The findings provide significant insights into the clinical use of these medications and are expected to serve as a guide for future research.

Method

This study focused on human research examining the effects of ketamine and esketamine on cognitive processes. A comprehensive literature review was conducted to evaluate the effects of ketamine and esketamine on cognitive functions, attention, and other cognitive processes. The literature search was carried out in January 2024 using academic databases such as PubMed, Google Scholar, and Web of Science. A systematic and extensive review of studies investigating the effects of ketamine and esketamine on cognitive functions was performed. Using keywords such as 'ketamine,' 'esketamine,' 'cognitive processes,' 'attention,' and 'cognitive functions,' a total of 18 studies were included in the research.

The inclusion criteria encompassed studies conducted with human subjects that investigated the effects of ketamine or esketamine on cognitive processes. These studies were required to include specific assessments of cognitive functions, attention, and other cognitive processes. Only studies published in English and Turkish were included in the evaluation. Exclusion criteria consisted of animal studies, in vitro research, and studies examining the cognitive effects of drugs other than ketamine and esketamine. Additionally, opinion articles, review papers, and meta-analyses were not included in the study.

Tables are presented that detail the study characteristics and measurement parameters related to the use of ketamine (from the most recent to older studies) and esketamine (from the most recent to older studies), as well as findings evaluating their cognitive effects in the treatment of TRD. According to the PRISMA flow diagram used in the study, the number of studies reviewed is systematically presented in Figure 1.

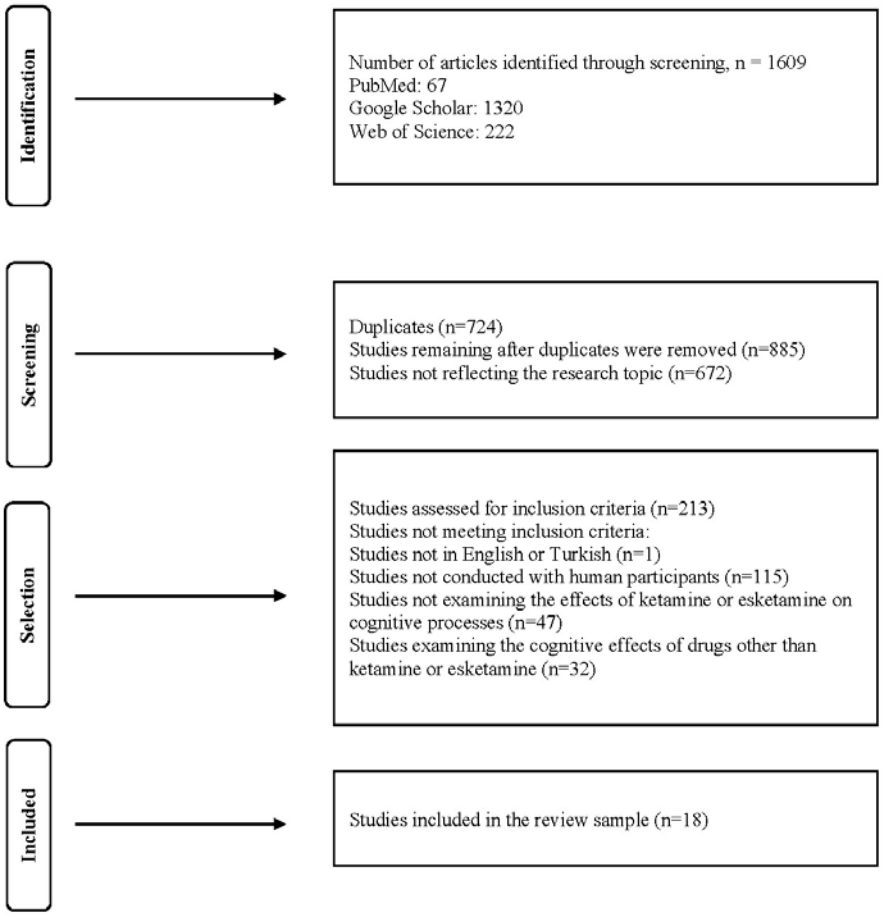

Figure 1. Identification of studies via databases and registers

Results

In Table 1, neuropsychological outcomes were obtained from 1,213 patients. For single-dose (R-S)-ketamine studies, the intervals between patient drug administration and assessment in studies using valid neuropsychological performance measures were as follows: 1 study 40 minutes (n = 25) (Murrough et al. 2014), 1 study 24 hours (n = 25) (Sterpenich et al. 2019), 1 study 3 days (n = 71) (Chen et al. 2018), 1 study 7 days (n = 38) (Phillips et al. 2022).

For four-infusion (R-S)-ketamine studies, the intervals between patient drug administration and assessment were: 1 study 7 days (n = 68) (McIntyre et al. 2021). For six-infusion (R-S)-ketamine studies, the intervals between patient drug administration and assessment were: 1 study 7 days (n = 15) (Shiroma et al. 2014), 5 studies 13 days (n = 321) (Zhou et al. 2018, Zheng et al. 2019, Zheng et al. 2020, Shiroma et al. 2020, Zhou et al. 2021), and 1 study 3 weeks (n = 28) (Wilkinson et al. 2021). In the large intranasal S(+)-ketamine study, assessments were conducted at 40 minutes (n = 389) (Wajs et al. 2020, Pepe et al. 2023b) 24 hours (n = 102) (Araújo-de-Freitas et al. 2021, Lan et al. 2023), and 4 weeks (n = 146) (Ochs-Ross et al. 2020, Pepe et al. 2023a).

Table 1. Use of ketamine and esketamine: study characteristics and measurement parameters

Research	Sample (Number of Patients/ Age Range)	Active Substance	Study Design	Treatment Parameters	Depression Severity Scales
Phillips et al. 2022	38/18-65	Ketamine	Ketamine/Placebo/Midazolam Crossover Design	0.5 mg/kg ketamine or 30 μg/kg midazolam, 40-minute infusion	MADRS
Araújo-de-Freitas et al. 2021	51/18+	Ketamine/esketamine	Esketamine/Ketamine/Placebo Controlled	0.25 mg/kg and 0.5 mg/kg esketamine or ketamine, 40-minute infusion	MADRS
McIntyre et al. 2021	68/18-75	Ketamine	Ketamine/Placebo Controlled	0.5 mg/kg infusion for those with >20% reduction in QIDS-SR-16 total score, 0.75 mg/kg infusion for inadequate response	QIDS-SR-16
Wilkinson et al. 2021	28/18-65	Ketamine	Randomized	0.5 mg/kg, 40-minute infusion	HAMD-17
Zhou et al. 2021	111/18-65	Ketamine	Open-label Observation	0.5 mg/kg, 40-minute infusion	HAMD-17
Shiroma et al. 2020	43/18-75	Ketamine	Ketamine/Placebo/Midazolam Crossover Design	0.5 mg/kg ketamine or 0.045 mg/kg midazolam, 40-minute infusion	IDS-C30
Zheng et al. 2020	19/18-65	Ketamine	Open-label Observation	0.5 mg/kg, 40-minute infusion	HAMD-17
Sterpenich et al. 2019	10/38-58	Ketamine	Open-label Observation	0.5 mg/kg, 40-minute infusion	MADRS
Zheng et al. 2019	64/18+	Ketamine	Open-label Observation	0.5 mg/kg, 40-minute infusion	HAMD-17
Chen et al. 2018	71/21-65	Ketamine	Ketamine/Placebo Controlled	Intravenous ketamine (0.5 mg/kg or 0.2 mg/kg) or normal saline (placebo), 40-minute infusion	HAMD-17
Zhou et al. 2018	84/18-65+	Ketamine	Open-label Observation	0.5 mg/kg, 40-minute infusion	HAMD-17
Murrough et al. 2014	25/21-80	Ketamine	Open-label Observation	0.5 mg/kg, 40-minute infusion	IDS-C30
Shiroma et al. 2014	15/18-70	Ketamine	Open-label Observation	0.5 mg/kg, 40-minute infusion	HAMD-17
Lan et al. 2023	51/13-18	Esketamine	Esketamine/Placebo Controlled	0.25 mg/kg esketamine or 0.02 mg/kg midazolam, 40-minute infusion	HAMD-17
Pepe et al. 2023a	8/19-59	Esketamine	Open-label Observation	Initial dose 28 mg or 56 mg, subsequent doses 56 mg or 84 mg	MADRS
Pepe et al. 2023b	25/18+	Esketamine	Case Series	First month 56 mg twice a week, following 8 weeks 84 mg, weekly doses	MADRS
Ochs-Ross et al. 2020	138/65+	Esketamine	Esketamine/Placebo Controlled	Flexible dose esketamine or placebo (28 mg, 56 mg, or 84 mg), twice a week for 4 weeks	IDS-C30
Wajs et al. 2020	364/18+	Esketamine	Open-label Observation	Starting dose ≥65 years 28 mg or <65 years 56 mg, adjusted doses <65 years 56 or 84 mg, ≥65 years 28, 56, or 84 mg	MADRS

HHAMD-17: Hamilton Depression Rating Scale (17 items), IDS-C30: Inventory of Depressive Symptomatology - Clinician Rated 30, MADRS: Montgomery-Åsberg Depression Rating Scale, QIDS-SR-16: Quick Inventory of Depressive Symptomatology - Self-Report 16 (Quick Inventory of Depressive Symptomatology - Self-Report 16)

Table 2. Cognitive effects of ketamine and esketamine in depression treatment: assessment parameters and study findings

Research	Outcome Measurement Parameters	Results
Ketamine Research		
Phillips et al. 2022	MADRS, MMSE, TMT-A, TMT-B, Digit Span, CVLT-II, Rey Complex Figure Test, Stroop Color and Word Test (computerized version), AMI-SF, QIDS-SR16	A decrease in depression levels and an increase in processing speed and verbal learning scores were observed, however, no significant improvement was noted in visual learning and working memory.
Araújo-de-Freitas et al. 2021	MADRS, WASI, WAIS-III, Corsi Block-Tapping Test	A decrease in depression levels and improvements in cognitive performance and auditory-verbal episodic memory tasks were observed.
McIntyre et al. 2021	MADRS, QIDS-SR-16, DSST, TMT-B, PDQ-5-D	A decrease in depression levels and an improvement in cognitive performance were observed. Increases in visual attention, mental flexibility, and motor speed, as well as a reduction in self-reported cognitive difficulty scores were noted.
Wilkinson et al. 2021	MADRS, QIDS-SR-16, Go/No-Go Task	A decrease in depression levels and positive effects on cognitive flexibility in emotional Stroop and go/no-go tasks were observed. Additionally, a reduction in errors and omissions in the go/no-go task was noted.
Zhou et al. 2021	MADRS, MCCB	A decrease in depression levels, along with an increase in processing speed and verbal learning scores, as well as improvements in visual learning and working memory, were observed.
Shiroma et al. 2020	MADRS, Cosgate Computerized Test Battery	No significant change in depression levels was reported, however, changes between groups were observed over time. A decrease in processing speed was noted in the single-infusion group, while the six-infusion group showed improvements in processing speed and visual memory.
Zheng et al. 2020	MADRS, MCCB	A decrease in depression levels and an improvement in processing speed were observed, while other cognitive functions remained stable.
Sterpenich et al. 2019	MADRS, HDRS-21, BDI-II, Reward Task, Emotional Evaluation Task	A decrease in depression levels, improvement in attention and visual memory performance, a reduction in delayed responses, and a decrease in delayed responses to positive cues in the game-like reward task were observed. No significant effects were found in the emotional evaluation task, although response times were faster.
Zheng et al. 2019	MADRS, MCCB	A decrease in depression levels, along with significant improvements in verbal learning and processing speed, were observed.
Chen et al. 2018	HDRS-17, Go/No-Go Task	A decrease in depression levels, along with a reduction in errors and omissions in the go/no-go task, was observed.
Zhou et al. 2018	HAMD-17, MCCB	A decrease in depression levels, along with increased neurocognitive performance in processing speed and verbal learning, was observed. The likelihood of an antidepressant response to ketamine infusion was higher in individuals without psychiatric comorbidities and in those with better visual learning abilities.
Murrough et al. 2014	MADRS, WRAT-3, WAIS-III, MCCB, BACS, CPT-I/P, HVLT	A decrease in depression levels and an increase in processing speed were observed, though no significant improvements were found in other cognitive domains. However, a temporary decline in verbal learning and recall performance occurred immediately after treatment due to the acute psychoactive effects of ketamine.
Shiroma et al. 2014	MADRS, CBB	A decrease in depression levels, along with improvements in attention performance and visual memory scores, were observed.
Esketamine Research		
Lan et al. 2023	MADRS, MCCB, SSI-5	In the group receiving esketamine, a greater decrease in depression levels, as well as higher antidepressant response and remission rates, were observed compared to the group receiving midazolam.

Pepe et al. 2023a	MADRS, DSST, TMT-B, PDQ-D5, HARS, CGI	A decrease in depression levels, a reduction in anxiety, and an increase in general cognitive function scores were observed during the same period, while a decline was noted in cognitive flexibility and visual planning abilities scores. A reduction in self-reported cognitive difficulty scores was also reported.
Pepe et al. 2023b	MADRS, HARS, DSST, BDI, SHAPS, SAS, PDQ-D5	A decrease in depression and anxiety levels, along with improvements in attention, processing speed, and cognitive flexibility, were observed.
Ochs-Ross et al. 2020	MADRS, CGI-S, PHQ-9, SDS	A decrease in depression levels and improvements in high-level cognitive function measures, including visual, verbal, and working memory, as well as executive functions, were observed. A slight slowdown in the simple reaction time test was noted in both treatment groups from baseline.
Wajs et al. 2020	MADRS, Cogstate Computerized Test Battery	A decrease in depression levels was observed, with cognitive performance remaining stable or slightly improved in patients under 65. In patients over 65, improvements or stability in visual and verbal learning, working memory, and executive functions were noted, while a slowdown in simple and choice reaction times, along with significant variability in response times, was detected in this age group.

AMI-SF: Affective Neuroscience Personality Scales-Short Form, BACS: Brief Assessment of Cognition in Schizophrenia, BDI-II: Beck Depression Inventory-II, CBB: Cambridge Brain Computerized Test, CGI: Clinical Global Impression, CPT-I/P: Continuous Performance Test-I/II, CVLT-II: California Verbal Learning Test-II, DSST: Digits Symbol Substitution Test, HARS: Hamilton Anxiety Rating Scale, HDRS: Hamilton Depression Rating Scale, HVLT: Hopkins Verb Memory Test, MCCB: MATRICS Consensus Cognitive Battery, MMSE: Mini Mental State Examination, PDQ-5-D: Perceived Deficits Questionnaire-Depression Version, PHQ-9: Patient Health Questionnaire-9, SAS: Self-Assessment Scale, SDS: Sheehan Disability Scale, SHAPS: Snaith-Hamilton Pleasure Scale, SSI-5: Sheehan Disability Scale-5, TMT: Trail Making Test, WAIS-III: Wechsler Adult Intelligence Scale-III, WASI: Wechsler Abbreviated Scale of Intelligence, WRAT-3: Wide Range Achievement Test-3

Discussion

Effects of Ketamine Treatment on Depression and Cognitive Functions

1. Clinical Efficacy

Studies have examined the clinical efficacy of ketamine on TRD from various perspectives. Specifically, ketamine infusions administered at a dose of 0.5 mg/kg have been reported to result in rapid improvement in depressive symptoms (Chen et al. 2018, McIntyre et al. 2021, Phillips et al. 2022). These infusions provided a significant reduction in patients' depressive symptoms, with more effective outcomes observed within 24 hours post-treatment. In the study by Zheng et al. (2020), after six infusions, a response rate of 65% and a remission rate of 50% were achieved (see Table 1).

Freitas et al. (2021) reported that ketamine treatment led to improvements in memory and processing speed, while Phillips et al. (2022) noted that this treatment provided clinically significant reductions in depression. These findings highlight the notable short-term effects of ketamine as well as its potential long-term benefits. However, the study by Murrough et al. (2014) indicated that the response to treatment was influenced by individual factors, particularly variables such as processing speed and age, suggesting that ketamine efficacy may vary based on personal differences. Furthermore, Sterpenich et al. (2019) emphasized that ketamine treatment could lead to both short-term and lasting improvements, underscoring the need to evaluate treatment progress within a broader context. In terms of the efficacy of combining ketamine with other treatment options, it has been shown that combining ketamine with cognitive behavioral therapy increased recovery rates (Wilkinson et al. 2021). These findings suggest that the use of ketamine in conjunction with psychotherapeutic approaches has the potential to enhance treatment efficacy (Table 1).

2. Safety Profile

The neurocognitive effects of ketamine vary depending on the administered dose, duration of use, and frequency of infusion. A single subanesthetic dose (10 mg/kg) of ketamine infusion has been found to improve neurocognitive performance and increase brain BDNF levels (Autry et al. 2011). However, ketamine infusions administered at an anesthetic dose (80 mg/kg) may lead to neurocognitive impairments by causing an increase in apoptotic cells, which negatively affects memory and learning processes (Zheng et al. 2020). Long-term ketamine use has been associated with impairments in spatial working memory and reduced hippocampal function (Morgan et al. 2014, Ding et al. 2016, Ke et al. 2018) (Table 1).

3. Cognitive Effects

The effects of ketamine on cognitive processes are most evident in areas such as attention, selective attention, learning, and memory. It has been shown to improve attention and selective attention processes by enhancing synaptic plasticity in the prefrontal cortex (Zanos et al. 2018, Yang et al. 2020). Additionally, ketamine has been found to promote short- and long-term memory performance by increasing neuroplasticity and elevating BDNF levels in the hippocampus (Duman and Aghajanian 2012, Lepow et al. 2021). Numerous studies have confirmed that ketamine supports cognitive performance, particularly by providing short-term improvements in memory and processing speed (Freitas et al. 2021, Shinohara et al. 2021, Jha and Trivedi 2023). The improvements in cognitive functions such as processing speed and short-term memory have also been linked to the recovery process of depression (Zhou et al. 2021, Grasso et al. 2024).

On the other hand, Murrough et al. (2014) emphasized that while ketamine provides short-term improvements in cognitive functions, these improvements vary based on individual differences. The study by Phillips et al. (2022) demonstrated inconsistencies between subjective and objective cognitive improvements. Furthermore, studies by McIntyre et al. (2021) and Chen et al. (2018) indicated that while ketamine treatment may improve processing speed and set-shifting tasks, some cognitive impairments may also appear. These findings suggest that the effects of ketamine on cognitive performance should be evaluated in the context of individual differences and the relationship between subjective and objective improvements (see Table 1).

4. Side Effects and Duration of Treatment

Different effects are observed depending on the dose of ketamine. High-dose and long-term ketamine administration can lead to structural changes in the hippocampal region, resulting in permanent cognitive impairments (Okubo et al. 2024). Ketamine administered at high doses (80 mg/kg) can disrupt memory and learning processes, causing an increase in apoptotic cells (Zheng et al. 2020). Additionally, long-term ketamine use has been found to impair spatial working memory and reduce hippocampal functions (Morgan et al. 2014, Ding et al. 2016, Ke et al. 2018, Okubo et al. 2024).

The effects of ketamine treatment have been extensively studied, and some side effects have appeared as notable. These side effects include dizziness, dissociative symptoms, and temporary cognitive impairments (Shiroma et al. 2014 2020, McIntyre et al. 2021). Chen et al. (2018) highlighted that ketamine treatment could pose a risk of short-term cognitive impairments and psychosis (see Table 2). On the other hand, Smith-Apeldoorn et al. (2022) noted that ketamine is generally well tolerated and that most side effects are mild. However, the study by Nikayin et al. (2022) suggested that prolonging the treatment duration may increase side effects. This underscores the necessity for careful monitoring and management during treatment. Langmia et al. (2022) examined the effects of treatment duration and dosage on ketamine's efficacy and found that treatment duration could influence both the antidepressant effects of ketamine and the management of its side effects. Therefore, careful consideration of treatment duration and dosage protocols is required.

The effects of ketamine may vary by age group. In older individuals, long-term use may increase the risks of cardiovascular side effects and neurotoxicity, with health issues such as hypertension and arrhythmia being among these risks (Gupta et al. 2021). In adolescents, the effects of ketamine are more complex, adolescence is a period when neuroplasticity is at its peak and ketamine's effects on synaptic plasticity can be pronounced. However, the potential negative effects on prefrontal cortex and hippocampal development complicate the treatment process (Acevedo and Siegel 2022). While the rapid antidepressant effects of ketamine in adolescents offer promising results, more research is needed to determine the safety of long-term use (Pardossi et al. 2024).

Effects of Esketamine Treatment on Depression and Cognitive Functions

1. Clinical Efficacy

Research on the efficacy of esketamine in depression treatment shows that this therapy has the potential to rapidly and significantly reduce symptoms. In the study by Wajs et al. (2020), 52.6% of patients receiving esketamine treatment responded positively, with 31.6% in remission. These findings support the clinical efficacy of esketamine and suggest that it could be a promising option for challenging cases like treatment-resistant depression. Similarly, Pepe et al. (2023a) reported significant improvements in symptoms of depression, anhedonia, sleep disturbances, and anxiety with esketamine treatment. These effects of esketamine are thought to be related to its NMDA receptor antagonism and its impact on the glutamatergic system (Johnston et al. 2024) (Table 2). Intranasal esketamine stands out as a more easily administered alternative to intravenous ketamine. This method offers a practical solution, particularly in cases of TRD (Wajs et al. 2020, Lan et al. 2023).

Intranasal administration allows the drug to enter the bloodstream directly without passing through the gastrointestinal system, bypassing first-pass metabolism and the blood-brain barrier, thereby offering an effective pharmacokinetic profile (Canuso et al. 2018). The rapid absorption of the drug through the nasal mucosa ensures the therapeutic effect begins quickly, enabling the desired outcome with lower doses (Daly et al. 2019). However, absorption through the nasal mucosa can be influenced by numerous factors, which introduce some limitations to the method (Popova et al. 2019) (Table 2).

2. Safety Profile

The safety profile of esketamine is a crucial consideration during treatment. Maher et al. (2023) emphasize the need for careful monitoring of esketamine treatment. This underscores the necessity of closely monitoring and managing potential risks during therapy (Price and Price 2024). Notably, two fatal cases during treatment (one due to cardiac and respiratory failure, the other a suicide) clearly indicate the importance of closely observing esketamine's safety profile (Sanders and Brula 2021). Additionally, the potential increase in suicide risk requires extremely careful management of the treatment process (Hashimoto 2020). However, clinical trials suggest that the cognitive effects of esketamine generally remain stable or improve over time with therapeutic use (Nikayin et al. 2022). Thus, while esketamine appears to be both an effective and practical option for the treatment of TRD, further research is necessary, particularly considering the potential limitations of intranasal administration (Table 2).

3. Cognitive Effects

Research indicates that esketamine generally maintains cognitive performance or improves areas such as processing speed, executive functions, and working memory (Lan et al. 2023, Pepe et al. 2023a 2023b). These improvements contribute to mitigating the cognitive impairments caused by depression, positively supporting the treatment process (Ochs-Ross et al. 2023, Pepe et al. 2023b) (Table 2).

The effects of esketamine on cognitive functions may vary by age. Specifically, in patients aged 65 and older, negative cognitive effects such as slowed reaction times have been reported (Krystal et al. 2024). This highlights the need for more cautious administration of esketamine in elderly individuals. However, some studies have observed significant increases in cognitive processing speed, although limited changes were reported in other cognitive domains (Lan et al. 2023).

The primary mechanism behind esketamine's rapid antidepressant effect is explained by its antagonistic action on NMDA receptors. This effect enhances neuroplasticity, quickly alleviating the cognitive and emotional symptoms of depression (Wajs et al. 2020). Research shows that esketamine produces significant antidepressant effects in patients with treatment-resistant depression and improves cognitive processing speed (Zheng et al. 2020, Araújo-de-Freitas et al. 2021) (Table 2). However, the exact mechanisms underlying esketamine's pro-cognitive effects have not yet been fully explained. These effects are thought to be related to the glutamatergic system, BDNF, and neuroplasticity (Lee et al. 2016).

There are also concerns that esketamine may have neurotoxic effects at high doses and could lead to cognitive impairments in some individuals (Popova et al. 2019). These negative effects are associated with synaptic plasticity and neurogenesis processes, and further research is needed regarding the long-term cognitive effects.

4. Side Effects and Duration of Treatment

Most side effects occur shortly after dose administration and resolve within the same day. However, these side effects need to be carefully monitored throughout the treatment process. The duration of treatment and dosage play a crucial role in balancing side effects with the response to treatment (Dwyer et al. 2021).

Research on the cognitive effects of esketamine suggests that dose-dependent cognitive effects may be observed, but significant cognitive impairment is generally not reported (Araújo-de-Freitas et al. 2021). In patients with TRD, it has been emphasized that esketamine does not cause serious negative effects on cognitive functions. However, it is important to consider that side effects may vary across different age groups. In older individuals, esketamine treatment may lead to cognitive impairments and balance issues, which could negatively impact the response to treatment (Gupta et al. 2021). Additionally, side effects such as hypertension and urinary tract infections have been reported more frequently in elderly patients (Ceban et al. 2021).

There are concerns that esketamine treatment in adolescent patients may negatively affect neurological development and trigger psychosis-like symptoms (Ryan and Hosanagar 2023). In younger age groups, side effects such as high-risk behaviors and sleep disturbances have been observed (Kim et al. 2021). Therefore, it is emphasized that the long-term effects and safety profile of esketamine need to be further investigated in both

elderly and younger populations. Comprehensive and long-term studies are needed to better understand the effects of treatment duration and dosage on side effects and treatment response (Nikayin et al. 2022).

This study has several important limitations. First, the included studies generally have small sample sizes, which limits the generalizability of the findings. Additionally, many studies were conducted with short follow-up periods, making it difficult to develop a deeper understanding of the long-term efficacy and safety of ketamine and esketamine. There are significant variables among the studies, such as dosage regimens, administration methods (intravenous vs. intranasal), outcome measures, and geographical differences. This diversity makes it challenging to obtain consistent results regarding the use of ketamine and esketamine in TRD and MDD cases with suicidal ideation. Furthermore, only human studies were included, excluding animal and cell culture studies, which limits the examination of the findings' effects on broader biological models.

Conclusion

This study comprehensively examined the therapeutic potential of ketamine and esketamine and their effects on cognitive functions in patients with MDD and TRD. The findings highlight the efficacy of these drugs in depression treatment and their potential for cognitive improvements.

Ketamine, particularly when administered via intravenous infusion, shows significant antidepressant effects in MDD patients. Research has demonstrated that ketamine rapidly and meaningfully reduces depressive symptoms, with these effects becoming evident within 24 hours post-infusion (Daly et al. 2019, Fedgchin et al. 2019). This rapid improvement suggests that ketamine may help alleviate depression symptoms by enhancing neural plasticity through the glutamate system. However, further research is needed to determine the long-term sustainability of ketamine's rapid effects and its potential side effects. Although the short-term safety profile is generally positive, factors such as long-term effects, misuse potential, and risk of addiction must also be considered.

Esketamine, the enantiomeric form of ketamine, is typically administered in its intranasal form. Studies have shown that esketamine rapidly reduces depression symptoms and is particularly effective in patients with TRD. Esketamine's high response rates, along with improvements in anxiety, anhedonia, and overall quality of life, make it a promising option for patients with TRD. However, further research is clearly needed on the long-term safety profile and efficacy of esketamine.

In terms of cognitive functions, ketamine and esketamine have generally been found to produce neutral or positive effects. Ketamine has shown potential improvements in cognitive domains such as processing speed, verbal learning, and auditory memory. However, it is important to validate these effects with larger and more diverse samples to ensure generalizability. Additionally, more information is needed regarding the long-term effects and reliability of ketamine and esketamine on cognitive functions.

In conclusion, ketamine and esketamine are considered drugs with significant potential in the treatment of MDD and TRD. However, more comprehensive research is needed on their long-term effects, safety profiles, and impacts on cognitive functions. Future studies will provide the necessary data to better understand the mechanisms of action, treatment continuity, and cognitive effects of ketamine and esketamine. Obtaining this information will contribute to the development of more effective and personalized approaches in the treatment of depression.

Future research can overcome these limitations by focusing on studies with larger sample sizes and multicenter trials. Working with more heterogeneous sample groups by increasing geographical diversity could enhance the generalizability of the results to a broader population. Additionally, incorporating long-term follow-up periods is crucial for understanding the persistence of antidepressant effects and potential long-term side effects. Such comprehensive and long-term studies are expected to make significant contributions to the deeper evaluation of the effects of ketamine and esketamine and to the improvement of treatment approaches

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