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The Relationship Between Ketamine and Memory Impairment: A Systematic Review

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ABSTRACT

Increasing evidence supports that ketamine affects cognitive function, but various studies have reported dissenting opinions. This study aimed to investigate the potential correlation between Ketamine usage and memory deterioration, which is crucial for informing clinical practice and public health interventions. A systematic review was conducted, and six databases were scanned according to the PRISMA guidelines. As a result, 50 studies were analyzed to investigate the relationship between Ketamine and memory deterioration. It was found that most studies provided evidence for the claim that there is a negative association between Ketamine and cognitive function, specifically in the realm of memory. Some studies emphasized gender differences; however, their results were inconclusive. Studies have also found that the impact of ketamine is not limited to cognitive functions; it extends to other aspects such as depression, suicidal ideation, and neurocognitive functions. In conclusion, it is evident that there is an association between Ketamine and memory deterioration however, this relationship is challenging to develop and further studies are required.

Keywords: Cognition, Ketamine, Memory, N-Methylaspartate

Ketamin ve Bellek Bozuklukları Arasındaki İlişki: Bir Sistematik Derleme

Sistematik Derleme

Süreç

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ÖZET

Ketaminin bilişsel işlevleri etkilediğine dair bulgular giderek artsa da çeşitli çalışmalarda farklı görüşler ortaya koyulmuştur. Bu çalışma, klinik uygulamalar ve halk sağlığı müdahaleleri hakkında bilgi vermede çok önemli olan Ketamin kullanımı ile bellek bozuklukları arasındaki potansiyel ilişkiyi araştırmayı amaçlamaktadır. Çalışmada sistematik derleme yöntemi benimsenerek PRISMA kılavuzuna göre altı veri tabanı taranmış, Ketamin ve bellek bozuklukları arasındaki ilişkiyi araştıran 50 çalışma analize dahil edilmiştir. Çoğu çalışma, Ketaminin bilişsel işlevler, özellikle de bellek üzerinde olumsuz bir etkisi olduğunu göstermektedir. Bazı çalışmalar cinsiyet farklılıklarını vurgulamış; ancak bunların sonuçları yetersiz kalmıştır. Çalışmalar ayrıca Ketaminin etkisinin bilişsel işlevlerle sınırlı olmadığını; depresyon, intihar düşüncesi ve nörobilişsel işlevler gibi diğer yönler üzerinde de etkili olduğunu ortaya koymuştur. Sonuç olarak Ketamin ve bellek bozuklukları arasında bir ilişki olduğu açıktır, ancak bu ilişkinin tam anlamıyla açıklanabilmesi için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Biliş, Ketamin, Bellek, N-Metilaspartat

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Introduction

Ketamine hydrochloride, commonly referred to as Ketamine is a widely used dissociative anesthetic that is used medically for the induction and maintenance of anesthesia. It is considered one of the safest anesthetics, in contrast to opiates, ether, and propofol.[1,2] Nowadays Ketamine usage had varied to include depression treatment, suicidality, chronic pain, migraines, obsessive compulsive disorder, and even some post-traumatic stress disorder (PTSD) symptoms.[3-5] Introduced in 1962 for use as an anesthetic and an analgesic (pain reliever) and also for use in minor surgery, Ketamine is an old medicine. In 1970, the U.S. Food and Drug Administration (FDA) approved the drug, and it quickly became the most widely used battlefield anesthetic during the Vietnam War.[6] Since then, more researchers have been interested in its impact on mental health and have been involved in further investigating it and how it can be used to enhance or manage mental health crises.[7]

Ketamine and its usages

Ketamine is one of the most well-known forms of psychoplastogen. Ketamine impacts multiple receptors and pathways in the brain and body. Ketamine has a predominant action on two very important neurotransmitters: glutamate and gamma-aminobutyric acid (GABA). In fact, as the Brain & Behavior Research Institute points out, these two chemical messengers have opposite effects: “glutamate is the most common of the brain’s ‘excitatory’ neurotransmitters, while GABA has an opposite, inhibitory, role.” This combination has been shown to be an important outcome not only in enhancing mood but also in decreasing suicidal ideation.[8,9]

Ketamine was and is still being used for different purposes; it can provide pain relief and short-term memory loss, such as amnesia, during medical procedures. Another important use for Ketamine is sedation in general anesthesia because it is an induction and maintenance agent. Ketamine is also used to control symptoms of depression, respiratory depression, and acute suicidal ideation by blocking the N-methyl-D-aspartate (NMDA) site.[10-15]

Side effects of ketamine

Just like any other drug, Ketamine also has side effects, including both mental and physical. The most common mental side effects include sedation, dream-like state, decreased focus, agitation, anxiety, hallucinations, difficulty thinking, and many more. Physical side effects of ketamine include involuntary eye movements, seizures, nausea, vomiting, and elevated blood pressure. Although ketamine activates the sympathetic nervous system, which typically leads to tachycardia, there are documented cases where decreased heart rate occurs, influenced by factors such as individual physiological responses and dosage.[15,16] Frequent use of ketamine can lead to damage to various major organs, including the digestive tract, urinary tract, and brain. Ketamine impact on the brain leads to induction of long-term cognitive deficits, which was found among frequent users. Frequent ketamine users exhibit numerous cognitive impairments, but particularly a specific decline in spatial working memory.[17-18]

Ketamine and memory

Most other antidepressants act on one of the "monoamine" neurotransmitters, such as serotonin, norepinephrine, or dopamine. Ketamine, on the other hand, is believed to work in a way that targets glutamate, the most common excitatory brain chemical messenger. It supports and strengthens synaptic connections by coordinating the brain's ability to process cognitive thoughts, emotions, and neuroplasticity. Therefore, glutamate acts to direct one of the key agents in learning and remembering, which is forming responses to past experiences.

The role of the NMDA receptor as a key component in learning is supported since the levels of ketamine in the chronic and acute state associated with spatial memory deficits in human beings, and due to the fact that there is the existence of a high density of the NMDA, high-affinity non-competitive NMDA acid in the hippocampus. This study will establish the relationship between memory deficits and frequent ketamine use by finding the relevance from the literature.[16]

Method

This study used a systematic review method to collect, analyze, and interpret the data. In the systematic review, studies published on the relevant subject are scanned in detail. The studies are included in the review in line with the inclusion criteria, and the findings obtained are synthesized quantitatively and qualitatively.[19] This systematic review study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (Attachment 1). PRISMA is a guide that provides transparency and accountability between papers in the presentation of results, specifying standards for reporting the results of systematic reviews.[20] In the current study, six databases were scanned in November 2023, and different combinations of the determined keywords were searched in the titles and abstracts of the studies using boolean operators (Table 1).

Table 1. Search Strategy

Databases	EBSCO, MEDLINE/PubMed, Science Direct, Scopus, Web of Science Core Collection, WILEY
Keywords	NMDA, Ketamine, Memory, Cognition
Inclusion/Exclusion	• Published in a peer-reviewed journal • In English • Research article • About Ketamine effects on memory during or after treatment • Available in full text

EndNote version 21.0, Clarivate Analytics, which is "a database application that is used to store, manage, and find bibliographic information", was used to extract the studies from the databases. Then, the titles and abstracts of the studies were examined individually and chosen according to the inclusion criteria. 50 studies that comply with the relevant criteria were determined as a result of the screening, and those studies were included in the scope of the review.

Ensuring validity and reliability in qualitative research can be explained by the concepts of credibility and confirmability. While credibility provides internal validity, confirmability provides external reliability.[21] The current study research's method, data, findings, and results were explained in a way that will provide the maximum benefits for the researchers. All included studies were analyzed in an unbiased and impartial manner with their sources. In this study, the studies included in the scope of the study were coded into a database using the Microsoft Office Excel program according to the pre-determined categories.

The research questions of this systematic review are as follows:

- What is the most used route for Ketamine?
- What is the most used dosage for Ketamine?
- If any, which other drugs were used in addition to Ketamine?
- Which scales were used the most to assess memory?
- What other scales were used the most in addition to memory assessment?
- Is Ketamine usage a contributive agent in memory deterioration?
- Does the effect of Ketamine differ among genders?
- What factors are mostly investigated with Ketamine use and its effect on memory?

Findings

All the studies that were included in this systematic review were based on the results of the inclusion and exclusion criteria, and they were examined in detail based on two aspects: characteristics of the studies and qualitative synthesis. In this section of the study, the findings will be analyzed in detail based on these two aspects.

Characteristics of the studies

A total of 50 studies were analyzed by the year of publication, and it was found that the publication years ranged from 1983 to 2022. Research on this topic was relatively limited during the late 1990s and early 2000s; however, there was a significant surge in research by the 2010s, followed by a subsequent decline as of 2022, as can be seen in Figure 1.

Studies were conducted using three different methods: clinical, experimental, and scale. The clinical method was the most used by 76%, followed by the experimental method by 18%, and the scale method came last with only 6% (Table 2). Most of the studies (80%) were interventional design and 20% were observational design. The universe sizes of the studies varied between nine and 1614 with an average of 104. 80% of the studies included both genders. Among these studies, eight were conducted only on male participants and six included only female participants (Table 2).

Detailed information about the studies, such as route and dose of Ketamine, memory, and other measurements, and the main findings are given in detail in Table 4. The studies were examined in detail for the application route of Ketamine, and it was found that most studies (72%) have used the intravenous method. Ketamine was not always applied alone; most of the time, it was combined with other drugs including Methadone and Morphine as opioids/analgesics, Propofol and Midazolam as anesthetics and sedatives/hypnotics, Haloperidol as Antipsychotics, and other drugs such as Saline and Methamphetamine (Table 2). It was found that increasing Ketamine doses leads to temporarily impaired cognitive functions (22-24). However, despite this variability, studies suggest that Ketamine, even at relatively low doses, can adversely affect cognitive functions (22, 23, 25-47).

It was also found that 59 different memory scales were used, and the most used was the MATRICS Consensus Cognitive Battery (n=8), followed by the Cogstate Brief Battery (n=6) (Attachment 2). 28% of the scales used were for working memory assessment and 20% were for general memory assessment. Other scales were also used to assist other parts of the memory, such as verbal, visual, and autobiographical memory (Table 3). In addition to scales for memory assessment, other scales were used in line with the specific purposes of the studies, such as the Montgomery–Asberg Depression Rating Scale (n=13), Brief Psychiatric Rating Scale (n=8), Clinician-Administered Dissociative States Scale (n=7) and Hamilton Depression Rating Scale (n=7) (Attachment 3). Most of the scales (66%) used were for mental health assessment followed by cognitive assessment (%13) and addiction assessment (5%) (Table 3).

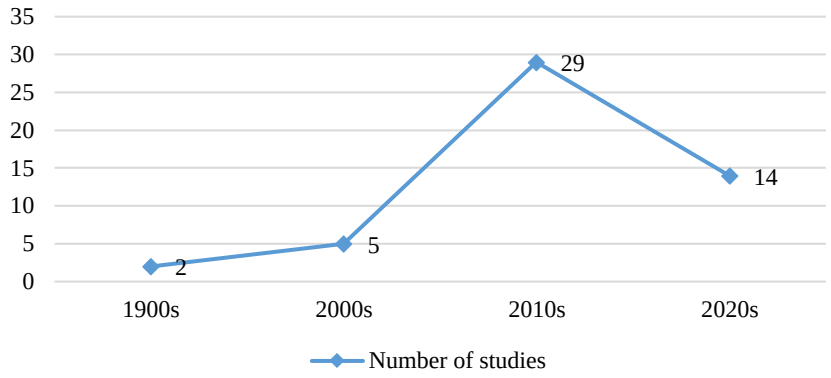

Figure 1. Distribution of studies by years

Table 2. Descriptive Findings of the Studies

Variable		Frequency (n)	Percentage (%)
Study Method	Clinical	38	76
	Experimental	9	18
	Scale	3	6
Study Design	Interventional	40	80
	Observational	10	20
Sample Gender	Only Female	3	6
	Only Male	4	8
	All	40	80
	N/A	3	6
Ketamine Route	Intravenous	36	72
	Nasal	2	20
	Oral	1	4
	Oral or nasal airway insertion	1	2
	N/A	10	2
Other Drugs	Anesthetics and Sedatives/Hypnotics	9	18
	Opioids/Analgesics	5	10
	Antipsychotics	1	2
	Other	15	30
	N/A	20	40

Table 3. The Type of Memory Scales Used in the Studies

	Frequency (n)	Percentage %
The Types of Memory Scales		
Working Memory Assessment	24	28
General Memory Assessment	17	20
Verbal Memory Assessment	12	14
Visual Memory Assessment	7	8
Autobiographical Memory Assessment	5	6
Other Memory Assessments	20	24
The Types of Other Scales		
Mental Health Assessment	84	66
Cognitive Assessment	17	13
Addiction Assessment	6	5
Personality Assessment	5	4
Psychomotor Assessment	5	4
Functioning Assessment	5	4
Diagnostic Assessment Tools	2	2
N/A	3	2

Table 4. Ketamine Findings Of The Included Studies

Study	Route and Dose	Other drugs (if any)	Memory Measurements	Other Measurements	Main Finding
(48)	Intravenous 0.5 mg/kg	Saline	Hopkins Verbal Learning Test-Revised (HVLT-R-DR) Controlled Oral Word Association Test (COWAT) Autobiographical Memory Interview – Short Form (AMI-SF) Medical College of Georgia Complex Figure Test (MCGCFT) Self-reported Global Self Evaluation of Memory (GSE-My)	Clinical Anxiety Scale (CAS) Clinical Global Impression (CGI) Brief Psychiatric Rating Scale (BPRS) Quick Inventory of Depressive Symptomatology— Self Report (QIDS-SR) EuroQol 3-level version (EQ-5D-3L)	The study found that ketamine treatment did not offer any cognitive or efficacy benefits compared with saline treatment. A minority of patients experienced psychological effects related to ketamine upon awakening from ECT, but overall, no serious safety or tolerability problems were observed.
(32)	Intravenous 20 and 40 mg/70 kg/h	N/A	Picture-encoding/recognition paradigm	Bond and Lader visual analog scale	At the 40 mg dose, a significant reduction in recognition picture recall performance characterized by an increase in the number of misses was observed.
(49)	N/A 0.5 mg/kg	N/A	Groton Maze Learning Test One-back test Two-back test International Shopping List Task Continuous Paired Associative Learning One Card Learning Test Groton Maze learning delayed International shopping list delayed	Clinician-administered PTSD Scale (CAPS-IV)	This study found that repeated ketamine infusions did not result in a significant decline in any measures of cognition. In contrast, there was a notable improvement in working memory after the completion of the infusion series.
(25)	N/A N/A	N/A	Authors' own questionnaire	Pelvic pain and urgency/frequency (PUF)	The study found that female ketamine offenders were more likely to develop severe cognitive impairment than males.
(50)	Intravenous 0.5 mg/kg	N/A	MATRICS Consensus Cognitive Battery (MCCB)	Beck Scale for Suicide Ideation (SSI)-part I Hamilton Depression Rating Scale adapted from the 17-item HAMD Global Assessment Scale (GAS)	The study found that ketamine as an NMDA receptor antagonist significantly improves working memory in patients with MDD.
(26)	Nasal 3.8 ± 2.7 g / day	N/A	Cogstate Brief Battery	Positive and Negative Syndrome Scale	The study found that ketamine-associated persistent psychosis patients had more severe symptoms than non-psychotic ketamine users. Both ketamine-associated persistent psychosis and schizophrenia patients had similar levels of cognitive impairment, worse than non-psychotic ketamine users, but not significantly different from each other after adjusting for demographic characteristics and antipsychotic dose.

(27)	Intravenous 0.23 mg/kg	N/A	IntegNeuro battery	Positive and Negative Syndrome Scale (PANSS) Clinician-administered Dissociative Symptoms Scale (CADSS) Visual Analog Scale (VAS)	The study found that ketamine can disrupt the ability to direct and sustain attention, response inhibition, working memory, verbal fluency, executive function, serial processing, immediate and delayed free verbal recall, speed of processing, reasoning, problem-solving, and emotion recognition.
(51)	Intravenous 0.5 mg/kg	N/A	Autobiographical Memory Interview – Short Form (AMI-SF) Autobiographical Fluency Task (AFT)	Hamilton Depression Rating Scale (HDRS) Beck Depression Inventory (BDI) Brief Psychiatric Rating Scale Visual analog scales (VAS) Structured Clinical Interview for DSM-IV Antidepressant treatment history form	The study found that subjects reported slight improvements or little change, suggesting that ketamine was not associated with memory impairment.
(29)	Intravenous 0.23 mg/kg–0.58mg/kg/h	Saline	The spatial WM task	Positive and Negative Syndrome Scale (PANSS)	The study found that even at higher doses, the effects of ketamine on perception, attention, working memory impairments, and declarative memory are relatively subtle.
(40)	Intravenous 3.4 g/d	N/A	Authors' own questionnaire	N/A	The study found that memory impairment was the most frequently reported long-term symptom by inpatients with ketamine dependence.
(30)	Intravenous up to 2 mg/kg	Propofol	Cambridge Automated Neuropsychological Test Battery Spatial Recognition Memory task (CANTAB SRM)	Hamilton Depression Rating Scale (HDRS) Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that memory impairment was the most frequently reported long-term symptom by individuals with ketamine dependence.
(31)	Oral or nasal airway insertion 0.5–0.74 mg/kg	Propofol	Authors' own questionnaire	Wisconsin Sedation Scale (WSS)	The study found that the incidence of memory loss after emergency department procedural sedation and analgesia (ED PSA) involving premixed ketamine-propofol (KP) administered sequentially is infrequent. This outcome is associated with moderate sedation levels and propofol doses less than 0.75 mg/kg.
(23)	Intravenous 0.3–0.15 mg/kg	Dexmedetomidine	Cambridge Neuropsychological Test Automated Battery (CANTAB)	Cambridge Neuropsychological Test Automated Battery (CANTAB)	The study found a modest association between reduced psychomotor speed and accuracy and the concentrations of ketamine, norketamine, and Dexmedetomidine in the blood. In addition, a negative correlation was found between the blood concentrations of ketamine, norketamine, and Dexmedetomidine and

					performance on memory tasks. Notably, concurrent administration of ketamine with Dexmedetomidine but not with fentanyl results in synergistic effects on psychomotor performance and memory, while avoiding executive dysfunction.
(22)	Intravenous 8 mg/kg/h	Norketamine	Visuospatial working memory (SWM)	Visual Analogue Scale (VAS) Reaction/movement time (RTI) Stockings of Cambridge (SOC)	The study found that increasing doses of ketamine temporarily impaired higher-order cognitive functions, including visuospatial working memory and spatial planning.
(24)	Intravenous 250–300 ug/dl	N/A	Wechsler Memory Scale-Third Edition (WMS-III) Hopkins Verbal Learning Test (HVLT)	Beck Depression Inventory-II (BDI-II) State Trait Anxiety Inventory Minnesota Multiphasic Personality Inventory-2 (MMPI-2) McGill Pain Questionnaire Wechsler Adult Intelligence Scale-III) Connors' Continuous Performance Test (CPT)	This study found that deep ketamine infusion may not have a negative impact on cognitive function with prolonged treatment.
(34)	Intravenous 0.25 mg/kg	Nimodipine	Hopkins Verbal Learning Test (HVLT)	Brief Psychiatric Rating Scale (BPRS) Dissociative States Scale (CADSS) Biphasic Alcohol Effects Scale (BAES) Comparable Volume of the Ethanol Scale	The study found that both ketamine and nimodipine have additive effects on recall that were independent of the presence of cues intended to enhance memory retrieval, suggesting that each drug influenced memory encoding rather than memory retrieval.
(52)	Intravenous 0.5 mg/kg	N/A	Consensus Cognitive Battery (MCCB)	Montgomery–Asberg Depression Rating Scale (MADRS) Hamilton Anxiety Rating Scale (HAMA)	The study found that ketamine is harmful to neurocognition in chronic users and decreased performance on pattern recognition memory tasks and spatial working memory tasks. Furthermore, chronic ketamine users also suffer from deficits in verbal learning, visual learning, selective attention, and verbal fluency.
(38)	N/A 1 mg/kg	Etomidate	Folstein Mini-Mental State Examination	Montgomery– Asberg Depression Scale	The study found that the effect of ECT on memory is mediated by glutamate at N-methyl-D-aspartate receptors, suggesting that N-methyl-D-astarte antagonists may offer protection from memory dysfunction during ECT.
(39)	Intravenous 0.5 mg/kg	Lamotrigine	MATRICS Consensus Cognitive Battery (MCCB)	Montgomery–Asberg Depression Rating Scale (MADRS) Psychiatric Rating Scale (BPRS)	The study found that subjects who showed significant clinical response to ketamine within a 24-h period had more severe

				Clinician-Administered Dissociative States Scale (CADSS)	neurocognitive impairments, specifically on tasks that require information processing and working memory.
(41)	Intravenous 1.0 mg/kg	Equianalgesic	German Hamburg– Wechsler Intelligence Scale Immediate digital recall Anterograde Amnesia	Freiburg Personality Inventory Intelligence Quotient	The study found that ketamine isomers induce less tiredness and cognitive impairment and cause fewer declines in concentration capacity and primary memory.
(53)	Intravenous 0.5 mg/kg	Saline	California Verbal Learning Test short form (CVLT-II) Rey Complex Figure Test Columbia Autobiographical Memory Interview Short Form (AMI-SF)	Montgomery– Asberg Depression Rating Scale Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR) Mini Mental State Examination Trail Making Test Parts A and B Stroop Color and Word Test	The study found that repeated ketamine treatment had no negative cognitive side effects, especially in the short term, adding to the growing body of evidence supporting the safety of ketamine and its impact on cognitive outcomes.
(42)	Intravenous 1–1.5 mg/kg	Thiopental	Wechsler Adult Intelligence Scale Rey auditory verbal learning test (RAVLT) Verbal fluency test	Hamilton Depression Rating Scale (HDRS) Benton visual retention test Trail making test Rey– Osterrieth complex figure test	The study found that subjects who used ketamine had worse results on some verbal memory measurements.
(54)	Intravenous 0.5 mg/kg	N/A	The N-back task	Montgomery– Asberg Depression Rating Scale (MADRS) Hamilton Anxiety Rating Scale (HAM-A) Brief Psychiatric Rating Scale (BPRS)	The study found that subjects showed great symptomatic improvement and increased working memory load within 4h of ketamine administration.
(55)	N/A 10 mg/kg	Psilocybin	EEG/ERP Recording	Altered State of Consciousness (ASC-R)	The group receiving ketamine showed significant improvements in verbal learning memory.
(56)	Intravenous 0.5 mg/kg	N/A	Cogstate Brief Battery	Hamilton Depression Rating Scale (HDRS) Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that after the last ketamine infusion, there was a significant improvement in the scores of visual memory, simple working memory, and complex working memory.
(57)	Intravenous 0.5 mg/kg	Midazolam	Cogstate Brief Battery	Brief Psychiatric Rating Scale (BPRS) Clinician-Administered Dissociative States Scale (CADSS) Young Mania Rating Scale (YMRS) Montgomery–Asberg Depression Rating Scale (MADRS)	Ketamine resulted in stable or improved neurocognitive functioning in most domains. These findings suggest the potential usefulness of complex working memory as a predictor of ketamine treatment response and its positive effects on neurocognition.
(43)	Intravenous 0.25 mg/kg	N/A	Berlin Affective Word List (BAWL)	Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that ketamine affects MDD symptoms differently. It also found that the largest symptom reduction was in the cognitive domain.

(58)	Intravenous 0.12 mg/kg	Phosphodiesterase 10A inhibitor (TAK-063)	A-X Continuous Performance Test (AX-CPT) CNS Vital Signs Cognitive Battery	Psychotomimetic States Inventory (PSI) Columbia Suicide Severity Rating Scale (C-SSRS)	The study found that ketamine can induce changes in the BOLD signal in multiple regions of the brain during the resting state and working memory task.
(46)	N/A 2.06 mg/kg	Methadone	The two-back task	CAS (Chinese Affect Scale) CES-D (Catchment-Area Epidemiology Survey-Depression) Raven's Progressive Matrices Test Minnesota Multiphasic Personality Inventory-2 Barratt's Impulsivity Scale Version 11 The Iowa Gambling Task (IGT)	The study found that ketamine users did not show deficits in decision-making but exhibited strong impulsivity, antisocial personality, and poor response inhibition and working memory at levels similar to those of methadone users.
(47)	N/A N/A	N/A	Wechsler Memory Scale-Third Edition (WMS-III) Rey– Osterrieth Complex Figure (ROCF) Wisconsin card sorting test (WCST)	Beck Depression Inventory (BDI) Hospital Anxiety Depression (HADSA) Structured Clinical Interview for DSM-IV Severity of Dependence Scale (SDS)	The study found that ketamine users suffered from cognitive impairments, including verbal/visual memory and executive function.
(59)	Intravenous 0.5mg/kg	N/A	Consensus Cognitive Battery MATRICS	Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that working memory and visual learning did not show significant improvement with ketamine treatment.
(60)	Intravenous 0.5mg/kg	N/A	Consensus Cognitive Battery MATRICS	Sheehan Disability Scale (SDS) Global Assessment of Functioning (GAF) Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that working memory and visual learning did not show significant improvement with ketamine treatment.
(61)	Intravenous 0.5 mg/kg	N/A	Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Letter–number sequencing Wechsler Memory Scale-Third Edition (WMS-III) Brief Visuospatial Memory Test-Revised Hopkins Verbal Learning Test-Revised (HVLT-R)	Montgomery–Asberg Depression Rating Scale (MADRS)	The study found no significant improvement in working memory or visual learning after six infusions of ketamine.
(62)	Intravenous 0.5 mg/kg	Saline	Consensus Cognitive Battery (MCCB)	Hamilton Depression Rating Scale (HAMD-17)	The study found that neurocognitive function did not deteriorate after six ketamine infusions, whereas verbal learning and speed of processing improved over 13 and 26 days of observation, respectively.
(63)	Intravenous 0.3 mg/kg	Propofol	Mini-Mental State Examination (MMSE)	Hamilton Depression Rating Scale (HAMD-24)	The study found that ketamine anesthesia (KP) had a lower incidence of cognitive function impairment than the propofol anesthesia group (P).
(64)	N/A 0.5 mg/kg	Morphine Metoprofen	Mini-Mental State Examination (MMSE) Digital symbol substitution test	Visual Analogue Scale (VAS)	The study found that ketamine did not modify mood, cognitive, or memory functioning.
(65)	Intravenous	Saline	Working memory task and go/no-go task	Hamilton Depression Rating Scale (HDRS)	The study found that a 0.5 mg/kg dose of ketamine infusion can be slightly beneficial

	0.2 mg/kg or 0.5 mg/kg				for the cognitive function of patients with treatment resistance disorder (TRD).
(66)	N/A N/A	N/A	Brief Assessment of Cognition in Schizophrenia (BACS)	Conners' Continuous Performance Test (CPT) Wisconsin Card Sorting Test (WCST) Iowa Gambling Task (IGT) The Barratt Impulsiveness Scale (BIS)	The study found that the experience of ketamine use was not linked to verbal and working memory.
(28)	Intravenous 0.23 mg/kg bolus over 1 min followed by 0.58 mg/kg/h constant infusion for ~45 minutes	PF-04958242	fMRI Hopkins Verbal Learning Test (HVLT)	Positive and Negative Symptom Scale (PANSS) Clinician-Administered Dissociative States Scale (CADSS)	The study found that ketamine can significantly increase the reaction time during the spatial working memory task.
(67)	Intravenous 0.5 mg/kg	N/A	Cogstate Brief Battery	Hamilton Depression Rating Scale (HDRS) Beck Depression Inventory-II (BDI-II)	The study found that ketamine did not affect working memory performance.
(68)	Intravenous 0.5 mg/kg	Midazolam	Neurocognitive battery	Hamilton Depression Rating Scale (HDRS) Suicidal Idea (SSI) Beck Depression Inventory (BDI) Profile of mood states (POMS) Young Mania Rating Scale (YMRS) Systematic Assessment for Treatment of Emergent Events-General Inquiry (SAFTEE) Clinician-Administered Dissociative States Scale (CADSS) Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression	There was a correlation between memory improvement after ketamine administration.
(33)	N/A 100 ml/kg	Neuroleptan aesthesia	Patients' self-report	Authors' own questionnaire	The study found that patients in both the neurolept group (NLA group) and ketamine group had suffered from difficulties with memory and concentration after 3 months of surgery.
(35)	Intravenous 0.26 mg/kg	Haloperidol	Recall test Wisconsin Card Sorting Test (WCST)	Brief Psychiatric Rating Scale (BPRS) Clinician-Administered Dissociative States Scale (CADSS) Extrapyramidal Symptom Rating Scale Barnes Akathisia Scale	The study found that ketamine produced a delay-dependent impairment in word recall with no significant effect on immediate recall and more prominent impairments of post-distraction and delayed recall.
(36)	Intravenous 50 mg/kg	Saline	Clinician-Administered Dissociative States Scale (CADSS) Systematic Assessment for Treatment of Emergent Effects	Montgomery– Asberg Depression Rating Scale (MADRS)	The study found that after 4 h of ketamine infusion, patients felt strange or unreal, had

				Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR) Hamilton Anxiety Rating Scale (HAM-A) Brief Psychiatric Rating Scale – Positive subscale (BPRS+) Young Mania Rating Scale (YMRS)	poor memory, and had weakness or fatigue.
(37)	Oral N/A	D-serine (DSR)	TesteIdentical Pairs (CPT-IP) Digit Memory Task Rey Auditory Verbal Learning Test (RAVLT) Category Fluency Test Benton Visual Retention Test (BVRT)	Visual Analogue Scale (VAS)	The study found that ketamine led to worse performance in verbal memory tasks.
(69)	Intravenous 0.5 mg/kg	Midazolam	MATRIC Consensus Cognitive Battery (MCCB)	Montgomery–Asberg Depression Rating Scale (MADRS)	The study found that ketamine had no specific effect on cognitive performance.
(70)	Nasal spray 28 mg, 56 mg, or 84 mg	N/A	Cogstate Brief Battery Hopkins Verbal Learning Test-Revised (HVLT-R)	Montgomery– Asberg Depression Rating Scale (MADRS) Clinical Global Impression–Severity (CGI-S) Patient Health Questionnaire 9-Item (PHQ-9) Sheehan Disability Scale (SDS) Columbia Suicide Severity Rating Scale (C-SSRS) Clinician-Administered Dissociative States Scale (CADSS) Brief Psychiatric Rating Scale (BPRS)	The study found that there was a slight improvement in function (visual, verbal, and working memory, executive function) in both treatment groups: esketamine/antidepressant; antidepressant/placebo
(44)	Intravenous 0.25 mg/kg	Propofol	Cogstate Brief Battery	N/A	The study found that mixing ketamine with propofol for sedation in colonoscopy led to fewer complications such as respiratory depression and hypotension, but it also led to more impairment in cognitive functions.
(45)	N/A N/A	Methamphetamine	Brief Assessment of Cognition in Schizophrenia (BACS)	N/A	The study found that the ketamine group performed worse than the METH group in the domains of verbal memory, working memory, attention and processing speed, and composite battery scores.
(71)	Intravenous 0.5 mg/kg	N/A	MATRICS Consensus Cognitive Battery (MCCB)	Montgomery– Asberg Depression Rating Scale (MADRS) Suicidal Idea (SSI)	The study found that six ketamine infusions led to an improvement in the speed of processing and verbal learning, which was partly accounted for by the improvement in the severity of depression symptoms over time.

Qualitative synthesis of studies

Qualitative synthesis of the 50 studies is reported on the basis of their content. The studies directly examining memory and ketamine use, which is the main focus of this research, were examined and found that 13 studies (26%) found ketamine enhanced memory functions,[49-51,54-57,62,63,65,68,70,71] 26 studies (52%) found it impairs the memory, concluding that ketamine can cause a deterioration in memory.[22,23,25-47,52] These studies have revealed the negative impact of ketamine on memory functions. More specifically, we discussed the observed decrease in recognition picture-recall performance at a specific dosage.[26,29,31-34] According to these studies, ketamine negatively impacted a broad spectrum of cognitive functions, including attention, response inhibition, working memory, verbal fluency, executive function, serial processing, and various aspects of memory recall. These findings emphasize the negative influence of ketamine on cognitive functions, warranting concern regarding its potential impact on both short-term and long-term memory function. Eleven studies (22%) found that ketamine had no impact on memory.[24,48,53,58-61,67,69,72,73]

Despite the majority of studies including both genders, only two of them have investigated gender differences, with one study finding that female ketamine users displayed a higher likelihood of developing severe cognitive impairment compared with their male counterparts,[25] and the other study displayed the opposite, with male ketamine users appearing to be more prone to suffer from memory-related problems compared with their female counterparts.[31] Some studies have focused their investigation on one gender; four of these studies included only male participants.[32,34,56,58] While one study reported a positive impact on memory,[56] two studies found that ketamine was a factor that deteriorated memory among male participants.[32,34] Three other studies investigated only female participants.[33,52,72] One study found no impact on memory,[72] and two studies found a negative impact.[33,52]

There were various factors mostly investigated with ketamine use and its effect on memory. Some studies investigated the effect of ketamine on memory among participants with *depression or suicidal ideation* (n=17). These studies found an association between ketamine, depression, suicidal ideation, and cognitive functions. 13 studies investigated the *neurocognitive effects and performance* of ketamine use and found a complex interplay between ketamine and neurocognitive functions.[36,49-53,56,57,59-62,65,67-70] While ketamine may initially have acute harmful effects on some cognitive domains in individuals with major depressive disorder or PTSD, repeated ketamine administration appears to reduce depressive symptoms and, in turn, leads to an improvement in various cognitive domains, including attention, working memory, verbal, and visuospatial memory. The findings also underline the potential benefits of ketamine in improving neurocognitive function in individuals who suffer from treatment-resistant depression, suggesting a mood-independent pro-cognitive effect, particularly in processing speed. The observed improvements in neurocognitive outcomes emphasize the intricate relationship between ketamine, cognitive function, and mental health outcomes.[22-24,26-28,35,49,56,57,62,69,73] Six studies applied *Electroconvulsive Therapy (ECT)* with Ketamine and their results varied. While administering Ketamine alongside ECT may lead to better antidepressant efficacy than certain anesthetics, it can also lead to a worsening in verbal memory. The impact of Ketamine on cognitive functions during ECT remains inconclusive, with some studies suggesting potential protective effects on memory, especially compared with other anesthetics. However, a randomized trial found no evidence of cognitive or efficacy benefits from low-dose Ketamine adjunctive to ECT for depression.[30,38,42,48,51,63]

Discussion and Conclusion

This study was designed to review studies examining the association between Ketamine and memory impairment. Among the included studies, certain themes were discovered from full-text readings, and those topics are written in italics in the qualitative synthesis of the study section. After analyzing the full texts of the included studies, it is important to highlight some of their limitations.

Limitations

One of the most notable limitations of these studies is the lack of long-term follow-up. Several studies have investigated the cognitive impact of Ketamine on short-term periods, neglecting to discuss its long-term outcomes. Therefore, it is recommended that future studies include extended follow-up periods to assess the persistence of cognitive effects and potential risks associated with prolonged ketamine use.

Another limitation of the study was the sample size and characteristics. Most of the studies had a small sample size, which may reduce the reliability and generalizability of the findings, emphasizing the need for larger cohorts in future studies. Studies also failed to compare genders and racial and ethnic groups. Future research should include participants with diverse characteristics and backgrounds.

There were also some limitations based on the design of the studies. Several studies did not have control groups, which may prevent the ability to compare outcomes between treatment and non-treatment conditions. In addition, studies conducted with an open-label design are susceptible to biases and placebo effects, potentially influencing the interpretation of treatment outcomes. Various other limitations such as specific population restrictions, incomplete data, study termination, and lack of examination of certain cognitive domains hinder the comprehensiveness and reliability of the research findings, indicating the need for improved study methodologies in future investigations.

This study also has some limitations. As mentioned in the Methods section, inclusion and exclusion criteria were determined for the search strategy. One of the exclusion

criteria was languages other than English; therefore, studies published in other languages were excluded from the review. In addition, only studies published in peer-reviewed journals were included; thus, chapters, conference papers, and dissertations were excluded. There were some studies meeting the search criteria, but the full text was inaccessible. While acknowledging these limitations, the findings of this study offer valuable insights poised to expand our current understanding of Ketamine, shedding light on both its potential benefits and associated side effects.

Conclusion

As a result of this study, it becomes evident that there is an association between Ketamine and memory deterioration; however, this relationship is challenging to develop. The complexities of the included studies necessitate a nuanced understanding of the correlation between Ketamine and memory deterioration. In light of these considerations, healthcare professionals and researchers should approach the issue comprehensively. Thus, it is recommended to include educational initiatives and awareness campaigns to inform individuals, particularly those at risk, about the potential consequences of Ketamine use on memory function. In addition, early detection and intervention strategies among vulnerable populations should be prioritized.

Based on the results of this systematic review, future studies should:

- Focus on longitudinal studies with qualitative components to provide insights into the multifaceted relationship between Ketamine and memory deterioration.
- Examine the effects of various doses of ketamine, particularly as an adjunctive anesthetic for ECT in elderly patients, while balancing efficacy and safety.
- Explore the neural mechanisms underlying the effects of ketamine on suicidal ideation using neuroimaging techniques and focus on functional outcomes, particularly long-term functioning, in addition to reductions in suicide.
- Include control groups, use techniques to assess brain changes, and investigate the potential pro-cognitive effects of Ketamine in larger studies, while ensuring comprehensive evaluation of cognitive function.
- Focus on psychological risk factors for Ketamine use and investigate cognitive problems specific to Ketamine users.

These studies might provide a deeper understanding of the factors influencing this association, which will help develop more effective prevention and intervention strategies.

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