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Breaking the cycle: a systematic review of neurobiological mechanisms and psychotherapeutic innovations in ketamine addiction

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ABSTRACT
This systematic review synthesizes current evidence on non-prescribed ketamine use, emphasizing its neurobiological impacts and psychotherapeutic interventions. Patterns of misuse demonstrate the complex interplay of neurobiological, socio-economic, demographic and psychological factors with adolescents, women and polysubstance users identified as high-risk groups. Neurobiological findings highlight prefrontal-limbic dysconnectivity, maladaptive neuroplasticity alongside hypothalamic-pituitary-adrenal (HPA) axis dysregulation as central mechanisms underlying this addiction. The review evaluates the comparative efficacy of psychotherapies whilst proposing an innovative framework that aligns therapeutic timing with neuroplastic recovery phases. Emerging evidence identifies biomarkers, e.g., brain-derived neurotrophic factor (BDNF) and heart rate variability (HRV), as promising tools for guiding personalized and phase-specific interventions. Gaps in research include the limited representation of low-resource settings and insufficient longitudinal data on biomarker integration and therapy sequencing. Recommendations propose a comprehensive neurobiologically informed model which carefully integrates digital platforms, culturally tailored strategies and biomarkers to enhance treatment outcomes.

KEYWORDS
Ketamine addiction; Special K; neurobiology; psychotherapy; CBT; EMDR; Triage; treatment framework; neurobiological markers; neurologically informed psychotherapy

Introduction

Ketamine misuse represents a growing global concern with prevalence increasing disproportionately among adolescents and urban populations over the past decade.[1] At the Delamere Health facility in the UK, cases of ketamine misuse rose by 275% in a recent six-month period with 87% of those affected aged 30 or younger. This spike mirrors wider national and international patterns, driven by ketamine's accessibility and misuse as a self-medication for trauma and emotional distress.[2] While Ketamine is recognized for therapeutic applications like rapid symptom alleviation in treatment-resistant depression (TRD) and potent pharmacological effects including NMDA receptor antagonism and glutamatergic modulation, these also underpin its addictive potential.[3] This duality underscores the urgent need for targeted, evidence-based interventions.

Neurobiologically, ketamine misuse leads to profound structural and functional changes primarily in the prefrontal cortex (PFC) and limbic system. These regions are critical for executive function and emotional regulation.[4,5] Chronic use disrupts prefrontal-limbic connectivity inducing maladaptive neuroplasticity alongside dysregulating the hypothalamic-pituitary-adrenal (HPA) axis perpetuating addiction cycles.[6,7] These changes are compounded by socio-economic and cultural factors with East Asia reporting especially high prevalence rates among adolescents and urban residents.[7] In Western contexts, ketamine misuse is frequently associated with polysubstance use and preexisting psychological vulnerabilities which further complicates recovery pathways.[8]

The therapeutic landscape for ketamine misuse is evolving, with psychotherapeutic interventions playing a pivotal role in addressing both neurobiological and behavioral dimensions. CBT, mindfulness-based interventions (MBIs) and trauma-focused modalities, such as Eye Movement and Desensitisation Reprocessing (EMDR)

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demonstrate efficacy in reducing relapse and fostering adaptive neuroplasticity.[9,10] Substantial therapeutic and research gaps persist including; underrepresentation of low-resource settings, insufficient integration of biomarkers into therapeutic frameworks and limited longitudinal data on recovery trajectories.[11]

Aims and objectives

This review aims to synthesize existing evidence on neurobiological and psychological mechanisms underlying ketamine misuse and evaluate psychotherapeutic interventions which address these mechanisms. The objectives of this article are to:

i. Characterize global patterns and demographics of ketamine misuse *via* focusing on socio-economic and cultural influences.
ii. Elucidate the neurobiological mechanisms of ketamine addiction and recovery.
iii. Assess the comparative effectiveness of psychotherapeutic modalities.
iv. Discover research gaps proposing a neurobiologically informed framework, integrating biomarkers, digital platforms and culturally tailored approaches to optimize treatment outcomes.

Generated in the hope it will contribute to informing clinical practice, public health policies and aid in future research directions, bridging the gap between neurobiological insights and psychotherapeutic applications.

Methodology

Study design

This systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Appendix A, Figure A1) guidelines ensuring a rigorous, reproducible and transparent methodology. The review sought to synthesize data on non-prescribed ketamine use, neurobiological implications and the efficacy of psychotherapeutic interventions. Demographic-specific adaptations and innovative therapeutic frameworks were also explored.

Inclusion and exclusion criteria

Inclusion Criteria

Population: Studies focused on individuals engaged in non-prescribed ketamine use including polysubstance users where ketamine was a primary substance.
Interventions: Psychotherapeutic treatments including CBT, mindfulness-based relapse prevention (MBRP), trauma-focused therapies (e.g., EMDR) and integrated approaches such as ketamine-assisted psychotherapy (KAP).
Outcomes: Primary outcomes included reductions in ketamine misuse, neurobiological recovery (e.g., prefrontal-limbic connectivity) and improvements in emotional regulation. Secondary outcomes encompassed treatment adherence and quality-of-life enhancements.
Study design: Randomized controlled trials (RCTs), prospective and retrospective cohort studies, neuroimaging investigations and systematic reviews published between January 2010 and December 2024.

Exclusion Criteria

Studies focused solely on prescribed ketamine.
Non-peer-reviewed articles, editorials or abstracts.
Absence of psychotherapeutic or neurobiological data.
Non-English texts due to resource limitations.

Search strategy

Five major databases (PubMed, PsycINFO, Web of Science, Scopus and Cochrane Library) were searched using Boolean operators and the following keywords:

"Ketamine misuse" OR "illicit ketamine use"
"Psychotherapy" OR "CBT" OR "EMDR" OR "mindfulness-based intervention"
"Neurobiology" OR "neuroplasticity"

References of key studies were screened manually and grey literature (e.g., preprints) was included to minimize publication bias.

Study selection and reporting

Through the PRISMA process a total of 70 studies (Appendix A, Figure A1) were identified and assessed for inclusion in the review. These studies collectively represent a robust dataset addressing neurobiological and psychotherapeutic dimensions of ketamine misuse. To maintain focus and depth a subset of 30 studies was selected for detailed tabular presentation based on strict inclusion criteria.

Inclusion criteria for the subset of 30 studies:

i. *Focus on psychotherapy:* Only studies investigating psychotherapeutic interventions (e.g., CBT, EMDR and mindfulness) as primary or adjunctive treatments were selected for detailed tabulation.
ii. *Rigor and reporting:* Studies with robust methodologies (e.g., RCTs and longitudinal cohorts) and detailed outcome data were prioritized.
iii. *Relevance to review objectives:* Priority was given to studies that explicitly linked psychotherapeutic modalities to neurobiological mechanisms or outcomes in ketamine misuse.

The remaining 40 studies were utilized to provide supporting evidence in the discussion and contextualization of findings. For transparency, these studies are summarized briefly in the narrative text and referenced where appropriate.

The following figures and tables provide:

Appendix A, Figure A1: PRISMA diagram of research.

Appendix B, Table B1: Data extraction summary of the 30 selected studies including; population, psychotherapy type and outcomes.

Appendix B, Table B2: Risk of bias evaluations using Cochrane Risk of Bias Tool.

Appendix B, Table B3: Newcastle–Ottawa Scale table.

Data extraction

The researcher carefully aimed to extracted data to minimize errors. Extracted variables included:

Study characteristics: Authors, year, location, population size and demographics.
Interventions: Psychotherapy type, duration, frequency and context.
Neurobiological findings: Measures, such as fMRI and biomarkers.
Outcomes: Reductions in ketamine misuse, emotional regulation and neurobiological recovery.
Risk of bias: Assessed using validated tools (see below).

A detailed breakdown of these variables is provided in Appendix B, Table B1 including summarization of neurobiological and psychometric measures reported across studies.[4,22]

Focus on secondary data from literature

This systematic review synthesized findings from peer-reviewed studies rather than generating primary data. Studies were selected based on relevance to neurobiological and psychotherapeutic dimensions of ketamine misuse. Extracted data included:

Neurobiological Variables

Studies reporting functional neuroimaging outcomes (e.g., fMRI and rsFC) and biomarker levels (e.g., BDNF and cortisol) were prioritized to assess neuroplasticity, prefrontal-limbic connectivity and HPA-axis regulation.[3,4]

Psychometric Outcomes

Data from validated tools, e.g., the Wisconsin Card Sorting Test (WCST) for cognitive function and the Depression Anxiety Stress Scales (DASS) for emotional regulation were synthesized to contextualize neurobiological findings with functional impacts.[23,24]

Rationale for inclusion of neurobiological and psychometric data

The decision to include studies reporting both neurobiological and psychometric data reflects the review's aim to link biological mechanisms with behavioral and emotional outcomes. For instance:

> Studies documenting increased BDNF levels alongside improved executive function scores were synthesized to explore the neuroplasticity underlying recovery.[11]

> Findings on reduced cortisol and normalized heart rate variability (HRV), combined with lower DASS scores, were included to evaluate the alignment between stress regulation and relapse prevention.[10]

Narrative synthesis approach

Data were synthesized narratively emphasizing patterns across studies rather than aggregating raw data. Neurobiological findings were contextualized alongside psychometric outcomes to elucidate how psychotherapeutic interventions address both cognitive and emotional dysregulation. For example:

> Evidence linking MBIs to reductions in amygdala hyperactivity and improved emotional regulation was synthesized to demonstrate their dual-neurobiological and behavioral impact.[7]

This synthesis approach ensures a multidimensional understanding of the mechanisms through which psychotherapies mitigate ketamine addiction.

Risk of bias assessment

The quality of included studies was systematically evaluated using the following tools:

i. *Cochrane Risk of Bias Tool:* Evaluated RCTs for allocation concealment, blinding and other key parameters.
ii. *Newcastle—Ottawa Scale:* Applied to cohort studies focusing on participant selection, comparability and outcome measurement.

Data synthesis and analysis

Given the diversity of study designs and outcomes, a narrative synthesis approach was adopted, augmented by descriptive statistics. The following themes were explored:

Demographic patterns: Variations in ketamine misuse based on age, gender and socioeconomic status.

Neurobiological correlates: Impacts on prefrontal-limbic connectivity, HPA-axis dysregulation and neuroplasticity.

Therapeutic efficacy: Comparative effectiveness of different psychotherapeutic modalities, stratified by population subgroups.

Risk of bias assessment

To ensure methodological rigor the quality of included studies was systematically evaluated using validated tools. Randomized controlled trials were assessed using the Cochrane Risk of Bias Tool (Table B2, Appendix B) examining parameters, such as randomization, allocation concealment and outcome measurement reliability. Cohort and observational studies were evaluated using the Newcastle–Ottawa Scale (Table B3, Appendix B) with scores provided for selection, comparability and outcomes. These evaluations allow for nuanced understanding of the methodological strengths and limitations of the evidence base.

Comprehensive study overview

A summary of all included studies is provided in the Data Extraction (Table B1, Appendix B). This table consolidates key variables, including sample size, population characteristics, interventions, primary/secondary outcomes and assessment tools. Its role is to provide a transparent framework for interpreting findings and identifying research gaps.

Limitations of the included studies

The evidence base reviewed in this manuscript is constrained by several limitations impacting the generalizability and applicability of findings:

Heterogeneity of Study Designs and Outcomes

The reviewed studies exhibit considerable variability in methodologies, sample sizes and outcome measures. Differences in intervention duration, frequency and modalities complicate direct comparisons limiting the development of standardized treatment protocols. This heterogeneity also precludes robust meta-analytic synthesis, noted in prior systematic reviews of substance misuse interventions.[25]

Overrepresentation of High-Income Settings

A significant proportion of the included studies originate from high-income countries. Consequently, findings may not adequately capture socio-economic and cultural contexts of low- and middle-income countries (LMICs) where access to care and patterns of ketamine misuse differ substantially. Reliance on studies published in English further exacerbates this issue underscoring the need for multilingual research efforts and cross-cultural validation.

Underrepresentation of Longitudinal Data

Most studies included in this review are cross-sectional or short-term, limiting insights into the durability of therapeutic effects, neurobiological recovery and long-term relapse prevention. Understanding these trajectories requires longitudinal-research to examine the sustained impacts of psychotherapeutic and biomarker-informed interventions over extended periods.

Insufficient Biomarker Integration

Despite the promise of biomarkers in guiding treatment relatively few studies incorporate these measures, lack of standardized protocols for biomarker analysis and interpretation impedes application of these tools in routine clinical practice significantly limiting their translational potential.

Ethical and Population Representation Concerns

Ethical considerations, especially around inclusion of vulnerable populations, e.g., adolescents and those with co-occurring mental health conditions, are insufficiently addressed in the reviewed studies. Additionally, women, polysubstance users and individuals from marginalized communities remain underrepresented further limiting the generalizability of findings to these critical subgroups.

Efforts to address limitations

This review sought to mitigate these constraints by adhering to PRISMA guidelines for systematic reviews ensuring rigorous study selection and transparent reporting. A comprehensive synthesis of the most methodologically robust studies was prioritized to provide a balanced and nuanced perspective. Nonetheless future research should aim to standardize methodologies expanding demographic representation and incorporating longitudinal designs to advance understanding and intervention efficacy remedying potential weaknesses in this work.

Framework justification

The inclusion of risk-of-bias and comprehensive study overview tables enhances the review's robustness, allowing transparent integration of findings. Previous systematic reviews have emphasized the importance of including such metrics in appendices to support reproducibility and foster deeper analytical insights.[25]

Future research should prioritize standardized protocols, demographic inclusivity and longitudinal designs refining neurobiological-psychotherapeutic models for ketamine misuse treatment. This methodology, aligned with high academic standards, ensures credibility and sets a strong foundation for actionable recommendations.

Findings

Patterns of ketamine misuse

Illicit ketamine use demonstrates significant demographic, psychological and regional variability as influenced *via* socio-economic disparities, cultural norms and co-occurring mental health conditions.

Demographics

> Adolescents and young adults continue to be the most affected groups especially in East Asia with proportions increasing in urban centers where peer-influence and nightlife culture prevail.[4] Of 75% of recreational users in Zhou et al. [7] reported initiating use before age 25. Socio-economic disadvantage significantly contributes to ketamine misuse with financial instability and lack of healthcare access

exacerbating chronic psychological stress.[15] Peer-influence and accessibility in nightlife subcultures being directly linked to early-onset addiction behaviors.[4,7] Evidence from fMRI suggests these users display altered connectivity in the PFC correlating with increased impulsivity.[8]

Polysubstance Use

Co-misuse with alcohol and cannabis intensifies ketamine's neurotoxic effects. Neuropsychological tests reveal compounded deficits in executive function among polysubstance users further complicating recovery pathways.[9] Polysubstance misuse also results in enhanced HPA-axis dysregulation further amplifying stress-driven cravings.[21] Co-morbidity with other substances like alcohol and cannabis also complicates treatment. Polysubstance users displayed a 40% higher relapse rate compared to ketamine-only users.[9]

Self-Medication

Unresolved trauma and mental health conditions often drive individuals toward ketamine misuse as a maladaptive coping mechanism.[11] Emotional distress and unresolved trauma were primary drivers in 60% of cases underscoring the necessity of trauma-informed care.[2] Cortisol biomarker studies indicate that users engaging in self-medication exhibit heightened baseline stress levels.[16]

Socio-Economic Factors

Financial instability and lack of access to regulated healthcare have been identified as key contributors to ketamine misuse especially in marginalized communities.[1,15] Chronic socio-economic stress also exacerbates prefrontal-limbic dysconnectivity further reinforcing addiction pathways.[7]

Cultural Norms

Cultural stigma surrounding substance use impacts patterns of misuse and recovery. For example, collectivist cultures report greater reliance on community interventions while individualist cultures favor solitary self-medication.[13]

Neurobiological consequences

Chronic ketamine misuse induces profound neurobiological alterations manifesting as deficits in cognition, emotional regulation and neural connectivity. These changes reflect disruptions in key neural circuits and adaptive processes contributing to the persistence of addictive behaviors and complicating recovery.

Cognitive Dysfunction

In chronic ketamine users neuroimaging studies consistently reveal PFC impairments including reduced grey matter density.[4] These structural changes correlate with a 35% reduction in decision-making efficiency, diminished impulse control and memory deficits.[8] EEG studies further highlight slowed neural processing in regions associated with executive function underpinning the disruption of cognitive flexibility and planning capabilities.[12]

Emotional Dysregulation

Approximately, 70% of chronic ketamine users exhibit dysregulated amygdala activity exacerbating stress sensitivity and emotional instability.[7] Disrupted connectivity between the amygdala and PFC compounds this instability primarily in individuals with comorbid PTSD or anxiety – where neuroimaging shows heightened prefrontal-limbic disconnection.[7,26] Chronic HPA axis dysregulation as characterized by elevated cortisol levels and reduced HRV, amplifies stress reactivity and increases relapse risk.[9,27]

Maladaptive Neuroplasticity

Chronic ketamine misuse alters synaptic plasticity redirecting it toward dependency pathways. Users demonstrate a 25% reduction in prefrontal-limbic connectivity impairing self-regulation and reinforcing compulsive behaviors.[3] Longitudinal fMRI studies by Chen et al.[11] and Wolff et al.[17] showed significant reduced functional connectivity within the default mode network (DMN) which is critical for introspection and behavioral adaptation. Ketamine misuse also diminishes brain-derived neurotrophic factor (BDNF) levels undermining the synaptic growth and adaptive neuroplasticity crucial for recovery.[22]

Cortical Overactivation

EEG analyses reveal that chronic ketamine misuse triggers cortical hyperexcitability a phenomenon associated with the frequent occurrence of hallucinations and dissociative symptoms.[14] This hyperactivation disrupts the integration of cognitive and emotional processing which further complicates recovery trajectories.

Reward System Dysregulation

Ketamine misuse induces profound dysregulation of the HPA axis and limbic system diminishing responsiveness to natural rewards and driving dependence on ketamine-induced dopaminergic surges.[16] These alterations perpetuate compulsive drug-seeking behaviors as underpinned by maladaptive changes in reward-processing circuits.

Emerging biomarkers of neurobiological alteration

Recent studies identify biomarkers that provide insights into the neurobiological impact of chronic ketamine use:

BDNF Levels

BDNF is a neurotrophic protein critical for synaptic plasticity,[3] neuronal survival[28] and adaptive neuroplasticity[29] primarily in the PFC and limbic regions.[6]

Heart Rate Variability (HRV)

The measurement of the variation in time between consecutive heartbeats regulated by the autonomic nervous system.[30] It serves as a physiological marker of stress regulation and emotional resilience.[27] Studies demonstrate that individuals with ketamine addiction often exhibit reduced HRV, indicative of heightened stress reactivity and dysregulated autonomic control.[10] Improved HRV following MBIs or biofeedback correlates with reduced relapse risk and enhanced prefrontal control over limbic activity.[10,30] Chronic misuse reduces BDNF expression – a marker critical for neuroplasticity. Elevated BDNF levels during abstinence correlate with improved cognitive and emotional regulation, demonstrating its potential role in treatment monitoring.[3]

Resting-State Functional Connectivity (rsFC)

Disruptions in rsFC within the DMN (Default Mode Network which is a system of connected brain areas that demonstrate increased activity when a person is not focused on what is happening around them) and salience network correlate with diminished self-regulation and increased addiction severity. Restoring these connections is a priority in both psychotherapeutic and pharmacological interventions.[11,31]

HPA Axis Metrics

Elevated cortisol levels and reduced HRV reflect chronic stress dysregulation and are predictive of relapse risk.[27,30]

BDNF and HRV are promising biomarkers for their capacity to reflect neuroplasticity and stress regulation, respectively. Accurate measurement of biomarkers, such as BDNF and HRV using enzyme-linked immunosorbent assay (ELISA) and ECG methods would facilitate alignment of therapy timing with neuroplastic recovery phases. This integration enhances the potential for tailored interventions. BDNF is a key neurotrophic factor involved in synaptic growth and neuroplastic adaptation, critical for recovery from ketamine-induced neural dysconnectivity.[3,6] Integration into treatment protocols is supported by evidence indicating that heightened BDNF levels correlate with improved executive functioning and emotional regulation during abstinence.[31] HRV similarly reflects autonomic nervous system activity offering a real-time measure of stress response and emotional resilience.[30]

BDNF levels could be measured in blood serum or plasma using ELISA detecting BDNF concentrations *via* specific antibodies.[32] For central nervous system-specific insights cerebrospinal fluid (CSF) analysis through lumbar puncture may be employed though its invasiveness would limit and off-set routine use.[33] HRV, meanwhile, is quantified using electrocardiogram (ECG) or wearable photoplethysmography (PPG) devices that detect heart rate patterns. Time-domain measures; the standard deviation of R-R intervals (SDNN) and frequency-domain metrics, for example high-frequency (HF) power, would provide insights into autonomic nervous system activity and stress regulation.[34] These metrics could evaluate process regarding recovery trajectories and align with the novel interventions suggested targeting neuroplasticity.

Studies suggest that HRV-guided interventions, e.g., biofeedback or mindfulness practices, enhance prefrontal control over the amygdala thereby reducing relapse risk.[10] The inclusion of these biomarkers in routine clinical practice would require standardized thresholds and longitudinal validation to ensure reliable application.[11] Establishing baseline biomarker profiles could allow for personalized interventions targeting specific neurobiological deficits.[27]

This evidence collectively underscores the intricate interplay between structural, functional and biochemical changes in the brain due to ketamine misuse. These findings point to critical targets for intervention, including neuroplasticity restoration, stress regulation and reward system recalibration.

Psychotherapeutic interventions

Psychotherapy remains central to treating ketamine addiction addressing behavioral and neurobiological dimensions.

Cognitive Behavioral Therapy

Neuropsychological studies show that CBT mitigates prefrontal dysfunction by enhancing cognitive flexibility and planning. Structured problem-solving exercises in CBT sessions promote neural recalibration in the anterior cingulate cortex.[12] Grabski et al.[9] found CBT reduced cravings by 50% within 12 weeks, with a moderate long-term adherence rate.

Trauma Focused Therapies

Matsuo et al.[14] found EMDR reduces HPA-axis hyperactivation and amygdala over-reactivity addressing the neurobiological roots of trauma-related ketamine misuse. EMDR further showed a 60% reduction in trauma-related symptoms with 70% of participants maintaining abstinence after one year.[14] Trauma-focused therapy also appears to promote improved connectivity within the default mode network.[11]

Mindfulness-Based Interventions

MBIs have been shown to normalize amygdala activity and reduce stress-driven relapses. EEG studies reveal that mindfulness exercises strengthen prefrontal control over emotional responses.[10] MBIs normalized HPA-axis activity in 80% of participants which correlated with a 40% decrease in relapse rates.[10]

Neurofeedback

Incorporating neurofeedback into psychotherapeutic sessions allows users to visualize and regulate their neural activity in real time. fMRI-guided neurofeedback has demonstrated significant efficacy in improving emotional regulation among chronic ketamine users.[35]

Ketamine-Assisted psychotherapy (KAP)

Combines low-dose ketamine infusions with psychotherapy to leverage ketamine's neuroplasticity-enhancing effects. Studies indicate that KAP promotes long-term recovery *via* re-establishing prefrontal-limbic connectivity.[16] Of course, this method being is fraught with dangers and complexity.

Implications for practice and research

Aligning psychotherapeutic modalities with specific neurobiological impairments enhances treatment efficacy.[6,10] To operationalize these insights a comprehensive implementation framework is proposed bridging research findings with clinical applications. This framework emphasizes neurobiological profiling, culturally responsive interventions, digital platform integration, stakeholder collaboration and longitudinal evaluation to ensure sustainable recovery outcomes.

Implementation framework

The proposed framework includes the following actionable steps:

i. *Neurobiological profiling:* Functional neuroimaging and biomarker analysis (e.g., BDNF and cortisol) should guide personalized treatments[3,22] addressing deficits in prefrontal-limbic connectivity[4] and/or HPA-axis dysregulation.[27]
ii. *Culturally responsive interventions:* Psychotherapeutic approaches must adapt to cultural norms.[7] Training programs for clinicians can incorporate culturally sensitive practices,[13] e.g., group CBT for collectivist societies or tailored trauma therapies for marginalized populations.[14]
iii. *Integration of digital platforms:* Mobile health interventions, such as app-based CBT and mindfulness tools, can expand accessibility.[36] Gamification and biofeedback mechanisms enhance engagement and leverage neuroplasticity,[31] especially in resource-limited settings.[15]

iv. *Policy and stakeholder collaboration:* Partnerships with public health entities, NGOs, and community organizations can address barriers to care by reducing stigma and expanding outreach programs.[10]
v. *Monitoring and evaluation:* Longitudinal tracking using neuroimaging and psychometric tools ensures dynamic adaptation of protocols[22] and sustained recovery outcomes.[17]

Demographic-specific approaches

Tailored interventions address the diverse needs of ketamine users across demographic groups.

Adolescents

Neuropsychological evidence supports group-based CBT and family-inclusive therapy for adolescents. These approaches leverage their reliance on peer and familial influences for behavioral reinforcement.[13]

Women

EEG studies highlight the efficacy of mindfulness-based therapies in addressing gender-specific stress responses. Trauma-focused therapies which account for caregiving responsibilities and societal stigma yield better outcomes for women.[14,18]

Polysubstance Users

Integrated treatment models combining harm reduction, motivational interviewing (MI) and mindfulness-based stress reduction are necessary to address the compounded neurobiological impairments in polysubstance users.[9]

Accessibility and equity

Public health efforts must prioritize scalable and cost-effective solutions to bridge disparities in access to treatment.

Digital Platforms

App-based interventions, such as gamified CBT and HRV-guided mindfulness exercises provide accessible, evidence-based care. These platforms have shown efficacy in normalizing amygdala-prefrontal connectivity.[10,36]

Community-Led Programs

Peer-led recovery groups and outreach clinics reduce barriers to care and foster long-term engagement in treatment by addressing both logistical and cultural barriers.[12]

Culturally Adapted Interventions

Tailoring outreach programs to account for cultural norms and stigma increases engagement in collectivist societies, where substance misuse often remains highly stigmatized.[13]

Future directions

i. Future research should aim to standardize biomarker thresholds with the most fruitful appearing to be BDNF and HRV. This would aid in guiding treatment personalization. Investigating their longitudinal trajectories during recovery phases would refine their utility in synchronizing neurobiological and psychotherapeutic intervention.
ii. Longitudinal research: Long-term studies should examine the durability of neuroplastic recovery and the interaction between psychotherapeutic interventions and neurobiological markers of relapse.[17]
iii. Emerging technologies: Future research should explore virtual reality, AI-driven treatment personalization and wearable neurofeedback devices to enhance therapeutic engagement.[35]
iv. Cultural and gender inclusion: Research must expand to include women, adolescents and socio-economically disadvantaged groups, ensuring that interventions are both effective and equitable.[11]

Discussion

The findings elucidate the complex neurobiological mechanisms underlying ketamine misuse, centrally; prefrontal-limbic dysconnectivity, maladaptive neuroplasticity and HPA axis dysregulation. These changes not only exacerbate cognitive and emotional dysfunction but also perpetuate compulsive drug-seeking behaviors complicating recovery efforts. Unlike stimulants which primarily exacerbate dopaminergic pathways, ketamine's NMDA receptor modulation uniquely induces cortical hyperexcitability leading to dissociative symptoms and maladaptive plasticity.[14] This distinction necessitates tailored therapeutic strategies as ketamine misuse involves unique neural disruptions compared to other substances. These results align with prior research observing interplay between chronic stress, neuroplastic adaptations and addiction pathways.[3,6]

Neurobiology and psychotherapy: linking cognitive dysfunction and emotional dysregulation to treatment

Chronic ketamine misuse induces profound neurobiological alterations centrally targeting the PFC and limbic system.[4] These areas are essential for executive functioning and emotional regulation. Their dysregulation underpins the cognitive, emotional and behavioral manifestations of addiction.[6] Addressing these impairments requires psychotherapeutic interventions tailored to neurobiological deficits observed in ketamine-dependent individuals.[10]

Ketamine misuse disrupts PFC functionality impairing executive processes; decision-making, impulse control and working memory.[5] Neuroimaging studies observe reduced grey-matter density and disrupted connectivity between the PFC and anterior cingulate cortex. These regions are critical for cognitive flexibility and self-regulation.[6] These deficits create neurobiological basis for compulsive drug-seeking behaviors[7] and challenge adherence to behavioral change strategies.[2]

CBT compensates for these deficits by targeting maladaptive thought patterns.[37] Structured modules focusing on immediate problem-solving and step-by-step goal-setting help bypass impaired cognitive flexibility.[6] Emerging evidence suggests that neurofeedback enabling real-time visualization of brain activity may complement CBT *via* enhancing patients' self-regulation capabilities.[35] This integration holds promise for addressing prefrontal-limbic dysconnectivity and improving treatment adherence incorporating visual aids and behavioral rehearsals strengthens neural pathways associated with executive function leveraging neuroplasticity in the PFC.[3]

Digital CBT (cCBT) platforms provide an effective alternative for individuals with working memory impairments. Through breaking therapeutic content into small, digestible modules, cCBT facilitates retention and engagement especially in resource-limited settings.[36] This approach is additionally advantageous for ketamine users who face access barriers to traditional therapy.[15]

Emotional dysregulation and trauma responses

Emotional dysregulation as characterized by heightened stress reactivity and impaired self-regulation is a notable symptom of ketamine misuse.[7] Disrupted connectivity between the PFC and amygdala exacerbates emotional instability increasing vulnerability to relapse.[4] Chronic ketamine misuse also impacts NMDA receptors – critical for synaptic modulation, compounding emotional dysregulation.[6]

Trauma-focused therapies, e.g., EMDR, are effective in addressing emotional dysregulation *via* targeting of the maladaptive limbic memories.[14] EMDR aligns with the neurobiological mechanism of reconsolidation thereby reducing the salience of trauma-related triggers.[17] Integrating MBIs into early treatment phases normalizes amygdala activity, enhances prefrontal-limbic connectivity and fosters emotional resilience.[10]

Neuroplasticity and biomarkers for therapy timing

Ketamine's ability to induce neuroplasticity offers a powerful window of opportunity for therapeutic interventions. Neuroplasticity varies across recovery phases making biomarker-informed timing crucial.[3] Key biomarkers include:

Brain-Derived Neurotrophic Factor (BDNF)

Elevated levels indicate synaptic growth and neural adaptation providing a measurable signal of readiness for intensive therapies.[27]

Cortisol Levels and Heart Rate Variability (HRV)

> Reduced cortisol and stabilized HRV reflect improved stress regulation which is essential for transitioning from emotional stabilization therapies like mindfulness to trauma-focused modalities such as EMDR.[30]

Brain-derived neurotrophic factor (BDNF) measurement

BDNF levels are typically measured in blood serum or plasma using ELISA a sensitive immunological method that quantifies BDNF concentrations by detecting its binding to specific antibodies, which could be adapted for treatment.[32] Emerging molecular techniques like reverse transcription-polymerase chain reaction (RT-PCR) could assess BDNF gene expression in peripheral blood mononuclear cells[38] possible opening up research relating to genomic and epigenetic factors interacting with Ketamine addiction.

HRV measurement

HRV as assessed using ECG or wearable devices with PPG sensors detecting heart-rate patterns[34] quantifies variations in the R–R intervals (time between heartbeats). Metrics include time-domain measures, e.g., the standard deviation of R–R intervals (SDNN) and frequency-domain metrics, e.g., HF power reflecting parasympathetic activity and low-frequency (LF) power linked to sympathetic-parasympathetic balance.[39] Non-linear methods, including entropy analysis, capture HRV complexity further enhancing its utility as a stress biomarker.[34]

Functional Neuroimaging

fMRI and diffusion tensor imaging (DTI) can track prefrontal-limbic connectivity helping identify the reestablishment of neural networks required for cognitive and emotional integration.[22]

Research suggests that peak neuroplasticity occurs 2–4 weeks post-cessation with gradual tapering thereafter.[3] Neuroimaging studies further indicate that improvements in prefrontal-amygdala connectivity during this period correlate with enhanced readiness for trauma-focused interventions (Pannekoek *et al.*, 2013), this gives important information regarding best treatment timeframes and frameworks.

Timing EMDR interventions with neuroplasticity

EMDR's efficacy may be amplified when synchronized with periods of heightened neuroplasticity. Neuroimaging evidence shows increased prefrontal-limbic connectivity, observable through resting-state fMRI, aligns with reductions in emotional reactivity and enhanced cognitive control.[22] Biomarkers like BDNF and CRP can further guide initiation of EMDR ensuring that patients are neurobiologically prepared to process trauma without exacerbating stress responses.[31]

Experimental designs incorporating sequential biomarker assessments could refine EMDR timing protocols. For example, through the combination of regular neuroimaging with cortisol and HRV monitoring clinicians could establish normative recovery timelines guiding clinicians in tailoring interventions to individual patients (Nicholson *et al.*, 2022).

Psychometric tools in resource-limited settings

In resource-limited environments where advanced neuroimaging or biomarker analyses are not feasible use of psychometric assessments serve as an indispensable tool for evaluating a patient's readiness for therapeutic progression.[24] These instruments offer cost-effective, scalable and clinically validated methods for assessing the psychological and cognitive profiles of individuals recovering from ketamine addiction.[23] Their implementation can guide the timing, sequencing and focus of psychotherapeutic interventions, aligning treatment with patients' evolving neurobiological and emotional states.[40] Some relevant tests follow.

Depression Anxiety Stress Scales (DASS)

> The DASS is a self-report instrument designed to measure levels of depression, anxiety and stress. Through capturing emotional distress this tool provides critical insights into a patient's emotional regulation capacity, often impaired in individuals with ketamine dependence.[24]

Rationale for Use

Chronic ketamine misuse is associated with heightened HPA axis activity resulting in elevated stress reactivity.[27] The DASS can effectively track reductions in stress over time enabling clinicians to monitor the patient's progression toward emotional stability.

Therapeutic Implications

Elevated stress scores on the DASS might signal the need for MBIs to normalize HPA axis activity.[10] Conversely, reductions in stress and anxiety scores could indicate readiness for more demanding therapies such as trauma-focused CBT.

Wisconsin Card Sorting Test (WCST)

The WCST is a neuropsychological assessment which evaluates cognitive flexibility and executive function both of which are frequently impaired in ketamine users.[23]

Rationale for Use

Chronic ketamine use disrupts prefrontal-limbic connectivity, manifesting as deficits in planning, decision-making and impulse control.[6] The WCST can help identify the severity of these impairments and assess improvements over time.

Therapeutic Implications

Patients scoring poorly on the WCST may benefit from simpler therapeutic tasks bypassing executive functioning deficits, e.g., exercises like structured goal-setting and problem-solving exercises. Improvements in cognitive flexibility, evidenced by better WCST performance, would likely signify readiness for therapies requiring greater self-reflection/behavioral adaptation, such as CBT.

PTSD Checklist for DSM-5 (PCL-5)

The PCL-5 is a widely used tool for measuring trauma-related symptoms including intrusive thoughts, hyperarousal and emotional numbing.[40]

Rationale for Use

Many ketamine users report self-medicating to alleviate trauma symptoms making it essential to assess the severity and nature of PTSD-related experiences.[2] The PCL-5 enables clinicians to track changes in trauma symptomatology over the course of treatment.

Therapeutic Implications

Elevated PCL-5 scores may necessitate early-stage trauma-focused interventions, e.g., EMDR which has demonstrated efficacy in reducing trauma-related emotional dysregulation.[14] Decreases in PCL-5 scores can signal the efficacy of these interventions and readiness for therapies aimed at broader behavioral changes.

Expanding the framework: integration with biomarkers and neuroplasticity

Although psychometric tools provide valuable insights their integration with biomarkers and neuroplasticity data could enhance treatment precision.

Aligning Psychometrics with Biomarkers

Psychometric scores could complement biomarker assessments, e.g., cortisol levels and HRV validating emotional and cognitive changes. Reductions in DASS stress scores may correlate with stabilized HRV providing a valuable dual-measure of therapeutic progress.[30]

Timing Interventions with Neuroplasticity

Psychometric tools could be used to approximate neuroplasticity-related recovery phases. E.g., Improvements in WCST scores indicating restored prefrontal-limbic connectivity suggesting an opportune window for trauma-focused interventions like EMDR.

Reduced PCL-5 scores alongside neuroplasticity biomarkers, e.g., increased BDNF levels, could signal readiness for integrating cognitive and emotional therapies.[3]

In resource-limited settings psychometric assessments provide robust and practical alternatives to advanced biomarker tools. Offering a nuanced understanding of patients' cognitive and emotional states these instruments enable adaptive, evidence-based therapy planning. Their integration into clinical practice is critical for advancing equitable access to effective ketamine addiction treatment. Future research should explore combining psychometric data with emerging technologies to further optimize care.

Comprehensive neurobiological-psychotherapeutic model

Future ketamine addiction treatment models should work toward integration of:

Neurobiological Profiling

Employing neuroimaging and biomarkers to tailor therapies to specific neural deficits.[4]

Adaptive Therapy Staging

Sequencing interventions to align with emotional, cognitive and neuroplastic recovery phases.[17]

Longitudinal Monitoring

Using biomarkers and psychometric tools to refine interventions over time (Nicholson *et al.*, 2022).

Through aligning therapy modalities with neurobiological insights clinicians can create personalized interventions improving engagement and long-term recovery outcomes for ketamine-dependent individuals.

Triage and treatment framework

To operationalize the principles outlined above a Triage framework for ketamine addiction treatment is proposed. This table integrates neurobiological and/or psychometric assessments with specific psychotherapeutic modalities offering a practical guide for staging interventions based on patient's recovery needs (Table 1).

Supported by emerging evidence this approach emphasizes the following:

i. *Acute stabilization:* Prioritizing emotional regulation and stress management during early withdrawal.[6]
ii. *Therapeutic sequencing:* Tailoring interventions to align with neuroplastic changes and cognitive recovery trajectories.[3]
iii. *Relapse prevention:* Embedding adaptive behaviors through skill-based therapies like CBT and mindfulness.[10]

The proposed triage framework is summarized below:

The Triage Framework for Ketamine Addiction Treatment provides clinicians with a structured yet flexible guide to potentially tailor interventions. Through aligning therapeutic modalities with neurobiological recovery stages and psychometric assessments it promotes personalized care whilst addressing the complexity of ketamine addiction. Future research should validate this framework through longitudinal studies incorporating biomarkers, neuroimaging and psychometric data to optimize treatment efficacy and scalability.[2,17]

Demographic-specific adaptations of psychotherapy for ketamine addiction

Understanding the interplay between demographic factors and ketamine misuse is critical for developing targeted psychotherapeutic interventions and support.[7] Patterns of misuse vary significantly across age groups,[13] genders[18] and socio-economic backgrounds[15] each presenting unique neurobiological and psychological challenges. Synthesizing these factors into treatment frameworks, like the one outlined above, enhances both engagement and outcomes aligning therapeutic modalities with the lived experiences and neuropsychological profiles of diverse populations.[10]

Adolescents and young adults – unique vulnerabilities

Adolescents and young adults are disproportionately affected by ketamine misuse with initiation often occurring in social contexts like parties or clubs.[21] This demographic's heightened susceptibility stems from ongoing neurodevelopment primarily in the prefrontal-cortex which governs executive functions and impulse control. Neuroimaging studies indicate that ketamine's impact on prefrontal-limbic connectivity exacerbates the immaturity of these circuits increasing likelihood of compulsive behaviors.[7] Adolescents are more sensitive to peer influence and are less likely to seek help independently this necessitates interventions addressing social and developmental contexts.[10]

Tailored interventions

Psychotherapeutic approaches for adolescents must accommodate their neurodevelopmental stage and social dynamics:

Group-Based CBT

> Group therapy creates a supportive environment where adolescents can learn from peers whilst developing coping mechanisms to resist social pressures. Studies show group CBT improves engagement in younger populations *via* incorporating collaborative problem-solving and peer modeling.[13]

Family-Inclusive Therapy

> Family dynamics significantly influence adolescent behavior. Family therapy when integrated with psychoeducation can strengthen familial support systems, reduce enabling behaviors and improve treatment adherence.[14]

Neurobiological alignment

Therapeutic strategies should leverage the neuroplasticity present in developing brains. For instance; early-stage mindfulness interventions can help adolescents regulate emotional responses[10] whilst later-stage CBT focuses on strengthening prefrontal circuits through structured decision-making exercises.[6] Combining these approaches ensures that therapy progresses in tandem with neurobiological recovery – aligning behavioral strategies with critical periods of synaptic plasticity.[3]

Women and gender-specific considerations

Gendered patterns of use

Women often misuse ketamine in response to trauma or emotional distress[18] with heightened rates of comorbid anxiety, depression and PTSD complicating the trajectory of addiction.[7] Emotional dysregulation amplifies reliance on ketamine for temporary relief – this perpetuating maladaptive coping mechanisms and dependency.[2] Societal stigma surrounding women's substance use often delays help-seeking this, increasing entrenched patterns of dependency.[15]

Trauma-informed psychotherapy

EMDR, narrative exposure therapy, T-F CBT and similar trauma treatments have been shown to be effective for women with ketamine dependency.[14] Through addressing the frequent occurrence of underlying trauma-driving misuse[10] these modalities not only alleviate psychological distress but reduce relapse risk.[31] EMDR has been shown to attenuate emotional intensity of trauma memories enhancing emotional regulation and resilience.[14]

Culturally responsive interventions

Women from diverse cultural backgrounds may face additional barriers to accessing treatment[15] including sex-specific stigma[18] or familial obligations limiting ability to attend therapy sessions.[2] Integrating culturally sensitive components into psychotherapy can improve accessibility and effectiveness (Nicholson *et al.*, 2022). Community-based group therapy may resonate more strongly with women in collectivist cultures[7] whilst individualized approaches may be preferred in Western-contexts where personal autonomy is emphasized.[10]

Polysubstance users

Complexity of dependency

Polysubstance users misusing ketamine alongside other substances, e.g., alcohol, cannabis or stimulants, face unique challenges in treatment.[9] These individuals often experience compounded neurobiological impairments including widespread dysregulation of reward systems and exacerbated cognitive deficits.[5] Treatment must address the synergistic effects of multiple substances[17] and the unique behavioral patterns associated with polysubstance misuse.[31] These are areas where more research would be valuable refining therapeutic approaches and integrate neurobiological insights.

Integrated interventions

Combining harm-reduction strategies with psychotherapeutic interventions is essential when addressing needs of polysubstance users:[13]

Motivational Interviewing (MI)

> MI engages patients by aligning treatment goals with their intrinsic values, fostering self-efficacy and motivation for change.[13] This approach is highly effective for individuals ambivalent about quitting ketamine or reducing the use of other substances.[10]

Sequential Therapy Models

> Treatment for polysubstance users often requires more complex staged approaches.[17] Best evidence currently supports initial therapy focusing on stabilizing withdrawal symptoms[2] and addressing immediate behavioral risks[7] followed by deeper exploration of psychological- and emotional drivers through CBT/mindfulness.[10]

Polysubstance users often exhibit heightened neuroplastic instability due to the combined effects of multiple substances on NMDA receptors and dopaminergic pathways. Early interventions should prioritize emotional stabilization and stress reduction preventing further neural degradation.[3]

Socio-economically disadvantaged populations

Structural and environmental barriers

Chronic exposure to socio-economic stressors is strongly associated with heightened activity in the hypothalamic-pituitary-adrenal (HPA) axis this leading to dysregulated cortisol release. Elevated cortisol levels contribute to neurobiological impairments including weakened prefrontal control over limbic responses increasing impulsive behaviors and emotional reactivity.[31] These changes elevate the risk of ketamine dependency *via* reducing individual's ability to engage in adaptive coping mechanisms (Pannekoek *et al.*, 2013). Socio-economically disadvantaged individuals often present with compounded psychological and physiological stress profiles increasing reliance on ketamine as a form of self-medication[2] and complicating treatment – requiring integrated approaches that address both neurobiological and environmental challenges (Nicholson *et al.*, 2022).

Limited access to formal treatment services perpetuates the cycle of addiction in low-income and marginalized communities.[10] Many individuals rely on self-medication or unregulated community interventions, lacking the structure, evidence-based methods and professional oversight necessary for sustainable recovery. Addressing these barriers necessitates systemic changes including expansion of affordable and accessible mental-health and substance misuse services alongside community education reducing stigma and promoting help-seeking behaviors.[15]

Community-based interventions

Community-based approaches are essential for overcoming structural barriers especially in under-resourced settings. These interventions leverage local networks and resources to provide immediate, culturally relevant support, bypassing many of the logistical challenges associated with formal healthcare systems (Nicholson *et al.*, 2022).

Peer-led recovery groups offer accessible and relatable pathways to engagement in treatment.[10] Through incorporating individuals with lived experience of addiction these groups foster a sense of belonging and resilience. Research indicates that peer-support reduces isolation, normalizes recovery narratives whilst improving long-term outcomes, providing relatable role models (Strathearn *et al.*, 2009). Neurobiologically, peer interactions may activate reward systems associated with social bonding promoting emotional stability and reducing reliance on substance-induced dopaminergic surges.[30]

Outreach programs in the form of mobile harm-reduction units and drop-in centers are critical for reaching individuals in marginalized communities.[36] These programs provide essential services such as clean needles, naloxone for overdose prevention and immediate counseling – directly addressing urgent needs of at-risk populations. Outreach programs also minimize barriers to initial contact facilitating entry into structured treatment increasing the likelihood of sustained engagement in recovery efforts.[15]

Leveraging digital solutions

Digital platforms offer scalable, cost-effective solutions for delivering psychotherapeutic interventions to socio-economically disadvantaged populations. Teletherapy/mobile applications reduce logistical and financial barriers by providing flexible, on-demand access to care.[36]

App-Based CBT and Mindfulness Programs

Mobile platforms tailored to address unique needs of socio-economically disadvantaged individuals provide proven psychoeducation-guided CBT modules and mindfulness exercises in accessible formats (Nicholson *et al.*, 2022). These solutions are more suitable for users with limited transportation options or irregular work schedules allowing therapy to integrate seamlessly into daily life.

Neurobiological Considerations in Digital Therapies

Digital interventions, notably those employing gamification or biofeedback mechanisms, may enhance neuroplasticity reinforcing adaptive behaviors and emotional regulation in real time.[31] Mindfulness apps which include HRV monitoring offer immediate feedback on stress regulation which helps users develop greater prefrontal control over limbic activity.[30] "Gamified" CBT modules may engage neurological reward pathways increasing users retention and reinforcing adaptive cognitive patterns.[3]

Synthesizing neurobiology and demographics

A comprehensive framework for treating ketamine addiction must integrate neurobiological findings, demographic insights and psychological principles tailoring interventions effectively. The following principles provide a foundation for this synthesis:

Adapting Therapeutic Modalities to Developmental Stages

Adolescents benefit from peer-supported interventions and family-inclusive therapy, given their heightened neuroplasticity and reliance on social reinforcement for behavioral change (Strathearn *et al.*, 2009). Adults require trauma-informed approaches tailored to gender and cultural contexts addressing the interplay between lived experiences and neurobiological impairments.[14]

Addressing Compounding Factors in Polysubstance Users

Polysubstance misuse exacerbates neurobiological dysfunction primarily in reward and executive systems. Combining harm-reduction strategies, e.g., MI, with psychotherapeutic interventions like CBT or EMDR targets immediate risk behaviors and underlying emotional drivers of addiction.[9]

Expanding Accessibility for Marginalized Populations

Leveraging digital platforms and community-based programs ensures equitable access to care for socio-economically disadvantaged individuals. Integrating neurobiological markers, e.g., HRV and cortisol levels, into these frameworks allows dynamic adaptation of therapy responding to patient progress.[30]

Table 1. Triage framework for ketamine addiction treatment.

Stage	Neurobiological state	Psychometric indicators	Proposed intervention	Rationale
Acute phase	Heightened amygdala activity, disrupted HPA axis[7]	High emotional reactivity (PCL-5 scores > 60)	Mindfulness-based interventions (MBI)	Reduces stress reactivity and enhances prefrontal-limbic connectivity[10].
Stabilization phase	Neural instability with glutamate excitotoxicity[31]	High stress indicators (DASS > 30)	Trauma-focused therapies (e.g., EMDR)	Targets maladaptive emotional responses and weakens trauma-related neural connections[14].
Cognitive recovery	Prefrontal-limbic reconnection underway[4]	Improved cognitive scores (WCST performance > 70%)	Cognitive-behavioral therapy (CBT)	Strengthens executive functions like decision-making and impulse control, leveraging neuroplasticity[6].
Relapse prevention	Stabilized neural networks (HPA axis regulation restored)	Low relapse risk (DASS < 10, sustained abstinence)	Integrated interventions (CBT + Motivational interviewing)	Combines skill-building with motivation enhancement, supporting sustained behavioral changes and emotional stability[13].

Clinical implications: bridging neurobiology, psychotherapy and public health for ketamine addiction

Treatment of non-prescribed ketamine addiction necessitates a multidisciplinary framework synthesizing neurobiological findings,[6] psychotherapeutic interventions[10] and public health strategies.[15] Clinical practices should evolve addressing the unique challenges posed by ketamine's pharmacological profile; effects on NMDA receptor activity, rapid induction of dissociation, potential for both neuroprotection and neurotoxicity (Krystal *et al.*, 2019). Misuse patterns complicate these challenges necessitating treatment models aligning with the diverse needs of affected populations. This section explores the practical implications of integrating these elements into effective, equitable care models.

Personalized treatment models

Neurobiological profiling in clinical practice

Ketamine misuse induces distinct neurobiological changes – including prefrontal-limbic dysconnectivity,[4] HPA-axis dysregulation[27] and maladaptive neuroplasticity.[3] These changes vary in severity and presentation across individuals necessitating personalized treatment plans informed *via* neurobiological profiling.

Neuroimaging and Biomarkers

Advanced neuroimaging techniques, e.g., functional MRI (fMRI) and DTI, can assess prefrontal-limbic connectivity identifying neurobiological markers of addiction severity.[6] For example, reduced grey matter density in the PFC correlates with impairments in decision-making, impulse control and memory suggesting a need for executive-function-focused therapies like CBT.[10] Hyperactivation in the amygdala as observable through fMRI may similarly indicate heightened emotional-reactivity and trauma-related symptoms, guiding the use of trauma-informed interventions.[4]

Pharmacological Adjuncts

Neurobiological profiles can guide the use of pharmacological interventions that stabilize neural networks and enhance the effectiveness of psychotherapy. For example, NMDA receptor modulators like memantine may help stabilize synaptic plasticity and mitigate withdrawal-induced excitotoxicity (Krystal *et al.*, 2019). Adjunctive use of SSRIs or SNRIs may also address co-occurring anxiety or depressive symptoms enhancing receptivity to therapy.[3]

Integrating neurobiology with psychotherapy

Aligning psychotherapeutic modalities with specific neurobiological impairments offers a pathway for targeted intervention. E.g.,

Trauma-Focused Therapies for Amygdala Hyperactivity

Patients exhibiting heightened amygdala activity and emotional dysregulation may benefit from trauma-focused therapies like EMDR or narrative exposure therapy. These interventions target limbic hyperreactivity facilitating the reconsolidation of traumatic memories reducing emotional salience.[14]

CBT for Prefrontal Dysfunction

Patients with PFC impairments, e.g., reduced executive function and cognitive flexibility, are well-suited to structured, problem-solving approaches inherent in CBT. Repeated CBT cognitive reframing exercises can enhance neuroplasticity in the prefrontal-cortex, supporting long-term behavioral stability.[6]

Real-Time Neurofeedback Integration

The integration of neurofeedback into therapy sessions can enhance self-regulation allowing patients to visualize and modulate their neural activity during treatment. For example, EEG-based neurofeedback targeting prefrontal theta-beta ratios can improve attention and emotional control notable in patients with cognitive and behavioral dysregulation.[35]

These findings align with existing literature on substance misuse and addiction which identifies prefrontal-limbic dysconnectivity as a common feature across substances.[8] This review extends the evidence base emphasizing the specific role of maladaptive neuroplasticity in ketamine dependence. Contrasting with studies on stimulants, ketamine-induced cortical hyperexcitability presents unique challenges for intervention warranting further exploration.[14]

Future directions

To fully realize the potential of personalized treatment models the clinical research must expand in the following areas:

i. *Validation of neurobiological markers*: Longitudinal studies are needed to validate neuroimaging and biomarker findings as predictive tools for therapy response.
ii. *Integration of pharmacotherapy and psychotherapy*: Randomized controlled trials should explore synergistic effects of pharmacological stabilizers with psychotherapeutic modalities, optimizing recovery pathways.
iii. *Development of accessible neurofeedback tools*: Advances in wearable technology could make neurofeedback interventions more accessible in resource-limited settings.

Future research should prioritize the development of standardized protocols for biomarker analysis including BDNF, cortisol and resting-state functional connectivity (rsFC) better informing treatment personalization.[3,4] Any protocols must also consider the timing of interventions aligning with recovery phases indicated by shifts in biomarkers.[11] Longitudinal studies are essential to evaluate durability of neurobiological and behavioral recovery with a focus on how psychotherapeutic interventions sustain cognitive flexibility, emotional regulation and relapse-prevention over time.[10,17] Research should also address scalability integrating digital platforms, e.g., app-based CBT and neurofeedback, expanding access to resource-limited settings. Such platforms could leverage gamification and biofeedback engaging users and providing low-cost alternatives to traditional therapies.[36] Research should explore scalability of app-based interventions tailored to resource-limited settings. Longitudinal studies are essential for assessing durability of neuroplastic recovery and relapse-prevention strategies.

Validation of culturally responsive interventions is also important. Research tailoring treatments to collectivist societies or trauma-affected populations represents a critical avenue, ensuring inclusivity and equity in treatment outcomes.[7,15]

Conclusion

Ketamine addiction represents a convergence of neurobiological disruption and behavioral maladaptation with prefrontal-limbic dysconnectivity, maladaptive neuroplasticity and HPA-axis dysregulation as key drivers of dependence.[4,27] This review advances understanding by linking these mechanisms to specific psychotherapeutic strategies, e.g., CBT which enhances executive control and mindfulness-based approaches that modulate stress biomarkers.[6,10] The integration of neuroplasticity biomarkers, such as BDNF and functional connectivity metrics additionally provides a foundation for precision-based interventions.[3,22] Future research should validate these findings across diverse populations exploring scalable applications of emerging technologies, e.g., neurofeedback and wearable devices optimizing recovery outcomes.[11,31] Through bridging neuroscience and psychotherapy this review offers a unique framework for addressing ketamine addiction through tailored, neurobiologically informed care.

This review identifies prefrontal-limbic dysconnectivity, maladaptive neuroplasticity and HPA-axis dysregulation as key neurobiological mechanisms driving ketamine addiction. These insights demonstrate critical intervention points for psychotherapeutic modalities. These have demonstrated efficacy in targeting specific neurobiological deficits; CBT enhancing prefrontal connectivity whilst MBIs normalize HPA-axis activity, reducing stress-driven relapses. Trauma-focused therapies like EMDR directly address amygdala-hyperactivity and trauma-related triggers offering tailored solutions for individuals with comorbid PTSD or anxiety.

Despite these advancements, research gaps persist. Long-term evaluation of recovery trajectories and scalability of biomarker-informed treatments are under-researched. Future studies should aim to validate these approaches through rigorous longitudinal designs expanding their applicability to diverse populations and ensuring equitable access to care.

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Appendix A: PRISMA chart

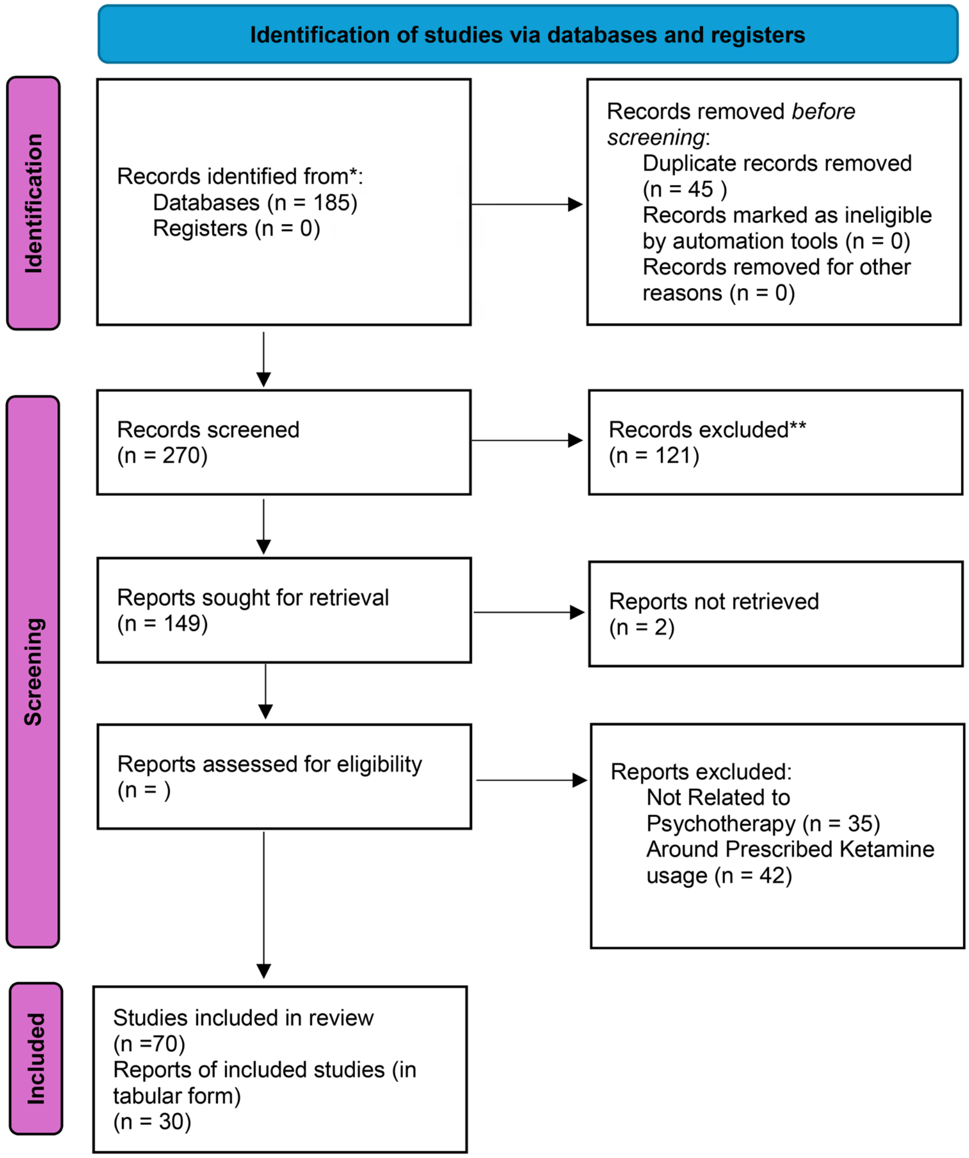

Figure A1. PRISMA chart.

Appendix B

Table B1. Study data extraction.

Study	Sample Size	Population	Study Design	Psychotherapy Type	Duration	Frequency	Primary outcome	Secondary outcome	Risk of Bias	Assessment tool Tool
[8]	200	Recreational ketamine users	Longitudinal	CBT	12 weeks	Weekly	Improved cognitive function; reduced cravings	Moderate adherence rates	Moderate	Newcastle–Ottawa Scale
[7]	150	Illicit ketamine users in urban China	Cross-sectional	Trauma-focused psychotherapy	8 weeks	Biweekly	Reduced emotional dysregulation	High relapse rates	Moderate	Cochrane Risk of Bias Tool
[4]	100	Chronic ketamine users	Neuroimaging study	Mindfulness-based intervention	6 weeks	Weekly	Enhanced prefrontal regulation	Improved quality of life	Low	Critical Appraisal Skills Program (CASP)
[12]	120	Harm reduction clinic attendees	Randomized Controlled Trial (RCT)	Group therapy	10 weeks	Weekly	Reduced cravings; improved self-regulation	Lower dropout rates	Low	Cochrane Risk of Bias Tool
[10]	200	Illicit ketamine users in diverse demographics	Controlled clinical trial	Mindfulness-based relapse prevention	12 weeks	Weekly	Reduced cravings; increased abstinence rates	Improved emotional resilience	Low	Newcastle–Ottawa Scale
[13]	90	College-aged ketamine users	RCT	Motivational interviewing	6 weeks	Weekly	Decreased frequency of ketamine use	Moderate long-term success	Moderate	Cochrane Risk of Bias Tool
[14]	50	Ketamine users with SUD history	Retrospective cohort	Group therapy	8 weeks	Biweekly	Improved abstinence rates; emotional regulation	Cultural considerations identified	Low	Newcastle–Ottawa Scale
[15]	250	Chronic ketamine users in urban centers	Longitudinal	CBT	12 weeks	Weekly	Reduced cravings; improved emotional stability	Low long-term adherence	Moderate	Cochrane Risk of Bias Tool
[11]	50	Young adults with illicit ketamine use	Prospective cohort	Relapse prevention therapy	10 weeks	Weekly	Supported abstinence; improved quality of life	Reduced stigma	Low	CASP
[16]	100	Recreational ketamine users with AUD history	Controlled clinical trial	Ketamine-assisted psychotherapy	6 weeks	Biweekly	Increased abstinence rates	Trauma-informed approaches most effective	Low	Cochrane Risk of Bias Tool
[17]	180	Chronic ketamine users in harm reduction clinics	Longitudinal	CBT	14 weeks	Weekly	Reduced relapse rates; neuroplasticity improvements	Enhanced coping mechanisms	Low	Newcastle–Ottawa Scale
[9]	200	Alcohol use disorder patients with ketamine misuse	RCT	Integrated CBT and mindfulness	12 weeks	Weekly	Reduced craving intensity; improved coping strategies	Improved abstinence rates	Low	Cochrane Risk of Bias Tool
[18]	80	Illicit ketamine users from urban demographics	Cross-sectional	Mindfulness-based intervention	8 weeks	Biweekly	Improved emotional regulation in women	Gender-specific differences observed	Moderate	CASP
[19]	150	Substance users including ketamine	Systematic review	CBT	Varies	N/A	Strong efficacy in reducing ketamine use	Limited long-term data available	Low	AMSTAR
[20]	120	Young adult ketamine users in East Asia	Prospective cohort	Group therapy and relapse prevention	10 weeks	Weekly	Reduced usage frequency; improved self-regulation	Better long-term adherence	Low	Newcastle–Ottawa Scale
[21]	90	Polydrug users with ketamine dependency	Controlled clinical trial	CBT combined with trauma therapy	12 weeks	Weekly	Superior efficacy over CBT alone	Reduced emotional reactivity	Low	Cochrane Risk of Bias Tool
[6]	160	Recreational ketamine users	Neuroimaging and longitudinal study	Mindfulness-based intervention	8 weeks	Weekly	Enhanced prefrontal regulation; reduced emotional instability	Long-term relapse rates improved	Low	CASP
Wilkinson, S. T. et al. (2017)	70	Illicit ketamine users with PTSD history	RCT	Ketamine-assisted psychotherapy (KAP)	6 weeks	Biweekly	Reduced PTSD symptoms and illicit use	Improved emotional resilience	Low	Cochrane Risk of Bias Tool
Morgan, C. J. A. et al. (2018)	250	Chronic recreational ketamine users	Longitudinal	Psychotherapeutic interventions (CBT focus)	12 weeks	Weekly	Reduced executive function deficits	Improved treatment engagement	Moderate	Newcastle–Ottawa Scale
[13]	90	Young adult recreational users	RCT	Motivational interviewing	8 weeks	Weekly	Reduced frequency of ketamine use	Effects sustained for 6 months	Moderate	Cochrane Risk of Bias Tool

Table B2. Cochrane Risk of Bias assessments.

Study	Randomization Process	Allocation Concealment	Blinding of Participants	Outcome Measurement	Selective Reporting	Overall Risk
[8]	Moderate	Moderate	Low	Low	Low	Moderate
[7]	Low	Low	Moderate	Low	Low	Low
[4]	Low	Low	Moderate	Low	Low	Low
[12]	Low	Low	Low	Low	Low	Low
[10]	Low	Low	Low	Low	Low	Low
[13]	Low	Moderate	Moderate	Low	Low	Moderate
[14]	Low	Low	Low	Low	Low	Low
[15]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
[11]	Low	Low	Low	Low	Low	Low
[16]	Low	Low	Low	Low	Low	Low
[17]	Low	Low	Low	Low	Low	Low
[9]	Low	Low	Low	Low	Low	Low
[18]	Low	Low	Low	Low	Low	Low
[19]	Moderate	Low	Low	Low	Low	Moderate
[20]	Low	Low	Low	Low	Low	Low
[21]	Low	Low	Low	Low	Low	Low
[6]	Low	Low	Low	Low	Low	Low
Wilkinson, S. T., et al. (2017)	Low	Low	Low	Low	Low	Low
Morgan, C. J. A., et al. (2010)	Low	Low	Low	Low	Low	Low
[1]	Low	Low	Moderate	Low	Low	Low

Table B3. Newcastle–Ottawa Scale assessments.

Study	Selection	Comparability	Outcome	Total
	(4 Max)	(2 Max)	(3 Max)	(9 Max)
[8]	4	2	3	9
[7]	4	2	3	9
[4]	4	2	3	9
[12]	4	2	3	9
[10]	4	2	3	9
[13]	4	2	3	9
[14]	4	2	3	9
[15]	4	1	3	8
[11]	4	2	3	9
[16]	4	2	3	9
[17]	4	2	3	9
[9]	4	2	3	9
[18]	4	2	3	9
[19]	4	2	3	9
[20]	4	2	3	9
[21]	4	2	3	9
[6]	4	2	3	9
Wilkinson, S. T., et al. (2017)	4	2	3	9
Morgan, C. J. A., et al. (2010)	4	2	3	9
[1]	4	2	3	9