Review paper

Ketamine as a prophylactic agent against post-traumatic stress disorder

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Abstract

Considering the persisting lack of remission among many patients with a stress-related disorder when treated with psychotherapy or antidepressants, the need for stress resilience-enhancing pharmacotherapy is a clinically unmet need. Ketamine's current efficacious use in the treatment of major depressive order (MDD) and post-traumatic stress disorder (PTSD) indicates its potential as a novel treatment. This review will address the existing use of ketamine as a therapeutic PTSD treatment, discuss the mechanisms and safety of the drug, and overview current literature regarding its use as a prophylactic stress resilience-enhancer. Rodent studies have demonstrated that ketamine's fear-attenuating effects may stem from its interaction with stress, making dosage and timing of prophylactic treatment especially crucial. Other work has revealed that ketamine's transformative spatio-temporal effects on the neurotransmitter network, rather than on the concentrations of individual neurotransmitters could be beneficially modulated to alter the ratio of its dissociative and therapeutic effects. Further studies translating these results among humans and addressing areas for innovation that may apply to PTSD treatment are necessary to continue exploring ketamine's novel potential. This may increase our understanding of ketamine's interactive and preventative mechanisms, thus shedding light on the pathophysiology of stress and fear consolidation as a whole.

Keywords

Ketamine, Post-traumatic stress disorder, Pharmacotherapy, Prophylactic, Resilience, Stress, N-Methyl-D-Aspartate, Fear expression, Dissociative effect, Neurotransmitter

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Introduction

Post-traumatic Stress Disorder (PTSD) has an estimated lifetime prevalence of 6.8% among United States Americans, a number that trends higher among females and veterans who are exposed to sexual or combat-related violence (1). The potentially chronic and debilitating psychiatric disorder is characterized by intrusive thoughts, memories, and flashbacks as well as cognitive, affective, and behavioral symptoms in response to reminders of a past traumatic event (2). Further, affected individuals may display avoidance of situations which bear resemblance to a traumatic event, selective amnesia regarding the events of the trauma, symptoms mirroring major depressive disorder (including feelings of detachment, hopelessness, and emotional negativity), and alterations in reactive behavior such as irritability, self-destructive actions, hypervigilance, and sleep disturbance (2).

Psychiatric comorbidity is also common in PTSD patients, contributing to the complexities and the risks associated with the disorder. The National Comorbidity Survey, a general survey of psychiatric disorders in the general US population, found that 44% of women and 59% of men with PTSD also had three or more psychiatric disorder diagnoses, with depressive disorders, anxiety disorders, and substance use disorders being particularly common (3).

The current gold standard in PTSD treatment is trauma-related psychotherapy, such as Cognitive Processing Therapy (CPT), trauma-focused Cognitive Behavioral Therapy, and Prolonged Exposure (PE) therapy, as well as pharmacotherapy, including SSRI and SNRI antidepressant medication (4,5).

First-line trauma-focused therapy has, however, demonstrated limitations among military and veteran populations. A review of randomized controlled trials (RCTs) involving psychotherapy for patients with military-related PTSD (6) found that 60 to 72% of patients receiving CPT and PE retained their diagnosis after treatment. Though meaningful symptom improvement was observed in 49% to 70% of patients and this improvement occurred at a higher rate among CPT and PE patients than waitlist and treatment-as-usual controls, trauma-focused interventions do yield relatively high non-responsive rates and relatively low remission rates.

Along with psychotherapy, pharmacotherapy plays a role in PTSD symptom reduction and in addressing comorbid conditions - but with similar limitations. The underlying pathophysiology of PTSD has previously been attributed to failures in stress-response relating to biological pathways such as corticotropin releasing hormone (CRH) abnormalities, hypothalamic–pituitary–adrenal (HPA) axis abnormalities, and dysfunction in noradrenergic, serotonergic, and glutamatergic systems (7), though drugs acting specifically on serotonergic systems have been particularly effective. Typically implemented along with trauma-focused psychotherapy, pharmacotherapy can entail both first and second line treatment. Currently, only the

SSRIs sertraline and paroxetine are approved by the Food and Drug Administration for treatment of PTSD, and other medications for PTSD are considered off-label use. Sertraline, paroxetine, and the SNRI venlafaxine, which all target serotonergic receptors in the amygdala and other neural fear circuitry, are most recommended for patients as they typically have the most substantial benefit, while use of benzodiazepines and monotherapeutic antipsychotics is not recommended (4,8).

However, despite SSRIs being considered the first-line pharmacotherapeutic treatment for PTSD, response rates among patients rarely exceed 60% and less than 20-30% of the patients achieve full remission (9). SNRIs, typically recommended as second-line treatment after SSRIs, have shown a similarly significant yet limited success rate. In a 6-month, double-blind, placebo-controlled trial (10), the SNRI venlafaxine yielded a 50.9% remission rate for adult outpatients while the placebo yielded a 37.5% remission rate. While this result does speak to the effectiveness of the drug over a short-term, continuous treatment period, remission was not achieved in a large part of the tested population. With even highly recommended treatment techniques yielding limited results, there is a need for improvement in existing PTSD treatments and the development of novel, evidence-based treatments which may be able to provide symptom relief and remission to previously non-responsive groups.

The definitive neurobiological mechanism of PTSD remains unknown, a key barrier to developing effective pharmacological treatment, but, along with pathophysiological errors in stress-response pathways, structural, genetic, and neurochemical causes have all been suspected. Some researchers have discovered decreased hippocampal volume in patients with both recent onset and persisting, combat-related PTSD compared to matched controls without the disorder via MRI measurement (11,12). Other studies have found a relationship between genetic polymorphisms and environmental occurrences, including a study of earthquake survivors that found a statistically significant relationship between 5-HTTLPR and 5-HTTVNTR polymorphisms and PTSD diagnosis after earthquake exposure (13) and a study which found that four SNPs of the FKBP5 gene interacted with severity of child abuse as a predictor of adult PTSD symptoms (14). Others have suggested that low plasma cortical levels and high CSF norepinephrine concentrations in PTSD patients are the result of decreased adrenocortical responsiveness and greater CNS noradrenergic activity respectively (15,16), indicating a neurochemical upset of stress arousal levels. Further, the disorder's relationship to synapse connectivity and memory formation has motivated some researchers to attribute its effects to alterations in the GABA inhibition system after a traumatic event (17). Re-establishing balance of excitatory glutamate and inhibitory GABA neuronal action as well as inhibitory regulation of GABA neurons may be crucial to pharmacologically influencing consolidation, expression, and extinction of fear conditioning.

The relationship between the GABAergic system and PTSD may also explain the efficacy of the dissociative anesthetic ketamine in experimental PTSD pharmacotherapeutic treatment. A randomized, double-blind, crossover trial conducted by Feder *et al.* (18) compared effects of a single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) and a single infusion of the control midazolam (0.045 mg/kg) in forty-one chronic PTSD patients. Rapid reduction of PTSD and comorbid depressive symptoms occurred based on an assessment of mean difference in Impact of Event Scale-Revised scores 24 hours after the infusion in patients who had received ketamine. This rapid-acting nature of ketamine is mimicked in its antidepressant properties, as its off-label use for treatment-resistant MDD demonstrated that ketamine has a very rapid efficacy rate, with a peak effect within 24 hours after a single IV infusion, though it has little sustained effect after 1 to 2 weeks (19). This fast action contrasts the delayed effect of traditional antidepressants, including SSRIs. In another study by Feder *et al.* (20), 30 patients with chronic PTSD were randomly assigned to receive six infusions of ketamine (0.5 mg/kg) or a control midazolam (0.045 mg/kg). Measurements of PTSD symptom severity from baseline to after the 2 weeks of infusion via CAPS-5 and MADRS scores showed that 67% of participants in the ketamine group were responders while only 20% in the midazolam group were, a significantly greater improvement. Among those who received ketamine, symptom improvement was maintained for a median of 27.5 days following the course of infusions. Overall, significant improvements and tolerability in the patient population after repeated ketamine infusions demonstrate the promise of ketamine as PTSD treatment.

The possibility of prophylaxis, particularly chemoprophylaxis, as a prevention method to treat PTSD continues to be raised. An RCT conducted by Delahanty *et al.* (21) has studied the use of low-dose hydrocortisone to prevent the emergence of post-traumatic stress symptoms and depression symptoms in traumatic injury patients. After a ten-day course of either hydrocortisone or a placebo, three-month post-trauma interviews were conducted among patients, and those who received hydrocortisone self-reported fewer symptoms and greater health-related quality of life. Similar studies have found that immediate administration of both morphine and beta-blocker propranolol appeared to limit fear conditioning and mitigate PTSD symptom development (22,23). However, another RCT conducted by Stein *et al.* (24) found that 14 days of beta-blocker propranolol treatment in patients with acute physical injury yielded no significant benefit over a placebo with regards to depressive or post-traumatic stress symptoms during outcome assessments 1, 4, and 8 months later. Nonetheless, the continued study of and search for new prophylactic treatment options should be explored to better understand the ability of pharmacotherapy to prevent the development of PTSD in trauma injury patients. Considering the aforementioned use and novel potential of ketamine in the treatment of diagnosed PTSD, its prophylactic potential must also be explored.

Ketamine's mechanism of action

Ketamine is a dissociative anesthetic known for its use as a surgical anesthetic and analgesic in both hospital and veterinary practice. Notable recent breakthroughs in ketamine use also include the 2019 FDA-approval of the nasal spray esketamine, which can be prescribed to those with treatment-resistant depression (25). This change has prompted a rise in demand for therapy augmented by intravenous administration of the drug for the off-label treatment of MDD, PTSD, and other disorders, and the opening of ketamine infusion clinics has become widespread across the United States and the world (26).

Ketamine acts as a noncompetitive antagonist, binding to N-methyl-D-aspartate (NMDA) ionotropic glutamate receptors. It has an affinity towards NMDA receptors on inhibitory γ-aminobutyric acid (GABA) interneurons (27) which, when suppressed, disinhibit downstream glutamatergic neurons and consequently cause an excitatory burst of glutamate (28). This surge of extracellular glutamate is associated with ketamine's psychotomimetic and dissociative effects (29,30), and also acts on α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. Stimulation of AMPA receptors leads to opening of voltage-dependent Ca^{2+} channels and therefore potentiation of BDNF and mTORC1 signaling pathways, thus increasing the synthesis of proteins contributing to synapse maturation and formation (28,31,32). Increasing synapse plasticity and strength builds new, active neural connections, and though its full scope has yet to be unraveled, this mechanism has prompted consideration of ketamine's potential as an antidepressant and treatment for PTSD, as well as other conditions that repress the brain's wiring.

Interestingly, the enantiomers of ketamine, (R)-ketamine and (S)-ketamine, have varying potency as NMDA receptor antagonists and distinct degrees of both antidepressant effect and psychotomimetic side effects (33), a phenomenon which must be considered when evaluating each enantiomer's potential to effectively treat patients. Ketamine also exerts effects on non-NMDA receptors, potentially interacting with opioid receptors (mu, delta, and kappa), monoaminergic receptors, and muscarinic receptors, but specific, glutamate-independent mechanisms of action and their consequences are still uncertain (34). Further, ketamine is thought to produce both functional and electrophysiological dissociation between thalamo-neocortical and limbic systems (34), accounting for its sedative qualities.

Ketamine's antagonistic behavior towards NMDA receptors and glutamatergic systems is most crucial to understanding its potential for PTSD treatment because memories, including traumatic ones, are consolidated when activation of glutamate NMDA receptors leads to changes in post-synaptic plasticity (35). Further, following a stress-induced glutamate release the NMDA receptor system may facilitate the formation of traumatic memories and promote morphological hippocampal damage (36). NMDA antagonists can block fear conditioning in the hippocampus (37), therefore potentially limiting glutamate-induced structural damage as well as the

acquisition and recall of traumatic memories seen in PTSD.

Rationale for prophylactic ketamine use

Brachman *et al.* identified ketamine-induced stress resilience in a 2015 study (38) in which mice were administered with a single dose of saline or ketamine. One week later, the mice remained group-housed or were subjected to either the chronic social defeat (SD) stress model for two weeks, learned helplessness (LH) training, or chronic corticosterone (CORT) model for three weeks. Ketamine was found to protect against depressive-like behavior following SD at a 30 mg kg^{-1} dose, and particularly protected mice from stress-induced increase in immobility time - which is used to detect depressive-like hopeless, despair, and negative mood in rodents - during a subsequent 6 minute Forced Swim Test (FST) as well as from stress-induced social avoidance of an aggressor mouse during the Dominant Interaction (DI) social test. These findings were supported by the LH experiment, in which mice treated with ketamine had decreased latency to escape compared to those not treated, as well as by the CORT model, in which mice treated with a single ketamine dose had decreased FST immobility, decreased latency to grooming after a sucrose splash test (ST), and decreased latency to feed in the novelty suppressed feeding test (NSF). No significant change to FST immobility was found after a 10 mg kg^{-1} or 90 mg kg^{-1} dose in the SD model or after a 10 mg kg^{-1} or 30 mg kg^{-1} dose in the CORT model, indicating the importance of dosage on ketamine's prophylactic effect when it comes to decreasing stress-induced, depressive-like behavior.

McGowan *et al.* studied ketamine's prophylactic effects on the development of PTSD using a three-shock Contextual Fear Conditioning (CFC) extinction paradigm, in which freezing behavior during re-exposure tests is used to measure fear memory consolidation (39). Mice were injected with a single 30 mg kg^{-1} dose of saline or ketamine, and one hour, one week, or one month later underwent CFC. Ketamine was found to significantly reduce freezing behavior during extinction trials (which first occurred 4 days after CFC) in mice treated with it one week prior to CFC compared to those administered with saline, but not in mice given ketamine one hour or one month prior or in mice given it during or after CFC. Both groups of mice exhibited comparable levels of freezing behavior during CFC encoding, subsequent extinction trials, reinstatement, and secondary extinction trials, but the aforementioned distinction between freezing behavior in the first extinction trial demonstrates that ketamine can buffer fear expression when administered as a prophylactic 1 week before CFC. Administering ketamine after CFC but before extinction did not result in altered feared expression, and ketamine administration one week or one hour before reinstatement increased attentiveness but also did not alter fear expression. Ketamine administered 1 hour after a strong reinstatement protocol (3 shocks instead of one) did reduce fear expression, indicating a possible blocking of memory consolidation in relation to strength of the stressor. However, ketamine administration 1 day after reinstatement did not alter fear expression. Therefore, McGowan's study is the first of its kind to demonstrate that a critical

window for ketamine administration exists in order for the drug to have significant prophylactic effect.

A follow-up study by McGowan *et al.* (40) replicated their previous results and performed metabolomics analysis of the brain (both hemispheres of the prefrontal cortex and hippocampus) and plasma following prophylactic ketamine treatment to identify markers of enhanced stress resilience. A 3-shock CFC and re-exposure treatment was performed once again, with a no-shock control group undergoing the same exposure procedure without shocks. Blood and brain tissue extractions from the mice occurred two hours after CFC re-exposure. Analysis of these tissue and plasma samples found that pyrimidine and purine metabolism was significantly altered in the HPC, PFC, and plasma after ketamine treatment and CFC in comparison to saline-treated mice and the no-shock control. Pyrimidine and purine metabolism have also been implicated in antidepressant treatment response in another rodent study conducted by Park *et al*. (41), where increased purine and pyrimidine metabolism was found in mice chronically treated with the SSRI paroxetine. Therefore, the effect of prophylactic ketamine on purine and pyrimidine metabolism after stress suggests that several mechanisms of successful antidepressant treatment may overlap with those of ketamine. McGowan's study additionally found that a total of eight metabolites were changed in both brain regions and in both hemispheres after ketamine treatment and complete CFC re-exposure. Precursors and metabolites for inhibitory neurotransmitters (GABA, taurine, alanine) increased while those for excitatory neurotransmitters (tyrosine, serine, phenylalanine) decreased. These changes didn't occur to the same extent in ketamine-treated mice not exposed to stress, indicating that ketamine's effect on the metabolome and behavior relates specifically to the occurrence of a stressful experience and may create protection through increasing inhibition.

In a 2008 study (42), McGhee *et al.* found that prevalence of PTSD measured by the PTSD Checklist-Military (PCL-M) in US army burn patients who received perioperative ketamine was lower than patients who did not receive ketamine. Out of the 147 burn casualties who completed the PCL-M and underwent at least one operation, PTSD prevalence was reported to be 27% for those who had received ketamine and 46% for those who had not. This was viewed as especially significant as the patients receiving ketamine often had more severe injuries, longer stays in intensive care units, and more surgeries in order to recover. The amount of morphine received by patients and their burn sizes were not found to predict PTSD development, therefore ketamine was concluded to cause plausibly decreased PTSD prevalence in patients. However, a follow-up 2014 McGhee study (43) found that receiving perioperative ketamine has no effect on PTSD prevalence in burned US service members. In this study of a larger sample size of 289 patients, those who received ketamine once again experienced more severe injuries, greater burn areas, longer hospital stays, and a larger number of surgical operations. No statistically significant difference in PTSD prevalence between ketamine-receiving and non-ketamine-

receiving groups was found but, importantly, ketamine administration to patients did not appear to increase PTSD prevalence either.

This aligns with McGowan's findings that post-exposure ketamine (beyond a specific window of administration) isn't effective in reducing fear response and Brachman's findings that ketamine administered following a stressor doesn't prevent stress-induced, depressive-like behaviors. It also mirrors the results of an additional 2015 Juven-Wetzler study (44) in which immediate ketamine treatment was ineffective in preventing post-traumatic stress responses in an animal model for PTSD. This study, which administered mice with 15 mg kg^{-1} of ketamine one hour after stress exposure, found that such administration may even be detrimental over longer periods of time. It can therefore be concluded that timing of ketamine administration is crucial, particularly when it comes to considering prophylactic potential and the way in which ketamine interacts with stress, with the significant biomolecular implications of this interaction being particularly apparent in McGowan's aforementioned metabolic analysis. Lack of control of burn severity among patients and of ketamine dosage, the latter of which McGowan's SD model experiment found to have major significance on prophylactic effect, must also be considered as a limitation when understanding the implications of McGhee's results.

In an effort to understand the brain circuitry behind ketamine-induced stress resilience, Mastrodonato *et al.* tested whether prophylactic ketamine injection alters neural activity in the HPC or PFC (45). Mice were injected with 30 mg kg^{-1} of saline or ketamine then underwent Social Defeat one week later. In one set of experiments, processing of the brains of sacrificed mice found that ΔFosB expression increased in the ventral dentate gyrus and ventral CA3 (vCA3) of social defeat mice but not in control saline-treated or non-stress-exposed mice. In a second set of experiments, mice were injected with viral vectors into the vCA3 in order to either silence or overexpress ΔFosB before prophylactic ketamine administration. Interestingly, silencing of ΔFosB activity in the vCA3 inhibited prophylactic ketamine efficacy, indicating that ΔFosB activity in vCA3 may be necessary for such efficacy, while overexpression of ΔFosB was comparable to ketamine's prophylactic effects. In a third set of experiments, $ArcCreER^{T2}$ x ChR2-EYFP mice, a strain in which neural ensembles activated by a single experience can be indelibly labeled, were used to quantify memory traces representing a CFC experience following prophylactic ketamine administration. CFC experience-related memory changes, particularly an increase in the number of c-fos+ cells and the percent of co-labeled cells, were found in the vCA3 but not in the ventral dentate gyrus. Overall, this study demonstrates that ketamine's protective action may have to do with changes in neurons in the vCA3 relating to an individual stressor. Mastrodonato's identification of the role of the ventral hippocampus in ketamine treatment is also supported by a 2022 study by Ryan *et al.* (46), which utilized fiber photometry to identify fear generalization pathways of activity in the ventral hippocampus. These pathways were altered by prophylactic (R,S)-

ketamine treatment on generalized fear. The study also found that BDNF Val66Met mice, which have impaired activity-dependent release of BDNF, were resistant to the prophylactic effects of (R,S)-ketamine, indicating that both BDNF signaling and neuronal action in the ventral hippocampus may play an integral role in modulating the fear-attenuating effects of prophylactic ketamine.

A more recent Mastrodonato study (47) found that the prophylactic effect of (R,S)-ketamine (racemic ketamine) is sex-dependent, age-dependent, and dose-dependent. Varying doses of (R,S)-ketamine or of saline were administered to adolescence (5-week-old) and aged (24-month-old) mice of both sexes. One week later, the mice underwent 3-shock CFC and were assessed for behavioral despair, avoidance, perseverative behavior, locomotion, and contextual fear discrimination. The mice experienced re-exposure 5 days later and underwent aforementioned behavioral tests once again. (R,S)-ketamine was found to be effectively prophylactic in adolescent mice but not in aged mice, with ketamine-treated adolescent males and females displaying less immobility on the FST and more traveling on the Open Field (OF) test than both their aged and saline-treated counterparts. Based on further behavior assessed in the Elevated Plus Maze (EPM) and marble-burying task, researchers concluded that prophylactic (R,S)-ketamine decreases stress-induced behavioral despair in adolescent male mice and decreases fear behavior and compulsive behavior in adolescent female mice.

In another set of this study's experiments, assessment of saline and ketamine-treated adolescent mice with 3-shock CFC delivered 1 month after treatment (as opposed to one week) revealed that prophylactic (R,S)-ketamine can have long-lasting effects in adolescent mice. Behavioral analysis 5 days after CFC found that (R,S)-ketamine prophylactic protection, against fear in adolescent male mice and against stress-induced behavioral despair and compulsive behavior in adolescent female mice, can last up to 1 month following a single injection. Further processing of the brains of tested mice was used to quantify Cyclooxygenase 2 (Cox-2) expression in order to determine prophylactic (R,S)-ketamine's effects on brain inflammation levels and found that, in ketamine-treated adolescent male mice, lower Cox-2 expression levels were present in the vCA3 relative to saline-treated mice. As (R,S)-ketamine did not impact Cox-2 expression in any other groups, the vCA3 may have a distinct, mediating role in prophylactic (R,S)-ketamine efficacy in adolescent male mice. Overall, this supports Mastrodonato's previous findings of the vCA3's role in prophylactic ketamine's neuronal action. It also indicates that sex and age must be considered in future studies relating to ketamine's pharmacology.

Overview of the prophylactic effect of ketamine in select rodent studies

Study: Ketamine as a Prophylactic Against Stress-Induced Depressive-like Behavior (38)
Subjects: Male 129S6/SvEvTac mice (8–10 weeks old)
Ketamine dosage: 10, 30, or 90 mg kg^{-1}

Protocol: SD model for two weeks, 1 week after dose
Primary measures: FST, DI, EPM
Primary outcomes: 30 mg kg^{-1} ketamine dosage, not 10 or 90 mg kg^{-1} decreased FST immobility time compared to saline-treated mice, indicating ketamine-induced stress resilience at a specific dosage. No effect on EPM occurred, so no evidence of prophylactic anxiolytic effect is demonstrated.

Study: Ketamine as a Prophylactic Against Stress-Induced Depressive-like Behavior (38)
Subjects: Male 129S6/SvEvTac mice (8–10 weeks old)
Ketamine dosage: 30 mg kg^{-1}
Protocol: LH model for two weeks, 1 week after dose
Primary measures: Shock escape protocol
Primary outcomes: Ketamine-treated mice had decreased latency to escape compared to saline-treated mice, indicating ketamine-induced resilience to LH stress.

Study: Ketamine as a Prophylactic Against Stress-Induced Depressive-like Behavior (38)
Subjects: Male C57BL/6NTac mice (8 weeks old)
Ketamine dosage: 10, 30, or 90 mg kg^{-1}
Protocol: CORT model for three weeks, 1 week after dose
Primary measures: FST, ST, NSF
Primary outcomes: At a 90 mg kg^{-1} dose, ketamine was most effective in decreasing immobility time during the FST, decreasing latency to grooming after a ST, and decreased latency to feed in NSF compared to saline-treated mice, indicating protective effect of ketamine at a higher dose.

Study: Prophylactic Ketamine Attenuates Learned Fear (39)
Subjects: Male 129S6/SvEvTac mice (8 weeks old)
Ketamine dosage: 30 mg kg^{-1}
Protocol: 3-shock CFC, 1 day, 1 week, or 1 month after dose
Primary measures: Extinction trials beginning 4 days after stress
Primary outcomes: Mice treated with ketamine 1 week (but not 1 day or 1 month) prior to stress exhibited less freezing behavior during their first extinction trial than saline-treated counterparts, indicating that ketamine can effectively buffer fear expression if administered 1 week before a CFC stressor.

Study: Prophylactic Ketamine Attenuates Learned Fear (39)
Subjects: Male 129S6/SvEvTac mice (8 weeks old)
Ketamine dosage: 30 mg kg^{-1}
Protocol: 3-shock CFC 1 hour before dose
Primary measures: Extinction trials beginning 4 days after stress

Primary outcomes: Mice treated with a single dose of ketamine 1 hour after CFC did not have altered fear expression.

Study: Prophylactic Ketamine Attenuates Learned Fear (39)
Subjects: Male 129S6/SvEvTac mice (8 weeks old)
Ketamine dosage: 30 mg kg^{-1}
Protocol: 3-shock CFC 1 week before dose, or 95 hours before dose
Primary measures: Extinction trials beginning 1 week after dose, or 1 hour after dose
Primary outcomes: Mice treated with ketamine before extinction (either one week before or one hour before) did not have altered fear expression, indicating that ketamine administration after the encoding of a stressor doesn't have a prophylactic effect.

Study: Prophylactic Ketamine Attenuates Learned Fear (39)
Subjects: Male 129S6/SvEvTac mice (8 weeks old)
Ketamine dosage: 30 mg kg^{-1}
Protocol: 1-shock or 3-shock reinstatement 1 week after dose
Primary measures: FST, OF
Primary outcomes: Injection of ketamine 1 week before 1-shock or 3-shock reinstatement of a stressor doesn't buffer fear expression as both ketamine and saline-treated mice had comparable immobility in the FST and comparable roaming in the OF. Ketamine-treated mice did have more rearing bouts in the OF, indicating increased attentiveness, though this effect wasn't present after a stronger reinstatement trial.

Study: Prophylactic Ketamine Attenuates Learned Fear (39)
Subjects: Male 129S6/SvEvTac mice (8 weeks old)
Ketamine dosage: 30 mg kg^{-1}
Protocol: 1-shock or 3-shock reinstatement 1 hour before dose, or 3-shock reinstatement 1 day before dose
Primary measures: Extinction Trials
Primary outcomes: Ketamine injection 1 hour after 3-shock (but not after 1-shock) reinstatement buffered fear expression via reduced freezing during extinction. Injection 1 day after reinstatement did not alter fear expression, indicating that a specific window of administration and strength of stressor may play a role in ketamine's ability to decrease fear expression.

Study: Prophylactic ketamine alters nucleotide and neurotransmitter metabolism in brain and plasma following stress (40)
Subjects: Male 129S6/SvEvTac mice (8 weeks old)
Ketamine dosage: 30 mg kg^{-1}
Protocol: 3-shock CFC 1 week after dose

Primary measures: Context re-exposure 2 hours prior to sacrifice (PFC, HPC, blood plasma extraction)
Primary outcomes: Ketamine attenuated fear response during context re-exposure compared to saline. Prophylactic ketamine was also found to alter metabolites (particularly metabolites involved in purine and pyrimidine metabolism) and alter amino-acid derived neurotransmitters and their precursors in the PFC, HPC, and plasma. These changes only occurred in mice treated with ketamine and exposed to stress, indicating ketamine's interaction with stress may cause these metabolomic changes.

Study: Prophylactic (*R,S*)-Ketamine Is Effective Against Stress-Induced Behaviors in Adolescent but Not Aged Mice (47)
Subjects: Male or female 129S6/SvEv adolescent (5-week-old) or aged (24-week-old) mice
Ketamine dosage: 10, 30, or 100 mg kg^{-1}
Protocol: 3-shock CFC 1 week after dose
Primary measures: Context re-exposure, FST, OF, EPM, MB
Primary outcomes: Both male and female (R,S)-ketamine-injected adolescent mice had decreased fear expression compared to their aged and saline-treated counterparts, indicating differences in prophylactic effect by age. Significant differences between aged and adolescent female mice in the MB task but not the EPM task and vice versa for male mice also indicates distinct prophylactic effect by sex.

Study: Prophylactic (*R,S*)-Ketamine Is Effective Against Stress-Induced Behaviors in Adolescent but Not Aged Mice (47)
Subjects: Male or female 129S6/SvEv adolescent (5-week-old) mice
Ketamine dosage: 10 (female) or 30 (male) mg kg^{-1}
Protocol: 3-shock CFC 1 month after dose
Primary measures: Context re-exposure, FST, OF, EPM, MB
Primary outcomes: In adolescent mice, prophylactic effects of ketamine can last up to 1 month after a single dose. The significantly lower freezing of time of male mice during context re-exposure indicates fear expression buffering and the significantly lower immobility time during day 2 of the FST as well as the burying of fewer marbles in the MB task by female mice (compared to saline-treated counterparts) indicates reduced stress-induced behavioral despair and reduced compulsive behavior.

Study: Prophylactic (*R,S*)-Ketamine Is Effective Against Stress-Induced Behaviors in Adolescent but Not Aged Mice (47)
Subjects: Male or female 129S6/SvEv adolescent (5-week-old) or aged (24-week-old) mice
Ketamine dosage: 10, 30, or 100 mg kg^{-1}
Protocol: CFD 1 week after dose

Primary measures: Context discrimination ratios
Primary outcomes: In adolescent but not aged mice, prophylactic ketamine at certain doses can facilitate contextual fear discrimination.

Study: Prophylactic (*R,S*)-Ketamine Is Effective Against Stress-Induced Behaviors in Adolescent but Not Aged Mice (47)
Subjects: Male or female 129S6/SvEv adolescent (5-week-old) or aged (24-week-old) mice
Ketamine dosage: 10 (female) or 30 (male) mg kg^{-1}
Protocol: 3-shock CFC 1 week after dose
Primary measures: Context re-exposure, FST, OF, EPM, MB (HPC, DG, CA3 extraction)
Primary outcomes: In adolescent male mice, (R,S)-ketamine-treated mice had lower Cox-2 expression levels in the vCA3 than their saline counterparts. (R,S)-ketamine did not impact Cox-2 expression in any other groups, indicating that vCA3 may have a distinct mediating role in prophylactic (R,S)-ketamine efficacy in adolescent male mice.

Study: Prophylactic Ventral CA3 Activation Mediates Prophylactic Ketamine Efficacy Against Stress-Induced Depressive-like Behavior (45)
Subjects: Male 129S6/SvEvTac mice
Ketamine dosage: 30 mg kg^{-1}
Protocol: SD 1 week after dose
Primary measures: FST, DI, NSF, EPM (HPC, PFC extraction)
Primary outcomes: Prophylactic ketamine administration was found to increase ΔFosB expression in the ventral HPC of stressed mice compared to their saline and non-stressed counterparts.

Study: Prophylactic Ventral CA3 Activation Mediates Prophylactic Ketamine Efficacy Against Stress-Induced Depressive-like Behavior (45)
Subjects: Male 129S6/SvEvTac mice (injected with AAV–GFP or AAV–ΔJunD viruses into vCA3 2 weeks before dose)
Ketamine dosage: 30 mg kg^{-1}
Protocol: 3-shock CFC 1 week after dose
Primary measures: Context re-exposure, FST, OF, EPM, (vCA3 extraction)
Primary outcomes: Viral injections of ΔJunD into vCA3 blocked attenuation of learned fear and depressive-like behavior in ketamine-treated mice, indicating that transcriptional ΔFosB activity in vCA3 may be necessary for prophylactic ketamine efficacy.

Study: Prophylactic Ventral CA3 Activation Mediates Prophylactic Ketamine Efficacy Against Stress-Induced Depressive-like Behavior (45)

Subjects: Male 129S6/SvEvTac mice (injected with injected with AAV–GFP or AAV–ΔFosB viruses into vCA3 2 weeks before dose)
Ketamine dosage: 30 mg kg^{-1}
Protocol: 3-shock CFC 1 week after dose
Primary measures: Context re-exposure, FST, OF, EPM, (vCA3 extraction)
Primary outcomes: In virus-injected ΔFosB mice both saline and ketamine-treated mice had low levels of freezing compared to saline-injected GFP mice. However, ΔFosB overexpression occluded ketamine's effect on immobility time in the FST. This indicates that ΔFosB overexpression mimics ketamine's prophylactic efficacy for attenuating learned fear but not for depressive-like behavior.

Study: Prophylactic Ventral CA3 Activation Mediates Prophylactic Ketamine Efficacy Against Stress-Induced Depressive-like Behavior (45)
Subjects: $ArcCreER^{T2}$ x ChR2-EYFP mice
Ketamine dosage: 30 mg kg^{-1}
Protocol: 3-shock CFC 1 week after dose (5 hours after 4-OHT tagging injection)
Primary measures: Context re-exposure (DG and CA3 extraction)
Primary outcomes: In the vCA3 of tested mice, the number of c-fos^{+} cells and the percent of co-labeled cells increased following prophylactic ketamine administration, indicating that ketamine may be effective at attenuating learned fear by altering vCA3 neural ensembles.

Study: Prophylactic Ventral CA3 Activation Mediates Prophylactic Ketamine Efficacy Against Stress-Induced Depressive-like Behavior (45)
Subjects: Male 129S6/SvEvTac mice
Ketamine dosage: 30 mg kg^{-1}
Protocol: OF, NOR, PF paradigms 1 week after dose
Primary measures: Locomotion, object recognition memory, context discrimination ratios
Primary outcomes: Though prophylactic ketamine treatment did not alter locomotion or object recognition memory, suggesting it does not alter non-fear learning, ketamine-treated mice expressed decreased fear generalization and accelerated contextual discrimination.

Safety of ketamine treatment

Limited data has been collected on ketamine's side effects in humans in a clinical setting. The drug's nature as a dissociative anesthetic has been cause for further careful study before true risk is established.

In the study conducted by Feder *et al.* comparing the effects of a single ketamine infusion to a midazolam control (18), no significant psychotic or manic symptoms were observed or measured by the implemented Clinician-Administered Dissociative States Scale, the Brief Psychiatric Rating Scale, and the Young Mania Rating Scale. Any

dissociative symptoms were short-lived and resolved 120 minutes from the infusion's start, though it's notable that one participant dropped out after feeling uncomfortable with the infusion's dissociative effects. In addition, three patients required acute treatment with β-blockers during ketamine infusion because of blood pressure elevation. Based on Patient-Rated Inventory of Side Effects (PRISE), the most common adverse effects of ketamine in the 24 hours following infusion were headache, nausea/vomiting, restlessness, poor coordination, and blurred vision. In the Feder study which provided two weeks of ketamine infusions to patients (20), similar effects were observed. PRISE reported the most common adverse effects as blurred vision, dizziness, and fatigue. Once again, dissociative symptoms emerging during the infusions were transient and resolved after 120 minutes. One patient required acute treatment for elevated blood pressure during their fifth infusion. No significant psychotic or manic symptoms were observed, although one participant withdrew from the study after the first two infusions due to lack of improvement and concern over worsening of their PTSD symptoms.

Overall, in Feder's studies IV ketamine was demonstrated to be safe and generally well-tolerated treatment. Dissociative symptoms did occur but were transient, and no measurable signs of worsening chronic PTSD symptoms were observed after ketamine administration in small, RCT populations.

A study by Schönenberg *et al.* (48) retrospectively screened 56 moderately injured accident victims who had received either racemic ketamine (which contains both R and S enantiomers), S-ketamine, or opioids during emergency ambulance transportation. Based on a one-year post-accident assessment of acute and current PTSD symptoms using the Peritraumatic Dissociative Experiences Questionnaire, Acute Stress Disorder Scale, and Impact of Event Scale, acute symptomatology was found to be strongly increased in subjects who received (S)-ketamine and slightly increased in those who received racemic ketamines compared to opioids. Current PTSD symptoms were also found to be significantly higher in (S)-ketamine subjects compared to both racemic ketamines and opioids. These findings suggest that ketamine received in early trauma may lead to stronger dissociative symptoms and enhanced formation of traumatic memories. The differences noted between racemic and S-ketamine may also demonstrate that ketamine's S-enantiomers contribute more significantly to the drug's negative psychoactive properties, particularly over a long-term period.

McGhee's aforementioned follow-up study of perioperative ketamine effects on PTSD prevalence in burned US service members (43) refutes Schönenberg's findings, however, as it found that though prevalence of PTSD was not significantly decreased in patients who received ketamine, it was not increased either.

With safety being a key consideration in whether prophylactic ketamine or other novel prophylactic pharmacotherapies addressing PTSD prevention may be tested in humans, it's clear that more research of its current treatment effects must be undertaken. While expected

dissociative side effects in infusion studies are transient and little risk is apparent, these side effects may be more potent or have longer-lasting impact based on factors relating to the type of trauma a patient experiences and the time that ketamine is administered in relation to that trauma. The enantiomer of ketamine used also may play a significant role in the safety of a ketamine infusion, as Schönenberg suggests.

Areas for future research

Expectancy bias

Lii *et al.* studied the potential masking of ketamine's antidepressant effects in a recent study that has yet to be peer reviewed (49). Forty patients with diagnosed MDD took part in a triple-masked, randomized, placebo-controlled trial in which they were given either a single ketamine dose (0.5 mg kg^{-1}) or a placebo saline dose infused over the course of 40 minutes. This infusion occurred while each patient experienced anesthetized surgery. Results were measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) on the first, second, and third day post-infusion. Findings indicated a strong antidepressant response in both groups, but no significant difference in results between ketamine and placebo-treated patients. The unique premise of this experiment, in which doses were delivered during surgical anesthesia, may indicate that this result was due to anesthesia's inhibition of cortical neurons (which are implicated in glutamate bursts in some models of ketamine's mechanism of action) or due to anesthesia's action on opioid receptors (which may also have attenuated ketamine's effect). The latter cause is in conjunction with a 2018 crossover study's findings that naltrexone-induced opioid receptor antagonism reduces antidepressant effect in ketamine-treated patients (50). In this study, Williams *et al.* found that, without activation of the opioid system, dissociative and psychotomimetic effects were still present, but these effects were not sufficient in producing significant, MADRS-measured antidepressant results. Therefore, interactions of surgical anesthesia with the opioid system could similarly mask ketamine's antidepressant properties. Lii *et al.*'s interpretation of their own result counters this notion, however, as they suggest that the lack of difference in antidepressant effect between ketamine and a placebo demonstrates that successful masking, which limits subject-expectancy bias, determines ketamine's efficacy as an antidepressant. While a major limitation of this study is that treatment expectancies weren't measured prior to randomization (other limits include differences in lengths and types of surgeries as well as types of general anesthetic agents used), the studied effect of subject-expectancy bias in microdosing treatment of other psychedelic drugs is notable, with positive expectations being associated with improved mental health-related outcomes (51).

Such research on expectancy bias indicates that a primary enhancer of ketamine's antidepressant effects may be psychotherapy programs or simply the experience of seeing a medical professional. It also helps to potentially explain sub-anesthetic ketamine's rapidly reached peak efficacy and shines a cautionary light on unmasked trials which have studied ketamine's treatment efficacy. It would be beneficial to expand measurement and

consideration of expectancy bias to sub-anesthetic ketamine infusion treatment of both depression and PTSD. Such expansion would also be vital to future prophylactic research in humans, as to ascertain and account for the effect of bias in ketamine's preventative use.

Separation of dissociative and therapeutic effects

Williams *et al.*'s aforementioned 2018 study (50) warrants further investigation into how ketamine's effect on the brain's opioid system determines its efficacy as an antidepressant and as PTSD treatment. This is particularly important in understanding whether ketamine can serve as effective PTSD or antidepressant treatment when its dissociative effects, which have previously been correlated with its antidepressant effects (52), are inhibited. Such knowledge is crucial to being able to treat patients with certain comorbidities and/or pre-existing risk of psychosis, considering that ketamine has been shown to exacerbate psychotic features in schizophrenia patients (53). It also may increase the overall safety of ketamine infusion by reducing its primary adverse effect. However, it's currently unknown which systems are implicated in the mediation of the drug's characteristic dissociative effects – though Williams *et al*'s study implies that the opioid system does not play a major role, meaning dissociative properties may instead be attributed to NMDA receptor antagonism or additional mechanisms. Further research should replicate results of full opioid receptor antagonism on ketamine's effect and entail further investigation of ketamine's NMDA receptor-independent antidepressive properties. As the need for such research reveals, a major gap in current knowledge is a lack of definitive understanding of how the components of ketamine's mechanism produce a combined effect.

Other information that may lead to the reduction of ketamine's hallucinogenic effect without inhibiting treatment revolves around the reconfiguration of neural networks (as opposed to the manipulation of a single neurotransmitter or system). A study by Wang *et al.* (54) researched the cortical concentrations and networks of neurotransmitters in mice under esketamine-induced anesthesia. Continuous microdialysis sample collection and EEG recording of the mice yielded results which indicated that esketamine infusion significantly increased glutamate, adenosine, histamine, and 5-HT levels above their baseline in periods of late anesthesia and post-return of the righting reflex (post-RORR) in the medial prefrontal cortex (mPFC). Further, overall neurotransmitter correlations were reduced and simplified between the start of esketamine-induced anesthesia and full recovery. Surprisingly, connections between neurotransmitter networks were entirely absent during the post-RORR stage of recovery - a disruption of the mPFC which may explain the drug's dissociative effect. Further exploration of the effects of both anesthetic and non-anesthetic ketamine infusion on other brain regions is warranted as, though the mPFC is widely used for anesthesia-related detection, its use in this study limits the application of findings to other cortical regions. Despite this limitation, Wang *et al.*'s finding is notably in conjunction with previous work indicating the reconfiguration of

neurotransmitter networks and correlations in the prefrontal cortexes of mice under isoflurane-induced anesthesia (55). While these findings were primarily associated with the frontal association subdivision of the mouse PFC and did not find significant alteration in concentrations of serotonin, histamine, glutamate, and GABA between waking and isoflurane anesthesia states, they indicate that other anesthetics may share a similar effect in the reduction of neurotransmitter connections. Further comparisons between ketamine and other types of anesthesia may help elucidate some of its definitive mechanisms in relation to neural networks. This information may reveal how ketamine's dissociative effects could be minimized beyond the drug's influence on specific neurotransmitter levels and instead with respect to its broader potential to restructure the neurotransmitter correlation network.

Comparisons between ketamine and other drugs with hallucinogenic properties which have been utilized as therapeutic treatment in recent years may also provide insight. In a 2021 study by Hesselgrave *et al.* (56), mice were treated with both psilocybin and the 5HT2A/2C antagonist ketanserin, which is thought to suppress perceived psychotomimetic effects of psilocybin in human subjects (57). Psilocybin infusions in this study - both with and without accompanying ketanserin infusion - were found to produce behavioral antidepressant effects, elevated AMPA/NMDA ratios, and restored synaptic strength in cortico-mesolimbic reward circuits. This indicates that key elements of MDD and PTSD treatment can occur independently of hallucinogenic effect, and, while 5-HT2AR activation may still influence antidepressant and synaptic mechanisms over time, provides a potential method of minimizing psilocybin's psychedelic effects without sacrificing its therapeutic value. While psilocybin as a tryptamine psychedelic differs in much of its mechanism of action from dissociative anesthetic ketamine, Wang *et al.*'s aforementioned study on ketamine-induced neurotransmitter reconfiguration (54) found that increased EEG-detected gamma oscillation during anesthesia and recovery in mice had a positive correlation with 5-HT concentration, thus indicating that ketamine's conscious-altering action may also significantly involve the serotonin system. More research is needed to determine if the use of a serotonin receptor antagonist or an alternative system-targeting antagonist during ketamine infusion may dull its dissociative effects while preserving its antidepressant, stress-attenuating, and synaptic-restructuring ones. The potential of such separation has vital implications for the validity, maximization, and expanded use of ketamine as treatment, and could reduce the risks of it and other drugs with hallucinogenic properties in treating vulnerable patients – therefore making human studies of ketamine's prophylactic effect more feasible.

fMRI methodology

Another realm of research yet to be adequately explored in the use of ketamine to treat PTSD is fMRI imagery. In a study by Carhart-Harris *et al.* (58), fMRI protocol was used to analyze psilocybin-induced transition into the psychedelic state in healthy volunteer subjects, measuring cerebral blood flow and blood-oxygen level-dependent signaling in order to

identify pharmaco-physiological interactions. Their findings implicated decreases in connectivity and activity of neural hubs, particularly the mPFC and posterior/anterior cingulate cortex, in psilocybin's alteration of cognition. Despite these informative results, very few existing studies have similarly used fMRI methodology to further understand the dissociative or therapeutic mechanisms of ketamine.

One such study by Roy *et al.* (59) utilized a combination of resting state fMRI signals and blood samples (PBMC assays) to identify molecular markers of ketamine treatment in adolescents with Treatment-Resistant Depression (TRD). This study, though limited by a small sample size, is distinct in its focus on the adolescent age group. After completing a two-week program of six infusions, the five subjects deemed responsive to the treatment based on altered scores on the Children's Depression Rating Scale-Revised (CDRS-R) had a notable increase in nucleus accumbens entropy after ketamine, as well as insulin-induced upregulation of *p*mTOR/mTOR and *p*GSK3β/GSK3β expression - which may serve as markers of clinical response if replicated with a larger sample size. Resting state fMRI-elucidated change in nucleus accumbens entropy also associates neural flexibility with ketamine response in adolescents with TRD. While these findings were limited by further factors, including a lack of a placebo control group, the analysis of neural changes only at ketamine's peak clinical response (24 hours after the final infusion of the program), and the lack of a multimodal imaging approach, these considerations (as well as the hypotheses generated by this study) may be applied to future work involving fMRI's contributions to both TRD and PTSD ketamine treatment.

Another fMRI study by Masaki *et al.* (60) used rodent subjects to determine the antidepressant effects of (R,S)-, (R)-, and (S)- ketamine compared with those of another NMDA receptor antagonist, MK-801. Significant, positive responses to both 10 mg kg^{-1} (R,S)-ketamine and (S)-ketamine infusions were detected in the cortex, nucleus accumbens, and striatum. Similarly positive and locomotor activity-increasing fMRI responses were detected after a 0.10 mg kg^{-1} infusion of MK-801, while negative responses in parts of the rodent brain were detected after a 10 mg kg^{-1} (R)-ketamine infusion. These findings provide insight into the differences between the mechanisms of (R)- and (S)-ketamine, with (R)-ketamine not acting on NMDA receptors in the same pattern as (S)-ketamine and MK-801 in order to have an antidepressant effect. The use of fMRI analyses to better understand the neuropharmacological differences of enantiomers illustrates how such differences may be used in the evaluation of ketamine's effectiveness, safety, and multipurpose nature. It may also assist with the identification of the ideal ketamine enantiomer for use in specific clinical cases (based on variables of type of disorder for treatment or time of dosage for prophylaxis). Further, it emphasizes the strong potential and necessity for integration of fMRI technology in the elucidation of the mechanisms behind ketamine's stress resilience-enhancing effects.

Studies utilizing fMRI have also notably explored another proposed mechanism of depression and ketamine's action against it. Depression has previously been considered a perceptual disorder, in part due to its associations with dysregulation of visual sensory processing and with center-surround suppression of visual motion (61,62). Spies *et al.* investigated the effect of esketamine on fMRI resting-state functional connectivity (rsFC) of the whole brain (63). In this study, 27 healthy subjects were given either a twenty-minute ketamine or saline placebo infusion and dynamic rsFC was subsequently assessed with sliding window correlation, multiplication of temporal derivatives, and atlas methodology. Researchers determined that esketamine had a negative influence on dynamic rsFC relating to visual processing networks, and interpreted this result to reflect the association of ketamine's antidepressant influence with its regulation of visual sensory processing. This inhibitory influence on sensory perception-based elements of depression may also relate to ketamine's influence on PTSD, which has similarly been modeled as a perception disorder due to atypical, fMRI-elucidated alterations in the visual processing of PTSD patients compared to trauma-exposed controls (64). Expanded research of ketamine's influence on the rsFC of the entire brain relating to both disorders may help shine further light on this potential sensory-based mechanism of action and the nature of the disorders themselves.

Microdosing

Unlike psilocybin microdosing, the effectiveness of off-label ketamine microdosing has not been sufficiently studied in clinical trials relating to PTSD treatment, though this method may assist in understanding of the drug's currently short-lived effect. An additional treatment field where ketamine microdoses may have therapeutic value is in buprenorphine precipitated opioid withdrawal (BPOW). Hailozian *et al.* analyzed one recorded case study (65) to explore the use of ketamine as a synergistic medication in the treatment of BPOW as both an alleviator of depressive symptoms and potentiator of buprenorphine's effectiveness. In this case study, an Opioid Use Disorder patient with severe BPOW was treated with a 1-hour ketamine infusion, a simultaneous buprenorphine dose, and a following month-long, extended-release buprenorphine dose. While results of the patient's continuous treatment and abstinence from fentanyl use must be replicated on a broader scale to elucidate if ketamine's pharmacological influence was truly a significant factor in their treatment, the versatility of singular or continuous ketamine microdoses should be considered for further research - both in synergistic and extended effect against disorders like PTSD.

An additional study by Ren *et al.* (66) investigated the effect of a single, sub-anesthetic dose of ketamine on post-operative anxiety and depression in colorectal cancer patients. Researchers divided 104 patients into three groups receiving varying ketamine dosages and one control group for a randomized, double-blind, placebo-controlled trial, then delivered an IV microdose infusion of either ketamine or saline to each patient five

minutes before anesthetized colorectal surgery. Subsequent patient scores on the Hospital Anxiety and Depression (HAD) scale and the Quality of Recovery-40 (QoR-40) questionnaire revealed that those who received a 0.3 mg kg^{-1} dosage of preoperative ketamine had significantly reduced anxiety and depression symptoms as well as elevated analgesic benefit. Further, patients in the 0.3 mg kg^{-1} group exhibited reduced inflammatory factors (based on serum measurement of TNF-α, IL-6, and IL-8 levels). The differences in scores and inflammatory factors between those who received a 0.1 mg kg^{-1} ketamine dose, a 0.2 mg kg^{-1} ketamine dose, and a control saline dose were not significant, emphasizing the importance of dosage concentration on ketamine's effect, particularly when delivering a single dose. While no significantly adverse effects were noted in ketamine groups compared to controls and, interestingly, no differences were noted in the respiratory and conscious recovery of all groups, this study is limited by its small sample size and warrants further research into an effective dosage range and protocol for preoperative infusions. It strongly indicates that exploratory prophylactic research may benefit from examining the use of off-label, sub-anesthetic microdose infusions of ketamine in establishing stress resilience. Future RCTs which examine the use of preventative ketamine microdosing within various situations and treatment time periods are needed to confirm this trajectory.

Summary and Conclusion

PTSD continues to be a difficult condition to treat, with even first-line treatments such as Cognitive Processing Therapy and SSRI antidepressants not yielding remission in many patients. Off-label, novel treatment must often be turned to in these resistant cases. Ketamine's interaction with the GABAergic system through the antagonism of NMDA receptors and increase of BDNF levels likely accounts for its current efficacy as a novel treatment administered as IV infusion therapy. Its benefits include fast action, as it takes effect as little as 24 hours after an infusion, though its outcomes are transient and relatively short-lasting. Despite concerns of the drug's dissociative properties worsening symptoms, recent studies indicate that, for the vast majority of patients, dissociative effects are short-lived and clinical use of ketamine as a whole will not worsen the conditions of patients. Even so, incomplete understanding of the drug's mechanism of action means that safety measures must be implemented in future studies with and current treatment of humans.

Ketamine's prophylactic potential is supported by rodent studies, in which a ketamine infusion one week before implementation of a stressor has been shown to increase stress resilience and attenuate fear. Ketamine was also found to interact specifically with stress, as measured by metabolomic changes in ketamine-treated, stress-exposed mice and by neuronal activity in the vCA3 relating to an altered stressor-based response in ketamine-treated mice. A future experiment which silences the vCA3 cells activated during CFC context re-exposure is necessary to solidify this interaction as a core component of prophylactic ketamine's effect on fear expression. Further research has also indicated that ketamine's prophylactic effectiveness is both time sensitive and

dependent on the dosage given to mice, as well as on the sex and age of mice.

However, no adequately controlled study of this prophylactic potential for stress resilience in humans has occurred. As current research on patients receiving ketamine infusion treatment and emergency or perioperative ketamine has, for the most part, not indicated worsening of PTSD symptoms or higher risk of diagnosis after ketamine infusion, studies in humans are warranted to better understand ketamine's mechanisms, effectiveness in both a treatment and prophylactic setting, and potential side effects. Further research in rodents must also occur in order to ensure results are replicable and translatable, as well as to help establish standards of prophylactic ketamine treatment based on the variables of injection timing, dosage, sex, and age. Additionally, past studies assessing ketamine's effects on depression and making comparisons to psilocybin microdosing reveal the need to research ketamine's mechanisms with respect to the impact of subjectivity bias, the insights provided by fMRI technology, and the differentiation between the causes of ketamine's dissociative versus therapeutic effects - which may lead to better understanding and greater accessibility of the drug's therapeutic action.

The novel potential of ketamine and other possible prophylactic agents should not be overlooked. Further exploration of such agents can promote better understanding of the nature of fear memory consolidation and facilitate solutions which achieve stress resilience or PTSD remission in vulnerable and treatment-resistant populations.

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