Ketamine as a Potential Therapy for Post-Traumatic Stress Disorder: Review

Khalid Yasseen

University of California, Berkeley

Abstract

Post-traumatic stress disorder (PTSD) is a chronic and debilitating mental illness that afflicts millions of individuals. With limited treatment options available, research has been focused on studying new and alternative treatments for PTSD. One such promising treatment is a widely used anesthetic, ketamine, which has been shown to have success as an antidepressant treatment. PTSD symptoms have been linked to the neurobiological glutamatergic system which relies heavily on N-methyl-D-aspartate (NMDA) receptors. Under stress conditions, the NMDA receptors are hyperactivated and lead to neurobiological changes that explain PTSD symptomology such as fear conditioning and intrusive memories. Ketamine, as an NMDA receptor antagonist, is believed to be a potential therapy for PTSD patients. This paper discusses evidence for the implication of the glutamatergic system as well as reasons for the proposed efficacy of ketamine. Lastly, a thorough literature review of current data and understanding of ketamine's effect on PTSD patients and symptomology is presented and discussed.

Keywords: PTSD, NMDA, Ketamine, Stress, Fear, Depression, Glutamate

Introduction

Post-traumatic stress disorder (PTSD) is a chronic and debilitating mental illness that develops after experiencing a severe emotionally or physically traumatic event (Feder et al., 2014). PTSD is associated with symptoms such as hyper or anxious arousal, intrusive nightmares and flashbacks, and avoidance of thoughts and reminders of the trauma (Feder et al., 2014; Krystal et al., 2017). This illness afflicts millions of individuals, and makes up 8% of the Ameican population at any given time (Averill et al., 2017; Pradhan, Kluewer D'Amico, Makani, & Parikh, 2016). Traumas that result in PTSD include combat and military trauma, sexual violence and rape, and any actual or threated death or injury that inflicted the individual, family or a close friend (Liriano, Hatten, & Schwartz, 2019). PTSD is also comorbid with depression, drug abuse, and suicide; patients respond poorly to most treatments, and only few have demonstrated significant success (Feder et al., 2014; Kelmendi et al., 2016; Pradhan et al., 2016). The molecular pathophysiology of PTSD implicates the hypothalmic-pituatary-adrenal (HPA) axis and glutamatergic pathways as potential mechanisms due to their involvement in memory-formation and stress response, thus presenting a potential drug target (Averill et al., 2017; Feder et al., 2014; Girgenti, Ghosal, LoPresto, Taylor, & Duman, 2017; Krystal et al., 2017).

Ketamine is a fast-acting genreal anesthetic that, unlike other anesthetics, does not promote respiratory depression (Averill et al., 2017; Sinner & Graf, 2008; White, Way, & Trevor, 1982). Ketamine has been a promising potential intervention with a reputation as a treatment against major depressive disorder (MDD) and biplar disorder (Abdallah, Sanacora, Duman, & Krystal, 2015; Averill et al., 2017; Pradhan et al., 2016). Its mechanism of action involves the inhibiton of N-methyl-D-aspartate (NMDA) receptors which are activated by glutamate binding in the central nervous system (Averill et al., 2017; Sinner & Graf, 2008; White

et al., 1982). With the involvement of glutamate in the stress mediation response in PTSD, ketamine is thought to be a potential treatment since it acts to inhibit glutamate action in the brain. This literature review aims to present current understanding of ketamine's effect on patients with post-traumatic stress disorder, with a thorough review of PTSD pathophysiology and ketamine's known mechanism of action.

PTSD Physiology

PTSD is charcterized by symptoms of re-experiencing, avoidance, and hyperarousal following a traumatic event that is extraordinary to normal life stressors (Kelmendi et al., 2016). PTSD symptoms are not temporally consistent and may develop years after the trauma, which makes PTSD heterogenous; symptom occurance is unpredictable and like depression, is a collection of unique symptoms (Kelmendi et al., 2016). Furthermore, PTSD presentation is confounded by comorbid disorders such as depression, anxiety, and addiction (Kelmendi et al., 2016). Only two medications have been approved by the Food and Drug Administration (FDA) for the pharmacological treatment of PTSD: paroxetine (Paxil) and sertraline (Zoloft) (Berger et al., 2009; Kelmendi et al., 2016). Unfortunatley, these drugs produce a response rate of no more than 60% with only 30% of patients achieving remission (Berger et al., 2009; Pradhan et al., 2016). Thus, it is imperative to find a novel therapeutic agent for the treatment of PTSD.

Current PTSD medications target the serotonergic system of the brain, however the discovery of new medications requires exploring other neurobiological systems. The neurobiology of PTSD identifies multiple other relevant axes including the HPA axis as well as the noradernergic and glutamatergic systems that are involved in PTSD symptomology. Specifically, there is substantial evidence that the glutamatergic system is active in brain areas involved in the stress response and in fear conditioning associated with PTSD (Bailey, Cordell,

Sobin, & Neumeister, 2013; Chambers et al., 1999; Koenigs & Grafman, 2009; Myers, Carlezon, & Davis, 2011; Nair & Ajit, 2008; Pitman et al., 2012). Functional imaging of PTSD patients suggests that the amygdala mediates the expression of fear conditioning, which is the conditioning of a fear response to a stimulus (Koenigs & Grafman, 2009; Myers et al., 2011). Moreover, the prefrontal cortex (PFC) is thought to regulate fear extinction, which is the decline of the fear conditioned response, although results have been shown to be paradoxical (Bremner, 2006; Myers et al., 2011). Functional imaging shows PTSD is associated with ventromedial PFC hypoactivity, while ventromedial PFC lesioning causes PTSD resistance; however, medial PFC lesioning demonstrated modulation of emotional responsiveness via amygdala inhibition (Bremner, 2006; Koenigs & Grafman, 2009). Lastly, the hippocampus is involved in memory formation, and its morphology in PTSD patients has been studied (Bremner, 2006). It was shown that PTSD patients have smaller hippocampal volumes, increased amygdala function, and decreased PFC function (Bremner, 2006). Pitman et al., 2012 found increased glutamate transmission in different brain regions including the PFC, amygdala, and hippocampus of rats exposed to an acute stress event. Furthermore, the increased level of glutamate released post-stress exposure has been connected to subsequent structural damage of the hippocampus (Bremner, 2006; Pitman et al., 2012; Ravindran & Stein, 2009).

The glutamatergic system involves the amino acid glutamate as an excitatory neurotransmitter. The primary source of glutamate in the cortex comes from excitatory pyramidal neurons and indicates the importance of glutamate in the processes of the central nervous system including learning, memory, and plasticity (Chambers et al., 1999; Kelmendi et al., 2016). There are two receptor types present in the glutamatergic system; ionotropic and metabotropic receptors. When activated, ionotropic receptors open ion channels that then

produce inhibitory or excitatory post-synaptic potentials as a result of ion flow through the channels. Metabotropic receptors are coupled to secondary messengers and activate a signaling cascade whose downstream effects cause inhibition or excitation of the neuron. An important ionotropic receptor in PTSD pathophysiology that is activated by glutamate is the N-methyl-D-aspartate (NMDA) receptor. Although not covered in this review, metabotropic receptors such as mGluR5 are thought to be promising drug targets (Holmes et al., 2017).

The NMDA receptor is a protein that is located within the neuronal membrane (transmembrane) and facilitates the movement of Na^+, K^+, and Ca^{2+} ions. It is voltage-gated, meaning it requires a specific cell potential to be open, but also ligand-gated, which requires the binding of an activator (i.e. glutamate) (Sinner & Graf, 2008). Glutamate activation of NMDA allows Ca^{2+} influx into the neuron, which leads to post-synaptic plasticity changes (Ravindran & Stein, 2009). Calcium forms a complex with protein calmodulin, which triggers induction of long-term potentiation, which is the basis of neuronal plasticity (Sinner & Graf, 2008).

The role of the NMDA ionotropic receptor in PTSD pathophysiology has been demonstrated by a number of studies (Bailey et al., 2013; Chambers et al., 1999; Kelmendi et al., 2016; Myers et al., 2011; Nair & Ajit, 2008; Pitman et al., 2012). The action of the NMDA receptor is relevant to the synaptic plasticity that drives learning, memory and behavior (Chambers et al., 1999; Kelmendi et al., 2016; Myers et al., 2011). NMDA receptors are also thought to play a role in fear extinction based on rat studies where NMDA antagonists were injected directly into the amygdala (Falls, Miserendino, & Davis, 1992; Ravindran & Stein, 2009). In rat models of PTSD, an increased density of NMDA receptors in the hippocampus and an unusually high glutamate level in the PFC were found (Pitman et al., 2012). Bailey et al., 2013 demonstrated that NMDA receptors were involved in fear conditioning. Furthermore,

NMDA receptor activation has revealed to increase spontaneous and intrusive memories, leading researchers to believe increased NMDA receptor activity to be a risk factor for PTSD (Liriano et al., 2019; McGhee, Maani, Garza, Gaylord, & Black, 2008). Evidently, NMDA receptors play a large role in PTSD pathophysiology through stress responses and fear conditioning, thus fear extinction is a desired outcome by the action of NMDA antagonists (Bailey et al., 2013; Falls et al., 1992; Kelmendi et al., 2016; Myers et al., 2011; Nair & Ajit, 2008; Ravindran & Stein, 2009).

Ketamine

Ketamine is an anesthetic drug that produces hypnotic (sleep-inducing), analgesic, and amnesic effects (Sinner & Graf, 2008). Chemically, it is identified as (+/-) 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone, with a molecular weight of 274.4 M (Sinner & Graf, 2008). It is both water and lipid soluble, which expands its range of administration but also allows it to cross the blood-brain barrier (Sinner & Graf, 2008). Ketamine is a noncompetitive NMDA glutamate receptor antagonist that induces and maintains anesthesia (Abdallah et al., 2015; Hartberg, Garrett-Walcott, & De Gioannis, 2018; White et al., 1982). In biochemistry, proteins contain an active site which is specific for a substrate, in the case of NMDA receptors its active site is specific to glutamate. Ketamine does *not* compete for binding with glutamate; it binds to the NMDA receptor elsewhere and prevents glutamate binding and channel opening, hence its noncompetitive nature. Ketamine also has an optically active S-enantiomer, which is known to bind NMDA with a much higher affinity; a mixture of the S and R enantiomers is termed “racemic” (Sinner & Graf, 2008; White et al., 1982). Some studies have demonstrated neuroprotective effects of ketamine in vitro, which is thought to be related to neurotoxicity that is induced as a result of increased glutamate and NMDA receptor density; however, this data has

yet to be replicated in humans (Himmelseher, Pfenninger, & Georgieff, 1996; Sinner & Graf, 2008). Ketamine is special in that it has a wide threapeutic range (the dosage range expected to achieve an effect), and as a result overdose is nearly impossible (Cooney et al., 2017; Sinner & Graf, 2008).

Ketamine has shown great promise as a treatment against multiple mental disorders, such as bipolar disorder and MDD (Abdallah et al., 2015; Averill et al., 2017; Chen et al., 2019; Pradhan et al., 2016). Abdallah et al., 2015 performed a thorough review of ketamine literature for MDD that concluded that there is great and well-replicated evidence that ketamine has rapid antidepressant effects. It was shown that neuronal atrophy and synaptic depression in the PFC were associated with stress and depression, and that enhancing the brain-derived neurotropic factor (BDNF) and mammalian target of rapamycin complex-1 (mTORC1) signaling pathways reversed these effects (Abdallah et al., 2015). The antidepressant effects of ketamine occurs through a mechanism in which a glutamate surge leads to activation of another glutamate ionotropic receptor called AMPA, which then activates a post-synaptic neuroplasticity pathway that involves BDNF and mTORC1 (Abdallah et al., 2015; Girgenti et al., 2017). A recent study explored ketamine augmented with an NMDA-agonist, D-cycloserine, as a therapy for treatment-resistant depression through a randomized double-blind placebo-controlled trial (Chen et al., 2019). The researchers found that the D-cycloserine did not have a superior antidepressant response in conjuction with ketamine versus ketamine alone, but did find prolonged antisuicidal effect in groups treated with D-cycloserine (Chen et al., 2019). The results of this trial not only support ketamine's antidepressant effect, but give further insight into stress and depressive pathophysiology through the understanding of the effects of D-cycloserine on neurobiology. With this information, researchers have begun to consider ketamine at a subanesthetic dose as a

possible therapeutic for PTSD, which shares similar pathophysiology and symptomology to MDD. It is apparent that the involvement of the glutametergic system and the NMDA receptors in PTSD pathophysiology suggest ketamine to be a potentially efficacious therapeutic agent in alleviating PTSD symptoms.

Ketamine and PTSD

Animal Studies.

Ketamine's effect on PTSD has been studied in a number of animal models (Brachman et al., 2016; Girgenti et al., 2017; Zhang et al., 2015). The earlist of these studies developed an animal model where mice were subjected to a fear stimulus (in the form of an inescapable footshock) to simulate PTSD (Zhang et al., 2015). Another time-dependent sensitization (TDS) model restrained rats for 2 hours, then placed them in water for 20 minutes where they were forced to swim (Zhang et al., 2015). Ketamine was given to the rats during a recovery period, and sertraline (Zoloft) was used as a positive control (Zhang et al., 2015). The results showed that these were good models for PTSD, and that ketamine managed to reverse the effects significantly better than sertraline (Zhang et al., 2015). The behavior of the mice was measured by aversive freezing, and repeated ketamine administration significantly increased the time spent in the context of the fear stimulus (Zhang et al., 2015). For the TDS model, the contextual aversive freezing was enhanced and ketamine treatment successfully alleviated those effects (Zhang et al., 2015). Lastly, Zhang et al., 2015 also found that ketamine managed to normalize BDNF levels in the hippocampus, which is usually decreased as a result of stress. A similar model was utilized by Brachman et al., 2016 to explore the prophylactic effects of ketamine for depressive behavior. Mice were given ketamine or saline (negative control), then exposed to various stressors; the authors concluded that ketamine was able to block stress-induced behavior

and induce stress resiliance (Brachman et al., 2016). These studies not only further understanding regarding ketamine's role in stress and fear conditioning, but also managed to demonstrate efficacious methods to develop animal PTSD models. If ketamine is able to exert similar neurobiological effects, such as increasing BDNF proteins in humans, then PTSD symptoms should be alleviated following ketamine administration.

PTSD has been shown to involve a bias toward perceiving neutral stimuli as threatening, which is connected to impaired fear extinction (Girgenti et al., 2017; Krystal et al., 2017). Girgenti et al., 2017 performed a rat investigation focused on the mechanism of fear extinction and ketamine's affect on this pathway. Rats were conditioned to a footshock stimulus and their freezing activity was measured before and after ketamine infusion, similar to the Zhang et al., 2015 PTSD model (Girgenti et al., 2017). The brain tissues were analyzed via Western blotting (protein immunprecipetation) to understand ketamine effects on the rat brains (Girgenti et al., 2017). It was found that the ketamine infusion activates the mTORC1 cascade and continued synaptic actions in the medial PFC, which mediates enhanced fear extinction (Girgenti et al., 2017). Fear extinction for patients with PTSD can allow recovery and remission from the trauma incident, and the findings of this paper support that possibility in humans. As mentioned previously, the mTORC1 cascade is implicated in stress and depression pathophysiology, and ketamine is shown to activate this cascade. If ketamine is able to exert similar neurobiolgical effects and stimulate the mTORC1 signaling pathway in humans, then PTSD symptoms should be alleviated following ketamine administration.

A 2018 animal study by Hou, et al. developed a PTSD induced rat model using a modified single-prolonged stress (SPS) by exposing the animal to a single inescapable foot shock, known as SPS&S (Wang et al., 2008). The researchers confirmed the effecteviness of the

model by behavioral observation as well as a noted BDNF protein level decrease (Hou et al., 2018). A single ketamine administration reversed PTSD behaviors in rats and increased the BDNF protein level which helped alleviate the rat stress responses (Hou et al., 2018). The results of these animal studies strongly suggest that ketamine can have an anti-PTSD effect in humans by decreasing the stress response, mediating fear extinction, and establishing stress resilience. However, animal models do not serve as perfect parallels to humans, thus it is important to review the known effects of ketamine on PTSD human patients.

Human Studies.

So far, limited human experimental studies have been performed assessing the effects of ketamine for PTSD patients. Published work utilize sub-optimal methods including case studies and retrospective analysis, but there are a few randomized, controlled trials (Abdallah et al., 2019; Albott et al., 2018; D'Andrea & Sewell, 2013; Feder et al., 2014; Hartberg et al., 2018; McGhee et al., 2014, 2008; Mion, Le Masson, Granier, & Hoffmann, 2017; Pradhan, Mitrev, Moaddell, & Wainer, 2018; Pradhan et al., 2017; Schönenberg, Reichwald, Domes, Badke, & Hautzinger, 2005, 2008; Womble, 2013).

1. Case Studies.

A case study by Womble, 2013 followed a 26-year old male combat veteren with diagnosed PTSD and chronic MDD. The patient was administered ketamine under propofol anesthesia, and then followed up with his psychiatrist, where it was revealed that his symptoms had abated from Day 1 until Day 14 (Womble, 2013). The patient experienced normal sleep with no nightmares, and found satisfaction in activities and increased social well-being (Womble, 2013). After 14 days, the patient relapsed into his depressive state prior to the infusion (Womble, 2013).

Another case report by D'Andrea & Sewell, 2013 followed a 23-year old male combat veteran with PTSD symptoms 6 months after a 15-month deployment. The patient had been tried on a variety of anti-depressants and atypical antipsychotics, as well as a number of psychotherapy forms (D'Andrea & Sewell, 2013). He was hospitalized three times with only short term and incomplete improvement after treatment (D'Andrea & Sewell, 2013). This patient's disease course was severe and unrelenting, and with a pregnant wife and his mother's recent sudden death, ketamine antidepressant therapy was approved and intiated (D'Andrea & Sewell, 2013). Ketamine was administred under propofol anesthesia, and upon awakening the patient had immediate and dramatic improvement in mood and personality; follow-up revealed functional improvement, motivation, and normalized sleep (D'Andrea & Sewell, 2013). The patients PTSD Checklist-Military (PCL-M) score decreased 37 points, from 66 to 29 (D'Andrea & Sewell, 2013). After 15 days, irritability, negative thinking and anhedonia recurred and the patient returned to his previous state within 24 hours (D'Andrea & Sewell, 2013). Although these case studies are sub-optimal forms of ascertaining ketamine's effect as a general PTSD therapeutic, they present good reason to investigate it further.

2. Retrospective Studies.

A retrospective study by Hartberg et al., 2018 investigated oral ketamine efficacy in contrast to intravenous (IV) or intramuscular (IM) administrations for both PTSD and treatment-resistant depression patients in an outpatient setting. The study used hospital and clinic admissions as the dependent variable, and found that these admissions significantly decreased (171 pre, 65 post, $p < 0.001$) after oral ketamine treatment (Hartberg et al., 2018). The study had a follow-up period of 3 years and observed dosage amount and frequency, which showed a decrease over time (suggesting lack of drug dependence) (Hartberg et al., 2018). Most

importantly, it was cited that IV ketamine limitations included a short relapse rate, and that oral ketamine is thought to eliminate that limitation (Hartberg et al., 2018). These findings suggest that ketamine may be beneficial for PTSD patients, especially through an oral route of administration. Another paper performed a retrospective analysis on burn patients in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) service members treated at a military center who received ketamine perioperatively (McGhee et al., 2008). In this analysis, 147 burn victims fit the inclusion criteria, with 119 patients receiving ketamine during surgery and 28 who did not (McGhee et al., 2008). It was found that the prevalence of PTSD in the ketamine population was significantly lower than patients who didn't receive ketamine ($p= 0.044$) (McGhee et al., 2008). In a follow-up study, McGhee et. al, 2014 performed a retrospective analysis on burn victims from the San Antonio Military Medical Center given the PCL-M after 30 days of injury. There were 289 burned service members, with 189 receiving ketamine and 100 who did not (McGhee et al., 2014). In accordance to their previous paper, patients who had multiple operations and larger burns were administered ketamine (McGhee et al., 2014). The paper supported the conclusion that ketamine did not increase PTSD development, however there was no significant difference in the rate of PTSD development between the two groups (McGhee et al., 2014). These two analyses support ketamine's potential as a PTSD therapeutic and may support a hypothesis that ketamine exerts its anti-PTSD effects long after trauma exposure.

Another retrospective study attempted to link pre-hospital and hospital ketamine use to PTSD development in war-wounded soldiers, and found that the ketamine was not a risk factor for the excarbation or development of PTSD (Mion, Le Masson, Granier, & Hoffmann, 2017). This study was important in establishing that ketamine used in the military setting did not aide in

the development of PTSD, and further confirms the potential for ketamine as an anti-PTSD therapeutic agent. A retrospective study by Schönenberg et al., 2005 attempted to determine if ketamine administration in accident victims increased the risk of PTSD symptoms. In this study, a 56 patient sample was assessed for PTSD symptoms using the Peritraumatic Dissociative Experiences Questionnaire (PDEQ) one year after the accident (Schönenberg et al., 2005). They found that patients who were administered the optically active S-enantiomer of ketamine, S-ketamine, had significantly increased PTSD symptoms, while patients who received racemic ketamine had only slightly increased PTSD symptoms (Schönenberg et al., 2005). In a follow-up study, Schönenberg et al., 2008 attempted to replicate the results from the previous study in the direct aftermath of a mild to moderate accident where the patient was treated in the emergency room. In this study, a 50 patient sample was assesed for PTSD symptoms using the PDEQ within 3 days of admission to the trauma unit (Schönenberg et al., 2008). Again, the patients treated with ketamine had a significant increase in PTSD symptoms in comparison to patients administered opiods or non-opiod analgesics (Schönenberg et al., 2008).

These results are contradictory to the aformentioned case studies and retrospective studies, although it is important to take into account the difference between a civilian and military patient sample. Furthermore, these studies provide further evidence for a hypothesis that necessitates ketamine administration long after trauma exposure, and not shortly after. Alternatively, these studies may suggest that ketamine's effect are dosage-dependent and that a subanesthetic dose may have more beneficial effects, while an anesthetic dose may have neurotoxic or stressful effects. Despite the benefit of these retrospective studies, to truly understand the causative effects of ketamine on the PTSD patient population, studies with an experimental controlled design are required.

3. Experimental Studies.

Focusing directly on ketamine as a drug therapy, an open-label drug study investigated ketamine's efficacy against PTSD and treatment-resistant MDD patients by administring IV ketamine (0.5 mg/kg) three times a week over a 12-day period (Albott et al., 2018). The study found that the ketamine treatments were efficacious in rapidly improving symptoms and sustaining those effects (Albott et al., 2018). Patients' PTSD mean score according to the DSM-V scale decreased by 33.3 points ($p < 0.0005$) and on the Montgomery-Asberg Depression Rating Scale (MADRS) decreased by 26.6 points ($p < 0.0005$) (Albott et al., 2018). The downside of the study was a remission rate of 80% for PTSD patients, with a mean relapse time of 41 days (Albott et al., 2018).

Another study followed the gold-standard experimental design, a randomized, double-blind, controlled trial using IV ketamine (0.5 mg/kg) and midazolam (0.045 mg/kg) as an active placebo. Midazolam is a benzodiazepine with anti-anxiolytic effects, with limited data to believe it has anti-PTSD effects (Braun, Greenberg, Dasberg, & Lerer, 1990; Cates, Bishop, Davis, Lowe, & Woolley, 2004; Feder et al., 2014; Jeffreys, Capehart, & Friedman, 2012; "Management of Posttraumatic Stress Disorder and Acute Stress Reaction 2017 - VA/DoD Clinical Practice Guidelines," 2017). The study found that a single ketamine dose was able to reduce core PTSD symptoms mean IES-R difference = 12.7, $p = 0.02$) with the effects persisting beyond 24 hours post-infusion (Feder et al., 2014). The mean difference in Impact of Event Scale-Revised (IES-R) score was 12.7 ($p = 0.02$) and the effects were superior to midazolam, which was used to strengthen the blind (Feder et al., 2014). The drug was well-tolerated and many patients, due to the persistent effect of the ketamine, were excluded from a second infusion (Feder et al., 2014).

In a pilot randomized, double-blind, placebo-controlled trial, ketamine was used in conjunction with Trauma Interventions using Mindfulness Based Extinction and Reconsolidation (TIMBER) cognitive therapy (Pradhan et al., 2018, 2017). In this study, 20 patients were treated with TIMBER and given either placebo or ketamine (0.5 mg/kg) (Pradhan et al., 2018). After 24 hours, there was no statistically significant difference between group outcomes, but the duration of effects were sustained for longer in the ketamine treated group (TIMBER-K = 34.44 days v. TIMBER-P = 16.50 days) (Pradhan et al., 2018). Furthermore, this study presented evidence of a potential biomarker, D-serine, that was elevated at baseline but significantly reduced following TIMBER and ketamine treatment (Pradhan et al., 2018).

Discussion

Although promising, these studies have their fair share of limitations. Firstly, there is a deficiency in the sample size, so future experimental studies should aim to recruit a much larger sample. Furthermore, the number of infusions and treatment length are too short and fail to establish a clear picture of ketamine's efficacy. The case studies and retrospective analyses described single adminsitrations of ketamine, and two of the three experimental studies also examined single ketamine administrations. In addition, with these studies and prior, the long-term use and safety of ketamine are ill-established and require further elucidation. Moreover, these few experimental studies utilized one dosage of ketamine (0.5 mg/kg) and did not further understanding of potential dose-dependent responses. It is clear that animal studies, case studies, and retrospective analyses are sub-optimal to experimental studies that are placebo-controlled, randomized, and double-blind. Despite the limitations of the experimental studies, the literature in combination point towards a powerful and promising PTSD alleviating effect. With a good understanding of PTSD pathophysiology, including NMDA receptor contribution and

BDNF/mTORC1 pathway importance, it won't be long before ketamine is fully studied in the patient population and its effects on PTSD pathophysiology is known.

Lastly, one of the main strengths of the Feder at al., 2014 paper happens to be its biggest limitation: the psychoactive placebo. In a reply to the Feder et al., 2014 paper, Dr. Keith Rasmussen pointed out the neurobiological effects of midazolam and challenged the results of the paper on the basis that ketamine could be a potentially better placebo than midazolam (Rasmussen, 2015). The researchers agreed that the placebo effect would be present in both drugs, but argued that despite this, since both drugs have neurobiological effects, the data could in fact show a superior therapeutic agent (Feder & Murrough, 2015). Granted the use of midazolam may have helped strengthen the blind, it is an additional confounding variable that can introduce doubt into the results of the study. Therefore, future studies should aim to use a pure negative control, such as saline, and for comparison a positive control, such as paroxetine (Paxil) or sertraline (Zoloft). Although a pure negative control has the potential to reveal the drug identity to the patient, it will be difficult to find an active placebo that can shield the blind and also have no neurobiological thereapeutic effect.

A recently published paper described an ongoing multisite, randomized, placebo-controlled, double-blind clinical trial investigating dose dependent ketamine efficacy for PTSD symptoms in veterens and active duty military (Abdallah et al., 2019). The study is using a 0.9% saline placebo and investigating two ketamine doses: 0.2 mg/kg or 0.5 mg/kg (Abdallah et al., 2019). This study aims to address the limitations of the two aforementioned studies including sample size, dosage, inactive placebo, and number of infusions (Abdallah et al., 2019). This trial is exciting and serves to be the first placebo-controlled trial to determine dose-related effects of ketamine, and its result will fall within FDA-guidelines for the approval of ketamine as drug for

the treatment of PTSD (Abdallah et al., 2019). With a clear lack of experimental studies of ketamine as an anti-PTSD drug, this ongoing clinical trial's results will be paramount in understanding the effects of ketamine on patients suffering with PTSD.

Conclusion

This literature review aimed to present current evidence for ketamine as a therapeutic agent for post-traumatic stress disorder. Ketamine is an NMDA-antagonist that is being recognized as a potential PTSD treatment (Averill et al., 2017; Krystal et al., 2017; Liriano et al., 2019). PTSD is charcterized by symptoms such as intrusive thoughts and nightmares, hyperarousal, and avoidance which result in the aftermath of a traumatic event or experience (Averill et al., 2017; Feder et al., 2014; Krystal et al., 2017). These symptoms have been connected to the glutamatergic system and are thought to be the result of NMDA receptor hyperactivation (Bailey et al., 2013; Chambers et al., 1999; Falls et al., 1992; Kelmendi et al., 2016; Liriano et al., 2019; McGhee et al., 2008; Myers et al., 2011; Nair & Ajit, 2008; Pitman et al., 2012; Ravindran & Stein, 2009). Ketamine is a widely used anesthatic that inhibits the action of the NMDA-receptor; it has demonstrated success against MDD and other mental illnesses such as bipolar disorder (Abdallah et al., 2015; Averill et al., 2017; Chen et al., 2019; Pradhan et al., 2016; Sinner & Graf, 2008; White et al., 1982). Animal studies of ketamine using PTSD rat models showed promising results as an effective anti-PTSD therapy (Brachman et al., 2016; Girgenti et al., 2017; Hou et al., 2018; Zhang et al., 2015). A few case and retrospective analyses demonstrated that ketamine was effective in reducing PTSD symptoms (D'Andrea & Sewell, 2013; Hartberg et al., 2018; Womble, 2013). Retrospective analyses in the military population showed that ketamine administration during surgery did not increase the liklihood or rate of developing PTSD (McGhee et al., 2014, 2008; Mion et al., 2017). A similar retrospective

analysis in the civilian population found increased PTSD symptoms directly after an accident as well as at least one year following if administered ketamine during treatment (Schönenberg et al., 2005, 2008). These studies suggests important factors in understanding ketamine's effects such as dosage (anesthetic v. subanesthetic) and timing (earlier v. delayed). Three experimental studies showed evidence that ketamine is effective for PTSD patients, however they suffer from small sample size and confounding variables (Albott et al., 2018; Feder et al., 2014; Pradhan et al., 2018). With the evidence that exists, ketamine is surely promising but requires further human experimental data, with the hopes that a current ongoing trial can bring forth this data (Abdallah et al., 2019). With PTSD being a debilitating disease afflicting many, the potential benefits of ketamine as an effective therapeutic agent are great.

References

Abdallah, C. G., Roache, J. D., Averill, L. A., Young-McCaughan, S., Martini, B., Gueorguieva, R., … Krystal, J. H. (2019). Repeated ketamine infusions for antidepressant-resistant PTSD: Methods of a multicenter, randomized, placebo-controlled clinical trial. *Contemporary Clinical Trials*, *81*(December 2018), 11–18. https://doi.org/10.1016/j.cct.2019.04.009

Abdallah, C. G., Sanacora, G., Duman, R. S., & Krystal, J. H. (2015). Ketamine and Rapid-Acting Antidepressants: A Window into a New Neurobiology for Mood Disorder Therapeutics. *Annual Review of Medicine*, *66*(1), 509–523. https://doi.org/10.1146/annurev-med-053013-062946

Albott, C. S., Lim, K. O., Forbes, M. K., Erbes, C., Tye, S. J., Grabowski, J. G., … Shiroma, P. R. (2018). Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. *Journal of Clinical Psychiatry*, *79*(3). https://doi.org/10.4088/JCP.17m11634

Averill, L. A., Purohit, P., Averill, C. L., Boesl, M. A., Krystal, J. H., & Abdallah, C. G. (2017, May 10). Glutamate dysregulation and glutamatergic therapeutics for PTSD: Evidence from human studies. *Neuroscience Letters*, Vol. 649, pp. 147–155. https://doi.org/10.1016/j.neulet.2016.11.064

Bailey, C. R., Cordell, E., Sobin, S. M., & Neumeister, A. (2013). Recent progress in understanding the pathophysiology of post-traumatic stress disorder: Implications for targeted pharmacological treatment. *CNS Drugs*, *27*(3), 221–232. https://doi.org/10.1007/s40263-013-0051-4

Berger, W., Mendlowicz, M. V., Marques-Portella, C., Kinrys, G., Fontenelle, L. F., Marmar, C. R., & Figueira, I. (2009, March 17). Pharmacologic alternatives to antidepressants in

posttraumatic stress disorder: A systematic review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, Vol. 33, pp. 169–180. https://doi.org/10.1016/j.pnpbp.2008.12.004

Brachman, R. A., McGowan, J. C., Perusini, J. N., Lim, S. C., Pham, T. H., Faye, C., … Denny, C. A. (2016). Ketamine as a Prophylactic Against Stress-Induced Depressive-like Behavior. *Biological Psychiatry*, *79*(9), 776–786. https://doi.org/10.1016/j.biopsych.2015.04.022

Braun, P., Greenberg, D., Dasberg, H., & Lerer, B. (1990). Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. *The Journal of Clinical Psychiatry*, *51*(6), 236–238. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2189869

Bremner, J. D. (2006). Traumatic stress: Effects on the brain. *Dialogues in Clinical Neuroscience*, *8*(4), 445–461.

Cates, M. E., Bishop, M. H., Davis, L. L., Lowe, J. S., & Woolley, T. W. (2004). Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. *Annals of Pharmacotherapy*, *38*(9), 1395–1399. https://doi.org/10.1345/aph.1E043

Chambers, R. A., Bremner, J. D., Moghaddam, B., Southwick, S. M., Charney, D. S., & Krystal, J. H. (1999). Glutamate and post-traumatic stress disorder: toward a psychobiology of dissociation. *Seminars in Clinical Neuropsychiatry*, Vol. 4, pp. 274–281. https://doi.org/10.153/SCNP00400274

Chen, M. H., Cheng, C. M., Gueorguieva, R., Lin, W. C., Li, C. T., Hong, C. J., … Su, T. P. (2019). Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: a double-blind randomized placebo–control study. *Neuropsychopharmacology*, *44*(12), 2112–2118. https://doi.org/10.1038/s41386-019-0480-y

Cooney, L., Loke, Y. K., Golder, S., Kirkham, J., Jorgensen, A., Sinha, I., & Hawcutt, D. (2017). Overview of systematic reviews of therapeutic ranges: methodologies and recommendations for practice. *BMC Medical Research Methodology*, *17*(1), 84. https://doi.org/10.1186/s12874-017-0363-z

D'Andrea, D., & Sewell, R. A. (2013, November 1). Transient resolution of treatment-resistant posttraumatic stress disorder following ketamine infusion. *Biological Psychiatry*, Vol. 74. https://doi.org/10.1016/j.biopsych.2013.04.019

Falls, W. A., Miserendino, M. J. D., & Davis, M. (1992). Extinction of fear-potentiated startle: Blockade by infusion of an NMDA antagonist into the amygdala. *Journal of Neuroscience*, *12*(3), 854–863. https://doi.org/10.1523/jneurosci.12-03-00854.1992

Feder, A., & Murrough, J. W. (2015, January 1). Ketamine for posttraumatic stress disorder - Reply. *JAMA Psychiatry*, Vol. 72, pp. 95–96. https://doi.org/10.1001/jamapsychiatry.2014.1751

Feder, A., Parides, M. K., Murrough, J. W., Perez, A. M., Morgan, J. E., Saxena, S., … Charney, D. S. (2014). Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial. *JAMA Psychiatry*, *71*(6), 681–688. https://doi.org/10.1001/jamapsychiatry.2014.62

Girgenti, M. J., Ghosal, S., LoPresto, D., Taylor, J. R., & Duman, R. S. (2017). Ketamine accelerates fear extinction via mTORC1 signaling. *Neurobiology of Disease*, *100*, 1–8. https://doi.org/10.1016/j.nbd.2016.12.026

Hartberg, J., Garrett-Walcott, S., & De Gioannis, A. (2018). Impact of oral ketamine augmentation on hospital admissions in treatment-resistant depression and PTSD: a retrospective study. *Psychopharmacology*, *235*(2), 393–398.

https://doi.org/10.1007/s00213-017-4786-3

Himmelseher, S., Pfenninger, E., & Georgieff, M. (1996). The effects of ketamine-isomers on neuronal injury and regeneration in rat hippocampal neurons. *Anesthesia and Analgesia, 83*(3), 505–512. https://doi.org/10.1213/00000539-199609000-00011

Holmes, S. E., Girgenti, M. J., Davis, M. T., Pietrzak, R. H., Dellagioia, N., Nabulsi, N., … Esterlis, I. (2017). Altered metabotropic glutamate receptor 5 markers in PTSD: In vivo and postmortem evidence. *Proceedings of the National Academy of Sciences of the United States of America, 114*(31), 8390–8395. https://doi.org/10.1073/pnas.1701749114

Hou, L., Qi, Y., Sun, H., Wang, G., Li, Q., Wang, Y., … Sun, L. (2018). Applying ketamine to alleviate the PTSD-like effects by regulating the HCN1-related BDNF. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 86*, 313–321. https://doi.org/10.1016/j.pnpbp.2018.03.019

Jeffreys, M., Capehart, B., & Friedman, M. J. (2012). Pharmacotherapy for posttraumatic stress disorder: Review with clinical applications. *Journal of Rehabilitation Research and Development, 49*(5), 703–716. https://doi.org/10.1682/JRRD.2011.09.0183

Kelmendi, B., Adams, T. G., Yarnell, S., Southwick, S., Abdallah, C. G., & Krystal, J. H. (2016). PTSD: from neurobiology to pharmacological treatments. *European Journal of Psychotraumatology, 7*(1), 31858. https://doi.org/10.3402/ejpt.v7.31858

Koenigs, M., & Grafman, J. (2009, October). Posttraumatic stress disorder: The role of medial prefrontal cortex and amygdala. *Neuroscientist*, Vol. 15, pp. 540–548. https://doi.org/10.1177/1073858409333072

Krystal, J. H., Abdallah, C. G., Averill, L. A., Kelmendi, B., Harpaz-Rotem, I., Sanacora, G., … Duman, R. S. (2017, October 1). Synaptic Loss and the Pathophysiology of PTSD:

Implications for Ketamine as a Prototype Novel Therapeutic. *Current Psychiatry Reports*, Vol. 19. https://doi.org/10.1007/s11920-017-0829-z

Liriano, F., Hatten, C., & Schwartz, T. L. (2019). Ketamine as treatment for post-traumatic stress disorder: A review. *Drugs in Context*, Vol. 8. https://doi.org/10.7573/dic.212305

Management of Posttraumatic Stress Disorder and Acute Stress Reaction 2017 - VA/DoD Clinical Practice Guidelines. (2017). Retrieved December 1, 2019, from https://www.healthquality.va.gov/guidelines/MH/ptsd/

McGhee, L. L., Maani, C. V., Garza, T. H., Slater, T. M., Petz, L. N., & Fowler, M. (2014). The Intraoperative Administration of Ketamine to Burned U.S. Service Members Does Not Increase the Incidence of Post-Traumatic Stress Disorder. *Military Medicine*, *179*(8S), 41–46. https://doi.org/10.7205/milmed-d-13-00481

McGhee, L. L., Maani, C. V, Garza, T. H., Gaylord, K. M., & Black, I. H. (2008). The correlation between ketamine and posttraumatic stress disorder in burned service members. *The Journal of Trauma*, *64*(2 Suppl). https://doi.org/10.1097/ta.0b013e318160ba1d

Mion, G., Le Masson, J., Granier, C., & Hoffmann, C. (2017). A retrospective study of ketamine administration and the development of acute or post-traumatic stress disorder in 274 war-wounded soldiers. *Anaesthesia*, *72*(12), 1476–1483. https://doi.org/10.1111/anae.14079

Myers, K. M., Carlezon, W. A., & Davis, M. (2011). Glutamate receptors in extinction and extinction-based therapies for psychiatric illness. *Neuropsychopharmacology*, Vol. 36, pp. 274–293. https://doi.org/10.1038/npp.2010.88

Nair, J., & Ajit, S. S. (2008). The role of the glutamatergic system in posttraumatic stress disorder. *CNS Spectrums*, Vol. 13, pp. 585–591. https://doi.org/10.1017/S1092852900016862

Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson, M. W., … Liberzon, I. (2012, November). Biological studies of post-traumatic stress disorder. *Nature Reviews Neuroscience*, Vol. 13, pp. 769–787. https://doi.org/10.1038/nrn3339

Pradhan, B., Kluewer D'Amico, J., Makani, R., & Parikh, T. (2016). Nonconventional interventions for chronic post-traumatic stress disorder: Ketamine, repetitive trans-cranial magnetic stimulation (rTMS), and alternative approaches. *Journal of Trauma & Dissociation*, *17*(1), 35–54. https://doi.org/10.1080/15299732.2015.1046101

Pradhan, B., Mitrev, L., Moaddell, R., & Wainer, I. W. (2018). D-Serine is a potential biomarker for clinical response in treatment of post-traumatic stress disorder using (R,S)-ketamine infusion and TIMBER psychotherapy: A pilot study. *Biochimica et Biophysica Acta - Proteins and Proteomics*, *1866*(7), 831–839. https://doi.org/10.1016/j.bbapap.2018.03.006

Pradhan, B., Wainer, I. W., Moaddel, R., Torjman, M. C., Goldberg, M., Sabia, M., … Pumariega, A. J. (2017). Trauma Interventions using Mindfulness Based Extinction and Reconsolidation (TIMBER) psychotherapy prolong the therapeutic effects of single ketamine infusion on post-traumatic stress disorder and comorbid depression: a pilot randomized, placebo-controlle. *Asia Pacific Journal of Clinical Trials: Nervous System Diseases*, *2*(3), 80. https://doi.org/10.4103/2542-3932.211589

Rasmussen, K. G. (2015, January 1). Ketamine for posttraumatic stress disorder. *JAMA Psychiatry*, Vol. 72, pp. 94–95. https://doi.org/10.1001/jamapsychiatry.2014.1621

Ravindran, L. N., & Stein, M. B. (2009, October 1). Pharmacotherapy of PTSD: Premises, principles, and priorities. *Brain Research*, Vol. 1293, pp. 24–39. https://doi.org/10.1016/j.brainres.2009.03.037

Schönenberg, M., Reichwald, U., Domes, G., Badke, A., & Hautzinger, M. (2005). Effects of

peritraumatic ketamine medication on early and sustained posttraumatic stress symptoms in moderately injured accident victims. *Psychopharmacology*, *182*(3), 420–425. https://doi.org/10.1007/s00213-005-0094-4

Schönenberg, M., Reichwald, U., Domes, G., Badke, A., & Hautzinger, M. (2008). Ketamine aggravates symptoms of acute stress disorder in a naturalistic sample of accident victims. *Journal of Psychopharmacology*, *22*(5), 493–497. https://doi.org/10.1177/0269881107082481

Sinner, B., & Graf, B. M. (2008). Ketamine BT. *Modern Anesthetics. Handbook of Experimental Pharmacology*, *182*, 313–333. https://doi.org/10.1007/978-3-540-74806-9_15

Wang, W., Liu, Y., Zheng, H., Wang, H. N., Jin, X., Chen, Y. C., … Tan, Q. R. (2008). A modified single-prolonged stress model for post-traumatic stress disorder. *Neuroscience Letters*, *441*(2), 237–241. https://doi.org/10.1016/j.neulet.2008.06.031

White, P. F., Way, W. L., & Trevor, A. J. (1982). Ketamine - Its pharmacology and therapeutic uses. *Anesthesiology*, *56*(2), 119–136. https://doi.org/10.1097/00000542-198202000-00007

Womble, A. L. (2013). Effects of ketamine on major depressive disorder in a patient with posttraumatic stress disorder. *AANA Journal*, *81*(2), 118–119. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L368767012%5Cnhttp://d27vj430nutdmd.cloudfront.net/23204/153253/8bd85f70035180d9a88a2f3935b05bd26d025930.1.pdf

Zhang, L. M., Zhou, W. W., Ji, Y. J., Li, Y., Zhao, N., Chen, H. X., … Li, Y. F. (2015). Anxiolytic effects of ketamine in animal models of posttraumatic stress disorder. *Psychopharmacology*, *232*(4), 663–672. https://doi.org/10.1007/s00213-014-3697-9