CHAPTER NINE

The emergence of ketamine as a novel treatment for posttraumatic stress disorder

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Abstract

A serious lack of effective pharmacotherapeutic interventions for posttraumatic stress disorder (PTSD) raises the urgent need for the development of novel treatments. Ketamine—a noncompetitive glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist in use for decades as an anesthetic and analgesic agent—has more recently been demonstrated to have rapid-onset antidepressant effects in patients with treatment-resistant depression (TRD). In the present review of ketamine as an emerging novel pharmacotherapeutic intervention for chronic PTSD, we discuss findings from the first proof-of-concept, randomized clinical trial (RCT) of single-dose intravenous ketamine in patients with chronic PTSD, as well as open-label studies and current practice. We introduce ongoing RCTs investigating the efficacy of repeated ketamine infusions in rapidly reducing symptoms and maintaining improvement in samples of individuals with PTSD stemming from civilian and military traumas. Additionally, we discuss mixed findings from published reports on ketamine administration in the acute aftermath of trauma.

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Studies in animal models of chronic stress have investigated molecular mechanisms underlying ketamine's effects, generating a shift in the conceptualization of PTSD as a disorder of impaired neural connectivity. We review animal studies examining the potential of ketamine to modify the expression of fear by altering memory reconsolidation or enhancing fear extinction, as well as others investigating ketamine administration prophylactically prior to stress exposure. We introduce the need for additional study in humans to evaluate whether ketamine might enhance the efficacy of psychotherapeutic interventions in individuals with chronic PTSD, harnessing a window of ketamine-induced neuroplasticity. While research on ketamine for PTSD is still in its early stages, it brings about the promise of novel and more effective treatments for this disabling condition.

1. Introduction

PTSD is a disabling and chronic condition arising after exposure to traumatic event—experiencing or witnessing actual or threatened death, serious injury, and physical or sexual assault. Approximately 8% of the general population will experience PTSD at some point in their lifetime (Kessler et al., 1995). In veterans of the Iraq and Afghanistan wars, its prevalence has been estimated at 14% (Schell and Marshall, 2008). Symptoms of PTSD comprise four clusters—re-experiencing of the traumatic event, avoidance of trauma-related stimuli, negative cognitions and mood with onset or worsening after the trauma, and trauma-related arousal and reactivity (American Psychiatric Association, 2013). Exposure to trauma is common in the United States and abroad, even among civilians (Kessler et al., 2017). Risk for PTSD differs by trauma exposure severity, cumulative number of traumas, and trauma type, with interpersonal trauma (physical and sexual assault in the context of a relationship) carrying the highest risk (Kessler et al., 2017). This condition is often co-morbid with other psychiatric disorders—particularly depression (Kessler et al., 1995)—and is equally or more impairing than many serious psychiatric conditions (Kessler, 2000).

Despite the prevalence, chronicity and seriousness of PTSD, current pharmacotherapies are often ineffective or insufficiently effective. The lack of helpful pharmacologic treatments for individuals suffering from this disorder has been labeled a "PTSD pharmacotherapy crisis" (Krystal et al., 2017b). Currently, there are only two FDA-approved medications for PTSD—selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine. Other off-label medications (other SSRIs, other antidepressant

classes, among others) are often ineffective or only lead to partial symptom improvement, requiring clinicians to combine medications without sufficient empirical evidence. Novel pharmacotherapies are urgently needed for this disorder, particularly interventions targeting the underlying mechanisms of disease.

2. Ketamine pharmacology and history

Ketamine, first approved as an anesthetic agent by the FDA in 1970 (Pfizer, 1970) is a noncompetitive glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist, originally derived from phencyclidine (PCP) in an attempt to reduce the dissociative effects of PCP (Domino, 2010; Li and Vlisides, 2016). A racemic mixture of the S-ketamine (or esketamine) and R-ketamine enantiomers, ketamine has a short elimination half-life of 2–4 h, and the advantage of not having significant respiratory depression effects. Anesthetic doses range from 1 to 2 mg/kg when administered as an intravenous (IV) bolus (Zanos et al., 2018). In addition to its antagonist activity at the NMDA receptor, ketamine also binds with lower affinity to a broad range of other receptors—including dopamine, serotonin, opioid, and others—and interacts with ion channels. Ketamine is primarily metabolized via demethylation to no rketamine, an active metabolite, which is in turn metabolized to hydroxynorketamines and dehydronorketamine (Zanos et al., 2018).

In addition to its uses as an anesthetic agent, ketamine has been used in clinical practice for analgesia and sedation in burn injury survivors (McGuinness et al., 2011), and for the treatment of certain forms of chronic pain, for example in patients with complex regional pain syndrome (Zhao et al., 2018). In psychiatry, IV ketamine administration was first investigated for the treatment of depression. Its rapid antidepressant effect has now been demonstrated in patients with treatment-resistant depression (TRD; Murrough et al., 2013), following the first report of its potential effectiveness in depressed patients 2 decades ago (Berman et al., 2000), with additional potential for the rapid reduction of suicidal ideation (Wilkinson et al., 2018). Further, intranasal administration of the ketamine enantiomer esketamine (Spravato) was recently approved by the Food and Drug Administration (FDA) as an adjunct to oral antidepressant medication for patients with TRD (Janssen Pharmaceuticals, 2019; Popova et al., 2019).

3. Ketamine and PTSD

3.1 Ketamine administered in the acute aftermath of trauma exposure

Given its use as an anesthetic and analgesic following acute physical injury, observational studies have examined the impact of ketamine administration acutely after trauma on the subsequent emergence of PTSD symptoms in physical accident victims. Schonenberg and colleagues reported results of the first study in a sample of 56 accident victims with moderate injuries, comparing the effects of a single or fractionated dose of racemic ketamine, esketamine, or opioids, administered in the ambulance—the first two combined with midazolam (Schonenberg et al., 2005). Patients with severe injuries were excluded. Participants completed self-report measures at a time point ranging between several months and 2 years post-injury. Compared with the racemic ketamine and opioid groups, patients who had received esketamine following their injury were found to exhibit significantly higher scores on the Dissociation, Reexperiencing and Avoidance subscales of the Acute Stress Disorder Scale (ASDS; Bryant et al., 2000), and significantly higher total score on the modified Peritraumatic Dissociative Experiences Questionnaire (PDEQ; Marmar et al., 2004), inquiring retrospectively about participants' peritraumatic experiences. Additionally, the esketamine group scored significantly higher on the Impact of Event Scale (IES; Horowitz et al., 1979), assessing current PTSD symptom levels. Patients in the racemic ketamine group had mildly elevated acute symptoms on the PDEQ, compared to those in the opioid group (Schonenberg et al., 2005). The same team of investigators conducted a prospective, naturalistic study of 50 accident victims with moderate injuries screened within 3 days of hospital admission, comparing a single or fractionated dose of racemic ketamine (combined with midazolam) to opioids and non-opioid analgesics (Schonenberg et al., 2008). Within 3 days post-hospital admission, patients who had received ketamine showed significantly higher levels of acute stress symptoms on the PDEQ and ASDS than those who had received opioids or other analgesic agents.

Based on findings from these two observational studies, the authors concluded that ketamine administration in the acute aftermath of trauma exposure might worsen risk of developing acute stress disorder and persistent PTSD symptoms. Some methodological issues complicate interpretation of these findings, however, including the authors' lack of adjustment in statistical analyses for injury severity within the mild-to-moderate range, as

well as subsequent findings from an unrelated database review of emergency care provided to soldiers injured in combat, suggesting that opioid medication (morphine)—which was employed as a comparison treatment in the Schonenberg studies—administered acutely after injury might reduce risk of PTSD symptom development (Holbrook et al., 2010). In addition, the lack of information regarding dosages and the frequent combination of midazolam with ketamine prevent any firm conclusions regarding the risk of ketamine administration in the acute aftermath of trauma.

By contrast, a study by McGhee and colleagues of 147 US service members found a lower prevalence of PTSD in those who had received ketamine during surgery (McGhee et al., 2008). This retrospective chart review study was conducted in burn victims who had undergone at least one surgery. Among the 119 patients who had received intraoperative ketamine, only 32 (27%) developed full PTSD—assessed with the PTSD Checklist Military Version (PCL-M; Weathers et al., 1994)—compared to 13 of 28 (46%) patients in the no-ketamine group, even though the ketamine group had more severe burns and a greater number of surgeries than the comparison group. Another retrospective chart review study by the same group, however, found no significant between-group difference in PTSD prevalence, despite significantly higher injury severity and greater number of operations in the ketamine group (McGhee et al., 2014). This second study was conducted in a sample of 289 burned US service members, with assessments completed at least 1 month post-injury. PTSD prevalence in those who had received intraoperative ketamine was 24 out of 100 (24%), and in the no-ketamine group 51 of 189 (27%), suggesting that intraoperative ketamine administered in the aftermath of trauma does not increase risk of developing PTSD. One key difference between the Schonenberg and the McGhee studies is that the latter involved intraoperative ketamine administration, and thus likely higher doses of ketamine, also in combination with other drugs, complicating comparisons across studies.

A subsequent, larger retrospective matched cohort study of US service members injured in combat found no difference in the prevalence of PTSD associated with administration of ketamine for analgesia (Highland et al., 2020). In this sample of 1158 injured service members, 107 patients received ketamine during hospitalization while 1051 did not receive ketamine. There was no between-group difference in rates of positive PTSD screen, assessed with the PCL Civilian Version (Ruggiero et al., 2003) at a time point ranging between 30 and 365 days post-injury. In summary, there is no clear evidence to date that ketamine administered in the aftermath

of trauma is beneficial in preventing the development of PTSD, and concern still remains that ketamine might be detrimental in this context.

Of note, a study in a prospective animal model of PTSD aimed to investigate this very question. Rats were administered increasing doses (0.5, 5, or 15 mg/kg) of intraperitoneal (IP) ketamine over 3 days, beginning 1 h after exposure to predator-scent stress (PSS) in soiled cat litter. Ketamine administration did not prevent "PTSD-like behavior" assessed 1 month after PSS exposure with the elevated plus maze and acoustic startle response (Juven-Wetzler et al., 2014). Further, the ketamine group exhibited significantly prolonged freezing responses when exposed to a trauma cue (unused cat litter) 31 days post-PSS exposure; a possible interpretation offered by the authors is that ketamine administered shortly after trauma exposure might affect consolidation of the trauma memory, with detrimental effects (Juven-Wetzler et al., 2014). In this study, the ketamine-exposed group also showed a reduced corticosterone response measured in serum 20 min after the first ketamine administration, suggesting a resulting suppression of the normal hypothalamic-pituitary-adrenal (HPA) axis response to stress. Finally, in a different study by another research group that instead employed a contextual fear conditioning (CFC) paradigm in mice, IP ketamine injection (30 mg/kg) 1 h following CFC did not reduce or increase freezing responses during later extinction training (McGowan et al., 2017).

3.2 Ketamine for the treatment of chronic PTSD

3.2.1 First randomized controlled trial

Meanwhile, despite concerns about potential adverse effects of ketamine administration to individuals in the acute aftermath of trauma, progress was being made in the development of ketamine as a potential rapid treatment intervention for patients with treatment-resistant depression (TRD; Zarate Jr. et al., 2006). Building on our research group's experience conducting clinical trials of ketamine for patients with TRD, we designed and conducted the first, proof-of-concept randomized controlled trial (RCT) of ketamine for patients with chronic PTSD at the Icahn School of Medicine at Mount Sinai, funded by the US Army Medical Research and Development Command (USAMRDC; Principal Investigator, Dennis Charney; Feder et al., 2014). Employing a cross-over, within-subject design, participants were randomized to receive single IV ketamine (0.5 mg/kg) and midazolam (0.045 mg/kg) infusions, separated by 2 weeks, in counterbalanced order. Infusions were administered over 40 min. Midazolam was employed as the control condition to allow better preservation of the study blind

(compared to the use of saline as placebo control), given the greater overlap of side effects between the two drugs, including potential acute dissociation. The study sample was composed of unmedicated individuals with chronic PTSD, predominantly civilians, with mean age [standard deviation (*SD*)] of 36 (10) years, and mean PTSD duration (*SD*) of 13 (13) years. A history of treatment-resistance was not required, and 46% of the sample reported past treatment with psychotropic medication.

Forty-one participants completed at least one infusion, and 29 completed both infusions—6 participants completed the study after the first infusion due to persistently improved symptoms 2 weeks after the first infusion. PTSD symptoms were assessed 24 h after each infusion, using the Impact of Event Scale—Revised (IES-R; Weiss & Marmar, 1997) as the primary outcome measure. At study completion, we showed that a single sub-anesthetic dose of IV ketamine was superior to midazolam in rapidly reducing PTSD symptom severity by 24 h post-infusion (Feder et al., 2014). While PTSD symptoms often began to recur 48 h post-infusion, seven participants exhibited sustained improvement 2 weeks after ketamine infusion, assessed with the Clinician-Administered PTSD (CAPS; Blake et al., 1995; Weathers et al., 2001). Ketamine also led to improvement in co-morbid depressive symptoms, and its effect on PTSD symptoms remained significant after controlling for depressive symptom levels pre-infusion and 24 h post-infusion (see Table 1). Results from this RCT suggested that ketamine has rapid beneficial effects on core PTSD and co-morbid depressive symptoms in patients with PTSD, when administered once the disorder has developed and has become chronic.

3.2.2 Side effects and safety considerations

In this first, single-dose ketamine RCT for PTSD, dissociative symptoms were observed to emerge transiently during infusion and resolved shortly after infusion end, with no evidence of worsening dissociative symptoms of the disorder. No clinically significant psychotic or manic symptoms were observed. Only one participant withdrew from the study due to discomfort experienced during ketamine infusion. Three participants received treatment with beta-blockers during ketamine infusion for blood pressure elevation; however, once the protocol was modified to exclude patients with blood pressure readings over 140/90 on two measurements, either at screening or pre-infusion baseline, no additional participants required beta-blocker administration. The most common side effects emerging during infusion were transient, and included blurred vision (37% with ketamine vs. 19%

Table 1 Clinical studies and case reports.

Authors	Year	Study design	Sample size	Sample	Ketamine dose	Assessment time points	Results
Ketamine for the treatment of chronic PTSD							
Clinical trials							
Feder et al.	2014	Randomized controlled trial; double-blind cross-over design	41	Patients with chronic PTSD, unmedicated	Single IV ketamine (0.5 mg/kg) and IV midazolam (0.045 mg/kg) infusions	24 h post-infusion (and up to 1 week post-infusion)	Significantly greater rapid reduction in PTSD symptoms 24 h post-ketamine infusion No significant difference in PTSD symptoms 1 week post-infusion
Albott et al.	2018	Open-label trial	15	Patients with co-morbid TRD and chronic PTSD, on concomitant psychotropic medications	Repeated IV ketamine (0.5 mg/kg), 6 infusions over 12 days	24 h post-infusion for all infusions (and up to 8 weeks after last infusion)	Rapid improvement in depressive and PTSD symptoms; median time to relapse in the 12 PTSD remitters was 41 days
Case reports							
Womble	2013	Case report	1	Veteran with chronic MDD and PTSD (age 26), 24-h medication washout	Single IV ketamine (0.5 mg/kg) infusion combined with other agents	Not stated	Rapid resolution of anxiety and depressive symptoms, including nightmares and sleep disruption, persisting for 14 days
D'Andrea et al.	2013	Case report	1	Veteran with chronic TRD and PTSD (age 23), 24-h medication washout	Single IV ketamine (35 mg) with propofol infusion	Not stated	Rapid improvement in PTSD along with depressive symptoms, persisting for 15 days
Donoghue et al.	2015	Case report	1	Chronic PTSD and severe emotional and aggressive outbursts (age 7)	Two single IV ketamine (10 mg) infusions combined with other agents, administered 3 months apart (for two procedures)	Not stated	Marked decrease in emotion dysregulation and physical aggression (previously treatment-refractory), persisting for 13 and 8 days after each infusion, respectively

Retrospective review							
Hartberg et al.	2018	Retrospective review of treatment data	37	Patients with TRD, several with co-morbid chronic PTSD or severe anxiety, on concomitant psychotropic medications	Repeated sublingual ketamine (0.5 mg/kg, titrated up by 20–50% to reach a final dose between 0.5 and 7.0 mg/kg); twice weekly or every other week	Pre-selected endpoint (median 31 months)	Significant reduction in hospital admissions (65%) and in inpatient hospitalization days (70%)
Ketamine administered in the acute aftermath of trauma exposure							
Retrospective studies							
Schönenberg et al.	2005	Retrospective and current symptom assessments	56	Accident victims with moderate injuries	Single or fractionated dose of S-ketamine, racemic ketamine, or opioids	Up to 2 years post-injury: Retrospective assessment of acute stress disorder symptoms Assessment of current PTSD symptoms	Substantially higher ASD and current PTSD symptom levels in the S-ketamine group; slightly higher acute symptoms in the racemic ketamine group
McGhee et al.	2008	Retrospective chart review	147	US service members who had sustained burns and underwent surgery	Intraoperative IV ketamine or no ketamine	Not stated	Lower prevalence of PTSD in the ketamine group

Continued

Table 1 Clinical studies and case reports.—cont'd

Authors	Year	Study design	Sample size	Sample	Ketamine dose	Assessment time points	Results
McGhee et al.	2014	Retrospective chart review	289	US service members who had sustained burns and underwent surgery	Intraoperative IV ketamine or no ketamine	30 or more days post-injury	No significant difference in PTSD prevalence between ketamine and no-ketamine groups
Highland et al.	2020	Retrospective, matched cohort, medical record review	1158	US service members injured during combat	IV ketamine or no ketamine (for analgesia)	Between 30 and 365 days post-injury	No significant difference in PTSD prevalence between ketamine and no-ketamine groups
Prospective studies							
Schönenberg et al.	2008	Prospective naturalistic study	50	Accident victims with moderate injuries	Single or fractionated dose of racemic ketamine, non-opioid analgesics, or opioids	Within 3 days of hospital admission	Higher ASD symptom levels in the ketamine group

ASD, acute stress disorder; IV, intravenous; PTSD, posttraumatic stress disorder; TRD, treatment-resistant depression.

with midazolam), dizziness (37% vs. 16%), dry mouth (24% vs. 6%), fatigue (24% vs. 16%), restlessness (21% vs. 3%), nausea/vomiting (21% vs. 0%), and headache (16% vs. 6%; Feder et al., 2014). Additional study is needed, and results from ongoing RCTs will yield further information about potential side effects related to repeated IV ketamine administration for PTSD, beyond a single infusion. If the efficacy of ketamine for PTSD is confirmed, administration of this treatment should be conducted in supervised settings, as it is done in the treatment of TRD, given its potential for abuse (Krystal et al., 2019). Given that cognitive impairment is associated with PTSD, the study of ketamine and cognition in PTSD patients will be important. In patients with MDD or TRD, initial findings suggest that short-term administration of ketamine does not adversely affect cognition—beyond transient effects during infusion—and that slower pre-treatment processing speed predicts greater improvement in depressive symptoms in response to ketamine (Murrough et al., 2015; Zhou et al., 2018).

3.2.3 Case reports

Additionally, some case reports described beneficial effects of single-dose IV ketamine administration on PTSD symptoms in individuals with chronic PTSD, albeit combined with other agents (see Table 1). These included the case of a 26-year-old veteran diagnosed with co-morbid PTSD and Major Depressive Disorder (MDD; Womble, 2013). After receiving a single IV infusion of ketamine (0.5 mg/kg for a total of 35 mg) combined with midazolam, propofol, and lidocaine, the patient reported that his anxiety and depressive symptoms rapidly resolved, with no recurrence of nightmares or sleep disruption for 14 days, at which point a full relapse of his symptoms began. In another case report of a single IV infusion of ketamine (35 mg) combined with propofol (34 mg) for the treatment of severe TRD and suicidal ideation in a 23-year-old veteran with co-morbid PTSD and TRD, the patient experienced a rapid reduction in PTSD symptoms along with his depressive symptoms (D'Andrea and Andrew Sewell, 2013). Symptom reduction persisted for 15 days post-infusion, followed by full symptom relapse.

A third case report described marked improvement of pronounced emotional and aggressive outbursts following ketamine infusion in a 7-year-old boy with chronic PTSD (Donoghue et al., 2015). The patient had received two separate IV ketamine infusions, 3 months apart, for two different medical procedures: 10 mg of ketamine combined with other agents for a tonsillectomy and 10 mg of ketamine for neuroimaging. Following each

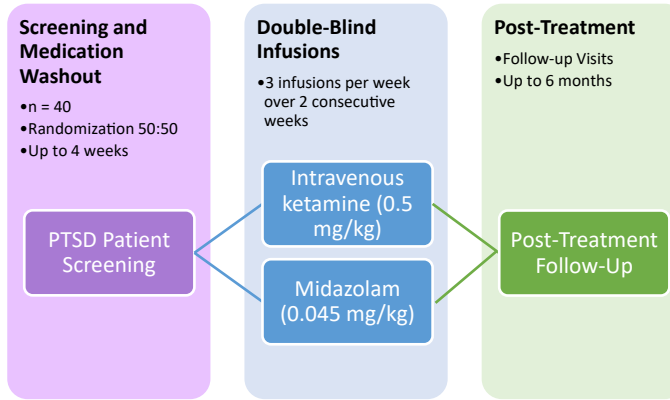
infusion, the boy exhibited a clear reduction in physical aggression and emotional dysregulation for 13 days following the first infusion, and for 8 days following the second infusion. Most notably, after the second infusion he was able to discuss his past trauma history with his therapist for the very first time.

3.2.4 A retrospective analysis and an open-label trial of repeated ketamine administration

More recently, results of a retrospective analysis and an open-label clinical trial in patients with TRD and co-morbid PTSD have been published. The retrospective study, in patients who had received long-term treatment with oral ketamine augmentation for TRD and co-morbid PTSD in an outpatient psychiatric practice, found a 70% reduction in the number of days spent in inpatient treatment and a 65% reduction in hospital admissions after ketamine treatment, compared to before treatment (Hartberg et al., 2018). In a recently completed open-label trial of 6 ketamine infusions administered to 15 veterans with co-morbid TRD and PTSD over 2 consecutive weeks, symptoms of both disorders improved significantly, with only transient dissociative symptoms. Ketamine administration was not associated with worsening of PTSD symptoms. Among the 12 participants whose PTSD symptoms remitted in response to ketamine, median time to relapse was 41 days (Albott et al., 2018; see Table 1).

3.2.5 Ongoing clinical trials

At present, there are two ongoing RCTs of repeated IV ketamine administration for PTSD. Our research group is conducting a parallel-arm RCT examining the efficacy of six IV ketamine infusions (administered three times per week over two consecutive weeks) compared to the control condition, six midazolam infusions, in patients with chronic PTSD. This study aims to replicate the findings from our initial RCT, and additionally evaluate the efficacy of repeated infusions in prolonging reduction of core PTSD and co-morbid symptoms (see Fig. 1). The sample is predominantly civilian, with all participants meeting DSM-5 criteria for chronic PTSD of at least moderate severity, assessed with the Structured Clinical Interview for DSM-5 (SCID-5; First et al., 2015) and confirmed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013). Concurrent psychotropic medications at stable doses are allowed, with the exception of opioids or long-acting benzodiazepines. History of treatment-resistance is not required,



Note: PTSD = posttraumatic stress disorder

Fig. 1 Randomized controlled trial of repeated intravenous ketamine infusions, currently in progress. PTSD, posttraumatic stress disorder.

and patients with no prior history of PTSD treatment are also eligible. Another ongoing, multi-site RCT aims to examine the efficacy of repeated IV ketamine infusions (twice a week for four consecutive weeks), compared to saline infusions, for antidepressant-resistant PTSD in a larger sample of veterans and active duty service members (Abdallah et al., 2019). The efficacy of two different doses of ketamine (0.5 and 0.2 mg/kg) will be compared. Additionally, novel clinical trials currently in progress have begun to examine whether ketamine can enhance the effect of exposure therapy on chronic PTSD symptoms (see below).

3.2.6 Current clinical practice

While initial results have identified ketamine as a promising novel therapeutic intervention for PTSD, the research is still in its early stages. In practice, however, many ketamine clinics originally set up to treat patients with TRD and other mood disorders have added a diagnosis of PTSD as a treatment indication. A survey conducted between 2016 and 2017 found that PTSD was the third most frequent disorder treated in these clinics (5.7% of 57 clinics surveyed), with MDD (72.5%) and bipolar disorder (15.1%) as the two most common disorders (Wilkinson et al., 2017a). Ketamine might appeal to patients with PTSD, as it is fast-acting, administered in the clinic, and does not require daily treatment, which may encourage medication adherence, a concern in this population (Jeffreys et al., 2012).

4. Mechanisms of action

Glutamate is the principal excitatory neurotransmitter in the brain. Glutamate transmission underlies learning and the encoding of new memories in the brain, including memories of traumatic events, through strengthening of synaptic connections between neurons (Malenka and Nicoll, 1999; Reul and Nutt, 2008). Animal studies have shown that exposure to chronic stress and the associated glucocorticoid release result in dendritic atrophy and synaptic loss in the hippocampus and the medial prefrontal cortex (mPFC; Popoli et al., 2011). These changes, mediated by glutamate excitotoxicity, bring about impaired connectivity in glutamatergic synapses in these brain regions (Radley and Morrison, 2005). These enduring changes in glutamatergic transmission resulting from chronic stress might also contribute to the onset and progression of psychiatric disorders, including PTSD (Popoli et al., 2011).

Much of what we know about the molecular mechanisms underlying the actions of ketamine came from studies in rodent models of chronic stress. In 2011, Li and colleagues reported that a single dose of IP ketamine administered to rats previously subjected to 21 days of chronic unpredictable stress led to rapid reversal of the behavioral deficits caused by chronic stress, as well as reversal of stress-induced synaptic atrophy and dysfunction in PFC pyramidal neurons, peaking 24 h post-administration (Li et al., 2011). A series of studies have now shown that a sub-anesthetic—but not full anesthetic—dose of ketamine causes a rapid increase in glutamate release, thought to stem from blockade of NMDA receptors located on γ-aminobutyric acid (GABA)ergic interneurons (Deyama and Duman, 2020). The resulting disinhibition of glutamate signaling triggers a cascade leading to increases in brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and other mediators. Downstream effects include increases in translation and synthesis of synaptic proteins, synaptogenesis, and maturation of synaptic spines (Deyama and Duman, 2020). Optimal PFC function is critical for adaptive responses to stress and fear extinction learning.

Investigators have proposed that persistent, recurrent intrusions experienced by individuals with chronic PTSD, often triggered by trauma reminders, represent a form of chronic stress that prolongs and worsens maladaptive biological changes, including synaptic atrophy, dysregulation of glutamatergic transmission, and disrupted connectivity in corticolimbic circuitry (Averill et al., 2017; Krystal et al., 2017a). Impairments in neural

connectivity might in turn contribute to persistent PTSD symptoms, in particular cognitive impairment, anhedonia, and reduced ability to experience positive emotions (Krystal et al., 2017a). Findings from neuroimaging studies in patients with major depressive disorder suggest that ketamine might work by normalizing connectivity in the PFC and other key brain regions (Abdallah et al., 2017; Evans et al., 2018). Neuroimaging studies in patients with PTSD pre- and post-ketamine administration are currently in progress.

In addition to evidence from animal models of chronic stress, the effects of ketamine administration have also been studied in animal models of PTSD. In a well-known PTSD model, rats displayed PTSD-like behaviors after receiving a single prolonged stress followed by foot shock. IP ketamine administration 2 weeks later, at a dose of 15 mg/kg, led to reversal of both PTSD-like behaviors and of the reduction in PFC BDNF levels (Hou et al., 2018). In another set of studies employing two different rodent models of PTSD (repeated inescapable foot shocks and time-dependent sensitization; TDS), repeated IP administration of ketamine reduced anxiety-like behaviors and contextual fear. Further, in the TDS PTSD model, ketamine administration was associated with increased hippocampal BDNF levels (Zhang et al., 2015).

5. Additional preclinical studies of relevance for PTSD and implications for human studies

While PTSD is increasingly understood as a disorder of impaired neural connectivity, abnormal fear processing and regulation are also thought to play a key role in the onset and maintenance of PTSD, thus presenting potential avenues for treatment intervention (Norrholm and Jovanovic, 2018). Psychophysiology and neuroimaging studies have identified impairments of fear extinction in individuals with PTSD (Milad et al., 2008, 2009; Wessa and Flor, 2007), assessed by repeated presentation of the conditioned stimulus without the unconditioned stimulus. Fear extinction is understood to be mediated by formation of a new memory that competes with the original fear memory, which is not itself modified (Schiller and Delgado, 2010). An additional, well-known phenomenon observed in patients with PTSD is over-generalization of fear responses to environmental stimuli that serve as trauma reminders (Jovanovic et al., 2012; Kaczkurkin et al., 2017). A recent study provided a computational account of fear learning and reversal in PTSD, showing that a dynamic learning rate parameter was related to

PTSD symptomatology, as well as the neural tracking of fear-conditioned cues in terms of their value, associability and prediction error (Homan et al., 2019).

Utilizing fear conditioning paradigms, animal studies have begun to examine whether ketamine administration affects fear extinction learning. In one study, ketamine administered IP 24 h after rats underwent fear conditioning (foot shocks paired with a tone) was shown to enhance fear extinction training, administered over the next three consecutive days (Girgenti et al., 2017). When tested the following week, rats in the ketamine group showed reduced return of fear when exposed to the original fear conditioning context, an effect that was mediated by mTORC1 signaling. These findings were replicated in a different study in fear-conditioned rats when ketamine was also administered IP; however, when administered IV, ketamine was instead associated with fear memory enhancement (Radford et al., 2018). While these opposite findings might be due to the different routes of ketamine administration, the reasons are not fully understood.

In a different study conducted in a mouse model of PTSD, induced by inescapable foot shocks, the combination of repeated IP ketamine administration over 22 days and a two-day fear extinction training reduced fear relapse, and was associated with increased BDNF levels in the medial PFC and hippocampus through reduction of *BDNF* gene methylation (Ju et al., 2017). Of note, a recent study in "fear-generalized mice" (higher behavioral generalization stemming from strong foot shock exposure) showed that a single subanesthetic dose of ketamine, administered IP 22 h after fear conditioning (but not prior to or right after fear conditioning), led to a significant reduction in fear generalization, lasting for at least 2 weeks (Asim et al., 2020). This effect was mediated by GluN2B-dependent BDNF signaling in the infralimbic PFC (a putative homolog of the human vmPFC), and was dose-dependent, as reduction of fear generalization was observed at ketamine doses of 15 and 30 mg/kg, but not 7.5 mg/kg.

In addition to extinction of fear memories, another key phenomenon of interest in the development of potential treatment interventions for PTSD is that of memory reconsolidation. Studies in the last decade have shown that after initial memory formation, when a memory is retrieved, it may destabilize and return to a labile state until re-stored through the process of reconsolidation, creating a window of opportunity for changing the memory in some way (Agren, 2014; Lee et al., 2017). Unlike fear extinction, reconsolidation allows modification of the original memory itself, via an updating mechanism, potentially preventing the reemergence of fear (Lee, 2009;

Monfils et al., 2009; Schiller et al., 2010). The effect of ketamine administration on fear memory reconsolidation was investigated in a recent animal study. Two weeks after rats underwent fear conditioning, IP ketamine administration right after reactivation of the fear memory resulted in a reduction of freezing, possibly indicating disruption of contextual fear reconsolidation (Duclot et al., 2016). As this study was not conducted in an animal model of PTSD, and did not fully examine a reconsolidation mechanism, further study is needed to understand the implications of these findings for the treatment of individuals with PTSD.

While gold-standard psychotherapeutic interventions for individuals with PTSD—including prolonged exposure (PE; Foa et al., 2007) and cognitive processing therapy (CPT; Resick and Schnicke, 1992)—are complex treatments, they are thought to work at least in part by harnessing the more basic mechanisms of fear memory reconsolidation and extinction (Lane et al., 2015). There is current active interest in studying whether ketamine administration can enhance the effectiveness of psychotherapeutic treatments for PTSD, with at least two current studies examining whether ketamine can enhance the efficacy and durability of exposure therapy in this patient population. Although both memory reconsolidation and extinction involve memory retrieval, they are distinct processes, and duration of exposure to the reminder appears to be important in determining which process is set in motion (Hu et al., 2018; Suzuki et al., 2004). Further, the older and stronger a particular memory is, the harder it is to modify by reconsolidation (Khalaf et al., 2018; Suzuki et al., 2004). Memory recall in itself will not always induce destabilization and may require specific conditions such as prediction error at the time of retrieval (Sinclair and Barense, 2019). Thus, a range of factors need consideration when designing combined ketamine and psychotherapy intervention studies for patients with PTSD, including timing of ketamine administration with respect to memory retrieval, ketamine dose, and frequency and duration of sessions, among others (Veen et al., 2018).

Of note, recently published studies not involving individuals with PTSD—one conducted in patients with TRD and the other in problem drinkers—have reported the effects of such combined interventions. In a small open-label study, 16 adults with severe TRD received four ketamine infusions (twice a week for 2 weeks), combined with cognitive-behavioral therapy (CBT) sessions on different days, and followed by additional weekly CBT sessions for 8 weeks. Preliminary findings suggest that combined treatment might prolong duration of symptom improvement in this patient

population, but additional research is needed (Wilkinson et al., 2017b). A different study examined whether ketamine administration could alter reconsolidation of reward memories in a sample of adults with high levels of drinking (on average 74 units of alcohol per week, with one unit being 8 g), but who did not meet diagnostic criteria for alcohol use disorder. A single dose of IV ketamine, administered right after reactivation of alcohol-related maladaptive reward memories, was associated with reduced urge to drink and subsequent alcohol consumption (Das et al., 2019).

A different research direction has been launched by a series of animal studies examining the effects of ketamine administered prior to stress exposure. Study results suggest that ketamine administered 1 week prior to stress exposure has a prophylactic effect. In an initial study, a sub-anesthetic dose of ketamine administered to mice 1 week before the animals were exposed to 2 weeks of social defeat stress-induced resilience, protecting against depressive-like behaviors resulting from stress exposure (Brachman et al., 2016). Prophylactic ketamine administration, albeit at a higher dose, had a similar effect in a different stress model, consisting of 3 weeks of corticosterone treatment (Brachman et al., 2016). In a subsequent study, ketamine was shown to attenuate fear learning when administered 1 week prior to contextual fear conditioning, but not 1 month or 1 h prior to conditioning (McGowan et al., 2017). Studies in humans are needed to investigate the potential of ketamine as a preventive agent against the deleterious impact of stress, especially in military and first responder populations repeatedly exposed to potentially traumatic events by virtue of their occupation, as well as discussion of any ethical and practical concerns.

6. Conclusion

While initial results from published studies are promising, more definitive answers are expected after completion of clinical trials of repeated ketamine administration for PTSD, currently in progress. In addition to potential replication of the rapid effect of a single IV ketamine infusion on chronic PTSD symptoms, ongoing clinical trials (e.g., NCT02397889, NCT02655692, NCT02727998, NCT04032301 on clinicaltrials.gov)—in both civilian and military samples—are investigating whether repeated ketamine infusions can sustain symptom reduction, and if so, for how long. These studies will also yield additional information on the safety of ketamine administration to patients with PTSD. If ketamine is confirmed to be effective for this disorder, future studies should investigate alternative routes

of administration that are more easily adaptable to outpatient clinical settings, such as the intranasal route. Additional studies will also be necessary to determine whether a primary diagnosis of PTSD can be added as a treatment indication for intranasal esketamine (Spravato), currently approved for TRD.

As reviewed above, another emerging research direction involves examining whether ketamine can enhance the effects of psychotherapeutic interventions for individuals with PTSD, harnessing a period of increased neuroplasticity induced by ketamine administration. While results from animal studies suggest that ketamine alters reconsolidation of fear memories as well as fear extinction, directionality of findings from those studies has been mixed, pointing to the need to identify the specific parameters under which ketamine and behavior might interact. Further, animal studies investigating whether ketamine administration can modify fear responses have employed basic fear conditioning models. Translational work in actual animal models of PTSD should yield important information for designing clinical trials of combined interventions for patients with chronic PTSD.

In parallel, as mentioned above human studies have begun to examine whether ketamine can enhance the effectiveness of prolonged exposure therapy in patients with PTSD. Additional studies should investigate the effect of ketamine on reconsolidation of fear memories, starting with healthy individuals to determine optimal timing and dose of ketamine administration, as well as optimal conditions for successful fear memory updating, then progressing to trials in patients with chronic PTSD. While we are still in the early stages of developing ketamine's full potential as a treatment for PTSD, this novel rapid-acting drug and its potential for modifying fear memory expression by harnessing a window of ketamine-induced neuroplasticity represent a welcome new research frontier for the treatment of this disabling condition, supported by translational neuroscience.

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Conflict of interest

Drs. Charney and Feder are named co-inventors on an issued patent in the United States, and several issued patents outside the United States, filed by the Icahn School of Medicine at Mount Sinai (ISMMS) for the use of ketamine as a therapy for PTSD. This intellectual property has not been licensed. In addition, Dr. Charney is named co-inventor on several issued US patents, and several pending US patent applications, filed by ISMMS for the use of ketamine as a therapy for TRD and suicidal ideation. ISMMS has entered into a licensing agreement with Janssen Pharmaceuticals, Inc. and it has and will receive payments from Janssen under the license agreement related to these patents. As a co-inventor, Dr. Charney is entitled to a portion of the payments received by the ISMMS. Since SPRAVATO (esketamine) has received regulatory approval for TRD, ISMMS and Dr. Charney as its employee and a co-inventor, will be entitled to additional payments, under the license agreement. Dr. Charney is named co-inventor on a patent application filed by the ISMMS for the use of intranasally administered neuropeptide Y for the treatment of mood and anxiety disorders. This intellectual property has not been licensed. Dr. Charney is a named co-inventor on several patents filed by ISMMS for a cognitive training intervention to treat depression and related psychiatric disorders. ISMMS has entered into a licensing agreement with Click Therapeutics, Inc., and has and will receive payments related to the use of this cognitive training intervention for the treatment of psychiatric disorders. In accordance with the ISMMS Faculty Handbook, Dr. Charney has received a portion of these payments and is entitled to a portion of any additional payments that the medical school might receive from this license with Click Therapeutics. Ms. Rutter and Dr. Schiller have no conflicts of interest to declare.

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