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PTSD (S Creech and L Sippel, Section Editors)

Augmenting the Treatment of PTSD with Ketamine—a Review

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Abstract

Purpose Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder with a lifetime prevalence of 6.1% in the general adult population. Clinical guidelines for the treatment of PTSD suggest the use of trauma-focused psychotherapies such as prolonged exposure (PE) and cognitive-behavioral therapy (CBT). As a second-level intervention, these guidelines suggest the use of psychotropic medications, mainly selective serotonin reuptake inhibitors (SSRIs). To date, however, studies have shown that both psychotherapeutic and psychopharmacologic treatments have limited efficacy, with remission rates around 40–70% and dropout rates of up to 50%. This paper reviews a new and emerging treatment approach of medication-augmented psychotherapy for PTSD, with an emphasis on augmenting prolonged exposure therapy (PE) with sub-anesthetic ketamine infusion. Based on animal and human research on fear extinction and memory reconsolidation, neurobiological changes that emerge following a ketamine infusion can enhance learning and thus benefit exposure-based psychotherapies for PTSD.
Summary Medication-augmented exposure-based psychotherapies represent a promising direction for the treatment of PTSD, with some positive results in small-scale studies. More

studies (phase 2 and 3) should be performed to determine if this multimodal treatment approach may help mitigate PTSD symptoms in trauma-exposed individuals who do not respond to standard monotherapeutic approaches.

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder with an estimated 1-year prevalence of 4% [1–3] and lifetime prevalence in the general population ranging between 4.6 and 6.1% [4]. Among US military personnel, PTSD rates are even higher, ranging from 19 to 22% [5], although a recent study of a general population-based sample of US veterans suggested a lifetime prevalence of 6.9% [6]. The disease course of PTSD may be chronic, with more than 40% of individuals with PTSD describing their symptoms as having a major negative effect on their social and/or occupational functioning even 10 years after the onset of the disorder [1, 7–10]. PTSD is also associated with psychiatric comorbidities such as major depressive disorder, significantly reduced health-related quality, psychosocial dysfunction, and increased morbidity and mortality [10, 11].

PTSD symptoms include intrusive thoughts of the traumatic event, avoidance of thoughts, places, and other reminders of the event, negative alterations in mood and cognition, and hyperarousal and reactivity. This disorder is often accompanied by sleep disturbances, social isolation, and cognitive dysfunction [11]. It is a heterogeneous disorder in which some might be more affected by intrusive symptoms such as recurrent flashbacks or dreams of the event, while others might be more affected by hypervigilance, sleep disturbance, and concentration difficulties [12].

The National Academies of Science, Engineering, and Medicine issued a report on the treatment of PTSD [13] where they concluded that exposure therapy is the most efficacious treatment. In 2017, the American Psychological Association (APA) issued clinical practice guidelines for PTSD, which included recommendations for both psychotherapeutic and pharmacotherapeutic treatments for this disorder [14]. In this document, the APA recommended the following psychotherapies for the treatment of PTSD: cognitive-behavioral therapy (CBT; [15]), cognitive processing therapy (CPT; [16]), cognitive therapy (CT; [17]), and prolonged exposure (PE; [18]). Other psychotherapies have been found to be moderately effective, and some, such as relaxation or Seeking Safety, were not found to be effective at all [14]. In its guidelines, APA recommended the following pharmacotherapies: fluoxetine, paroxetine, sertraline, and venlafaxine, with moderate level of evidence.

Although the above-mentioned treatments for PTSD are currently the most efficacious, the percentage of full remission from PTSD remains low, with studies suggesting that 30–60% fail to remit from the disorder [19, 20•, 21]. To date, no single pharmacological agent has been developed exclusively to treat PTSD. FDA-approved drugs for PTSD such as paroxetine and sertraline achieve 30% remission [22, 23]. In psychotherapy trials, there is a large percentage of dropout and non-responders, with large variability between reports, and the percentage of non-remitted patients can be as high as 50% [24]. Thus, current advances in both psychotherapeutic and pharmacotherapeutic treatments limited in providing full and lasting remission from PTSD.

As discussed below, some recent studies assessed the combination of psychotherapy and pharmacotherapy, in order to achieve better results in treating PTSD. In this review, we summarize extant literature regarding the potential clinical benefits associated with ketamine infusion and how it may help augment current trauma-focused psychotherapies such as prolonged exposure. Ketamine was first found to promote rapid improvement in depressive patients [25] and has been studied as a

potential treatment to other associated disorders, such as PTSD. Existing psychotherapies and pharmacotherapies for PTSD will be described briefly below as a basis for review.

Current treatments

Currently, several psychotherapies and pharmacological treatments are considered as evidence-based treatments (EBP) for PTSD. According to APA, the National Institute for Care and Health Excellence (NICE), and the Department of Defense/US Department of Veterans Affairs (DoD/VA) guidelines [14, 26, 27], evidence-based psychotherapy is the recommended intervention for PTSD patients. Strong evidences for CBT, CPT, CT, and PE suggest using one of these as a first-line treatment for PTSD. The latest DoD/VA guidelines also added strong recommendations for eye movement desensitization and reprocessing (EMDR; [28]), brief eclectic psychotherapy (BEP; [29]), narrative exposure therapy (NET; [30]), and written narrative exposure [27]. Briefly, the common ground of all these recommended psychotherapies is that they are trauma-focused therapies that include components of psychoeducation, exposure, and cognitive strategies in the treatment of PTSD.

When individual psychotherapy is not available or not preferred, these guidelines suggest the use of pharmacotherapy, with recommendations for sertraline, paroxetine, fluoxetine, or venlafaxine as monotherapies. While APA guidelines give the score of "moderate" to "low" evidence for all of the above pharmacotherapies, DoD/VA guidelines strongly recommend them (in the absence of individual psychotherapy). Other pharmacotherapies have either no or weak evidence. DoD/VA guidelines recommend strongly against the use of divalproex, tiagabine, guanfacine, risperidone, benzodiazepines, ketamine, hydrocortisone, or D-cycloserine, cannabis, or cannabis derivatives as monotherapy due to the lack of strong evidence for their efficacy and/or known adverse effect profiles and associated risks.

Augmenting psychotherapy with ketamine

As mentioned earlier, although efficacious, most treatments for PTSD are limited, with reported limited remission, resulting in large proportion of patients who do not remit and still meet diagnostic criteria for PTSD at the conclusion of treatment [19, 20•, 21–24]. Consequently, clinicians and researchers have examined augmentation therapies in which psychotherapeutic and pharmacotherapeutic interventions are combined. To date, however, studies examining the effect of PE augmentation with SSRIs found little to no effect [21, 31, 32]. Thus, in the next section, we will describe a promising emerging combined treatment of ketamine infusion + PE (KPE). As part of the role of the glutamatergic system in

PTSD, we will also briefly discuss another partial NMDA agonist D-cycloserine (DCS) that may enhance psychotherapy [33].

Ketamine

There is increasing evidence which points to the significant role of the glutamatergic system in the pathophysiology of PTSD [34]. Preclinical studies in rats, for example, found that under conditions of acute stress, there is a significant increase in glutamate transporters in the amygdala, hippocampus, and the prefrontal cortex (PFC). Irregularity in glutamate levels in the hippocampus and PFC has been implicated in animal models of PTSD [34]. The PTSD-glutamate connection may be rooted in the crucial role of NMDA receptors in the neuroplasticity of learning and memory [35]. In this respect, Bailey et al. suggested that NMDA agonists may help to enhance fear extinction among individuals diagnosed with PTSD [36].

Ketamine is a glutamate NMDA receptor antagonist, mostly used as an anesthetic [20•]. In contrast to DCS, an agonist for the NMDA receptor, ketamine is known for its dissociative properties. Interest in ketamine as a possible treatment for PTSD began when it was found to alleviate depressive symptoms [25, 37]. The potential effect of ketamine on PTSD and depression is supported by animal studies demonstrating that exposure to chronic stress causes atrophy in limbic brain regions associated with mood and fear learning, including the hippocampus, amygdala, and PFC [38–40]. Accumulating evidence also suggests that ketamine, in sub-anesthetic doses, promotes neurogenesis [39, 41•], cell proliferation [42], and synaptogenesis [39, 43].

Although PTSD symptoms are multifaceted, at its core, the disorder is associated with overgeneralization of fear responses and deficits in memory reconsolidation process in which the original trauma is "forever" stored in its original form and is resistant to spontaneous modifications after trauma recollection. Fear learning is a conditioned learning in which a previously natural cue (CS) was associated with an aversive (painful, life threatening, etc.) occurrence (US). After an association is established, the individual will respond to appearance of CS in a similar manner to that of the original US [44]. *Extinction* is the attenuation or disappearance of a previously learned response, after lack of association was present. Some theories contend that PTSD is basically a failure in extinction learning. Some studies have found that PTSD patients have impaired extinction learning [45, 46] or in learning in general [47] that is associated with heightened amygdala and sympathetic activity. *Reconsolidation* is a process that initiates destabilization of a memory, followed by a protein-synthesis–dependent restabilization phase, during which memories are activated into a labile state and can be stored in an altered form [48, 49]. Thus, after invoking CS, a specific time frame is open in which updating of the memory is possible [48, 50]. The amygdala and hippocampus were found to be associated with reconsolidation [48, 51].

Both extinction and reconsolidation play an important role in PTSD and many treatment agents target these processes in order to alleviate PTSD symptoms [44]. Indeed, studies have found that trauma-focused

psychotherapies (such as PE, TF-CBT, and EMDR) affect brain regions associated with fear extinction and reconsolidation, such as the amygdala, hippocampus, ventral PRF, and ACC [44, 52].

Pharmacological agents have also been suggested as a potential enhancement mechanism for extinction and reconsolidation. Fear extinction is linked to N-methyl-d-aspartate (NMDA) glutamatergic receptor activity in the basolateral amygdala, and as such, D-cycloserine (DCS), a NMDA receptor agonist, was suggested as a possible pharmacotherapy to facilitate fear extinction [44, 53]. Ketamine was also suggested as a potential initiator of reconsolidation, especially as it is also enhancing neurogenesis and synaptogenesis (as discussed above). A recent study [54] found that infusion of ketamine after learned fear reduced the fear-associated behavior of mice. Further, while brain-derived neurotrophic factor (BDNF) levels in the hippocampus were lower in rats after exposed to chronic stress, this effect was reversed by ketamine infusion [54]. Furthermore, [55] another study found that a single ketamine infusion of 15 mg/kg in rats alleviated PTSD-like symptoms by increasing the levels of BDNF in the PFC.

In the past few years, studies have showed converging evidence of reconsolidation [49, 50, 56, 57], which is important in fear learning and extinction [49, 50]. Recently, studies have found that neurogenesis plays an important role in reconsolidation [58, 59]. For example, Duclot et al. (2016) found that a single 10 mg/kg infusion of ketamine diminishes reactivation of feared memories in rats [60]. Thus, it seems that the use of ketamine might enhance the ability for memory reconsolidation and extinction, which may in turn help alleviate PTSD symptoms. Additional details regarding the role of ketamine in promoting synaptogenesis and neurogenesis are provided elsewhere [39, 61].

A few studies examined the effect of ketamine in anesthetic doses in mitigating PTSD symptoms in humans [62, 63]. These studies found that patients receiving ketamine (as part of a medical procedure) in anesthetic levels reduced severity of PTSD symptoms relative to non-ketamine-infused patients. A single case study reported that infusion of ketamine (as a treatment for depression) caused rapid and significant alleviation in PTSD symptoms that lasted for 15 days [64]. In 2014, Feder et al. published the first known RCT for ketamine as treatment for PTSD. In this crossover design study, individuals with PTSD were randomly assigned to two distinct groups: one group received a single infusion of ketamine (0.5 mg/kg infused over 40 min); the second group received a single infusion of midazolam (0.045 mg/kg over 40 min); midazolam was chosen due to its pharmacokinetic parameters and its non-specific behavioral effects are similar to those of ketamine. Two weeks later, the groups received the second medication. Results of this study indicated that PTSD levels were significantly lower after one infusions of ketamine. The effect persisted up to 7 days after infusion [65]. Feder et al. also assessed levels of dissociative symptoms associated with ketamine infusion, as this is a known risk in the treatment. They found that dissociative symptoms (when occurred) had peaked after 40 min and were fully resolved after 120 min. In 2018, Albott et al. studied the effect of repeated ketamine infusions on PTSD and treatment-resistant depressed patients [66]. In this study, 15 patients who suffered from both treatment-resistant depression (TRD) and chronic PTSD received 6 intravenous infusions (0.5 mg/kg for 40 min) for 2 weeks. Patients were monitored

for side effects before infusion and 40,100 and 160 min after infusion. Changes in PTSD and depressive symptoms were assessed using the PTSD Checklist for DSM-5 (PCL-5) [67] and Montgomery-Asberg Depression Rating Scale (MADRS) [68], respectively. At the end of treatment, 80% of patient had full remission of PTSD (PCL scores < 33). Median time to relapse, however, was 41 days, thus suggesting that although very effective, the treatment effect is transient.

Recently, a small study reported on the effect of combining ketamine infusion with mindfulness-based psychotherapy for PTSD. In this study, 20 patients were divided into two groups. The first group received one infusion of ketamine (0.5 mg/kg over 40 min); and the second group received saline. The patients received mindfulness-based psychotherapy, with the first treatment session during the infusion, two consecutive short session within a week after the infusion, and then 9 weekly sessions. Results revealed that the group that received ketamine showed reduced symptoms and longer lasting effect (34 ± 19 days) in comparison to the saline group (16 ± 11) [69]. Results of this study provide preliminary support for combining ketamine with psychotherapy to alleviate PTSD symptoms with longer lasting effect.

As ketamine was found to be associated with neurogenesis, synaptogenesis, and cell proliferation, all promote learning and extinction, it is reasonable to test the effect of ketamine on extinction-based treatment in humans, as a possible enhancer for this treatment. Thus, ongoing studies are assessing the efficacy of ketamine+PE (KPE) as a possible combined treatment for PTSD. A search in ClinicalTrials.gov for ketamine and PTSD yielded 13 results, of which four are not associated with PTSD, two completed the study (only ketamine infusion, without psychotherapy), one reported withdrawal, three unknown status, and three currently recruiting (one study also includes psychotherapy). Out of which, only two studies reported results [65, 66]. Other than that, no full scope clinical trial was published yet—as ketamine and PE seem like a promising future therapy, more studies should be conducted in order to provide evidence for the efficacy of this treatment approach.

Although the focus of this paper was to highlight the potential of ketamine to enhance the effectiveness of trauma-focused psychotherapy, it is important to note that there is one additional partial NMDA receptor agonist that may assist in the treatment of PTSD.

D-Cycloserine

D-Cycloserine (DCS) is a partial agonist at N-methyl-D-aspartate (NMDA) receptor. Antagonists for NMDA receptors have been found to block fear learning, thus suggesting that these receptors are associated with fear learning [70]. As extinction is also a form of new learning, researchers have hypothesized that NMDA agonists may help promote learning and in turn help mitigate PTSD symptoms [71]. DCS was studied as enhancer for PE and specifically virtual reality using PE (VPE). Details of the therapy can be found in [71]. Although a study found that DSC group (compared to placebo) had less PTSD symptoms in a 6-month follow-up [72], other studies failed to find a difference between DCS group and placebo or alprazolam groups [53] and one study even found that DCS group had poorer outcome, compared to placebo [71]. Recently, a review paper

addressed the RCT that studied the effect of DCS-augmented psychotherapy on individuals with PTSD [73]. Although some trials showed a promising effect of DCS-augmented therapy [72], recent studies showed little to no effect, compared to placebo augmentation or only psychotherapy [53, 71]. Thus, although promising, it seems that there is currently inconclusive evidence regarding the efficacy of D-cycloserine as augmentation therapy for PTSD.

As augmented trauma-focused psychotherapies is an emerging research field, other potential candidate agents such as oxytocin, MDMA, and yohimbine, among others, are currently under investigation worldwide, and have the potential to advance psychotherapy outcomes and retentions.

Conclusions

In this paper, we reviewed common interventions for PTSD. As of now, most suggested treatments have remission rates of about 40–70%. With that in mind, a new approach is presented here—enhancing psychotherapy with medications in order to achieve better (and sometimes faster) remission rates. Although some of these have shown promising results, there is a need of more RCTs in order to conclude the efficacy of each of the treatments.

Ketamine, a glutamate NMDA receptor antagonist, was found to promote extinction and alleviate PTSD-like symptoms in animal models [54, 55]. It is assumed that the ketamine mechanism of action is associated with increasing neurogenesis and BDNF levels in limbic areas of the brain (mainly, amygdala and hippocampus). Ketamine is used as a possible treatment for depression, with promising results [25, 37]. We presented three studies (one RCT) that examined the effect of ketamine infusion on PTSD levels. It seems that although there is rapid improvement, the symptom alleviation does not last for long. As the supposed mechanism of action in ketamine may affect memory reconsolidation, learning and more specifically, extinction learning, further research is needed to evaluate the efficacy of ketamine as an enhancer for extinction-based psychotherapies for PTSD (e.g., PE).

To summarize, as there is an urgent need for new and more effective approaches for treatment of PTSD, to date, not a single agent was developed exclusively for the treatment of PTSD. Augmenting psychotherapy with novel pharmacological agents to enhance therapeutic outcomes appears to be a promising direction that deserves further attention in larger clinical trials.

Compliance with Ethical Standards

Conflict of Interest

Or Duek declares that he has no conflict of interest. Benjamin Kelmendi declares that he has no conflict of interest. Ilan Harpaz-Rotem declares that he has no conflict of interest. Robert H. Pietrzak is a scientific consultant with Cogstate and received payment from them.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593–602. https://doi.org/10.1001/archpsyc.62.6.593.
2. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:617–27. https://doi.org/10.1001/archpsyc.62.6.617.
3. Kilpatrick DG, Resnick HS, Milanak ME, Miller MW, Keyes KM, Friedman MJ. National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria. J Trauma Stress. 2013;26:537–47. https://doi.org/10.1002/jts.21848.
4. Goldstein RB, Smith SM, Chou SP, Saha TD, Jung J, Zhang H, et al. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. Soc Psychiatry Psychiatr Epidemiol. 2016;51:1137–48. https://doi.org/10.1007/s00127-016-1208-5.
5. Seal KH, Bertenthal D, Miner CR, Sen S, Marmar C. Bringing the war back home: mental health disorders among 103 788 US veterans returning from Iraq and Afghanistan seen at Department of Veterans Affairs Facilities. Arch Intern Med Am Med Assoc. 2007;167:476–82. https://doi.org/10.1001/archinte.167.5.476.
6. Smith SM, Goldstein RB, Grant BF. The association between post-traumatic stress disorder and lifetime DSM-5 psychiatric disorders among veterans: data from the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III). J Psychiatr Res. 2016;82:16–22. https://doi.org/10.1016/j.jpsychires.2016.06.022.
7. Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. J Anxiety Disord. 2011;25:456–65. https://doi.org/10.1016/j.janxdis.2010.11.010.
8. Schnurr PP, Hayes AF, Lunney CA, McFall M, Uddo M. Longitudinal analysis of the relationship between symptoms and quality of life in veterans treated for posttraumatic stress disorder. J Consult Clin Psychol. psycnet.apa.org. 2006;74:707–13. https://doi.org/10.1037/0022-006X.74.4.707.
9. Schnurr PP, Lunney CA, Bovin MJ, Marx BP. Posttraumatic stress disorder and quality of life: extension of findings to veterans of the wars in Iraq and Afghanistan. Clin Psychol Rev Elsevier. 2009;29:727–35. https://doi.org/10.1016/j.cpr.2009.08.006.
10. Marmar CR, Schlenger W, Henn-Haase C, Qian M, Purchia E, Li M, et al. Course of posttraumatic stress disorder 40 years after the Vietnam War: findings from the National Vietnam Veterans Longitudinal Study. JAMA Psychiatry. jamanetwork.com. 2015;72:875–81. https://doi.org/10.1001/jamapsychiatry.2015.0803.
11. Rodriguez P, Holowka DW, Marx BP. Assessment of posttraumatic stress disorder-related functional impairment: a review. J Rehabil Res Dev. pdfs.semanticscholar.org. 2012:49, 649–665. https://doi.org/10.1682/JRRD.2011.09.0162.
12. Pietrzak RH, el- Gabalawy R, Tsai J, Sareen J, Neumeister A, Southwick SM. Typologies of posttraumatic stress disorder in the U.S. adult population. J Affect Disord. 2014;162:102–6. https://doi.org/10.1016/j.jad.2014.03.024.
13. Committee on Treatment of Posttraumatic Stress Disorder, Board on Population Health and Public Health Practice, Institute of Medicine. Treatment of posttraumatic stress disorder: an assessment of the evidence. National Academies Press; 2008, DOI: https://doi.org/10.3768/rtipress.2008.mr.0007.0809.
14. Courtois CA, Sonis J, Fairbank JA, Friedman M, Jones R, Roberts J, et al. Clinical practice guideline for the treatment of posttraumatic stress disorder (PTSD) in adults. Manuscript submitted for publication. 2017, DOI: https://doi.org/10.1310/sci2301-20;
15. Monson CM, Shnaider P. Treating PTSD with cognitive-behavioral therapies: interventions that work. American Psychological Association; 2014, DOI: https://doi.org/10.3389/fpsyg.2014.01239.
16. Resick PA, Monson CM, Chard KM. Cognitive processing therapy for PTSD: a comprehensive manual. Guilford Publications; 2016.
17. Ehlers A, Hackmann A, Grey N, Wild J, Liness S, Albert I, et al. A randomized controlled trial of 7-day intensive and standard weekly cognitive therapy for PTSD and emotion-focused supportive therapy. Am J Psychiatry. 2014;171:294–304. https://doi.org/10.1176/appi.ajp.2013.13040552.
18. Foa E, Hembree E, Rothbaum BO. Prolonged exposure therapy for PTSD: emotional processing of traumatic

experiences therapist guide. USA: Oxford University Press; 2007.

19. Helpman L, Papini S, Chhetry BT, Shvil E, Rubin M, Sullivan GM, et al. Ptsd remission after prolonged exposure treatment is associated with anterior cingulate cortex thinning and volume reduction. Depress Anxiety. 2016;33:384–91. https://doi.org/10.1002/da.22471.

20.• Kelmendi B, Adams TG, Yarnell S, Southwick S, Abdallah CG, Krystal JH. PTSD: from neurobiology to pharmacological treatments. Eur J Psychotraumatol. 2016;7:31858.

This review paper provides details on mechanism of mechanism of action of pharmacological treatments for PTSD, including ketamine and MDMA. https://doi.org/10.3402/ejpt.v7.31858.

21. Rauch SAM, Kim HM, Powell C, Tuerk PW, Simon NM, Acierno R, et al. Efficacy of prolonged exposure therapy, sertraline hydrochloride, and their combination among combat veterans with posttraumatic stress disorder: a randomized clinical trial. JAMA Psychiatry [Internet]. 2018;76:117–26.

Available from. https://doi.org/10.1001/jamapsychiatry.2018.3412.

22. Berger W, Mendlowicz MV, Marques-Portella C, Kinrys G, Fontenelle LF, Marmar CR, et al. Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic review. Prog Neuro-Psychopharmacol Biol Psychiatry. 2009;33:169–80. https://doi.org/10.1016/j.pnpbp.2008.12.004.

23. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. cochranelibrary.com; 2006;CD002795, DOI: https://doi.org/10.1002/14651858.CD002795.pub2.

24. Schottenbauer MA, Glass CR, Arnkoff DB, Tendick V, Gray SH. Nonresponse and dropout rates in outcome studies on PTSD: review and methodological considerations. Psychiatry. 2008;71:134–68. https://doi.org/10.1521/psyc.2008.71.2.134.

25. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47:351–4. https://doi.org/10.1016/S0006-3223(99)00230-9.

26. National Collaborating Centre for Mental Health (UK). Common mental health disorders: identification and pathways to care. Leicester (UK): British Psychological Society; 2012.

27. Ostacher MJ, Cifu AS. Management of posttraumatic stress disorder. JAMA. 2019;321:200–1. https://doi.org/10.1001/jama.2018.19290.

28. Shapiro F Eye movement desensitization and reprocessing (EMDR) therapy, 3rd Edition: Basic Principles, Protocols, and Procedures. Guilford Publications; 2017, DOI: https://doi.org/10.1103/PhysRevD.95.101303.

29. Lindauer RJL, Gersons BPR, van Meijel EPM, Blom K, Carlier IVE, Vrijlandt I, et al. Effects of brief eclectic psychotherapy in patients with posttraumatic stress disorder: randomized clinical trial. J Trauma Stress. 2005;18:205–12. https://doi.org/10.1002/jts.20029.

30. Schauer M, Schauer M, Neuner F, Elbert T. Narrative exposure therapy: a short-term treatment for traumatic stress disorders. Hogrefe Publishing; 2011.

31. Rothbaum BO, Cahill SP, Foa EB, Davidson JRT, Compton J, Connor KM, et al. Augmentation of sertraline with prolonged exposure in the treatment of posttraumatic stress disorder. J Trauma Stress. 2006;19:625–38. https://doi.org/10.1002/jts.20170.

32. Simon NM, Connor KM, Lang AJ, Rauch S, Krulewicz S, LeBeau RT, et al. Paroxetine CR augmentation for posttraumatic stress disorder refractory to prolonged exposure therapy. J Clin Psychiatry. 2008;69:400–5. https://doi.org/10.4088/JCP.v69n0309.

33. Sherwood AM, Prisinzano TE. Novel psychotherapeutics - a cautiously optimistic focus on hallucinogens. Expert Rev Clin Pharmacol. 2018;11:1–3.

34. Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, et al. Biological studies of post-traumatic stress disorder. Nat Rev Neurosci. 2012;13:769–87. https://doi.org/10.1038/nrn3339.

35. Chambers RA, Bremner JD, Moghaddam B, Southwick SM, Charney DS, Krystal JH. Glutamate and post-traumatic stress disorder: toward a psychobiology of dissociation. Semin Clin Neuropsychiatry. 1999;4:274–81. https://doi.org/10.153/SCNP00400274.

36. Bailey CR, Cordell E, Sobin SM, Neumeister A. Recent progress in understanding the pathophysiology of post-traumatic stress disorder: implications for targeted pharmacological treatment. CNS Drugs. 2013;27:221–32. https://doi.org/10.1007/s40263-013-0051-4.

37. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013;74:250–6. https://doi.org/10.1016/j.biopsych.2012.06.022.

38. Vyas A, Pillai AG, Chattarji S. Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. Neuroscience. 2004;128:667–73. https://doi.org/10.1016/j.neuroscience.2004.07.013.

39. Duman RS, Li N, Liu R-J, Duric V, Aghajanian G. Signaling pathways underlying the rapid antidepressant actions of ketamine. Neuropharmacology. 2012;62:35–41. https://doi.org/10.1016/j.neuropharm.2011.08.044.

40. McEwen BS. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. Eur J Pharmacol. 2008;583:174–85. https://doi.org/10.1016/j.ejphar.2007.11.071.

41.• Clarke M, Razmjou S, Prowse N, Dwyer Z, Litteljohn D, Pentz R, et al. Ketamine modulates hippocampal neurogenesis and pro-inflammatory cytokines but not stressor induced neurochemical changes. Neuropharmacology. 2017;112:210–20.

This paper provides an in depths explanation of the mechanism behind ketamine and neurogenesis. https://doi.org/10.1016/j.neuropharm.2016.04.021.

42. Bai X, Yan Y, Canfield S, Muravyeva MY, Kikuchi C, Zaja I, et al. Ketamine enhances human neural stem cell proliferation and induces neuronal apoptosis via reactive oxygen species-mediated mitochondrial pathway. Anesth Analg. 2013;116:869–80. https://doi.org/10.1213/ANE.0b013e3182860fc9.
43. Li N, Lee B, Liu R-J, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. science.sciencemag.org. 2010;329:959–64. https://doi.org/10.1126/science.1190287.
44. Smith NB, Doran JM, Sippel LM, Harpaz-Rotem I. Fear extinction and memory reconsolidation as critical components in behavioral treatment for posttraumatic stress disorder and potential augmentation of these processes. Neurosci Lett. 2017;649:170–5. https://doi.org/10.1016/j.neulet.2017.01.006.
45. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry. 2009;66:1075–82. https://doi.org/10.1016/j.biopsych.2009.06.026.
46. Garfinkel SN, Abelson JL, King AP, Sripada RK, Wang X, Gaines LM, et al. Impaired contextual modulation of memories in PTSD: an fMRI and psychophysiological study of extinction retention and fear renewal. J Neurosci. 2014;34:13435–43. https://doi.org/10.1523/JNEUROSCI.4287-13.2014.
47. Homan P, Levy I, Feltham E, Gordon C, Hu J, Li J, et al. Neural computations of threat in the aftermath of combat trauma. Nat Neurosci. 2019;22:470–6. https://doi.org/10.1038/s41593-018-0315-x.
48. Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature. 2000;406:722–6. https://doi.org/10.1038/35021052.
49. Schiller D, Monfils M-H, Raio CM, Johnson DC, Ledoux JE, Phelps EA. Preventing the return of fear in humans using reconsolidation update mechanisms. Nature. 2010;463:49–53.
50. Lee JLC, Nader K, Schiller D. An update on memory reconsolidation updating. Trends Cogn Sci. 2017;21:531–45. https://doi.org/10.1016/j.tics.2017.04.006.
51. Debiec J, LeDoux JE, Nader K. Cellular and systems reconsolidation in the hippocampus. Neuron. 2002;36:527–38. https://doi.org/10.1016/S0896-6273(02)01001-2.
52. Thomaes K, Dorrepaal E, Draijer N, Jansma EP, Veltman DJ, van Balkom AJ. Can pharmacological and psychological treatment change brain structure and function in PTSD? A systematic review. J Psychiatr Res. 2014;50:1–15. https://doi.org/10.1016/j.jpsychires.2013.11.002.
53. Rothbaum BO, Price M, Jovanovic T, Norrholm SD, Gerardi M, Dunlop B, et al. A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. Am J Psychiatry. 2014;171:640–8. https://doi.org/10.1176/appi.ajp.2014.13121625.
54. Zhang L-M, Zhou W-W, Ji Y-J, Li Y, Zhao N, Chen H-X, et al. Anxiolytic effects of ketamine in animal models of posttraumatic stress disorder. Psychopharmacology. 2015;232:663–72. https://doi.org/10.1007/s00213-014-3697-9.
55. Hou L, Qi Y, Sun H, Wang G, Li Q, Wang Y, et al. Applying ketamine to alleviate the PTSD-like effects by regulating the HCN1-related BDNF. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;86:313–21. https://doi.org/10.1016/j.pnpbp.2018.03.019.
56. Schiller D, Phelps EA. Does reconsolidation occur in humans? Front Behav Neurosci. 2011;5:24. https://doi.org/10.3389/fnbeh.2011.00024.
57. Deębiec J, Doyère V, Nader K, LeDoux JE. Directly reactivated, but not indirectly reactivated, memories undergo reconsolidation in the amygdala. Proc Natl Acad Sci U S A. 2006;103:3428–33.
58. Barker JM, Boonstra R, Wojtowicz JM. From pattern to purpose: how comparative studies contribute to understanding the function of adult neurogenesis. Eur J Neurosci. 2011;34:963–77. https://doi.org/10.1111/j.1460-9568.2011.07823.x.
59. Suárez-Pereira I, Carrión ÁM. Updating stored memory requires adult hippocampal neurogenesis. Sci Rep. 2015;5:13993.
60. Duclot F, Perez-Taboada I, Wright KN, Kabbaj M. Prediction of individual differences in fear response by novelty seeking, and disruption of contextual fear memory reconsolidation by ketamine. Neuropharmacology. 2016;109:293–305. https://doi.org/10.1016/j.neuropharm.2016.06.022.
61. Krystal JH, Abdallah CG, Averill LA, Kelmendi B, Harpaz-Rotem I, Sanacora G, et al. Synaptic loss and the pathophysiology of PTSD: implications for ketamine as a prototype novel therapeutic. Curr Psychiatry Rep. 2017;19:74.
62. Schönenberg M, Reichwald U, Domes G, Badke A, Hautzinger M. Effects of peritraumatic ketamine medication on early and sustained posttraumatic stress symptoms in moderately injured accident victims. Psychopharmacology. 2005;182:420–5. https://doi.org/10.1007/s00213-005-0094-4.
63. McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH. The correlation between ketamine and posttraumatic stress disorder in burned service members. J Trauma. 2008;64:S195–8.

Discussion S197–8. https://doi.org/10.1097/TA.0b013e318160ba1d.

64. D'Andrea D, Andrew SR. Transient resolution of treatment-resistant posttraumatic stress disorder following ketamine infusion. Biol Psychiatry. 2013;74:e13–4. https://doi.org/10.1016/j.biopsych.2013.04.019.

65. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA Psychiatry. 2014;71:681–8. https://doi.org/10.1001/jamapsychiatry.2014.62.
66. Albott CS, Lim KO, Forbes MK, Erbes C, Tye SJ, Grabowski JG, et al. Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. J Clin Psychiatry [Internet]. 2018;79:17m11634. Available from. https://doi.org/10.4088/JCP.17m11634.
67. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The ptsd checklist for dsm-5 (pcl-5). Scale available from the National Center for PTSD at www ptsd va gov 2013, DOI: https://doi.org/10.1055/s-0033-1351234;
68. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382–9. https://doi.org/10.1192/bjp.134.4.382.
69. Pradhan B, Mitrev L, Moaddell R, Wainer IW. 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. Biochim Biophys Acta, Proteins Proteomics. 2018;1866:831–9. https://doi.org/10.1016/j.bbapap.2018.03.006.
70. Zimmerman JM, Maren S. NMDA receptor antagonism in the basolateral but not central amygdala blocks the extinction of Pavlovian fear conditioning in rats: central amygdala, glutamate receptors and extinction of fear. Eur J Neurosci. 2010;17:no, DOI: https://doi.org/10.1111/j.1460-9568.2010.07223.x.
71. Litz BT, Salters-Pedneault K, Steenkamp MM, Hermos JA, Bryant RA, Otto MW, et al. A randomized placebo-controlled trial of D-cycloserine and exposure therapy for posttraumatic stress disorder. J Psychiatr Res. 2012;46:1184–90. https://doi.org/10.1016/j.jpsychires.2012.05.006.
72. Difede J, Cukor J, Wyka K, Olden M, Hoffman H, Lee FS, et al. D-cycloserine augmentation of exposure therapy for post-traumatic stress disorder: a pilot randomized clinical trial. Neuropsychopharmacology. 2014;39:1052–8. https://doi.org/10.1038/npp.2013.317.
73. Friedman MJ, Bernardy NC. Considering future pharmacotherapy for PTSD. Neurosci Lett. 2017;649:181–5. https://doi.org/10.1016/j.neulet.2016.11.048.

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