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Medication-Assisted Psychotherapy for PTSD

Effective treatment approaches for posttraumatic stress disorder (PTSD) include psychotherapy and pharmacotherapy, with treatment guidelines emphasizing trauma-focused treatments, such as prolonged exposure (PE) and cognitive processing therapy (CPT) as first-line interventions. Unfortunately, trauma-focused psychotherapies are efficacious only in approximately 50% of patients treated, indicating substantial need to improve these treatments (American Psychological Association, 2017). Over the past decade, the possibility of using medications to enhance the efficacy of psychotherapy, collectively known as medication-assisted psychotherapy (MAP), has been the focus of increased research efforts.

Rapid advances in the neuroscience of learning and memory and animal studies of drugs to reduce conditioned and unconditioned fears paved the way for translational research clinical trials in humans. MAP approaches for patients with fear disorders (including specific phobia, social anxiety disorder, panic disorder, and PTSD) typically involve the use of medications that are not therapeutic for PTSD as monotherapy, but rather the medications are dosed in conjunction with the delivery of a psychological intervention, with the aim of reducing the strength or dominance of the fear memories.

The recent rapid increase in the number of studies evaluating medications to enhance psychotherapies for fear disorders has led to a mix of terms that can be difficult for clinicians to follow. Although some authors have referred to medications used to improve trauma-focused therapies as “cognitive enhancers,” that term can encompass psychotropics used for a variety of other psychiatric purposes and lacks the specificity of how medications are applied in MAP studies. This article provides an overview of the status of MAP studies for PTSD, classifying medications into three

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categories based on their theorized mechanisms for enhancing psychological interventions: extinction enhancement, altered reconsolidation, and psychotherapy process catalysts.

Extinction learning involves the formation of new memories related to the fear cues and contexts (in PTSD, the reminders of the traumatic event). Persistent fear after trauma is sustained by avoidance behaviors (physical and mental) that prevent the patient from engaging with the fear memory. PE is a specific protocol for exposure therapy based partly on animal models of conditioning and learning which seek to reduce fear through repeated presentations of the feared stimuli without the presence of adverse consequences. During exposure therapy, feared stimuli can be presented in several ways, including the patient's imagination (imaginal), in real life (*in vivo*), or in virtual reality. This process is thought to lead to habituation and eventual extinction of fear by forming a new memory trace that competes for expression (activation) with the original fear memory when feared cues or contexts are encountered. Successful extinction learning occurs when the extinction memory is consistently dominant and the fear memory is rarely expressed. However, even after successful extinction learning, the fear memory can reemerge as the dominant memory: 1) if the fear cue is encountered in a context different from that in which extinction learning occurred (called “renewal” in the animal literature); 2) if a new stressor is encountered (“reinstatement”); or 3) simply with the passage of time (“spontaneous recovery”). Importantly, in this usage, adopted from the animal learning literature, “spontaneous recovery” refers specifically to the fear memory re-emerging and is a negative outcome; it should not be confused with recovery from the psychiatric illness, a positive outcome (Sevenster et al., 2018).

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Altered reconsolidation is a second approach to modifying fear, but one that does not employ the delivery of psychotherapy. In contrast to extinction, which aims to develop a new, less emotionally powerful memory trace associated with a person's trauma, altered reconsolidation aims to remodel the original memory. When retrieved, an established memory becomes briefly plastic, vulnerable to modification by pharmacological effects, before undergoing reconsolidation and returning to a new stable state. By altering the original fear memory, reconsolidation offers the advantages of being quicker than extinction training, and potentially avoids the problems of renewal, reinstatement, and spontaneous recovery of the fear experiences bound to the memory. To retrieve the traumatic memory in reconsolidation studies of PTSD, patients are usually dosed with the putative reconsolidation-altering drug and then asked to write a script of their traumatic experience(s) along with its associated emotions, without any provision of psychotherapy to activate and access the memory. At subsequent visits, patients listen to their recorded scripts after being dosed with the drug, with the goal of disrupting the memory as it is reconsolidated to diminish the associated fear. Evaluating whether reconsolidation was successfully altered requires assessment of PTSD symptoms or measurement of physiological responses to the trauma script at follow-up visits. Although not formally providing psychotherapy, MAP studies of altered reconsolidation have been performed in offices with psychotherapists, to allow for education, support, and crisis management if necessary (Wood et al., 2015; Brunet et al., 2018).

A third type of medication used in MAP studies is the psychotherapy process catalyst. Unlike the prior two approaches, these agents are not employed because of their ability to directly impact the biology of fear memories. Rather, these medications are designed to increase the patient's openness to experiencing and ability to tolerate feared memories, and to enhance the therapeutic alliance during therapy sessions. Low emotional activation during exposure sessions is associated with poorer outcomes to trauma-focused therapies; without emotional engagement, it is likely that both reconsolidation and extinction learning are diminished. By enabling greater engagement with fear memories, these medications permit the patient's traumatic events to be processed more fully (Feduccia and Mithoefer, 2018).

Neurobiology of Fear Memory Extinction and Reconsolidation

Fear is perhaps the most consistently preserved neural system between humans and other mammals, allowing for neurobiological, behavioral, and pharmacological studies in rodents to be translated into humans with greater confidence than other disorders such as depression. The complex biology of fear learning, extinction, and reconsolidation have been the subject of excellent recent reviews (Singewald et al., 2015). Although the neurobiological knowledge base is beyond the scope of this article, a brief summary of the aspects relevant to MAP studies is helpful to understand the rationale for the drugs used in this research.

The amygdala is the key brain structure involved in fear acquisition and consolidation, with glutamate signaling via *N*-methyl-D-aspartate (NMDA) receptors (specifically those containing *GuN2A* subunits) involved in the synaptic plasticity within the amygdala that establishes the fear memory. Fear inhibition and extinction learning depend extensively on interactions between the ventromedial prefrontal cortex

and the amygdala, with the hippocampus important for contextual aspects of extinction learning. Glutamate signaling via NMDA receptors (specifically those with *GuN2B* and *GuN2C* subunits) is involved in extinction learning. Blockade of glutamate receptors impairs both fear learning and extinction of fear. Both serotonin and norepinephrine are believed to contribute to fear acquisition, but of the two, only norepinephrine is involved in extinction learning. Higher levels of cortisol, the predominant glucocorticoid in humans, appears to protect against the establishment of fear after trauma but facilitate the consolidation of extinction learning. The biological processes underlying reconsolidation overlap substantially with those for original memory formation, though there are subtle differences. Important components of reconsolidation evaluated in MAP studies include norepinephrine binding to beta receptors and cortisol binding to glucocorticoid receptors (Kida, 2019).

Outcome Measures in MAP Trials

The type and timing of outcome measures are important considerations in MAP trials. Clinical outcomes have the greatest interest for clinicians, typically assessed by a change in PTSD symptoms or loss of PTSD diagnosis. Clinical "response" is also commonly reported but is inconsistently defined across trials. Because many patients benefit from PE in the absence of MAP, trials to test the added benefit arising from medication enhancement must be large enough to overcome the proportion that do well on PE alone (floor effects). To address this concern, MAP trials often have employed an abbreviated course of PE (i.e., under-dosing the therapy), with the aim of testing whether the medication can speed the rate of improvement. Potential benefits from accelerating treatment effects include reducing drop-out and treatment cost. However, the most important clinical applications of MAP are whether there are benefits that endure in the months post-therapy and whether MAP can prove useful for patients who failed to benefit from traditional trauma-focused therapies.

Several MAP studies have used physiologic measures of reactivity to trauma or fear cues as outcomes, including changes in startle, cortisol, heart rate, facial fear expression, and glucocorticoid receptor sensitivity. Patients with PTSD demonstrate several deficits in the ability to overcome fear, including impaired extinction of conditioned fear (i.e., requiring more exposures to safety cues to overcome initial fear learning) and heightened fear-potentiated startle responses during fear conditioning and extinction testing. The most common laboratory method for assessing fear learning and extinction in humans involves the use of startle paradigms. These models use aversive stimuli, such as loud noises or air blasts to the throat, presented simultaneously with neutral stimuli, such as the image of a colored shape. Through this pairing, the subject acquires a fear of the shape (fear acquisition). The strength of the fear learning is measured by the strength of the blinking reflex when exposed to the shape. During a subsequent session, the subject is exposed to the shape without the delivery of the aversive stimuli (extinction training), which leads to decline of fear responding to the shape, reflecting extinction learning or potentially altered reconsolidation.

Enhanced Extinction

In MAP studies aiming to enhance extinction, the medication is not given during the first 1-2 therapy sessions, when patients are oriented to treatment. Rather, the drug is dosed only during sessions

when the therapeutic exposures occur. PE treatment in MAP studies often varies from standard PE by excluding the between-session homework and *in vivo*: exposure components, when learning may be occurring in the absence of medication effects. Many PTSD MAP studies have omitted these components, providing only imaginal or virtual reality exposures in sessions to fully isolate the extinction-enhancing effects of the medication.

D-cycloserine

The most extensively studied drug used in MAP therapies is D-cycloserine (DCS). DCS was originally approved as an antibiotic for tuberculosis, but at low doses acts as a full agonist at GluN2C and a partial agonist at GluN2A, 2B, and 2D subtypes of the glutamate receptor.

There have been four published randomized controlled trials (RCTs) evaluating the efficacy of DCS augmentation of therapeutic exposure treatments for PTSD in adults (Mataix-Cols et al., 2017), and one in children and adolescents. (Scheeringa and Weems, 2014). Only one of these trials, applying a full course of 12 sessions of virtual reality exposure (VRE) therapy in 25 civilians with trauma related to the 9/11 World Trade Center terrorist attack, found DCS significantly improved clinical outcomes over placebo by the end of treatment (Difede et al., 2012). Notably, this trial differed from the unsuccessful trials in that it enrolled an exclusively civilian sample and had a very low drop-out rate of 12% (Difede et al., 2012). In addition, this trial used a higher dose of DCS (100 mg) and a longer period between dosing and therapy (90 minutes) compared to the negative trials (which used 50 mg dosed 30-60 minutes prior to therapy). The benefits of DCS over placebo in this study were even larger at the six-month follow-up than at the post-treatment assessment.

Two other, larger, adult trials (Rothbaum et al., 2014; de Kleine et al., 2012) and the pediatric trial (Scheeringa and Weems, 2014) found no significant benefits on primary clinical outcomes. However, secondary analyses of both adult trials found some support for DCS effects on extinction. De Kleine and colleagues found that patients with more severe PTSD symptoms who showed a slower response to the PE had superior outcomes with DCS at both the post-treatment and three-month follow-up timepoints (de Kleine et al., 2012). Rothbaum and colleagues found no benefit of DCS over placebo in a six session VRE PE trial on clinical measures, but two biological markers of fear reactivity, startle response and salivary cortisol concentrations, improved significantly more in the DCS than the placebo group between baseline and six-month follow-up (Rothbaum et al., 2014). Interestingly, these are the more objective and translational measures and were consistent with the animal studies.

Concerningly, one DCS MAP trial in male combat Veterans found significantly worse PTSD and depression outcomes at post-treatment in the DCS-treated group compared to the placebo group (Litz et al., 2012). In this trial, DCS/placebo was administered only 30 minutes prior to the start of therapy as part of an abbreviated course of six imaginal PE sessions (Litz et al., 2012). Post-hoc analyses found that compared to placebo-treated patients, DCS-treated patients had an increase in self-reported distress beginning with the second exposure session, suggesting that DCS may have increased fear learning after the session of exposure. A second trial also found that the degree of PTSD symptom improvement in the DCS arm (but not placebo arm) depended upon the amount of between session

extinction learning, with those with the greatest extinction learning showing better outcomes with DCS than placebo, but the opposite effect when between session learning was weak (Rothbaum et al., 2014). Biologically, these results suggest that DCS may enhance extinction learning if sufficient fear reduction during the session occurs but enhance fear learning via reconsolidation if fear remains high by the end of an exposure session, a finding supported by results of trials evaluating DCS MAP for other fear disorders. This association has been summarized that DCS (and other potential extinction-enhancing agents) can make good exposures better and bad exposures worse (Litz et al., 2012), though it should be noted that one placebo-controlled DCS MAP trial for PTSD trial did not find this association (de Kleine et al., 2015).

Methylene Blue

Methylene blue (MB), also known as methylthionium chloride, has been studied as an extinction enhancer, though it does not directly modulate neurotransmitters. Rather, MB stimulates mitochondrial metabolism preferentially in metabolically active cells by inducing cytochrome oxidase, leading to increases in oxygen consumption and adenosine triphosphate. Because extinction learning is a metabolically active process, MB can enhance the activity of neurons involved in extinction, potentially strengthening learning. Rodent studies and human MAP trials for phobic disorders have demonstrated MB can enhance extinction learning. However, in the only PTSD MAP trial to date, MB failed to prove superior to PBO among 42 patients receiving six sessions of imaginal PE (Zoellner et al., 2017).

Because MB increases metabolic activity at active synapses, it also has the potential to adversely enhance reconsolidation of the fear associated with a trauma memory, an effect observed in a claustrophobia trial of MB. An advantage of MB is that it can be administered after an exposure session, which can allow for withholding of the dose for patients having high levels of persisting fear at the end of an exposure session to avoid possible fear-strengthening effects. An additional concern with MB is that it is a potent inhibitor of monoamine oxidase (i.e., it is an MAOI). Consequently, it carries a warning of potential serotonergic syndrome if given to patients taking SSRIs or SNRIs. Finally, MB causes urine to turn a blue-green color, so adequate blinding requires use of a placebo capable of producing the same effect.

Yohimbine

Yohimbine is an alpha-2 receptor agonist that acts to increase norepinephrine release from the locus ceruleus, resulting in greater NE signaling in the amygdala, hippocampus and PFC. By increasing NE release, yohimbine acts to enhance emotional engagement with traumatic memories, often with increased subjective distress; this effect may be considered the opposite of that produced with benzodiazepines. Because low emotional engagement upon exposure to trauma cues has been associated with poorer outcomes with PE, the potential utility of yohimbine for fear disorders is to increase emotional distress and engagement with feared cues and memories during PE sessions. Thus, yohimbine is not theorized to enhance extinction by modulating the neurobiological components of extinction learning as occurs with DCS and MB, but rather by maximizing the exposure conditions known to optimize extinction learning in PE.

Yohimbine demonstrated efficacy in enhancing PE for claustrophobia and social anxiety, but only one RCT has evaluated its use in PTSD. Only one trial of yohimbine MAP for PTSD has been conducted, which used a single dose of yohimbine prior to the first exposure session (Tuerk et al., 2018). Patients receiving yohimbine reported significantly greater distress, heart rate, and blood pressure during the first PE exposure session, indicating greater emotional engagement with trauma memories. No patients experienced a panic attack, and no flashbacks were reported, after the oral administration of yohimbine; these potential side effects were of concern based on earlier studies in which intravenous yohimbine administration (0.4 mg/kg) to patients with PTSD had induced panic attacks in 42-70% and flashbacks in 31-40%. One week after dosing, the primary outcome of heart rate reactivity to trauma cues showed a significant reduction in the yohimbine compared to placebo group, potentially indicating enhanced inhibition of fear, though no benefits on PTSD severity at the end of a standard course of PE was observed. The study indicates that yohimbine can increase engagement with PE and thereby may improve the efficiency of PE therapy.

Glucocorticoids

The hypothalamic pituitary adrenal (HPA) axis is crucially involved in fear learning and extinction, with genetic, molecular, receptor, and hormonal components of the HPA axis implicated in the development and maintenance of PTSD symptoms (Dunlop and Wong, 2019). Glucocorticoids have complex effects on memory, being involved in both memory formation and reconsolidation while also diminishing retrieval of emotionally salient memories. Administration of glucocorticoids can facilitate extinction learning, possibly by potentiating the effects of NMDA receptors in the amygdala. These diverse effects have led to studies evaluating the therapeutic use of glucocorticoids for 1) enhancement of extinction learning, 2) altered reconsolidation of trauma memories, and 3) prevention of PTSD after trauma (Dunlop and Wong, 2019).

Glucocorticoid enhancement of fear extinction in humans was first demonstrated with hydrocortisone (an analogue of human cortisol) in patients with phobic disorders. In the first trial for extinction enhancement in PTSD conducted in 24 military Veterans, 30 mg of oral hydrocortisone given 20 minutes before sessions 3-10 of imaginal PE produced greater reductions over time than placebo in PTSD symptoms, though there was no difference in post-treatment CAPS scores (Yehuda et al., 2015). The beneficial effect appeared to be driven by a significantly lower drop-out rate in hydrocortisone-treated patients, suggesting that the drug helped reduce the distress associated with engaging in PE. A second trial of glucocorticoid effects was conducted in 27 Veterans undergoing 6-11 therapy sessions with VRE who took 0.5 mg of oral dexamethasone or placebo the night before their VRE sessions (Maples-Keller et al., 2019). In contrast to the first study, significantly more dexamethasone-treated patients dropped out of the study and no benefit in PTSD symptoms were found. These contrasting results may be explained from the divergent effects of the two glucocorticoids on circulating cortisol at the time of the exposure sessions. In contrast to hydrocortisone (the name applied to cortisol administered exogenously), dexamethasone suppresses endogenous cortisol and has limited ability to cross the blood-brain barrier, thereby diminishing activation of central nervous system (CNS) glucocorticoid receptors (Dunlop and Wong, 2019).

Altered Reconsolidation

Altered reconsolidation approaches to PTSD have been less extensively studied in humans than enhanced extinction. Preclinical studies and some human trials of patients with phobia have demonstrated the value of targeting reconsolidation for overcoming fear, though results in PTSD studies have been mixed. Three small trials involving single-session doses of propranolol (a beta-receptor blocker) or mifepristone (a glucocorticoid receptor antagonist) failed to produce evidence of altered reconsolidation or reduction of PTSD symptoms (Wood et al., 2015).

The best evidence of MAP to alter reconsolidation of trauma memories in patients with PTSD emerged from a placebo-controlled RCT of “pre-reactivation” propranolol involving 60 adults with PTSD, who were given the drug or placebo prior to the recall of the traumatic memory (Brunet et al., 2018). As opposed to the earlier unsuccessful reconsolidation trials applying a single session administration of propranolol, this study used up to six sessions of pairings, in which a mixture of both immediate-release and extended-release propranolol or placebo was administered 90 minutes prior to memory reactivation (Brunet et al., 2018). At the initial visit, one hour after ingesting the pills, patients wrote a one-page trauma narrative, which could take up to 30 minutes to complete, and then read the narrative to the study team member. At the subsequent visits, patients simply read the trauma script aloud once 90 minutes after the propranolol dosing. Differences between the propranolol and placebo groups in self-reported PTSD symptoms emerged by week 2 of treatment, with large and statistically significant gains evident by the end of treatment. Gains were evident at a six-month follow-up evaluation, though the proportion of the sample assessed at this point was small.

Another placebo controlled RCT with a relatively similar design to the successful propranolol trial was conducted using high dose oral dexamethasone (0.15 mg/kg) administered one hour prior to trauma memory reactivation (via writing or listening to personal trauma scripts) over four sessions approximately one week apart. Superior outcomes in PTSD symptoms were present in the dexamethasone-treated patients at the one- and three-months follow-up visits (Suris et al., 2017). Although the authors did not discuss this result as an altered reconsolidation paradigm, the administration of a memory-modifying agent during reactivation without concomitant delivery of psychotherapy suggests reconsolidation effects may have occurred. Interestingly, dexamethasone-treated patients were twice as likely to drop-out of this study as placebo-treated patients, a finding similar to that observed by Maples-Keller and colleagues (2019) in their study of low-dose dexamethasone.

A significant challenge to altered reconsolidation approaches for PTSD is that script-driven imagery may be inadequate to sufficiently destabilize the traumatic memory to allow for reconsolidation effects. One study in rodents indicated that administering DCS prior to traumatic memory reactivation could help reactivate difficult to retrieve memories, thus making them accessible for altered reconsolidation with pharmacologic intervention; one human trial applying this approach was unsuccessful (Wood et al., 2015). The timing of drug administration is a crucial variable for the success in altering reconsolidation. Reconsolidation begins just minutes after a memory is reactivated, so the pharmacologic agent must be ingested with sufficient time for the drug to reach necessary concentrations in

the CNS, though this also runs the risk of diminishing the chance of fully reactivating the memory at the time of trauma script exposure. Finally, definitive demonstration of reconsolidation alteration in humans is difficult because by administering a medication such as propranolol prior to memory reactivation, it is possible that the drug is simply interfering with recall of the trauma memory, rather than altering it. In addition, because altered reconsolidation should result in a weakened memory for long periods that cannot be reinstated, long-term follow-up of participants to test for the presence of this effect are required.

Psychotherapy Process Catalysts

MDMA

3,4-Methylenedioxymethamphetamine (MDMA) is a stimulant with the direct pharmacologic effects of increasing serotonin release and preventing the reuptake of serotonin, norepinephrine, and dopamine through actions at their respective monoamine transporters. Acute MDMA administration also enhances prolactin and oxytocin release. MDMA ingestion improves mood and affiliative behaviors, increases openness to experience, and allows patients to engage with traumatic memories with a diminished sense of imminent threat. Theories concerning how MDMA can enhance psychotherapy for PTSD emphasize the psychological constructs of reduced avoidance of traumatic material, increased acceptance of emotions related to trauma, and willingness to engage with traumatic memories. These effects have led to MDMA being considered as an “enactogen,” referring to its capacity to enhance inner awareness. Furthermore, MDMA can increase trust and thereby improve the therapeutic alliance. Beyond these psychological factors, MDMA has demonstrated enhanced extinction in fear conditioning studies with rodents, though concomitant SSRI administration interferes with this effect (Young et al., 2017).

MDMA-assisted psychotherapy has been manualized by the Multidisciplinary Association for Psychedelic Studies. Briefly, the therapy is conducted by two therapists (typically one female, one male) structured to alternate between periods of patient introspection and periods of interaction with the therapists. The therapy aims to engage the patient with past traumatic events without feeling overwhelmed by the intensity of feelings associated with the memories. The MDMA trials conducted to date have employed two or three 90-minute preparatory sessions before the MDMA dosing session. The trials used two or three MDMA dosing sessions, each given a month apart. Therapy on the day of the MDMA dosing session lasts about 8 hours. The MDMA is dosed at the beginning of the session, with the option of administering a second dose (50% of the original dose) after 90 minutes. The day following the MDMA dosing session, a 90-minute integration session is conducted, followed by three additional 90 minutes sessions over the subsequent weeks to further integrate and process their MDMA experience.

Six small RCTs of MDMA-assisted psychotherapy have been conducted that support its potential clinical utility. The initial doses of MDMA used in these studies ranged from 75-125 mg/d in the active arm; control arms used either placebo or lower doses (25-40 mg) of MDMA. Four of the trials have been published: two demonstrated statistically significant improvements in PTSD symptoms in the active MDMA arms (Mithoefer et al., 2011,

Mithoefer et al., 2018), whereas two others demonstrated large effect sizes that fell short of statistical significance (Mithoefer et al., 2019). Each trial included at least one year of follow-up, finding that benefits of the treatment were sustained for most patients (Mithoefer et al., 2013). The pooled data across the six trials (active MDMA arms: $n=72$; placebo/control arms $n=31$) found additional benefits on PTSD symptoms accrued with each MDMA dosing session (Mithoefer et al., 2019). The most common side effects attributable to MDMA were anxiety, dizziness, jaw clenching, reduced appetite and nausea. Suicidal ideation worsened more often in the active MDMA groups than placebo groups, and elevations in blood pressure and body temperature occurred. No concerns around impaired cognition were detected from neuropsychological testing, and no patients reported abuse of MDMA during follow-up (Mithoefer et al., 2019). The absence of abuse of MDMA by patients is unsurprising, given the clinical setting and non-reinforcing experience of revisiting trauma memories during the MDMA session.

Oxytocin

Oxytocin is another compound that may enhance the therapeutic alliance, though preclinical data suggest it also has independent extinction-enhancing effects. One placebo controlled RCT of 17 civilians with PTSD evaluated the efficacy of intranasal oxytocin (40 IU) administered 45 minutes prior to 8 PE sessions, finding non-significantly lower overall PTSD symptom scores in the oxytocin group (Flanagan et al., 2018). Other studies have failed to find benefit of oxytocin combined with psychotherapy.

Psychotherapy-Pharmacotherapy Combination Treatment

Combination treatment refers to the delivery of psychotherapy along with daily dosing of an antidepressant or other medication that directly targets PTSD symptoms. Beyond PTSD symptoms, patients in psychotherapy for PTSD may also be taking daily psychotropic medications for symptoms of comorbid disorders, such as major depression, obsessive compulsive disorder, or bipolar disorder. Combined treatment for PTSD is distinct from MAP in that administration of the medication is not limited to the psychotherapy sessions and is not used with the intent of modifying trauma memories. Rather, medications in combined treatment are generally considered to have effects on PTSD symptoms that are separate and additive to those achieved with psychotherapy. However, selective serotonin reuptake inhibitors (SSRIs) have actions that may enhance the efficacy of psychotherapy or the patient's experience of therapy. Specifically, SSRIs and ketamine raise brain-derived neurotrophic factor (BDNF) levels and SSRIs enhance the maturation and survival of new neurons in the hippocampus, actions which may be relevant to extinction learning in trauma-focused therapies (Eliwa et al., 2017). SSRIs may act to catalyze the psychotherapy process through their effects of increasing affiliative problem-solving behavior and increased attention to positive stimuli. SSRIs decrease amygdala activity and fear responses, which could have the positive effect of helping retain the patient in treatment. Conversely, by diminishing the emotional intensity of retrieved trauma memories, SSRIs may reduce the durability of gains achieved with cognitive behavior therapy after antidepressant discontinuation, as has been observed with the tricyclic antidepressant imipramine in panic disorder.

The effects of SSRIs on the durability of extinction learning after prolonged exposure therapy for PTSD have not been carefully assessed. Concomitant use of an antidepressant appeared to diminish the efficacy of DCS in a MAP trial for Obsessive-compulsive Disorder (OCD), suggesting that SSRIs may act to interfere with extinction learning. However, an individual participant meta-analysis of 21 DCS MAP trials for a variety of anxiety disorders and PTSD did not find that antidepressants reduced the efficacy of DCS for short or long-term outcomes (Mataix-Cols et al., 2017). Indeed, this analysis found that compared to patients not on an antidepressant, those taking an antidepressant during exposure therapy had significantly better outcomes at follow-up, irrespective of whether the patients had received DCS or placebo (Mataix-Cols et al., 2017).

Only two RCTs have specifically evaluated the efficacy of combined PE with an SSRI versus PE with placebo from the beginning of treatment (Schneier et al., 2012; Rauch et al., 2018). Only one found statistically significantly better outcomes at the end of treatment in the PE+SSRI arm, though the group differences weren't maintained at follow-up (Schneier et al., 2012). However, because patients were continued on SSRIs until the primary outcome assessment, it is not possible from these studies to interpret whether the better outcomes arose from the independent, additive anxiolytic or antidepressant effects of the SSRIs on PTSD symptoms, or whether the medication in fact enhanced the efficacy of PE. To fully assess this question, a PE+Placebo versus PE+SSRI trial (perhaps also with an SSRI+Psychotherapy control condition) would need to employ a taper off the SSRI/Placebo at the completion of the PE, with outcomes assessed 3 or more months after completing treatment. An important consideration in combination studies may be the duration of SSRI treatment in relation to the time of initiating the course of psychotherapy. In the first days after starting SSRI, fear processing and anxiety may increase, with the anxiolytic effects not emerging until after 1-2 weeks of daily dosing. Notably, two studies that used sequential combination of SSRIs and PE (adding PE after 10 weeks of open label SSRI or adding an SSRI or placebo after eight sessions of PE) did not find benefit of the combined treatments.

Future Directions

The studies reviewed herein identify the possibilities and challenges researchers face in continuing to develop MAP for clinical use. An important factor challenging the extension of encouraging results from MAP extinction and reconsolidation studies of specific phobias is the complexity of fear in PTSD. As opposed to a single cue in specific phobias, fear in PTSD is typically associated with multiple fear cues, and the contexts for traumatization can be diverse. In addition, PTSD is associated with persisting negative mood and cognitions, as well as hyper-arousal and insomnia, all of which may adversely impact learning to overcome fear. The effect of these variables likely varies across individuals with PTSD, and is affected by genetic predispositions, early history, trauma history, co-occurring disorders, social support, etc. There are also likely subtypes of PTSD that will respond differently to different interventions.

An additional challenge for MAP studies employing enhanced extinction and psychotherapy process catalysts is that their effect sizes must be large enough to overcome floor effects arising from the high rates of response to the psychotherapy alone. Enriching samples by selecting for treatment-resistant PTSD patients may

prove necessary to detect significant advantages for MAP interventions. An additional opportunity may lie in identifying physiological markers (moderators) at pre-treatment that can indicate which patients are likely to need a MAP approach to improve (Otto et al., 2016).

Convincingly demonstrating MAP benefits in clinical trials requires adequate blinding to treatment, particularly for drugs with obvious effects. MDMA has obvious and unmistakable effects (mydriasis, increased speech), and other MAP medications produce subtler, but still noticeable effects. Outcome assessment for trials involving these agents will require independent assessors, but this cannot fully control for the incomplete blinding of patients and therapists. DCS has no immediately apparent effects, allowing for confidence in blinding (de Kleine et al., 2012), and its excellent safety profile has even allowed for pilot testing of a MAP extinction enhancement trial using remote telehealth PE delivery (Olden et al., 2017).

For trials evaluating enhanced extinction, the possibility of ending a PE session in an unresolved high fear state poses the risk of reconsolidating the fear memory in a stronger state, potentially increasing drop-out, as has been observed in studies employing DCS (Litz et al., 2012) and dexamethasone (Maples-Keller et al., 2019). This risk cannot be avoided if the medication must be dosed prior to sessions to achieve adequate CNS levels at the time of extinction learning. Future studies should be mindful of this potentially important iatrogenic consequence of MAP. When the drug must be given prior to exposure, it may be prudent to delay giving the medication until after the first 1-2 sessions of exposure, when the extinction memory has been established, using MAP to strengthen that memory in later sessions. Ideally, a decision to administer an extinction-enhancing agent could be made after a session, when it is determined that the patient had a positive response to the exposure. MB can be dosed in this way, but yohimbine cannot. A recently concluded trial of DCS-assisted therapy for social anxiety disorder should be informative regarding the efficacy of post-exposure session dosing of DCS (NCT02066792).

Benzodiazepines may interfere with extinction learning, either by simply reducing emotional arousal and engagement with trauma material, or by direct antagonist effects on inhibitory learning. One trial using a low-dose benzodiazepine as a control arm (alprazolam 0.25 mg dosed before sessions) found partial support for the extinction-impairing effects of benzodiazepines during PE treatment at post-treatment and follow-up evaluations (Rothbaum et al., 2014). Whether other psychoactive drugs, such as anticholinergic medications, also interfere with reconsolidation is unknown. At a minimum, future MAP trials will need to track and control for the effects of concomitant psychotropic medications in MAP studies.

An understudied factor in MAP trials is the role of sleep and insomnia in enhancing or inhibiting memory consolidation/reconsolidation. A recent ground-breaking study in healthy adults demonstrated that the ability of a beta-blocker to disrupt the reconsolidation of learned fear requires a period of sleep after the fear memory reactivation (Kindt and Soeter, 2018). This finding suggests that a modification of MAP altered reconsolidation studies for PTSD (in which insomnia is a prominent symptom) may be to provide a sleep-promoting agent (particularly one devoid of GABAergic or anticholinergic effects, such as trazodone or suvorexant) on the night after the memory reactivation session.

FEATURED ARTICLES

Whether sleep promotion can enhance outcomes in extinction enhancement designs is also worthy of consideration.

There are many compounds, with mechanisms of action differing from those reviewed here, that have preclinical data supporting their potential use as MAP agents but have not yet been assessed in human trials of PTSD. The utility of cannabinoids and modulators of the endocannabinoid system have perhaps the greatest current interest (Hill et al., 2018), along with compounds targeting glutamate receptors, kappa opioid receptors, neuropeptide Y, and epigenetic mechanisms, such as histone deacetylase inhibitors (Singewald, 2015). Beyond medications, stimulation treatments, such as repetitive transcranial magnetic stimulation (Kozel et al., 2018), may have the potential to improve psychotherapy outcomes, as may exercise that has been shown to increase BDNF. Finally, there may be possibilities for MAP treatment in the prevention of PTSD. Cognitive behavioral therapy delivered soon after trauma can reduce the probability of developing PTSD, an effect that may be further enhanced if conducted with glucocorticoids as part of a MAP approach (Dunlop and Wong, 2019).

Conclusions

Each of the three approaches to MAP — enhanced extinction, altered reconsolidation, or psychotherapeutic process catalysts — offer promise, though much work remains to be done to establish their utility. Enhanced extinction approaches have the greatest pre-clinical support and fit most neatly into existing treatment delivery settings. However, convincing evidence of its efficacy in PTSD has been elusive and the issue of iatrogenic harms through unintentional strengthening of trauma memories is a concern. Altered reconsolidation holds out the promise of overcoming fear without having to go through the intense challenges of trauma-focused psychotherapy, but the evidence base and optimal trial designs are not well established. In 2017, the US Food and Drug Administration (FDA) granted Breakthrough Therapy designation to MDMA-assisted psychotherapy for PTSD, and in 2018 the agency agreed to the design of two pivotal phase III trials targeting 100 patients per trial (NCT03537014) (Mithoefer et al., 2019). Should these trials prove to be successful, MDMA-assisted psychotherapy is likely to be the first form of MAP to influence clinical practice. If approved, the FDA is likely to require a Risk Evaluation and Mitigation Strategy (REMS) for the clinical use of MDMA, similar to the REMS recently applied to esketamine, for monitoring of the cardiovascular effects and any other significant risks detected from the phase III trials.

FEATURED ARTICLES

Brunet, A., Saumier, D., Liu, A., Streiner, D. L., Tremblay, J., & Pitman, R. K. (2018). **Reduction of PTSD symptoms with pre-reactivation propranolol therapy: A randomized controlled trial.** *American Journal of Psychiatry*, 175, 427-433. doi:10.1176/appi.ajp.2017.17050481 *Objective:* The authors assessed the efficacy of trauma memory reactivation performed under the influence of propranolol, a noradrenergic beta-receptor blocker, as a putative reconsolidation blocker, in reducing symptoms of posttraumatic stress disorder (PTSD). *Method:* This was a 6-week, double-blind,

placebo-controlled, randomized clinical trial in 60 adults diagnosed with long-standing PTSD. Propranolol or placebo was administered 90 minutes before a brief memory reactivation session, once a week for 6 consecutive weeks. The hypothesis predicted a significant treatment effect of trauma reactivation with propranolol compared with trauma reactivation with placebo in reducing PTSD symptoms on both the Clinician-Administered PTSD Scale (CAPS) and the patient-rated PTSD Checklist-Specific (PCL-S) in an intention-to-treat analysis. *Results:* The estimated group difference in posttreatment CAPS score, adjusted for pretreatment values (analysis of covariance), was a statistically significant 11.50. The within-group pre- to posttreatment effect sizes (Cohen's d) were 1.76 for propranolol and 1.25 for placebo. For the PCL-S, the mixed linear model's estimated time-by-group interaction yielded an average decrease of 2.43 points per week, for a total significant difference of 14.58 points above that of placebo. The pre- to posttreatment effect sizes were 2.74 for propranolol and 0.55 for placebo. Per protocol analyses for both outcomes yielded similar significant results. *Conclusions:* Pre-reactivation propranolol, a treatment protocol suggested by reconsolidation theory, appears to be a novel and efficacious treatment for PTSD. Replication studies using a long-term follow-up in various trauma populations are required.

De Kleine, R. A., Hendriks, G.-J., Kusters, W. J. C., Broekman, T. G., & van Minnen, A. (2012). **A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder.** *Biological Psychiatry*, 71, 962-968. doi:10.1016/j.biopsych.2012.02.033 *Background:* Posttraumatic stress disorder (PTSD) is a complex and debilitating anxiety disorder, and, although prolonged exposure therapy has been proven effective, many patients remain symptomatic after treatment. In other anxiety disorders, the supplementary use of d-cycloserine (DCS), a partial agonist at the glutamatergic N-methyl-D-aspartate receptor, showed promise in enhancing treatment effects. We examined whether augmentation of prolonged exposure therapy for PTSD with DCS enhances treatment efficacy. *Methods:* In a randomized, double-blind, placebo-controlled trial we administered 50 mg DCS or placebo 1 hour before each exposure session to 67 mixed trauma patients, recruited from regular referrals, with a primary PTSD diagnosis satisfying DSM-IV criteria. *Results:* Although DCS did not enhance overall treatment effects, the participants having received DCS did show a stronger treatment response. Exploratory session-by-session analyses revealed that DCS yielded higher symptom reduction in those participants that had more severe pretreatment PTSD and needed longer treatment. *Conclusions:* The present study found preliminary support for the augmentation of exposure therapy with DCS, specifically for patients with more severe PTSD needing longer treatment.

Difede, J., Cukor, J., Wyka, K., Olden, M., Hoffman, H., Lee, F. S., & Altemus, M. (2014). **D-cycloserine augmentation of exposure therapy for post-traumatic stress disorder: A pilot randomized clinical trial.** *Neuropsychopharmacology*, 39, 1052-1058. doi:10.1038/npp.2013.317 Viewing post-traumatic stress disorder (PTSD) as a disorder of emotional learning, this study used a cognitive enhancer synergistically with virtual reality exposure (VRE) therapy for the treatment of PTSD. The main objective was to determine if a novel pharmacotherapy, D-cycloserine (DCS),

enhanced the efficacy of the psychotherapy. Pre-clinical studies suggest that when fear extinction occurs during DCS administration, neuroplasticity may be enhanced. VRE therapy is a particularly promising format to test the hypothesis that DCS enhances extinction learning, as sensory fear cues are standardized across patients. In a pilot randomized, double-blind, placebo-controlled trial, 100mg of DCS or placebo was administered 90min before each weekly VRE session, to ensure peak plasma concentrations during the sessions in 25 patients with chronic PTSD. The primary outcome measure was the Clinician Administered PTSD Scale (CAPS). Secondary outcome measures included the Beck Depression Inventory-II and the State-Trait Anger Expression Inventory-2. Assessments occurred at pre-treatment, following sessions 3, 6, 10, post-treatment, and at 6 months. The difference in CAPS between the VRE-DCS ($n=13$) and VRE-placebo ($n=12$) groups increased over time beginning at 6 weeks, with medium to large between-group effect sizes immediately post-treatment and 6 months later ($d=0.68$ and $d=1.13$, respectively). A similar pattern was observed for depression, anger expression, and sleep. PTSD remission rates were significantly greater for the VRE-DCS group (46% vs 8% at post-treatment; 69% vs 17% at 6 months). Patients in the VRE-DCS group showed earlier and greater improvement in PTSD symptoms compared with the VRE-placebo group. These results suggest a promising new treatment for PTSD.

Flanagan, J. C., Sippel, L. M., Wahlquist, A., Moran-Santa Maria, M. M., & Back, S. E. (2018). **Augmenting prolonged exposure therapy for PTSD with intranasal oxytocin: A randomized, placebo-controlled pilot trial.** *Journal of Psychiatric Research*, *98*, 64–69. doi:10.1016/j.jpsychires.2017.12.014 Posttraumatic stress disorder (PTSD) is a chronic, debilitating condition for which Prolonged Exposure (PE) therapy is highly efficacious. However, for some individuals, premature dropout and residual PTSD symptoms remain obstacles. The neuropeptideoxytocin is a promising candidate to enhance PE due to its ability to enhance 1) prosocial cognition and behavior, which are theorized to promote positive working alliance, and 2) extinctionlearning, which is the central mechanism of action underlying successful PE treatment. Despite a robust theoretical rationale, no studies to date have combined evidence-based psychotherapy for PTSD with oxytocin. This randomized, placebo-controlled, double-blind pilot trial examined the feasibility, safety, and preliminary efficacy of augmenting PE with oxytocin. Participants were 17 individuals with diverse index traumas. Participants self-administered intranasal oxytocin (40 IU) or matching placebo 45 min prior to each weekly PE therapy session. One adverse event occurred in the placebo group and three individuals dropped out (17.6%; 2 oxytocin group and 1 placebo group). The oxytocin group demonstrated lower PTSD and depression symptoms during PE, and had higher working alliance scores, although these differences did not reach statistical significance. Although preliminary, the findings support the feasibility of oxytocin combined with PE. Adequately powered studies are necessary to determine whether oxytocin enhances PE treatment outcomes and to examine potential mechanisms, such as accelerating extinction learning, enhancing early response, and preventing premature dropout.

Litz, B. T., Salters-Pedneault, K., Steenkamp, M. M., Hermos, J. A., Bryant, R. A., Otto, M. W., & Hofmann, S. G. (2102). **A randomized**

placebo-controlled trial of D-cycloserine and exposure therapy for posttraumatic stress disorder. *Journal of Psychiatric Research*, *46*, 1184-1190. doi:10.1016/j.jpsychires.2012.05.006

d-Cycloserine (DCS) is a partial NMDA receptor agonist that has been shown to enhance therapeutic response to exposure-based treatments for anxiety disorders, but has not been tested in the treatment of combat-related posttraumatic stress disorder (PTSD). The aim of this randomized, double-blind, placebo-controlled trial was to determine whether DCS augments exposure therapy for PTSD in veterans returning from Iraq and Afghanistan and to test whether a brief six-session course of exposure therapy could effectively reduce PTSD symptoms in returning veterans. In contrast to previous trials using DCS to enhance exposure therapy, results indicated that veterans in the exposure therapy plus DCS condition experienced significantly less symptom reduction than those in the exposure therapy plus placebo condition over the course of the treatment. Possible reasons for why DCS was associated with poorer outcome are discussed.

Maples-Keller, J. L., Jovanovic, T., Dunlop, B. W., Rauch, S., Yasinski, C., Michopoulos, V., ... & Rothbaum, B.O. (2019). **When translational neuroscience fails in the clinic: Dexamethasone prior to virtual reality exposure therapy increases drop-out rates.** *Journal of Anxiety Disorders*, *61*, 89-97. doi:10.1016/j.janxdis.2018.10.006

Posttraumatic stress disorder (PTSD) is characterized by exaggerated expression of fear responses to danger and safety cues. Translational research suggests that dexamethasone facilitates fear extinction in animal and human fear conditioning models. For this randomized, placebo-controlled trial ($N=27$), we aimed to translate these findings to the clinic by using virtual reality exposure (VRE) therapy for OEF/OIF/OND veterans with PTSD to determine whether dexamethasone will increase the efficacy of exposure therapy for VRE relative to placebo. VRE sessions involved imaginal exposure to the most traumatic war memories while viewing a computer-generated view of virtual Iraq or Afghanistan with multisensory stimulus options used to match patient's description of the trauma. VRE was effective in reducing PTSD symptoms but there was no interaction with dexamethasone. Drop-out rate was significantly higher in the dexamethasone group, with 10 of 13 (76.9%) participants in this group discontinuing, compared to only 4 of 14 (28.5%) in the placebo group, $\chi^2=6.31$, $p=0.02$. Results indicate that the dexamethasone group may have experienced an increase in PTSD symptoms, particularly re-experiencing, at session 2 following first drug administration. Contrary to study hypotheses, dexamethasone did not enhance exposure therapy outcomes and was associated with increased drop-out. This demonstrates potential pitfalls in translating neuroscience models to the clinic; future research carefully examining glucocorticoid mechanisms involved in therapy augmentation is warranted.

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., & Doblin, R. (2011). **The safety and efficacy of (+/-)-3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: The first randomized controlled pilot study.** *Journal of Psychopharmacology*, *25*, 439-452. doi:10.1177/0269881110378371 Case reports indicate that psychiatrists administered

±3,4-methylenedioxymethamphetamine (MDMA) as a catalyst to psychotherapy before recreational use of MDMA as 'Ecstasy' resulted in its criminalization in 1985. Over two decades later, this study is the first completed clinical trial evaluating MDMA as a therapeutic adjunct. Twenty patients with chronic posttraumatic stress disorder, refractory to both psychotherapy and psychopharmacology, were randomly assigned to psychotherapy with concomitant active drug ($n = 12$) or inactive placebo ($n = 8$) administered during two 8-h experimental psychotherapy sessions. Both groups received preparatory and follow-up non-drug psychotherapy. The primary outcome measure was the Clinician-Administered PTSD Scale, administered at baseline, 4 days after each experimental session, and 2 months after the second session. Neurocognitive testing, blood pressure, and temperature monitoring were performed. After 2-month follow-up, placebo subjects were offered the option to re-enroll in the experimental procedure with open-label MDMA. Decrease in Clinician-Administered PTSD Scale scores from baseline was significantly greater for the group that received MDMA than for the placebo group at all three time points after baseline. The rate of clinical response was 10/12 (83%) in the active treatment group versus 2/8 (25%) in the placebo group. There were no drug-related serious adverse events, adverse neurocognitive effects or clinically significant blood pressure increases. MDMA-assisted psychotherapy can be administered to posttraumatic stress disorder patients without evidence of harm, and it may be useful in patients refractory to other treatments.

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., ... & Doblin, R. (2018).

3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry*, 5, 486-497. doi:10.1016/S2215-0366(18)30135-4

Background: Post-traumatic stress disorder (PTSD) is prevalent in military personnel and first responders, many of whom do not respond to currently available treatments. This study aimed to assess the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for treating chronic PTSD in this population. **Methods:** We did a randomised, double-blind, dose-response, phase 2 trial at an outpatient psychiatric clinic in the USA. We included service personnel who were 18 years or older, with chronic PTSD duration of 6 months or more, and who had a Clinician-Administered PTSD Scale (CAPS-IV) total score of 50 or greater. Using a web-based randomisation system, we randomly assigned participants (1:1:2) to three different dose groups of MDMA plus psychotherapy: 30 mg (active control), 75 mg, or 125 mg. We masked investigators, independent outcome raters, and participants until after the primary endpoint. MDMA was administered orally in two 8-h sessions with concomitant manualised psychotherapy. The primary outcome was mean change in CAPS-IV total score from baseline to 1 month after the second experimental session. Participants in the 30 mg and 75 mg groups subsequently underwent three 100–125 mg MDMA-assisted psychotherapy sessions in an open-label crossover, and all participants were assessed 12 months after the last MDMA session. Safety was monitored through adverse events, spontaneously reported expected reactions, vital signs, and suicidal ideation and behaviour.

This study is registered with ClinicalTrials.gov, number NCT01211405. **Findings:** Between Nov 10, 2010, and Jan 29, 2015, 26 veterans and first responders met eligibility criteria and were randomly assigned to receive 30 mg ($n=7$), 75 mg ($n=7$), or 125 mg ($n=12$) of MDMA plus psychotherapy. At the primary endpoint, the 75 mg and 125 mg groups had significantly greater decreases in PTSD symptom severity (mean change CAPS-IV total scores of -58.3 [SD 9.8] and -44.3 [28.7]; $p=0.001$) than the 30 mg group (-11.4 [12.7]). Compared with the 30 mg group, Cohen's d effect sizes were large: 2.8 (95% CI 1.19–4.39) for the 75 mg group and 1.1 (0.04–2.08) for the 125 mg group. In the open-label crossover with full-dose MDMA (100–125 mg), PTSD symptom severity significantly decreased in the group that had previously received 30 mg ($p=0.01$), whereas no further significant decreases were observed in the group that previously achieved a large response after 75 mg doses in the blinded segment ($p=0.81$). PTSD symptoms were significantly reduced at the 12-month follow-up compared with baseline after all groups had full-dose MDMA (mean CAPS-IV total score of 38.8 [SD 28.1] vs 87.1 [16.1]; $p<0.0001$). 85 adverse events were reported by 20 participants. Of these adverse events, four (5%) were serious: three were deemed unrelated and one possibly related to study drug treatment. **Interpretation:** Active doses (75 mg and 125 mg) of MDMA with adjunctive psychotherapy in a controlled setting were effective and well tolerated in reducing PTSD symptoms in veterans and first responders.

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., Martin, S. F., Yazar-Klosinski, B., ... & Doblin, R. (2013). **Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: A prospective long-term follow-up study.** *Journal of Psychopharmacology*, 27, 28–39. doi:10.1177/0269881112456611

We report follow-up data evaluating the long-term outcomes for the first completed trial of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for chronic, treatment-resistant post-traumatic stress disorder (PTSD) (Mithoefer et al., 2011). All of the 19 subjects who received MDMA-assisted treatment in the original trial participated in the long-term follow-up (LTFU), with 16 out of 19 completing all of the long-term outcome measures, which were administered from 17 to 74 months after the original study's final MDMA session (mean = 45.4; $SD = 17.3$). Our primary outcome measure used was the Clinician-Administered PTSD Scale (CAPS). Secondary outcome measures were the Impact of Events Scale-Revised (IES-R) and the Neuroticism Extroversion Openness Personality Inventory-Revised (NEO PI-R) Personality Inventory. We also collected a long-term follow-up questionnaire. Results for the 16 CAPS completers showed there were no statistical differences between mean CAPS score at LTFU (mean = 23.7; $SD = 22.8$) ($t_{matched} = 0.1$; $df = 15$, $p = 0.91$) and the mean CAPS score previously obtained at Study Exit (mean = 24.6, $SD = 18.6$). On average, subjects maintained statistically and clinically-significant gains in symptom relief, although two of these subjects did relapse. It was promising that we found the majority of these subjects with previously severe PTSD who were unresponsive to existing treatments had symptomatic relief provided by MDMA-assisted psychotherapy that persisted over time, with no subjects reporting harm from participation in the study.

Rauch, S. A. M., Kim, H. M., Powell, C., Tuerk, P. W., Simon, N. M., Acierno, R., ... & Hoge, C. W. (2019). **Efficacy of prolonged exposure therapy, sertraline hydrochloride, and their combination among combat veterans with posttraumatic stress disorder: A randomized clinical trial.** *JAMA Psychiatry, 76*, 117-126. doi:10.1001/jamapsychiatry.2018.3412 *Importance:* Meta-analyses of treatments for posttraumatic stress disorder (PTSD) suggest that trauma-focused psychotherapies produce greater benefits than antidepressant medications alone. *Objective:* To determine the relative efficacy of prolonged exposure therapy plus placebo, prolonged exposure therapy plus sertraline hydrochloride, and sertraline plus enhanced medication management in the treatment of PTSD. *Design, Setting, and Participants:* The Prolonged Exposure and Sertraline Trial was a randomized, multisite, 24-week clinical trial conducted at the Veterans Affairs Ann Arbor Healthcare System, Veterans Affairs San Diego Healthcare System, Ralph H. Johnson Veterans Affairs Medical Center, and Massachusetts General Hospital Home Base Veterans Program between January 26, 2012, and May 9, 2016. Participants and clinicians were blinded to pill condition, and outcome evaluators were blinded to assignment. Participants completed assessments at weeks 0 (intake), 6, 12, 24, and 52 (follow-up). Participants ($N=223$) were service members or veterans of the Iraq and/or Afghanistan wars with combat-related PTSD and significant impairment (Clinician-Administered PTSD Scale score, ≥ 50) of at least 3 months' duration. Analyses were on an intent-to-treat basis. *Intervention:* Participants completed up to thirteen 90-minute sessions of prolonged exposure therapy by week 24. Sertraline dosage was titrated during a 10-week period and continued until week 24; medication management was manualized. *Main Outcomes and Measures:* The primary outcome was symptom severity of PTSD in the past month as assessed by the Clinician-Administered PTSD Scale score at week 24. *Results:* Of 223 randomized participants, 149 completed the study at 24 weeks, and 207 (180 men and 27 women; mean [SD] age, 34.5 [8.3 years]) were included in the intent-to-treat analysis. Modified intent-to-treat analysis using a mixed model of repeated measures showed that PTSD symptoms decreased significantly during the 24 weeks (sertraline plus enhanced medication management, 33.8 points; prolonged exposure therapy plus sertraline, 32.7 points; and prolonged exposure therapy plus placebo, 29.4 points; β , -9.39; 95% CI, -11.62 to -7.16; $P < .001$); however, slopes did not differ by treatment group (prolonged exposure therapy plus placebo group, -9.39; sertraline plus enhanced medication management group, -10.37; and prolonged exposure therapy plus sertraline group, -9.99; $P = .81$). *Conclusions and Relevance:* No difference in change in PTSD symptoms or symptom severity at 24 weeks was found between sertraline plus enhanced medication management, prolonged exposure therapy plus placebo, and prolonged exposure therapy plus sertraline.

Rothbaum, B. O., Price, M., Jovanovic, T., Norrholm, S. D., Gerardi, M., Dunlop, B., ... & Ressler, K. J. (2014). **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.** *American Journal of Psychiatry, 171*, 640-648. doi:10.1176/appi.ajp.2014.13121625 *Objective:* The authors examined the effectiveness of virtual reality exposure augmented with D-cycloserine or alprazolam, compared

with placebo, in reducing posttraumatic stress disorder (PTSD) due to military trauma. *Method:* After an introductory session, five sessions of virtual reality exposure were augmented with D-cycloserine (50 mg) or alprazolam (0.25 mg) in a double-blind, placebo-controlled randomized clinical trial for 156 Iraq and Afghanistan war veterans with PTSD. *Results:* PTSD symptoms significantly improved from pre- to posttreatment across all conditions and were maintained at 3, 6, and 12 months. There were no overall differences in symptoms between D-cycloserine and placebo at any time. Alprazolam and placebo differed significantly on the Clinician-Administered PTSD Scale score at posttreatment and PTSD diagnosis at 3 months posttreatment; the alprazolam group showed a higher rate of PTSD (82.8%) than the placebo group (47.8%). Between-session extinction learning was a treatment-specific enhancer of outcome for the D-cycloserine group only. At posttreatment, the D-cycloserine group had the lowest cortisol reactivity and smallest startle response during virtual reality scenes. *Conclusions:* A six-session virtual reality treatment was associated with reduction in PTSD diagnoses and symptoms in Iraq and Afghanistan veterans, although there was no control condition for the virtual reality exposure. There was no advantage of D-cycloserine for PTSD symptoms in primary analyses. In secondary analyses, alprazolam impaired recovery and D-cycloserine enhanced virtual reality outcome in patients who demonstrated within-session learning. D-Cycloserine augmentation reduced cortisol and startle reactivity more than did alprazolam or placebo, findings that are consistent with those in the animal literature.

Schneier, F. R., Neria, Y., Pavlicova, M., Hembree, E., Suh, E. J., Amsel, L., & Marshall, R. D. (2012). **Combined prolonged exposure therapy and paroxetine for PTSD related to the World Trade Center attack: A randomized controlled trial.** *American Journal of Psychiatry, 169*, 80-88. doi:10.1176/appi.ajp.2011.11020321 *Objective:* Selective serotonin reuptake inhibitors (SSRIs) are often recommended in combination with established cognitive-behavioral therapies (CBTs) for posttraumatic stress disorder (PTSD), but combined initial treatment of PTSD has not been studied under controlled conditions. There are also few studies of either SSRIs or CBT in treating PTSD related to terrorism. The authors compared prolonged exposure therapy (a CBT) plus paroxetine (an SSRI) with prolonged exposure plus placebo in the treatment of terrorism-related PTSD. *Method:* Adult survivors of the World Trade Center attack of September 11, 2001, with PTSD were randomly assigned to 10 weeks of treatment with prolonged exposure (10 sessions) plus paroxetine ($N=19$) or prolonged exposure plus placebo ($N=18$). After week 10, patients discontinued prolonged exposure and were offered 12 additional weeks of continued randomized treatment. *Results:* Patients treated with prolonged exposure plus paroxetine experienced significantly greater improvement in PTSD symptoms (incidence rate ratio=0.50, 95% CI=0.30-0.85) and remission status (odds ratio=12.6, 95% CI=1.23-129) during 10 weeks of combined treatment than patients treated with prolonged exposure plus placebo. Response rate and quality of life were also significantly more improved with combined treatment. The subset of patients who continued randomized treatment for 12 additional weeks showed no group differences. *Conclusions:* Initial treatment with paroxetine plus prolonged exposure was more efficacious than prolonged exposure plus placebo for PTSD related to the World

Trade Center attack. Combined treatment medication and prolonged exposure therapy deserves further study in larger samples with diverse forms of PTSD and over longer follow-up periods.

Singewald, N., Schmuckermair, C., Whittle, N., Holmes, A., & Ressler, K. J. (2015). **Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders.** *Pharmacology & Therapeutics*, 149, 150–190. doi:10.1016/j.pharmthera.2014.12.004 Pathological fear and anxiety are highly debilitating and, despite considerable advances in psychotherapy and pharmacotherapy they remain insufficiently treated in many patients with PTSD, phobias, panic and other anxiety disorders. Increasing preclinical and clinical evidence indicates that pharmacological treatments including cognitive enhancers, when given as adjuncts to psychotherapeutic approaches [cognitive behavioral therapy including extinction-based exposure therapy] enhance treatment efficacy, while using anxiolytics such as benzodiazepines as adjuncts can undermine long-term treatment success. The purpose of this review is to outline the literature showing how pharmacological interventions targeting neurotransmitter systems including serotonin, dopamine, noradrenaline, histamine, glutamate, GABA, cannabinoids, neuropeptides (oxytocin, neuropeptides Y and S, opioids) and other targets (neurotrophins BDNF and FGF2, glucocorticoids, L-type-calcium channels, epigenetic modifications) as well as their downstream signaling pathways, can augment fear extinction and strengthen extinction memory persistently in preclinical models. Particularly promising approaches are discussed in regard to their effects on specific aspects of fear extinction namely, acquisition, consolidation and retrieval, including long-term protection from return of fear (relapse) phenomena like spontaneous recovery, reinstatement and renewal of fear. We also highlight the promising translational value of the preclinical research and the clinical potential of targeting certain neurochemical systems with, for example d-cycloserine, yohimbine, cortisol, and L-DOPA. The current body of research reveals important new insights into the neurobiology and neurochemistry of fear extinction and holds significant promise for pharmacologically-augmented psychotherapy as an improved approach to treat trauma and anxiety-related disorders in a more efficient and persistent way promoting enhanced symptom remission and recovery.

Surís, A., Holliday, R., Adinoff, B., Holder, N., & North, C.S. (2017). **Facilitating fear-based memory extinction with dexamethasone: A randomized controlled trial in male veterans with combat-related PTSD.** *Psychiatry*, 80, 399–410. doi:10.1080/00332747.2017.1286892 *Objective:* Animal and preliminary human studies have demonstrated that glucocorticoids enhance the extinction of fear memories. Impaired extinction of fear memories is a critical component in the development and maintenance of posttraumatic stress disorder (PTSD). The purpose of this translational study was to determine the effectiveness of pairing a glucocorticoid with trauma memory reactivation as a novel intervention to treat PTSD and to measure the duration of the effect. *Method:* A total of 54 male veterans with combat-related PTSD in this double-blind, randomized, placebo-controlled trial received either four weekly glucocorticoid (dexamethasone [DEX]) or placebo administrations paired with a 45-second trauma memory reactivation task. PTSD

and depressive symptom severity were assessed at baseline and at one three, and six months. *Results:* Trauma memory activation paired with DEX versus trauma memory activation paired with placebo demonstrated a significantly greater reduction of PTSD symptoms for DEX at the one-month ($p=.037$) and three-month ($p=.036$) posttreatment assessments, but the difference was no longer evident at six months. DEX showed a nonsignificantly greater reduction of PTSD symptoms than placebo over the course of the study ($p=.067$). Significantly more veterans in the DEX group lost their diagnosis of PTSD at one month posttreatment compared to the placebo group, but the difference was not maintained at three or six months. DEX had no effect on depression symptoms. *Conclusions:* Despite insufficient power to test differences in PTSD symptom reduction, findings suggest that this novel intervention may have potential for treatment of combat-related PTSD.

Tuerk, P. W., Wangelin, B. C., Powers, M. B., Smits, J. A. J., Acierno, R., Myers, U. S., ... & Hamner, M. B. (2018). **Augmenting treatment efficiency in exposure therapy for PTSD: A randomized double-blind placebo-controlled trial of yohimbine HCl.** *Cognitive Behaviour Therapy*, 47, 351–371. doi:10.1080/16506073.2018.1432679 The alpha-2 adrenergic receptor antagonist, yohimbine, can facilitate fear extinction in animals and humans. One potential mechanism is increased noradrenergic activity and associated arousal in the presence of conditioned stimuli. Accordingly, yohimbine might augment prolonged exposure (PE) therapy for posttraumatic stress disorder (PTSD), where heightened exposure-oriented arousal is a theorized driver and empirical predictor of treatment success. A double-blind placebo-controlled randomized trial (NCT 01031979) piloted yohimbine augmentation in 26 males with combat-related PTSD. Participants were given one-time dose of yohimbine or placebo prior to the first imaginal exposure. Subsequently, both arms completed standard PE. The primary outcome was trauma-cued heart-rate reactivity a week after the drug/exposure visit, a highly specified, objective measure sensitive to incremental change. Secondary outcomes included arousal during the drug/exposure visit and slope of distress, PTSD, and depression over the course of PE. Consistent with hypothesis, yohimbine led to higher objective and subjective arousal during the drug/exposure visit and to lower trauma-cued heart-rate reactivity one-week later. One dose of yohimbine also led to greater between-session habituation and more rapid improvement on depression, but not PTSD, over the course of care. Results of this controlled pilot indicate support for continued investigation of yohimbine-augmented exposure therapy for PTSD.

Wood, N. E., Rosasco, M. L., Surís, A. M., Spring, J. D., Marin, M.-F., Lasko, N. B., ... & Pitman, R. K. (2015). **Pharmacological blockade of memory reconsolidation in posttraumatic stress disorder: Three negative psychophysiological studies.** *Psychiatry Research*, 225, 31–39. doi:10.1016/j.psychres.2014.09.005 Posttraumatic stress disorder (PTSD) may involve over-consolidated emotional memories of the traumatic event. Reactivation (RP) can return a memory to an unstable state, from which it must be restabilized (reconsolidated) if it is to persist. Pharmacological agents administered while the memory is unstable have been shown to impair reconsolidation. The *N*-methyl-d-aspartate (NMDA) partial agonist d-cycloserine (DCS) may promote memory destabilization.

In the three studies reported here, we investigated whether the β -adrenergic blocker propranolol or the glucocorticoid (GR) antagonist mifepristone, given at the time of traumatic memory reactivation, could reduce PTSD symptoms and physiological responding during subsequent traumatic imagery. Individuals with PTSD were randomized as follows: Study One: propranolol with memory reactivation ($n=10$) or without reactivation ($n=8$); Study Two: reactivation mifepristone ($n=13$), non-reactivation (NRP) mifepristone ($n=15$), or double placebo (PL) ($n=15$); Study Three: reactivation mifepristone plus d-cycloserine ($n=16$), or two placebos ($n=15$). Subjects underwent memory retrieval by describing their traumatic event. A week later they engaged in script-driven traumatic mental imagery, while heart rate (HR), skin conductance (SC), and facial electromyogram (EMG) responses were measured. There were no significant group differences in physiological responsivity or change in PTSD symptoms in any of the studies. These results do not support successful blockade of reconsolidation of traumatic memories in PTSD.

Yehuda, R., Bierer, L. M., Pratchett, L. C., Lehrner, A., Koch, E. C., Van Manen, J. A., ... & Hildebrandt, T. (2015). **Cortisol augmentation of a psychological treatment for warfighters with posttraumatic stress disorder: Randomized trial showing improved treatment retention and outcome.**

Psychoneuroendocrinology, 51, 589-597. doi:10.1016/j.psyneuen.2014.08.004 *Background:* Prolonged exposure (PE) therapy for post-traumatic stress disorder (PTSD) in military veterans has established efficacy, but is ineffective for a substantial number of patients. PE is also associated with high dropout rates. We hypothesized that hydrocortisone augmentation would enhance symptom improvement and reduce drop-out rates by diminishing the distressing effects of traumatic memories retrieved during imaginal exposure. We also hypothesized that in responders, hydrocortisone augmentation would be more effective in reversing glucocorticoid indices associated with PTSD than placebo augmentation. *Method:* Twenty-four veterans were randomized to receive either 30 mg oral hydrocortisone or placebo prior to PE sessions 3-10 in a double-blind protocol. Glucocorticoid receptor sensitivity was assessed in cultured peripheral blood mononuclear cells (PBMC) using the in vitro lysozyme inhibition test and was determined before and after treatment. Intent-to-treat analysis was performed using latent growth curve modeling of treatment effects on change in PTSD severity over time. Veterans who no longer met diagnostic criteria for PTSD at post-treatment were designated as responders. *Results:* Veterans randomized to hydrocortisone or placebo augmentation did not differ significantly in clinical severity or glucocorticoid sensitivity at pre-treatment. Hydrocortisone augmentation was associated with greater reduction in total PTSD symptoms compared to placebo, a finding that was explained by significantly greater patient retention in the hydrocortisone augmentation condition. A significant treatment condition by responder status interaction for glucocorticoid sensitivity indicated that responders to hydrocortisone augmentation had the highest pre-treatment glucocorticoid sensitivity (lowest lysozyme IC50-DEX) that diminished over the course of treatment. There was a significant association between decline in glucocorticoid responsiveness and improvement in PTSD symptoms among hydrocortisone recipients. *Conclusions:* The results of this pilot

study suggest that hydrocortisone augmentation of PE may result in greater retention in treatment and thereby promote PTSD symptom improvement. Further, the results suggest that particularly elevated glucocorticoid responsiveness at pre-treatment may identify veterans likely to respond to PE combined with an intervention that targets glucocorticoid sensitivity. Confirmation of these findings will suggest that pharmacologic interventions that target PTSD-associated glucocorticoid dysregulation may be particularly helpful in promoting a positive clinical response to PTSD psychotherapy.

Zoellner, L. A., Telch, M., Foa, E. B., Farach, F. J., McLean, C. P., Gallop, R., ... & Gonzalez-Lima, F. (2017). **Enhancing extinction learning in posttraumatic stress disorder with brief daily imaginal exposure and methylene blue: A randomized controlled trial.** *Journal of Clinical Psychiatry*, 78, e782-e789. doi:10.4088/JCP.16m10936 The memory-enhancing drug methylene blue (MB) administered after extinction training improves fear extinction retention in rats and humans with claustrophobia. Robust findings from animal research, in combination with established safety and data showing MB-enhanced extinction in humans, provide a foundation to extend this work to extinction-based therapies for posttraumatic stress disorder (PTSD) such as prolonged exposure (PE). Patients with chronic PTSD (DSM-IV-TR; $N=42$) were randomly assigned to imaginal exposure plus MB (IE + MB), imaginal exposure plus placebo (IE + PBO), or waitlist (WL/standard PE) from September 2011 to April 2013. Following 5 daily, 50-minute imaginal exposure sessions, 260 mg of MB or PBO was administered. Waitlist controls received PE following 1-month follow-up. Patients were assessed using the independent evaluator-rated PTSD Symptom Scale-Interview version (primary outcome), patient-rated PTSD, trauma-related psychopathology, and functioning through 3-month follow-up. Both IE + MB and IE + PBO showed strong clinical gains that did not differ from standard PE at 3-month follow-up. MB-augmented exposure specifically enhanced independent evaluator-rated treatment response (number needed to treat = 7.5) and quality of life compared to placebo (effect size $d=0.58$). Rate of change for IE + MB showed a delayed initial response followed by accelerated recovery, which differed from the linear pattern seen in IE + PBO. MB effects were facilitated by better working memory but not by changes in beliefs. The findings provide preliminary efficacy for a brief IE treatment for PTSD and point to the potential utility of MB for enhancing outcome. Brief interventions and better tailoring of MB augmentation strategies, adjusting for observed patterns, may have the potential to reduce dropout, accelerate change, and improve outcomes.

ADDITIONAL CITATIONS

American Psychological Association. (2017). *Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder*. Available at: <http://www.apa.org/ptsd-guideline/treatments/index.aspx>

This clinical practice guideline published by the American Psychological Association documents the underuse of trauma-focused psychotherapies to treat PTSD. The guideline strongly recommends treatment of PTSD with CBT, CPT, cognitive therapy, and PE, and suggests that brief eclectic psychotherapy, eye

movement desensitization and reprocessing, and narrative exposure therapy may be used. The guideline does not address potential use of MAP approaches to PTSD.

Buhmann, C. B., Nordentoft, M., Ekstroem, M., Carlsson, J., & Mortensen, E. L. (2016). **The effect of flexible cognitive-behavioural therapy and medical treatment, including antidepressants on post-traumatic stress disorder and depression in traumatized refugees: Pragmatic randomised controlled clinical trial.** *British Journal of Psychiatry, 208*, 252-259. doi:10.1192/bjp.bp.114.150961 This large study of 280 patients study evaluated the real-world effectiveness of combination treatment with flexible CBT and antidepressants in a refugee population with PTSD. After six months of treatment, there was no difference in PTSD symptoms across the four study arms (CBT and antidepressant, antidepressant alone, CBT alone, waitlist). Only 25% of the patients received any exposure components as part of their CBT, and the exposure treatments were limited. This trial demonstrates the large gap that exists for PTSD between clinical trials of efficacy and their translation to general clinical practice.

De Kleine, R. A., Smits, J. A. J., Hendriks, G.-J., Becker, E. S., & van Minnen, A. (2015). **Extinction learning as a moderator of d-cycloserine efficacy for enhancing exposure therapy in posttraumatic stress disorder.** *Journal of Anxiety Disorders, 34*, 63-67. doi:10.1016/j.janxdis.2015.06.005 The authors conducted four post-hoc analyses of their 2012 DCS MAP trial to test whether the degree of extinction learning moderated the efficacy of DCS augmentation for PTSD symptom improvement. In contrast to the results from animal studies and post-hoc analyses of other PTSD (and other fear disorders), they failed to find support for the assertion that DCS makes “good” exposures better and “bad” exposures worse. These results emphasize the challenges of using subjective measures of fear (i.e., Subjective Units of Distress) as opposed to more objective measures, such as psychophysiological testing.

Dunlop, B. W., & Wong, A. (2019). **The hypothalamic-pituitary-adrenal axis in PTSD: Pathophysiology and treatment interventions.** *Progress in Neuropsychopharmacology and Biological Psychiatry, 89*, 361-379. doi:10.1016/j.pnpbp.2018.10.010 This article presents a comprehensive review of the research implicating HPA axis functioning in the development and maintenance of PTSD, including the contributions of the HPA axis to fear learning and extinction. The authors also review the potential uses of glucocorticoids for the prevention of PTSD when administered after a traumatic event and the role of HPA-axis modulating drugs as treatments for PTSD, both as monotherapy agents or when used as part of MAP paradigms.

Eliwa, H., Belzung, C., & Surget, A. (2017). **Adult hippocampal neurogenesis: Is it the alpha and omega of antidepressant action?** *Biochemical Pharmacology, 141*, 86-99. doi:10.1016/j.bcp.2017.08.005 This article presents an extensive review of the processes underlying the generation of new neurons in the dentate gyrus of the hippocampus in adult mammals and the biological pathways by which antidepressants enhance this process. The authors propose that depression related to chronic stress etiologies is particularly responsive to the neurogenesis effects of

antidepressant medications, which may have implications for the use of antidepressants in PTSD.

Feduccia, A. A., & Mithoefer, M. C. (2018). **MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?** *Progress in Neuropsychopharmacology and Biological Psychiatry, 84 (A)*, 221-228. doi:10.1016/j.pnpbp.2018.03.003 This review provides a biologically-oriented discussion of the various mechanisms through which MDMA may lead to improved psychotherapeutic outcomes in PTSD. The authors frame the impact of MDMA on molecules relevant to central nervous system signaling in terms of their biological effects relevant to therapeutic changes in fear memories.

Hill, M. N., Campolongo, P., Yehuda, R., & Patel, S. (2018). **Integrating endocannabinoid signaling and cannabinoids into the biology and treatment of posttraumatic stress disorder.** *Neuropsychopharmacology, 43*, 80-102. doi:10.1038/npp.2017.162 The authors of this extensive review discuss the variety of ways in which the endocannabinoid system may be harnessed for therapeutic benefit for PTSD. Endocannabinoids impair retrieval and promote extinction of emotional memories, and thus may be a viable target for enhancing psychotherapeutic interventions. The authors cite the “overwhelming” evidence that endocannabinoid signaling is involved in fear memory extinction and point to fatty-acid amide hydrolase (FAAH) inhibitors, which block the metabolism of endocannabinoids, and other drugs worthy of further study.

Kida, S. (2019). **Reconsolidation/destabilization, extinction and forgetting of fear memory as therapeutic targets for PTSD.** *Psychopharmacology, 236*, 49-57. doi:10.1007/s00213-018-5086-2 The author provides an integrated review of the neurobiological processes involved in therapeutic interventions to alter traumatic memories. The review focuses on “cellular consolidation,” involving the intracellular signal transduction pathways involved fear memory formation, remodeling, and forgetting, as well as their regulation by glutamate receptors.

Kindt, M. & Soeter, M. (2018). **Pharmacologically induced amnesia for learned fear is time and sleep dependent.** *Nature Communications, 9*, 1316. doi:10.1038/s41467-018-03659-1 This study in healthy control subjects identified that a beta-adrenergic receptor antagonist (e.g., propranolol) can interfere with the reconsolidation of a reactivated fear memory only if the drug is present in a 2- to 3-hour window post-reactivation. Furthermore, the altered reconsolidation of the fear memory occurred only if the subjects had a night’s sleep after the dosing intervention. Without sleep, even after propranolol dosing, the fear memory was retained unchanged. This study has important implications for studies evaluating reconsolidation-altering interventions for PTSD, and the potential role of sedatives to improve outcomes.

Kozel, F. A., Motes, M. A., Didehban, N., DeLaRosa, B., Bass, C., Schraufnagel, C. D., ... & Hart, J. (2018). **Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: A randomized clinical trial.** *Journal of Affective Disorders, 229*, 506-514. doi:10.1016/j.jad.2017.12.046 This randomized, sham-controlled trial of 103 Veterans with PTSD

found significant benefits sustained for six months post-treatment when repetitive transcranial magnetic stimulation (rTMS) was delivered 30 minutes immediately prior to 12-15 CPT sessions. The form of rTMS used was low frequency (1 Hz) over the right dorsolateral prefrontal cortex (DLPFC), in contrast to the high frequency (10-20 Hz) rTMS delivered over the left DLPFC commonly used for major depression. Right-sided DLPFC rTMS decreases amygdala reactivity to threatening stimuli. Notably, the study only analyzed treatment completers with one-sided significance tests and did not use an “active” sham control for rTMS, so blinding of patients to their treatment arm may have been inadequate.

Mataix-Cols, D., Fernández de la Cruz, L., Monzani, B., Rosenfield, D., Andersson, E., Pérez-Vigil, A., ... & the DCS Anxiety Consortium. (2017). **D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders: A systematic review and meta-analysis of individual participant data.** *JAMA Psychiatry*, *74*, 501-510. doi:10.1001/jamapsychiatry.2016.3955 This meta-analysis of data from 1047 patients across 21 RCTs found that DCS augmentation of exposure-based CBT produced small benefits over placebo-augmentation across all psychiatric disorders studied. However, when limited to PTSD trials, the analysis found no benefits of DCS over placebo augmentation of PE, even though the study that found significantly worse outcomes from DCS augmentation was not included (Litz et al., 2012). Concomitant use of antidepressants did not negatively affect outcomes in the DCS treated patients.

Mithoefer, M. (2013). **MDMA-assisted psychotherapy: How different is it from other psychotherapy?** In R. Doblin & B. Burge (Eds.), *Manifesting minds: A review of psychedelics in science, medicine, sex, and spirituality*, (pp. 125-135). Berkeley: Evolver. In this article, Dr. Mithoefer, one of the key developers of MDMA-assisted psychotherapy, presents a straightforward summary of the form of therapy used during the 8-hour MDMA treatment sessions. Elements of anxiety management, exposure, cognitive restructuring, transference, and somatic manifestations are incorporated. More detailed description of the therapy is available in the on-line treatment manual: <http://www.maps.org/research-archive/mdma/MDMA-Assisted-Psychotherapy-Treatment-Manual-Version7-19Aug15-FINAL.pdf>

Mithoefer, M. C., Feduccia, A. A., Jerome, L., Mithoefer, A., Wagner, M., Walsh, Z., ... & Doblin, R. (2019). **MDMA-assisted psychotherapy for treatment of PTSD: Study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials.** *Psychopharmacology*, *236*, 2735-2745. doi:10.1007/s00213-019-05249-5 This article reviews the results of the six RCTs of MDMA used to enhance psychotherapy for PTSD. An overall large effect size (Cohen's $d = 0.8$) was found between high dose MDMA versus low dose MDMA/placebo when given over two or three dosing sessions. Of note, only about 10% of all participants had ever received either PE or CPT treatment, though a third reported having had eye movement desensitization and reprocessing therapy. The article describes how the results of these 6 small trials informed the design of the phase III trials now underway.

Olden, M., Wyka, K., Cukor, J., Peskin, M., Altemus, M., Lee, F. S., ... & Difede, J. (2017). **Pilot study of a telehealth-delivered medication-augmented exposure therapy protocol for PTSD.** *Journal of Nervous and Mental Disease*, *205*, 154-160. Retrieved from: https://journals.lww.com/jonmd/Fulltext/2017/02000/Pilot_Study_of_a_Telehealth_Delivered.14.aspx The authors present the results of an 11-patient pilot randomized placebo-controlled trial assessing DCS augmentation of 12-15 sessions of PE delivered via videoconferencing. The study establishes the feasibility of conducting MAP remotely with safe medications, which could increase access to efficacious care. Study participants reported high satisfaction and therapeutic alliance scores, though 36% of the patients dropped out, consistent with drop-out rates of in-person PE trials for PTSD.

Otto, M. W., Kredlow, M. A., Smits, J. A. J., Hofmann, S. G., Tolin, D. F., de Kleine, R. A., ... & Pollack, M. H. (2016). **Enhancement of psychosocial treatment with D-cycloserine: Models, moderators, and future directions.** *Biological Psychiatry*, *80*, 274-283. doi:10.1016/j.biopsych.2015.09.007 The authors present a thoughtful overview of DCS MAP trials across fear disorders, with the aim of identifying sources of discrepancy between studies and considerations for future study designs evaluating DCS. They emphasize the importance of end-session fear level as a moderator of the efficacy of DCS and the risks of enhanced reconsolidation of fear with DCS when end-session fear remains high. The authors also discuss the potential role of DCS in enhancing appetitive learning, with implications for addiction treatment, and the differences between clinical and experimentally induced fear for evaluating the extinction-enhancing effects of DCS.

Scheeringa, M. S. & Weems, C. F. (2014). **Randomized placebo-controlled D-cycloserine with cognitive behavior therapy for pediatric posttraumatic stress.** *Journal of Child and Adolescent Psychopharmacology*, *24*, 69-77. doi:10.1089/cap.2013.0106 This article reports on the only DCS MAP trial conducted in youth with PTSD, finding no benefit over placebo at end of treatment or at three-month follow-up. To avoid potential reconsolidation of fear effects early in treatment, DCS was administered beginning at the 5th session of a 12-session course of a specific youth-focused manualized CBT that incorporated graded exposure exercises in and out of the office. An important potential confound to the study results was that the DCS group was significantly more ill at baseline than the placebo group.

Sevenster, D., Visser, R. M., & D'Hooge, R. (2018). **A translational perspective on neural circuits of fear extinction: Current promises and challenges.** *Neurobiology of Learning and Memory*, *155*, 113-126. doi:10.1016/j.nlm.2018.07.002 The authors provide a review of fear extinction at the level of brain networks, integrating animal experiments with human neuroimaging studies, and discuss the neglected role of prediction error as a component of fear extinction. The authors also address the effect of pharmacological manipulations on the neural circuitry of fear extinction and prediction error.

Young, M. B., Norrholm, S., D. Khoury, L. M., Jovanovic, T., Rauch, S. A. M., Reiff, C. M., ... & Howell, L. L. (2017). **Inhibition of**

serotonin transporters disrupts the enhancement of fear memory extinction by 3,4-methylenedioxymethamphetamine (MDMA). *Psychopharmacology*, 234, 2883-2895. doi:10.1007/s00213-017-4684-8 Building off their previous work demonstrating that MDMA injected systemically or directly to the amygdala of mice 30 min prior to fear extinction training results in sustained fear memory extinction, the authors here evaluated the role of monoamine transporters in this MDMA effect. They found that serotonin transporter inhibition (i.e., co-administration of an SSRI) prevented MDMA from enhancing fear extinction, but that inhibitors of the norepinephrine and dopamine transporters did not reduce MDMA's extinction enhancement. In addition, blockade of serotonin type 2A (5HT2A) receptors also diminished MDMA's ability to enhance extinction. Because the serotonin transporter and 5HT2A are engaged by many antidepressant and antipsychotic medications, this study has direct implications for MDMA-assisted psychotherapy treatment.

ADDITIONAL CITATIONS *continued*