OXFORD

International Journal of Neuropsychopharmacology (2020) 23(6): 385–400

doi:10.1093/ijnp/pyaa018
Advance Access Publication: 14 March 2020
Review

REVIEW

Reviewing the Potential of Psychedelics for the Treatment of PTSD

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Abstract

There are few medications with demonstrated efficacy for the treatment of posttraumatic stress disorder (PTSD). Treatment guidelines have unequivocally designated psychotherapy as a first line treatment for PTSD. Yet, even after psychotherapy, PTSD often remains a chronic illness, with high rates of psychiatric and medical comorbidity. Meanwhile, the search for and development of drugs with new mechanisms of action has stalled. Therefore, there is an urgent need to explore not just novel compounds but novel approaches for the treatment of PTSD. A promising new approach involves the use of psychedelic drugs. Within the past few years, 2 psychedelics have received breakthrough designations for psychiatric indications from the US Food and Drug Administration, and several psychedelics are currently being investigated for the treatment of PTSD. This review discusses 4 types of compounds: 3,4-methylenedioxymethamphetamine, ketamine, classical psychedelics (e.g., psilocybin and lysergic acid diethylamide), and cannabinoids. We describe the therapeutic rationale, the setting in which they are being administered, and their current state of evidence in the treatment of PTSD. Each compound provides unique qualities for the treatment of PTSD, from their use to rapidly target symptoms to their use as adjuncts to facilitate psychotherapeutic treatments. Several questions are formulated that outline an agenda for future research.

Key words: PTSD, psychedelics, MDMA, ketamine, cannabinoids

Introduction

Posttraumatic stress disorder (PTSD) is a complex disorder with a host of neurobiological alterations (see Yehuda et al., 2015; Vermetten et al., 2018). During the last 2 decades, only 2 medications (i.e., paroxetine and sertraline) have been approved for the treatment of PTSD, both of which have demonstrated limited efficacy (Hoskins et al., 2015; Cipriani et al., 2018). Meanwhile, the search for and development of drugs with new mechanisms of action has stalled (Krystal et al., 2017b). Because of the limited efficacy of pharmacotherapeutic interventions, PTSD treatment guidelines (Department of Veterans Affairs and Department of

Received: September 17, 2019; **Revised:** February 12, 2020; **Accepted:** March 12, 2020

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Defense, 2017; National Institute for Health and Care Excellence, 2018) have unequivocally designated exposure-based psychotherapy as a first line treatment for PTSD. Yet, even after multiple modalities of psychotherapy, PTSD often remains a chronic illness, with high rates of psychiatric and medical comorbidity (Steenkamp et al., 2015; Bryant et al., 2016; Kitchiner et al., 2019). Therefore, there is an urgent need to explore not just novel compounds but novel approaches for the treatment of PTSD.

The complexity of PTSD makes pharmacological targeting of 1 specific neurotransmitter system (e.g., targeting stress reactivity with selective serotonin reuptake inhibitors or hyperarousal with beta-blockers) insufficient. The treatment of PTSD may require more than pharmacologically targeting dysregulated molecules and pathways associated with developing and sustaining PTSD symptom severity and may benefit from pharmacologically induced changes in the capacity to engage with traumatic material in psychotherapy (DePierro et al, 2019). This may imply an approach to therapy that is conceptually different from the currently available treatments.

Most of the currently used psychotherapies for the treatment of PTSD are exposure-based therapies, which rely on imaginal visualization of the traumatic events and exposure to trauma-related cues that trigger fear responses. The goal is to extinguish conditioned fear to cues associated with trauma by desensitization to fearful stimuli and learn that the trauma is not reenacted in real time. The approach is directive, and the role of the therapist is to instruct the patient to relive the trauma and to provide a cognitive framework for change (Resick et al., 2016). Many patients experience a reduction in PTSD symptoms after psychotherapy. However, 40–60% of patients do not respond adequately (Haagen et al., 2015; Steenkamp et al., 2017; Watkins et al., 2018). The processing of traumatic memories typically can be an emotionally challenging experience for PTSD patients. For some patients, emotional detachment, fragmentation of trauma memories, or an inability to complete sessions due to the inability to tolerate reexperiencing traumatic memories can lead to nonresponse and treatment dropout (Mott et al., 2014; Goetter et al., 2015). Engagement in psychotrauma-focused therapy may be difficult for some patients in particular, especially those with extreme affect dysregulation or with shame or guilt associated with the recall of traumatic memories.

The integration of the targeted use of certain psychoactive substances within a psychotherapeutic treatment may have the potential to address some of these challenges. The psychoactive properties of psychedelic drugs may be of particular interest within such a substance-assisted psychotherapy approach. The rationale behind this approach is that these drugs can catalyze the psychotherapeutic process, for example, by increasing the capacity for emotional and cognitive processing through pharmacologically diminishing fear and arousal, by strengthening therapeutic alliance through increased trust and rapport, or by targeting processes of fear extinction and memory consolidation.

After a several decades hiatus, psychedelics are increasingly being studied for the treatment of a range of psychiatric indications (Mithoefer et al., 2016; Kyzar et al., 2017). Within the past 2 years, the US Food and Drug Administration (FDA) has recommended 2 compounds (3,4-methylenedioxymethamphetamine and psilocybin), which are still on the US Drug Enforcement Administration's most restrictive schedule, a breakthrough therapy designation, and approved esketamine for treatment-resistant depression. Currently, several psychedelics are being investigated for the treatment of PTSD. In this article, we review the potential of 4 types of psychedelic compounds: 3,4-methylenedioxymethamphetamine (MDMA), ketamine, classical psychedelics (e.g., psilocybin and lysergic acid diethylamide [LSD]), and some cannabinoids.

Psychedelic Drugs in the Treatment of PTSD

The use of psychedelics as medicines has recently been called a new emerging paradigm (Nichols et al., 2017). Although many questions remain about the mechanisms of action and efficacy, psychedelic drugs have seen a renaissance in research on their therapeutic potential, ranging from the treatment of depression to substance use disorders and PTSD (Kyzar et al., 2017; Curran et al., 2018). Psychedelic drugs (sometimes referred to as hallucinogens or entactogens) refer to a category of compounds that can induce a wide range of psychological, cognitive, emotional, and physical effects (Nichols, 2004; Vollenweider and Kometer, 2010). For this review, we use a broad definition of psychedelic drugs, which includes substances such as MDMA, ketamine, and cannabis, whose pharmacological profiles differ substantially from the serotonergic "classical" psychedelics (such as psilocybin and LSD) but which all share the capacity for inducing an altered or opening of the sense of self.

Although psychedelic drugs are increasingly being studied for the treatment of PTSD, well-designed clinical studies are still scarce. In the following sections, we will summarize the available evidence for 4 types of psychedelics, providing background information and addressing the therapeutic rationale for each substance, the setting in which they are administered, and the current state of evidence for the treatment of PTSD. For an overview, see Table 1.

MDMA

Background

MDMA was first synthesized in 1912 as an intermediate substance in the synthesis of a hemostatic drug (Freudenmann et al., 2006). It only started gaining attention since the discovery of its psychoactive effects in the 1970s, after which several psychotherapists started using it as an adjunct to psychotherapy (Passie, 2018). In 1985, after MDMA became widely known as a "party drug," the US Drug Enforcement Administration placed it on schedule 1 of the Controlled Substances Act, and its therapeutic use became illegal (Passie, 2018). In spite of its initial therapeutic use, no clinical trials were conducted until the year 2000. Since then, MDMA has been investigated for the treatment of PTSD (e.g., Mithoefer et al., 2010, 2018), alcohol use disorder (Sessa et al., 2019), and social anxiety in autistic adults (Danforth et al., 2018). Because of the promising results, in August 2017, the FDA designated MDMA-assisted psychotherapy as a "breakthrough therapy" for the treatment of PTSD. A multicenter phase 3 trial is ongoing with several sites in the United States, Canada, and Israel, and another multicenter phase 2/3 trial has just started in several European countries.

Therapeutic Rationale

The main rationale behind MDMA-assisted psychotherapy is that MDMA acts as a catalyst to psychotherapy by reducing the fear response to anxiety-provoking stimuli, including previous trauma and traumatic memories. In addition, MDMA enhances introspection and increases interpersonal trust, which can benefit the therapeutic alliance. From a clinical perspective, MDMA alters cognition very slightly, produces only mild sensory alterations, and does not induce a clouding of consciousness, while patients sustain a clear memory of the experience (Passie, 2012). MDMA's fear-reducing effects and "trust-boosting"

Table 1. Psychedelic Substances in the Treatment of PTSD: Therapeutic Rationale, Administration, Setting, and Evidence

Substance	Therapeutic rationale[a]	Administration	Setting	Evidence
MDMA	• Increases release of serotonin, dopamine, norepinephrine, oxytocin, prolactin, vasopressin, and cortisol. • Serves as a catalyst to psychotherapy. • Increases fear extinction. • Reduces amygdala activity. • Reopens critical period for social reward learning. • Reduces fear response and shame. • Increases openness and interpersonal trust. • Increases emotional empathy. • Improves processing traumatic memories.	• Route of administration: oral. • Dose: 75–125 mg. • Duration of action: 4–8 h. • Administration at start of therapy session. • Multiple administrations (typically 3 sessions) spaced 1 mo apart.	• Clinical but aesthetically pleasant room. • Presence of 2 therapists. • Use of music to deepen and support therapeutic process. • Embedded within psychotherapeutic treatment (nondirective). • Multiple nondrug preparation and integrative sessions.	• Sustained reduction of PTSD symptoms. • Phase 2 RCT (n = 105) completed in 2016. • Phase 3 RCT expected to be completed in 2021. • Other indications: alcohol use disorder and social anxiety (in autistic adults).
Ketamine	• NMDA receptor antagonist. • Rapid (temporary) symptom reduction. • May serve as a catalyst to psychotherapy. • Increases synaptic plasticity. • Facilitates fear extinction and blocks memory reconsolidation. • May increase receptivity to therapeutic interventions. • May improve ability to process traumatic memories.	• Route of administration: i.v., i.m., intranasal, oral. • Dose: typically 0.50 mg/kg over 40 min. • Duration of action: 40–70 min. • Administration at start of treatment, beginning of therapy session, after memory retrieval, or without psychotherapy (depending on rationale). • Single or multiple administrations spaced days to weeks apart.	• Clinical room with no to minimal attention to aesthetics. • Psychological support varies from minimal support from nurse/psychiatrist to extensive support from psychotherapist. • Virtually no use of music. • Currently not embedded within psychotherapeutic framework. • No nondrug preparation and integrative sessions.	• Rapid (temporary) reduction of PTSD and depressive symptoms. • 1 RCT (n = 41) completed in 2014. • Multiple RCTs ongoing. • Increasing evidence for treatment of depression. • Other indications: anesthesia, depression, suicidality, alcohol and opiate addiction.
Classical psychedelics	• 5-HT2A receptor agonists. • Serve as a catalyst to psychotherapy. • Increase synaptic plasticity. • Can reduce amygdala reactivity during emotional processing. • Increase insightfulness and introspection. • Increase divergent thinking and mindfulness-related capacities. • May reduce avoidance. • Can increase emotional empathy. • Can induce emotional breakthrough experiences. • May resolve existential distress. • May increase access to traumatic memories.	• Route of administration: oral. • Dose: 10–25 mg (psilocybin), 50–200 µg (LSD). • Duration of action: 4–12 h. • Administration at beginning of therapy session. • Single or multiple administrations (typically not more than 3) spaced weeks to months apart.	• Clinical but aesthetically pleasant room. • Presence of 2 therapists/guides. • Use of music to deepen and support therapeutic process. • Often embedded within psychotherapeutic treatment (nondirective). • Multiple nondrug preparation and integrative sessions.	• No RCTs in PTSD. • Extensive psychotherapeutic use of LSD and psilocybin during first wave (1950–1970) of research with psychedelics. • Used in treatment of concentration camp syndrome in 1960s and 1970s. • Recent evidence from studies in other indications with high effect sizes. • Other indications: depression, substance use disorders, end of life anxiety, and obsessive-compulsive disorder.

Table 1. Continued

Substance	Therapeutic rationale[a]	Administration	Setting	Evidence
Cannabinoids	• Target the endocannabinoid system (e.g., CB1 and CB2 receptors). • Symptom management (insomnia and nightmares). • May serve as a catalyst to psychotherapy. • May increase fear extinction (decreased fear extinction with chronic use). • May improve ability to process traumatic memories.	• Route of administration: oral, sublingual, or inhaled (vaporized or smoked). • Dose: varying dosages and different ratios of THC/CBD. • Duration of action: 3–8 hours. • Daily administration in case of symptom management.	• Take-home prescription. As such, used in a variety of settings. • Depending on symptoms, used throughout the day or just before sleep.	• 1 small RCT (n = 10) with nabilone completed in 2015. • Multiple RCTs with medical cannabis ongoing. • Other indications: symptom management for multiple nonpsychiatric indications, e.g., multiple sclerosis and oncology (pain, cachexia, and nausea).

Abbreviations: CB1 and CB2, cannabinoid 1 and 2 receptors; CBD, cannabidiol; 5-HT2A, serotonin 2A receptor; LSD, lysergic acid diethylamide; MDMA, 3,4-Methylenedioxymethamphetamine; NMDA, N-methyl-D-aspartate; PTSD, posttraumatic stress disorder; RCT, randomized controlled trial; THC, tetrahydrocannabinol.
[a]Therapeutic rationale based on both (pre)clinical research and clinical observations.

properties aid in opening new avenues for therapeutic reprocessing. These effects may be used to facilitate imaginal exposure, cognitive restructuring, and corrective attachment.

Several papers have been published on the therapeutic mechanisms of MDMA-assisted psychotherapy (e.g., Mithoefer et al., 2016; Feduccia and Mithoefer, 2019). Both preclinical and clinical studies provide evidence for some of the proposed mechanisms. For example, MDMA has been shown to increase emotional empathy (Kuypers et al., 2017), prosocial behavior (Hysek et al., 2013), pleasantness of affective touch (De Wit and Bershad, 2019), and subjective ratings of closeness to others, openness, and trust (Schmid et al., 2014). MDMA-assisted psychotherapy has shown the ability to induce lasting changes in some personality traits (Mithoefer et al., 2018). Preliminary data indicate that increases in the trait of openness play a moderating role between treatment with MDMA-assisted psychotherapy and reductions in PTSD symptoms (Wagner et al. 2017).

On a neurobiological level, MDMA attenuates amygdala activity while activating the frontal cortex (Gamma et al. 2000; Carhart-Harris et al., 2015), the activity of which is often impaired in patients suffering from PTSD (see Francati et al., 2007; Dahlgren et al., 2018). MDMA also increases oxytocin levels, which is a potential contributing factor to experienced increases in interpersonal trust (Vizeli and Liechti, 2018). Oxytocin levels have been shown to mediate the prosocial effects of MDMA in animal studies (Thompson et al., 2007), and a recent study found that a single dose of MDMA in mice reopens the critical period for social reward learning, which required activation of oxytocin receptors in the nucleus accumbens, and endures beyond the acute effects of the drug (Nardou et al., 2019). The effects of MDMA on fear extinction and memory consolidation may be another contributing factor to its therapeutic potential for the treatment of PTSD (Young et al., 2017; Feduccia and Mithoefer, 2018). Ongoing research is testing whether these findings translate to humans as well (e.g., NCT03181763).

Setting

Typically, the use of MDMA is embedded within a psychotherapeutic treatment, with several non-drug preparatory sessions preceding and multiple integrative therapy sessions following each MDMA session. MDMA is administered in a clinical—but aesthetically pleasant—setting, with sessions lasting 5 to 8 hours. Patients are accompanied by 2 therapists whose role is to facilitate an introspective process in which the patient may revisit past experiences. An important difference with regular pharmacotherapeutic treatments of PTSD is that MDMA is used as an adjunct to psychotherapy. The role of MDMA is to occasion a mental and emotional state conducive to fuller engagement in the therapeutic process. Another important distinction is the nondirective approach. This approach emphasizes the importance of allowing the patient's own process to unfold. Although verbal interactions between the patients and therapists can be an important part of the sessions, patients are often encouraged to lie down, close their eyes, and go inwards while listening to a music playlist specifically selected for this therapy. Music has shown to play a central role in psychedelic-assisted psychotherapy (Kaelen et al., 2015; Barrett et al., 2018), and several playlists have been composed to assist and enhance the therapeutic process (Kaelen et al., 2018). The psychotherapeutic procedures and interventions follow a standardized treatment manual that has been developed for MDMA-assisted psychotherapy for PTSD (Mithoefer, 2017).

Administration

MDMA is typically administered orally in doses ranging from 75 to 125 mg (Mithoefer et al., 2019). In most studies, 1 to 2 hours after administration, a booster dose containing one-half of the initial dose is offered to prolong the effects. The duration of effects is 4 to 6 hours, often with some lingering effects in the hours afterwards (Mithoefer et al. 2010). MDMA is typically administered 2 to 3 times over the course of several months of nondrug psychotherapy.

Evidence in the Treatment of PTSD

The first clinical trial into the use of MDMA-assisted psychotherapy for the treatment of PTSD was conducted in Spain from 2000 to 2002 in 6 women with chronic PTSD secondary to sexual assault (Bouso et al., 2008). Patients received a low dose (50 or 75 mg MDMA) combined with several 90-minute nondrug psychotherapy sessions before and after the MDMA sessions. Reductions of PTSD symptoms were observed in both MDMA groups, but the small number of patients did not allow for statistical analysis. The most important conclusion that could be drawn from this study was that the administration of MDMA in this population seemed both physically and psychologically safe.

The results of the first randomized placebo-controlled trial (RCT) of MDMA-assisted psychotherapy for PTSD were published in 2010 (Mithoefer et al., 2010). Twelve treatment-resistant patients received 2 sessions with 125 mg MDMA (plus an optional booster of 62.5 mg), while 8 patients received a placebo. The results showed that 83% of the patients in the MDMA group did not meet the criteria for PTSD anymore, according to Clinician-Administrated PTSD Symptoms Scale (CAPS-IV) cutoff scores, compared with 25% in the placebo group. A long-term follow-up demonstrated that treatment effects were stable over a 3.5-year period (Mithoefer et al., 2013). These results were replicated in 2 other studies (Mithoefer et al., 2018; Ot'alora et al., 2018) in which MDMA-treated patients also showed increases in posttraumatic growth. A pooled analysis on 105 patients from 6 RCTs (Mithoefer et al., 2019) showed that patients who received MDMA experienced significantly greater reductions in PTSD symptom scores than patients in the control group (Cohen's $d = 0.8$). After 2 MDMA sessions, 54.2% of patients no longer met PTSD diagnostic criteria compared with 22.6% in the control group. Compared with data used for the FDA approval of paroxetine and sertraline, MDMA-assisted psychotherapy showed higher effect sizes and significantly lower dropout rates (Feduccia et al., 2019). Based on these results, the FDA granted MDMA a breakthrough therapy designation for the treatment of PTSD.

Safety and Potential Side Effects

Frequently reported side effects of MDMA include anxiety, tight jaw, headache, and fatigue (Feduccia et al., 2019; Mithoefer et al., 2019). Episodes of anxiety can occur when the first effects of MDMA become noticeable and can easily be coped with by psychotherapeutic support (Passie, 2012). In some cases, a slightly depressed mood has been reported (Liechti et al., 2001). MDMA is known to increase heart rate and blood pressure in a dose-dependent manner (Vizeli and Liechti, 2018). Therefore, some forms of hypertension and severe cardiovascular pathology are seen as contraindications. Slight hyperthermia as induced by MDMA presents no problem when used in a medical setting (Holze et al., 2020). Some authors (e.g., Parrott, 2014; Schenk and Newcombe, 2018) have raised concerns over a potential neurotoxicity and abuse liability of MDMA (e.g., Roger et al., 2009; Biezonski and Meyer, 2011; Heal et al., 2018). However, neither of those have occurred in medically supervised use of MDMA (e.g., Feduccia et al., 2019; Mithoefer et al., 2019).

Ketamine

Background

Ketamine, a noncompetitive N-methyl-D-aspartate-receptor antagonist, was first synthesized in 1962 and approved as an anesthetic in 1970. It is often categorized as a "dissociative psychedelic" (e.g., Sanz et al., 2018). Since the 1990s, ketamine-assisted psychotherapy has been used in the treatment of alcoholism and heroin addiction based on an aversion approach (Krupitsky and Grinenko, 1997; Krupitsky et al., 2007). During the last 2 decades, ketamine has been receiving increasing interest for the treatment of a variety of psychiatric indications. In the early 2000s, several clinical trials reported the rapid antidepressant properties of ketamine (Berman et al., 2000; Zarate et al., 2006). Since then, there has been an exponential growth in studies investigating its antidepressant effects (see Fond et al., 2014 for a meta-analysis) and its effects on suicidal ideation (see Wilkinson et al., 2018 for a meta-analysis). In March 2019, the FDA approved esketamine (1 of 2 enantiomers of ketamine) for the treatment of treatment-resistant depression. Ketamine has also been proposed as a candidate for targeting emotional memories (Veen et al., 2018), and it is increasingly studied for the treatment of PTSD (e.g., Feder et al., 2014; DePierro et al., 2019).

Therapeutic Rationale

In the treatment of depression, ketamine has very rapid effects, acting through glutamatergic and other signaling pathways (Murrough et al., 2013a). Although there is limited empirical evidence for mechanisms through which ketamine might reduce PTSD symptoms, several neurobiological mechanisms have been proposed. One hypothesis is that PTSD is a "synaptic disconnection syndrome" (e.g., Li et al., 2011; Duman et al., 2016; Krystal et al., 2017a). The therapeutic effects of psychedelic drugs like ketamine might be partially explained by their ability to rapidly increase synaptic and neuronal plasticity (Ly et al., 2018).

Ketamine could also target PTSD symptoms by its effects on glutamate signaling. The glutamate system has shown to play an essential role in several memory processes, such as reconsolidation and extinction learning (Nader, 2015). Ketamine enhances fear extinction in rodents (Girgenti et al., 2017) and has also shown the ability to block memory reconsolidation (Das et al., 2013; Duclot et al., 2016). Ketamine's effects on these memory processes suggest a potential role for its use within a substance-assisted psychotherapy framework. Due to its plasticity-enhancing effects, ketamine may also increase the receptiveness to psychotherapeutic interventions in the days following administration.

Administration of a subanesthetic dose of ketamine could then be considered an augmentation strategy for trauma-focused psychotherapy (Veen et al., 2018), suggesting that the integration of ketamine within a psychotherapeutic treatment could result in long-term remission of PTSD symptoms. A small number of practitioners have used ketamine within such a framework before, with promising results in the treatment of alcohol and heroin addiction (Krupitsky and Grinenko, 1997; Krupitsky et al., 2007), and in some other indications (e.g., depression and anxiety; Dore et al., 2019). Within a substance-assisted psychotherapy approach, the acute psychoactive effects of ketamine—ranging from sensory distortions and

hallucinations, to transformations in the self-concept, emotional attitudes to aspects of self and others, and changes in life values and purposes (Krupitsky et al., 1997)—could catalyze, deepen, or increase engagement in a psychotherapeutic process and facilitate reflections on psychological material presented during the acute subjective experience.

Setting

Different from the therapeutic use of MDMA, the current administration of ketamine is typically not approached from a substance-assisted psychotherapy framework. This is often reflected in the setting in which ketamine is applied. It is mainly being administered in clinical hospital rooms, without the use of music, and with little—if any—time spent on psychological preparation and integration of ketamine experiences. It must be noted that there can be a wide range of settings in which ketamine can be administered, from the stand-alone administration of ketamine to the use of ketamine with assisted forms of psychotherapeutic preparation and support. When ketamine is embedded within a substance-assisted psychotherapy framework, its use might benefit from a similar setting as used for MDMA- or psilocybin-assisted psychotherapy.

Administration

In the treatment of psychiatric indications, ketamine is typically administered intravenously in doses of 0.5 mg/kg over a period of 40 minutes (e.g., Feder et al., 2014; McGirr et al., 2015). Administered intravenously, the acute effects of ketamine last for 40 to 70 minutes. Ketamine can also be administered intramuscularly, intranasally, or orally. For the treatment of PTSD, ketamine has been studied as a single infusion intervention (Feder et al., 2014) and as a multiple infusion intervention (e.g., 6 administrations in 2 weeks; Albott et al., 2018). Different doses of ketamine can induce qualitatively different psychoactive effects, which can potentially be used for different treatment approaches. When its use is embedded within a psychotherapeutic treatment, it can be administered at different stages of therapy, depending on the therapeutic approach. For example, when the aim is to enhance fear extinction or to influence memory consolidation, it could be administered in low doses at the beginning of a psychotherapy session. Because of its ability to increase neuroplasticity, ketamine might also increase the receptiveness to inpatient exposure therapy when administered in higher doses at the day or several hours before a patient starts treatment.

Evidence in the Treatment of PTSD

The only RCT that studied ketamine for the treatment of PTSD compared a single i.v. infusion of 0.5 mg/kg ketamine with an i.v. infusion of 0.045 mg/kg midazolam in 41 patients with chronic PTSD and associated depressive symptoms (Feder et al., 2014). Ketamine infusion led to a significant and rapid reduction of PTSD symptom severity, which remained significant up until 7 days after this single infusion. These short-term improvements point to a temporary neurobiological working mechanism, as also observed in the use of ketamine for depression (see Fond et al., 2014).

As with the use of ketamine for depression (Murrough et al., 2013b), research suggests that the therapeutic effects of ketamine on PTSD can be enhanced—both in strength and duration—with repeated infusions. Albott et al. (2018) administered 6 i.v. ketamine infusions (0.5 mg/kg) over a 12-day period in 15 military veterans with comorbid PTSD and treatment-resistant depression. The remission rate for PTSD (defined as PTSD checklist for DSM-5 scores <33) was 80%, with a median time to relapse of 41 days.

To our knowledge, only 1 published study has attempted to treat PTSD with ketamine using an approach that is somewhat comparable with substance-assisted psychotherapy. Pradhan et al. (2017, 2018) combined the administration of ketamine with a mindfulness-based cognitive therapy in patients with refractory PTSD. Patients received a single i.v. dose of 0.5 mg/kg ketamine (or saline) over 40 minutes. Before the infusion, traumatic memories were activated in a controlled manner by making patients reflect on a personalized scripted narrative of their index trauma. In addition, during the infusion period, 2 cycles (10 minutes each) of a mindfulness exercise were practiced, aimed to facilitate the extinction of traumatic memories and the reconsolidation of novel calming memories. Ketamine-induced relaxation and dissociation augmented a state in which patients did not react fearfully to the traumatic memories but passively accepted them as they came (Pradhan et al., 2017). Patients in the ketamine group showed a significantly more durable reduction in CAPS-IV PTSD symptoms (for 34 days) than patients in the placebo group (for 16 days). This is a 5-times increase in the duration of response compared with a single administration of ketamine without any psychotherapy reported by Feder et al. (2014). However, improvement in PTSD symptoms was still relatively short-lived.

Safety and Potential Side Effects

Frequently reported side effects of ketamine include drowsiness, dizziness, nausea, visual and perceptual alterations, and dose-dependent dissociative effects (Rybakowski et al., 2016). In some cases, ketamine can induce short-lived anxiety. Such reactions can be minimized by supportive clinical settings (Aust et al., 2019; Dore et al., 2019). By its sympathomimetic effects, ketamine increases heart rate and blood pressure. Therefore, some forms of hypertension and severe cardiovascular pathology are seen as contraindications (Rybakowski et al., 2016). While acute psychoactive effects of ketamine are often considered undesirable side effects, from the perspective of a substance-assisted psychotherapy approach, some of these effects are thought to have therapeutic value (Krupitsky et al., 2007; Pradhan et al., 2017).

Classical Psychedelics

Background

Classical psychedelics comprise a group of several compounds, including psilocybin, LSD, and dimethyltryptamine (DMT), which share a common mechanism of action, mainly by agonistic action at the 5-HT2A receptor. In the 1950s and 1960s, many psychiatrists judged classical psychedelics as valuable tools when combined with psychotherapy. Over 700 scientific articles were published, and a few thousand patients were treated for several mental disorders, including neuroses, trauma, and alcoholism (Passie, 1997). In the mid-1960s, most psychedelic drugs were scheduled because of widespread use outside of the medical context, and research came to a halt. Since the 2000s, there is renewed interest in the therapeutic potential of these compounds. The focus varies from pharmacokinetics, mechanisms of action, and brain imaging studies to phase 2 trials for the treatment of several psychiatric disorders. Psilocybin has been studied for the treatment of depression (Carhart-Harris et al., 2016, 2017), tobacco and alcohol addiction (Johnson et al., 2014, 2017; Bogenschutz et al., 2015, 2018), obsessive-compulsive disorder (Moreno et al., 2006), and depression and anxiety in patients with life-threatening diagnoses (Grob et al., 2011; Griffiths

et al., 2016; Ross et al., 2016). Based on these studies, psilocybin recently received breakthrough designations from the FDA for use in depression. Currently, several trials with psilocybin- and LSD-assisted psychotherapy are being conducted in Europe and the United States. Although no formal clinical trials have yet investigated these substances for the treatment of PTSD, the available evidence (e.g., Leuner, 1981; Bastiaans, 1983) does warrant such an investigation.

Therapeutic Rationale

Findings of several recent studies suggest that the effects of classical psychedelics might be useful for the treatment of PTSD. As with ketamine, classical psychedelics induce several neurobiological changes that may be relevant for a psychotherapeutic application. Both psilocybin (Catlow et al., 2013) and DMT (Cameron et al., 2018) have been shown to facilitate fear extinction in animal studies and to promote neural plasticity in vivo and vitro, increasing neurogenesis, spinogenesis, and synaptogenesis (Ly et al., 2018). The plasticity-promoting properties of these substances might contribute to their rapid antidepressant and anxiolytic effects. Classical psychedelics have also been shown to decrease amygdala reactivity during emotion processing (Kraehenmann et al., 2015; Mueller et al., 2017). As patients with PTSD often show heightened amygdala reactivity (see Francati et al., 2007), this may increase the ability to process traumatic memories.

Other acute effects that substantiate their potential therapeutic role in the treatment of PTSD include increases in emotional empathy (Pokorny et al., 2017), increases in creative divergent thinking (Kuypers et al., 2016), enhanced mindfulness-related capacities (Soler et al., 2015; Sampedro et al., 2017), increased insightfulness (Kometer et al., 2015), reduced avoidance and increases in acceptance and connectedness (Watts et al., 2017), long-term increases in the personality trait of openness (Maclean et al., 2011; Lebedev et al., 2016), and emotional breakthrough experiences (Roseman et al,. 2019), which has shown to be a key mediator in long-term psychological change in other mental disorders. Classical psychedelics are also known to induce mystical-type experiences (Griffiths et al., 2011). Such experiences have shown to mediate therapeutic effects of psilocybin in nicotine addiction (Garcia-Romeu et al., 2014); reductions in anxiety, depression, and existential distress in patients with a life-threatening diagnosis (Griffiths et al., 2016; Ross et al., 2016); and improvements in depression (Roseman et al., 2018). However, it is currently unknown whether this type of experience also holds value for the treatment of PTSD.

Setting

The setting in which classical psychedelics are administered is very similar to that of MDMA. Their use is usually embedded within an extensive psychotherapeutic treatment with multiple nondrug preparatory and integrative sessions. Typically, psilocybin and LSD are administered in a comfortable and aesthetically pleasant setting under the guidance of a female/male therapist team. As with MDMA, the approach is nondirective, and interaction with the therapists or guides is often kept to a minimum, especially during the first few hours of the experience. Patients are encouraged to lie down, close their eyes, and go inwards while (in most treatment procedures) listening to specifically selected music (Kaelen et al., 2018). Classical psychedelics have also been used in more interactive and group settings with small to moderate doses to weaken psychological defenses, as was done with psycholytic therapy in the previous century (Passie, 1997). Appropriate contextualization within conventional psychotherapy and safety measures as well as competent verbal and nonverbal support are essential when this type of compound will be used when dealing with the complex symptoms of PTSD.

Administration

Psilocybin and LSD are typically administered orally at the beginning of a treatment session in doses ranging from 10 to 25 mg psilocybin or 50 to 200 µg LSD. The psychological effects of psilocybin last from 3 to 6 hours (Passie et al., 2002) and those of LSD last from 8 to 10 hours (Passie et al., 2008). Both substances are usually administered just a few times over the course of several months of nondrug psychotherapy.

Evidence in the Treatment of PTSD

Before PTSD was introduced as a psychiatric diagnosis in the third edition of the Diagnostic and Statistical Manual of Mental Disorders in 1980, LSD (and sometimes psilocybin and ketamine) was used in the Netherlands as a therapeutic tool in the treatment of what was then called concentration camp syndrome. The core of this therapy consisted of enabling clients to reexperience the traumatic event with appropriate emotional abreaction under therapeutic guidance. The main figure working with this approach was Dutch psychiatrist Jan Bastiaans (1983), who treated hundreds of patients. In a long-term follow-up study on 12 patients, all but 1 patient reported moderate to strong improvements after treatment with this method (Ossebaard and Maalsté, 1999). It is known from the literature on psycholytic treatments in the 1960s (Passie, 1997) that many traumatized patients have been treated with classical psychedelics; however, they were not diagnosed with PTSD due to the lack of this diagnosis in the diagnostic systems at the time.

To our knowlegde, since then no studies have investigated the potential of a classical psychedelic for the treatment of PTSD. However, the DMT-containing plant concoction ayahuasca recently has been proposed as a candidate for its treatment (Nielson and Megler, 2014; Inserra, 2018). Ayahuasca is usually prepared from the combination of the beta-carboline–containing *Banisteriopsis caapi* vine, which has monoamine oxidase inhibiting properties, and the DMT-containing leaves of *Psychotria viridis*. This strong psychoactive brew has been used for centuries by indigenous people in the Amazon for medicinal, spiritual, and other purposes (McKenna, 2004). Some researchers are currently collecting survey data on the use of ayahuasca for the treatment of PTSD. There are also plans to study ayahuasca for this indication in clinical trials (Labate et al., 2014).

Results from both past and recent studies suggest a potential role for classical psychedelics in the treatment of PTSD. However, there may be specific challenges with this approach due to the heightened arousal and sensitivity induced by these substances. In sum, there is tentative clinical evidence that these substances may be helpful with PTSD, but more rigorous studies are needed.

Safety and Potential Side Effects

Side effects of classical psychedelics include occasional transient episodes of nausea, vomiting, and physical discomfort (Carhart-Harris et al., 2016; Griffiths et al., 2016). Classical psychedelics can also induce psychologically challenging experiences, including anxiety and confusion (Johnson et al., 2018). However, such experiences can be part of the therapeutic process. With experienced therapists, they do not cause any serious problems (Grof, 1980; Leuner, 1981). Some patients may feel

emotionally vulnerable during the days following the experience, which stresses the importance of psychological support afterwards (Watts et al., 2017). Classical psychedelics can mildly increase heart rate and blood pressure. Therefore, some forms of hypertension and severe cardiovascular pathology are seen as contraindications (Johnson et al., 2018). Classical psychedelics are not toxic to the human organism and do not cause dependence or serious after effects (e.g., flashbacks) when used in medically supervised settings (Cohen, 1960; Malleson, 1971; Johnson et al., 2018).

Cannabinoids

Background

Cannabis has been used in Asia and the Middle East for medicinal, spiritual, and other purposes for thousands of years (Haney and Hill, 2018). Medicinal use of cannabis in the Western world started in the 19th century for the treatment of rheumatism, convulsions, and other indications (Zuardi, 2006). However, the medical use of cannabis declined since the early 20th century (Pisanti and Bifulco, 2017). Since the 1990s, after the endogenous cannabinoid (endocannabinoid) system was discovered, scientific studies into medicinal applications (e.g., pain relief, multiple sclerosis, and epilepsy) have been increasing again (Whiting et al., 2015; Haney and Hill, 2018). Meanwhile, the endocannabinoid system is seen as a promising pharmacological target for the treatment of several diseases, and its relevance for the treatment of PTSD is increasingly studied (Passie et al., 2012; Steenkamp et al., 2017; Hindocha et al., 2019). During the last 2 decades, several countries have legalized medical cannabis. Recently, the World Health Organization proposed rescheduling cannabis to allow for medical applications (Mayor, 2019).

Therapeutic Rationale

Cannabis contains more than 100 different cannabinoids, of which tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most studied (Berman et al., 2018). Several synthetic cannabinoids such as nabilone and dronabinol have been developed and studied as well (Freeman et al., 2019). Cannabinoids act on the endocannabinoid system, which plays a central role in emotional memories and is a crucial mediator of the hypothalamic-pituitary-adrenal response under stress (Ney et al., 2019). Exposure to chronic stress causes a downregulation of cannabinoid type 1 receptors (Morena et al., 2016), and several PTSD symptoms such as hyperarousal, sleeping problems, and intrusive memories seem to be facilitated by decreased endocannabinoid signaling (Passie et al., 2012; Hill et al., 2018). These findings support the potential role of cannabinoids for the treatment of PTSD.

Cannabis and synthetic cannabinoids differ from other psychedelic compounds in that they are mainly used and studied for the temporary relief of PTSD symptoms. However, they might hold potential for use within a substance-assisted psychotherapy model as well. Several cannabinoids, including THC and CBD, have shown the ability to increase fear extinction (Passie et al., 2012; Rabinak et al., 2013, 2014) and to disrupt fear memory reconsolidation (Stern et al., 2017). As fear extinction processes are essential for successful exposure therapy, and as PTSD patients have shown poorer fear extinction learning and recall than controls (Norrholm et al., 2011; Zuj et al., 2016; Ney et al., 2019), the efficacy of exposure therapies could possibly be enhanced with the targeted use of cannabis or certain cannabinoids. The acute psychoactive effects of cannabinoids could also offer benefits that might increase engagement in psychotherapy. For example, it has been shown that THC can reduce amygdala reactivity to threatening stimuli (Phan et al., 2008; Passie et al., 2012), an effect that might facilitate the processing of traumatic memories.

Setting

Medical cannabis and synthetic cannabinoids are commonly prescribed as a take-home medication for daily use to reduce PTSD symptoms. As such, cannabinoids are used in a variety of contexts. Although cannabinoids have not been studied within a substance-assisted psychotherapy model before, it is reasonable to assume this might benefit from a similar setting as used with other psychedelics, such as MDMA and psilocybin.

Administration

Cannabinoids can be administered by several routes. Synthetic cannabinoids are mainly administered orally, but medical cannabis is often administered sublingually as an oil or through a method of inhalation (e.g., vaporized or smoked). The duration of effects depends on the route of administration. The acute effects of cannabis or cannabinoids last around 6–8 hours when taken orally or sublingually and 2–3 hours when inhaled (Akram et al., 2019). The dose depends on the particular cannabinoid or cannabis strain and on the symptoms and particular needs of the patient. Cannabinoids can be used throughout the day or just before sleep.

Evidence in the Treatment of PTSD

Several studies have investigated the use of cannabinoids for the treatment of PTSD. In 1 study, 5 mg THC (sublingually) was prescribed twice daily as an add-on treatment to 10 outpatient patients who were taking another stable medication for their PTSD symptoms. A significant improvement in global symptom severity, sleep quality, frequency of nightmares, and hyperarousal symptoms was found (Roitman et al., 2014). However, these results have to be interpreted with caution due to the small sample size, lack of control group, and interfering other medications. The only placebo-controlled study with cannabinoids for PTSD has been done with nabilone, a synthetic cannabinoid that mimics THC. Ten PTSD patients from the Canadian military who were experiencing trauma-related nightmares received nabilone in a placebo-controlled trial with a cross-over design. After receiving nabilone for 7 weeks, patients showed significantly stronger improvements on the CAPS Recurring and Distressing Dream scores, Clinical Global Impression of Change scores, and scores of the General Well Being Questionnaire compared with when they received a placebo for 7 weeks (Jetly et al., 2015). These results confirm tentative findings from an open label chart review study of nabilone in 47 PTSD patients (Fraser, 2009) and a retrospective study on 104 male inmates (Cameron et al., 2014) in which nabilone had shown beneficial effects on several PTSD symptoms, nightmares, and sleeping problems in particular. A recent meta-analysis has called for high-quality studies to further examine the effects of cannabinoids on PTSD (Black et al., 2019).

Safety and Potential Side Effects

Frequently reported side effects of cannabinoids include dry mouth, dizziness, and fatigue (MacCallum and Russo, 2018). In a few cases, nausea and vomiting can occur. Especially if used in higher doses, cannabinoids can induce anxiety (Moreira and

Wotjak, 2009). The use of cannabinoids might be an additional risk factor for the development of psychotic disorders in susceptible individuals (Di Forti et al., 2019; Hamilton and Monaghan, 2019). Frequent recreational use of cannabis has also been associated with cognitive deficits, especially in adolescents (Levine et al., 2017). There is an ongoing discussion about the persistence of such effects (Schreiner and Dunn, 2012; Scott et al., 2018). Another potential risk factor is the development of cannabis use disorder in vulnerable individuals (Hasin et al., 2016). This emphasizes the importance of appropriate screening and monitoring of treatment.

Discussion

Exposure-based psychotherapy is unequivocally designated as a first-line treatment for PTSD. Yet, in many cases, PTSD remains a chronic illness, with high rates of psychiatric and medical comorbidity. Therefore, there has been an urgent need for novel interventions that can increase the efficacy of PTSD treatments. As this review shows, psychedelic drugs offer opportunities for a novel approach to the treatment of PTSD. Each of the reviewed compounds provides a unique potential, from their use to rapidly target the symptoms of PTSD to their use as adjuncts to facilitate psychotherapeutic treatments.

MDMA may allow patients to experience reduced fear and shame, and, at the same time, feelings of trust and safety, often of great importance in complex PTSD. This enables them to more easily revisit and process traumatic memories and gain openness and trust. Patients also feel more empathetic and experience an increased openness to new and constructive perspectives on their situation. They may experience an increased connection to others, changes in views on life values and purposes, and insights into the moral value of traumatic exposures or around existential issues. Integrated within a psychotherapeutic treatment, 2 to 3 sessions with MDMA have shown the ability to induce significant and sustained reductions in PTSD symptoms (Mithoefer et al., 2019).

Ketamine has thus far mainly been used as a standalone treatment for PTSD. Used this way, it has shown the ability to rapidly reduce the symptoms of PTSD (Feder et al., 2014). A single administration of ketamine seems to lead to relatively brief reductions in symptoms up to a week, but multiple infusions over the course of several weeks (Albott et al., 2018), or the combination with psychotherapeutic interventions (Pradhan et al., 2017, 2018), may extend therapeutic effects. The proper integration of ketamine within a substance-assisted psychotherapy framework might hold promise for long-term effects. Moreover, ketamine's ability to alter memory processes, such as increases in fear extinction or the disruption of memory reconsolidation, offers an exciting opportunity for an application in combination with exposure therapy (Veen et al., 2018). Currently, at least 2 studies (NCT03960658; NCT02727998) are exploring such an approach.

Classical psychedelics such as psilocybin and LSD have shown promising results for the treatment of a variety of psychiatric indications, but clinical trials focusing on the treatment of PTSD are still lacking. Observations from clinical use in the previous century (Leuner, 1981; Bastiaans, 1983; Ossebaard and Maalsté, 1999) and several of their acute psychoactive effects suggest a significant potential for treating PTSD. However, their partially unpredictable psychological effects might not make them the best candidates compared with other substances reviewed here. For example, compared with MDMA, their effects are more variable and instable and harder to predict and handle. Their sensitizing and affect-intensifying effects as well as the labilization of the general psychological state could be detrimental for at least some patients with PTSD. Although the fear response can also be reduced by classical psychedelics, this may be much more dependent on the psychological state of the patient. The psychological condition of many PTSD patients is unstable, and they are particularly vulnerable to increases in anxiety when reexperiencing traumatic memories, which in some cases can be amplified by classical psychedelics. Another difference from MDMA, which produces a relatively stable pattern of effects, is decreases in the sense of self and self-control. While alterations in the sense of self and self-control are mild with MDMA, classical psychedelics can reduce ego integrity and self-control more strongly, although in a dose-dependent manner.

For these reasons, classical psychedelics might have less potential for the treatment of PTSD than MDMA. Their potential might be maximized by a stringent patient selection, the use of lower doses, and specifically structured settings. In addition, clinical observations suggest that classical psychedelics may be more easily and effectively handled after patients have previously experienced MDMA (Gasser, 1996; Passie, 2012). MDMA can help patients experience an altered state of consciousness with reduced anxiety and an only mildly altered sense of self, which could help patients to become accustomed to an altered state of consciousness before a classical psychedelic might be considered. However, there has not been any formal research on such an approach.

Cannabinoids have mainly been used for the symptomatic treatment of PTSD. The only placebo-controlled trial has focused on the use of nabilone and demonstrated efficacy for treatment of insomnia and nightmares (Jetly et al., 2015). However, larger RCTs into the safety and efficacy of cannabinoids (and whole plant cannabis in particular) are necessary. There are important unknowns regarding dose, cannabinoid ratios, routes of administration, long-term risks, and side effects. Some clinical trials are currently being conducted (NCT02759185; NCT02517424) in which different strains of medical cannabis—with varying ratios of THC and CBD—are compared for treatment efficacy and safety in PTSD. As some cannabinoids have shown similar effects on extinction learning and memory reconsolidation as other psychedelics (Rabinak et al., 2013, 2014; Stern et al., 2017), they might hold promise for the use within a substance-assisted psychotherapy framework as well.

PTSD has been associated with an increased risk for developing cannabis use disorder in some cases (Hasin et al., 2016). Such extensive use of cannabis may have negative effects on PTSD symptoms (e.g., Bonn-Miller et al., 2013; Wilkinson et al., 2015). A possible explanation is that cannabis use can serve as a way to avoid unpleasant experiences (Bonn-Miller et al., 2007; Bordieri et al., 2014). Whether such use should be classified as problematic or as self-medication probably depends on the specific circumstances of each unique case. Chronic use of high amounts of cannabis has also been associated with reduced fear extinction learning (Papini et al., 2017). Although monitored prescription of medical cannabis in controlled dosages cannot be compared with excessive unsupervised use of cannabis from unknown sources, this does call for caution when prescribing cannabinoids on a daily basis. In such cases, close monitoring of the treatment is advised.

From the substances reviewed in the present paper, only cannabinoids have been studied as a take-home prescription for daily symptom control. In contrast, MDMA, ketamine, and classical psychedelics are only administered in a clinical setting

under direct supervision of a clinician, while patients with certain medical or psychological risk factors (e.g., high blood pressure, history of psychosis or bipolar disorder) are excluded through a specific screening process. When administered this way, using proper treatment and safety protocols, risks can be easily controlled (Johnson et al., 2018; Mithoefer et al., 2019).

The use of psychedelic compounds within a substance-assisted psychotherapy framework offers a novel method for the integration of pharmacotherapies and psychotherapies. As shown in this review, these substances may increase engagement with and the effectiveness of psychotherapeutic interventions due to a variety of psychological and neurobiological effects, such as an increased capacity for emotional and cognitive processing through pharmacologically diminished fear and arousal, increased insightfulness and introspection, strengthened therapeutic alliance through increased trust and rapport, increases in synaptic plasticity, or by targeting processes of fear extinction and memory consolidation.

The quest for optimization of these methods opens new areas for clinical and scientific exploration. One such area is the implementation of psychedelics in different psychotherapeutic treatment modalities. Most of the recent studies have used a relatively nondirective approach during drug sessions in which therapists follow each patients' unique unfolding inner process. It has yet to be tested whether more directive approaches, such as cognitive processing therapy, prolonged exposure, or Eye Movement Desensitization and Reprocessing, could also be used when patients are under the influence of psychedelics like MDMA or psilocybin.

Which therapeutic approach is the most appropriate might be dependent on several variables. For example, the use of ketamine or classical psychedelics in a dose that is high enough to significantly decrease the sense of self might benefit from a more nondirective approach, while the use of a lower dose that keeps the sense of self sufficiently intact for verbal interaction could potentially benefit from more directive psychotherapeutic approaches. Another variable to consider is the timing of the psychotherapeutic intervention relative to the administration of the psychedelic drug. During the acute drug effects, patients might benefit from particularly nondirective methods of psychotherapeutic interventions and support, while there could be more flexibility in the use of directive and nondirective approaches in the sessions before the administration of a psychedelic drug, when the acute effects of the drug are diminishing, or during sessions in the days and weeks following administration.

An example of a mixed approach is the combination of MDMA with cognitive behavioral conjoint therapy for PTSD (CBCT; Monson and Fredman, 2012), a therapeutic approach in which a PTSD patient's close relatives are directly involved in the treatment. Adding MDMA sessions to this approach could be particularly useful, as MDMA has shown to increase empathy (Kuypers et al., 2017) and interpersonal trust (Schmid et al., 2014). A pilot study on this approach added 2 MDMA sessions to CBCT during which the patient took the drug together with their partner. The nondrug sessions followed the relatively structured and directive CBCT protocol, while the MDMA sessions followed a more nondirective approach. Preliminary results of this study suggest that this is a promising approach (Wagner et al., 2019).

Other psychotherapeutic approaches that are increasingly being explored for the use in combination with psychedelic drugs are third-wave therapies such as acceptance commitment therapy (Walsh and Thiessen, 2018). These third-wave therapies represent a movement away from challenging or changing the content of internal experiences towards nonjudgmental acceptance of such experiences by emphasizing experiential methods. As Walsh and Thiessen (2018) report, these novel approaches are informed by concepts and practices that are rooted in contemplative spiritual practices and share potential mechanisms with acute effects of psychedelic drugs, including enhanced mindfulness, decentering, emotion regulation, and distress tolerance. These are all important elements for the treatment of PTSD. Exploring the use of psychedelic drugs within these new approaches might open a range of new possibilities to improve the efficacy of PTSD treatments.

To increase our understanding of the use of psychedelic drugs in the treatment of PTSD, we will lay out an agenda for future research. It is essential to generate more data regarding the safety and efficacy of psychedelics and to identify patients for whom these treatments might be indicated and effective. Contraindications in respect to specific symptom constellations and/or personality dispositions are another important area for research. There also is a need for an increased understanding of the diverse psychological states that these psychedelic compounds can induce from both a clinical and neurobiological perspective. These new studies will allow us to better understand putative biological mechanisms of action as well as to evaluate how these changes may augment the psychotherapeutic treatment of PTSD. The effects of these drugs, and neurobiological data obtained before and after treatment, may prompt a reverse translation to the biology of PTSD and increase our understanding of specific neurotransmitter trajectories and brain circuits involved in this approach to treatment and in recovery (DePierro et al., 2019; Heifets and Malenka, 2019). We also need to deepen our understanding of the role of psychotherapy and the setting in which these compounds are being administered to maximize safety and efficacy. In addition to considering their clinical efficacy, research on cost-effectiveness is required. Substance-assisted psychotherapy can be an expensive intervention, especially in terms of therapist time. Therefore, efficacy studies should include a health economic evaluation to allow informed future choices to be made with respect to funding and adoption by clinical services. Moreover, it will be important to consider where in the treatment trajectory these therapies might potentially be indicated and whether they should only be considered for treatment-resistant patients or also as first-line treatments. Lastly, there will be a need for specialized therapist training and supervision to work safely and effectively with these compounds and the complex psychological states they induce. If these drugs will be approved for use in licensed centers, they will require a new mental health care infrastructure that is capable of administering powerful psychoactive substances and integrating the intense inner experiences they produce.

When properly applied, according to published treatment manuals, new models of substance-assisted psychotherapy may offer a valuable contribution to the spectrum of existing pharmacological and psychotherapeutic treatments for PTSD. These interventions may not easily become a first-line treatment anytime soon, as they require specific expertise and environments, but they may boost explorations to implementing novel approaches to mental health infrastructures. For the large number of patients for whom PTSD has become a chronic illness, these approaches can be of immense value. If successfully implemented, many patients with PTSD could potentially recover, and the availability of psychedelics could herald a new era in the evidence-based care options that are available to patients with PTSD.

Acknowledgments

The authors thank the Nypels-Tans PTSD Fund at Leiden University for its financial support.

Statement of Interest

None.

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