Psilocybin for Trauma-Related Disorders

Amanda J. Khan, Ellen Bradley, Aoife O'Donovan, and Joshua Woolley

Contents

Abstract Posttraumatic stress disorder (PTSD) is a debilitating, chronic disorder and efficacy rates of current PTSD treatments are underwhelming. There is a critical need for innovative approaches. We provide an overview of trauma and PTSD and cite literature providing converging evidence of the therapeutic potential of psilocybin for PTSD. No study to date has investigated psilocybin or psilocybin-assisted psychotherapy (PAP) as treatments for PTSD. An open-label study in traumatized AIDS survivors found that PAP reduced PTSD symptoms, attachment anxiety, and demoralization. Several PAP trials show preliminary efficacy in facilitating confronting traumatic memories, decreasing emotional avoidance, depression, anxiety, pessimism, and disconnection from others, and increasing acceptance, self-compassion, and forgiveness of abusers, all of which are relevant to PTSD recovery. There is also early evidence that other classic psychedelics may produce large reductions in PTSD symptoms in combat veterans. However, this body of literature is small, mechanisms are not yet well understood, and the risks of using psychedelic

A. J. Khan, E. Bradley, A. O'Donovan, and J. Woolley (✉)
Department of Psychiatry, University of California, San Francisco, CA, USA
e-mail: amanda.khan@ucsf.edu; ellen.bradley@ucsf.edu; aoife.odonovan@ucsf.edu; josh.woolley@ucsf.edu

Curr Topics Behav Neurosci (2022) 56: 319–332
https://doi.org/10.1007/7854_2022_366
Published Online: 17 June 2022

compounds for trauma-related disorders need further study. In sum, evidence supports further investigation of PAP as a radically new approach for treating PTSD.

Keywords Psilocybin · Posttraumtic Stress Disorder · Psychedelics · Trauma · Treatment

1 Introduction

The recent resurgence of interest in using psychedelics in mainstream healthcare has led to numerous studies investigating their therapeutic potential for multiple psychiatric disorders (e.g., Galvão-Coelho et al. 2021; Mithoefer et al. 2018). Trauma-related disorders such as posttraumatic stress disorder (PTSD) have notoriously chronic or treatment-resistant trajectories and there is an urgent need for novel interventions (Steenkamp et al. 2020). The majority of psychedelic-assisted clinical trials for PTSD have focused on using MDMA (3,4-Methylenedioxymethamphetamine), an entactogen now designated as a Breakthrough Therapy for PTSD by the U.S. Food and Drug Administration (FDA) (Mithoefer et al. 2018). However, a different group of psychoactive compounds, "classic psychedelics," which includes psilocybin, lysergic acid diethylamide (LSD), and N,N-dimethyltryptamine (DMT), may provide important and unique therapeutic benefit for PTSD. In this chapter, we examine the theoretical framework for using psilocybin and other classic psychedelics to treat PTSD and trauma-related disorders and review relevant findings.

2 PTSD and Trauma-Related Disorders

Over 70% of the population will experience a traumatic event in their lifetime (e.g., Benjet et al. 2016). This number is likely even higher given that the current psychiatric diagnostic framework of trauma (American Psychiatric Association 2013) fails to capture experiences of racial trauma, emotional abuse and neglect, perpetration-based traumas (e.g., killing in combat), and institutional betrayal (e.g., Litz et al. 2009; Williams et al. 2018). Both the cumulative amount and type of trauma are important predictors of subsequent mental and physical health sequelae (Cloitre et al. 2009; Karam et al. 2014). Trauma exposure, particularly in childhood, can cause neurobiological, physiological, psychological, immunological, and epigenetic changes (e.g., Nemeroff 2004; Nöthling et al. 2020). The sequelae of trauma are numerous and include PTSD, depression, anxiety, suicidal thoughts and behaviors, personality disorders, somatic complaints, eating disorders, moral injury, substance use disorders, and psychotic disorder, cardiovascular, and autoimmune disorders (e.g., Chen et al. 2010; Cloitre et al. 2009; Litz et al. 2009; O'Donovan

et al. 2015; Shalev et al. 1998). In this chapter, we primarily focus on the specific psychological sequelae of PTSD, although trauma very likely plays a role in the development and maintenance of other disorders.

PTSD is a debilitating psychiatric disorder that involves re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal (American Psychiatric Association 2013). Stemming from exposure to traumatic event(s), PTSD is characterized by emotion dysregulation and can cause long-lasting impairments in social and occupational functioning (Ehring and Quack 2010; Rodriguez et al. 2012). Lifetime prevalence rates range widely (7–50%) depending on the population, with higher rates in veterans than civilians, and amongst those with interpersonal trauma (Fulton et al. 2015; Kessler et al. 2017). PTSD is associated with chronic symptom trajectories, increased psychiatric and medical morbidity, and decreased quality of life (Sareen et al. 2007).

Prevailing theoretical models of factors involved in the etiology and maintenance of PTSD are largely rooted in principles of (1) fear conditioning, with a focus on increased fear acquisition and impaired extinction, and (2) cognitive theory, emphasizing negative appraisals of the trauma and its meaning (Ehlers and Clark 2008; Foa and Kozak 1986). Beyond these models, individuals with PTSD are more likely to have insecure attachment styles, use avoidance-related emotion regulation strategies like suppression, and have strongly negative self- and other-concepts (e.g., Seligowski et al. 2015; Woodhouse et al. 2015). In addition, the extent to which a person perceives the trauma(s) as central to their identity and life story is a robust predictor of risk for and severity of PTSD (for review, see Gehrt et al. 2018). Indeed, how a person organizes their knowledge of self and consequently, others in relation to self appears central to PTSD. These self-other concepts can subsequently serve as reference points for interpreting everyday occurrences, which then contribute to the developing and/or strengthening of stable, global beliefs (Berntsen and Rubin 2006). Overall, these models highlight the breadth of important treatment targets robustly involved in PTSD.

Currently available evidence-based treatments (EBTs) for PTSD are inadequate (Steenkamp et al. 2020). Existing pharmacotherapies (e.g., selective serotonin reuptake inhibitors (SSRIs)) provide limited symptom relief and likely lack the specificity to address the unique neurobiology of PTSD (see Ostacher and Cifu 2019). Critically, up to 60% of patients do not respond adequately to medications (Watts et al. 2013), and latest clinical guidelines even advise against most available pharmacotherapies (Ostacher and Cifu 2019). Rooted in fear conditioning and cognitive models of PTSD, front-line psychotherapies include Prolonged Exposure (PE) and Cognitive Processing Therapy (CPT). Both treatments show moderate efficacy in reducing PTSD symptoms compared to waitlist and treatment as usual (e.g., Merz et al. 2019). However, as many as 60–72% of patients retain their PTSD diagnoses (see Steenkamp et al. 2015; Watts et al. 2013) and dropout rates reach up to 40% (e.g., Goetter et al. 2015). Some have theorized that fear conditioning models, while effective, may be too narrow to explain the breadth of symptoms associated with PTSD (e.g., Krystal et al. 2017; Markowitz et al. 2015). Indeed, trauma exposure and PTSD are both linked to structural, functional, and connectivity

alterations in brain networks responsible for not only fear conditioning, but also self-concept, emotion regulation, and memory (see review Liberzon and Abelson 2016; Akiki et al. 2017). In sum, development of alternatives to current pharmacologic and psychotherapeutic EBTs is essential for improving outcomes for this patient population.

3 Brief Review of Psilocybin

Psilocybin is the naturally occurring prodrug of psilocin (4-hydroxy-dimethyltryptamine) and has been used by Indigenous peoples of Central and South America for centuries (Wasson 1980). Psilocin is a serotonergic (5-hydroxytryptamine, 5-HT) agonist, primarily exerting its psychedelic effects through the 5HT2A receptors but also binding to 5HT2C, 5HT1A, and 5HT1B receptors (Halberstadt and Geyer 2011). Acutely, psilocybin can cause profound, dose-dependent changes in sensory perception and cognition including auditory and visual hallucinations and derealization (Barrett et al. 2015; Kometer and Vollenweider 2018) that last from 3 to 6 h after oral ingestion. Studies examining the clinical safety of oral dosages ranging from 0.29 to 0.43 mg/kg indicate psilocybin is generally well tolerated (Bogenschutz and Ross 2016), has low physiological toxicity, and is not associated with compulsive drug seeking (e.g., Tylš et al. 2014; van Amsterdam et al. 2011). Evidence from preclinical models, neuroimaging work, and clinical trials (Baumeister et al. 2014; Carhart-Harris et al. 2012; Catlow et al. 2013; Herzog et al. 2020; Kraehenmann et al. 2015; Kringelbach et al. 2020; Ly et al. 2018; Petri et al. 2014; Raval et al. 2021; Schindler et al. 2018) suggest that psilocybin and related compounds have the potential to alleviate PTSD symptoms via multiple mechanisms (see review by Vollenweider and Preller 2020). Further investigation is critical to understanding the effects of classic psychedelics for trauma-related disorders.

4 Review of the Empirical Literature of Psilocybin for Treating PTSD

To date, no studies have examined the efficacy of psilocybin as a PTSD treatment (see review Krediet et al. 2020) or have reported quantitative information on trauma exposure rates in participants. One study examined PTSD symptoms as a secondary outcome in a single-arm, open-label, trial of psilocybin-assisted group psychotherapy (Anderson et al. 2020). In a sample of 18 older, gay-identified, long-term AIDS survivors, PTSD severity declined from baseline to the end of treatment with gains maintained at 3-month follow-up with moderate effect sizes. However, only 3 of the 18 participants had a baseline PTSD severity score above clinical cut-off, limiting the conclusions that can be drawn. Attachment anxiety also significantly decreased

from baseline to 3-month follow-up in the same study (Stauffer et al. 2020), which is in line with research in healthy volunteers showing psilocybin acutely reduces rejection sensitivity (Preller et al. 2015).

Studies focused on depression and anxiety also point to psilocybin's ability to improve negative cognitions, avoidance, anxiety, and disconnectedness, overlapping symptoms between PTSD and other disorders. Four studies reported that psilocybin-assisted therapy reduces depression symptoms in patients with treatment-resistant depression (TRD) and in cancer patients (see meta-analysis Galvão-Coelho et al. 2021). Across all four studies, depression remission rates remained high (60–80%) at 3- or 6-month follow-up and patients reported being less pessimistic about their future (Watts et al. 2017). In follow-up qualitative interviews from one study (Watts et al. 2017), participants reported post-treatment shifts from avoiding traumatic memories and painful emotions to confronting and accepting them, increased understanding and compassion for past abusers, access to a fuller range of autobiographical material, and a sense of reconnection with self, others, and the world. In the three studies in cancer patients, psilocybin reduced trait anxiety related to having a life-threatening illness and some participants discussed unearthing and processing childhood traumas that were realized to be unhealed (Malone et al. 2018). Additionally, a prospective self-report study found psilocybin (and related compounds) reduced experiential avoidance, which in turn correlated with decreases in depression and suicide ideation (SI) (Zeifman et al. 2020). Finally, a cross-sectional self-report study in Black, Indigenous, and People of Color (BIPOC) who experienced racial trauma reported that increases in psychological flexibility following ingestion of psilocybin (and related compounds) were associated with decreases in posttraumatic stress symptoms (Davis et al. 2021; Williams et al. 2021). Although additional research focused on PTSD specifically is clearly needed, these findings provide some insight into how psilocybin may help trauma-related disorders across a range of trauma types.

5 Review of the Empirical Literature of Other Classic Psychedelics for Treating PTSD

To the best of our knowledge, no studies have investigated the potential of LSD to treat PTSD (see review Krediet et al. 2020). Given that it is also a 5HT2A agonist and facilitates associative learning (Romano et al. 2010), it may have similar therapeutic effects for PTSD as those theorized for psilocybin, but clinical evidence is needed. Ayahuasca (which includes the psychedelic tryptamine, DMT) has also been proposed as a candidate treatment for PTSD (e.g., Nielson and Megler 2014). Studies in rodents and healthy volunteers show that ayahuasca increases serotonin and induces alterations in activity in regions involved in episodic memory, contextual associations of emotional events, and reactivity (de Castro-Neto et al. 2013; Riba et al. 2006). Another study found DMT with pharmahuasca (Harmaline)

normalized trauma-induced reactive oxygen species production and PTSD associated gene expression that overlapped with human PTSD (Kelley et al. 2022). A recent open-label study examined the effectiveness of using 5-MeO-DMT (another psychedelic tryptamine found in several plants and certain desert toads) and ibogaine to treat PTSD in combat veterans ($N = 65$) (Davis et al. 2020). PTSD symptoms, suicidal ideation (SI), depression, anxiety, and psychological flexibility all showed significant reductions from 1 month pre- to 1 month post-treatment, with large effect sizes. Notably, the dual action on serotonergic (5-MeO-DMT) and Kappa opioid and NMDA (ibogaine) receptors may have provided unique, additive benefits; it is unclear whether using only one psychedelic agent would have yielded the same results. No study has empirically investigated 5-MeO-DMT or ibogaine as monotherapies for PTSD. In one large survey study assessing 5-MEO-DMT use and effects, 21% reported having PTSD and of those, 79% reported symptom improvement (18% no change, 3% worsening) (Davis et al. 2018). These findings suggest the potential of 5-MeO-DMT and ayahuasca for PTSD, but intervention studies evaluating each of these compounds are essential. Additionally, in an online survey study, participants reported improvements in PTSD symptoms following use of mescaline, another primarily serotonergic psychoactive alkaloid (Agin-Liebes et al. 2021).

LSD and ayahuasca also have demonstrated anxiolytic and antidepressant effects, facilitated engagement with salient memories, and improved positive self-other concepts that may be relevant for treating PTSD. In a placebo-controlled pilot study, LSD-assisted psychotherapy significantly reduced anxiety related to having a life-threatening illness (Gasser et al. 2014). Of the eight participants in the LSD condition, one did have PTSD, but no data regarding PTSD symptom changes were reported. In qualitative interviews a year later, participants reported treatment helped them confront memories and access emotion, which they viewed as helpful in restructuring their beliefs about trust and the world (Gasser et al. 2015). There is also evidence a single dose of LSD produces lasting reductions in anxiety in healthy volunteers (Schmid and Liechti 2018) and increases feelings of trust and closeness (Dolder et al. 2016), effects likely to benefit individuals with PTSD. In open-label and placebo-controlled trials in depressed participants, ayahuasca significantly reduced depression severity (Osório et al. 2015; Palhano-Fontes et al. 2019). These findings provide preliminary evidence that classic psychedelics can reduce anxiety, improve mood, and facilitate trauma processing.

6 Considerations for Other Trauma-Related Disorders

6.1 Complicated Grief

Complicated Grief (CG) is a distinct syndrome characterized by protracted and impairing grief in response to losing someone, causing more impairment and significant distress than traditional grief trajectories (American Psychiatric Association 2013). Core symptoms include pervasive yearning for the deceased, persistent

preoccupation with the deceased, and avoiding grief-related stimuli. There is preliminary evidence that psilocybin and ayahuasca reduce grief. Although no study has investigated psilocybin to treat CG, the psilocybin group therapy for demoralization trial did find significant decreases in CG symptoms, with improvement maintained at 3-month follow-up (Anderson et al. 2020). Two additional studies examined the effectiveness of ayahuasca for bereavement. In a small survey study, ayahuasca reduced grief and preoccupations and improved self-other forgiveness significantly more than peer-support grief groups (González et al. 2017). In a small sample of 50 bereaved individuals attending ayahuasca ceremonies, symptoms of grief significantly decreased from baseline to end of treatment and up to 12 months after (González et al. 2020). Acceptance and defusion mediated the improvement in grief symptoms. These findings are encouraging and future research should prioritize investigating the therapeutic potential of psilocybin and ayahuasca for CG.

6.2 Borderline Personality Disorder

Borderline personality disorder (BPD) is theorized as a trauma-related disorder with high rates of comorbidity with PTSD and notable symptom overlap (e.g., Cloitre et al. 2013). To date, no study has investigated the efficacy of psilocybin or classic psychedelics for treating BPD. Notably, three participants in the psilocybin group therapy trial in AIDS survivors met criteria for BPD (Anderson et al. 2020), but no data on BPD symptom changes were reported. Similarly, in a clinical trial of ayahuasca for TRD, 76% of participants had a cluster B personality disorder, but no data on personality disorder changes were reported (Palhano-Fontes et al. 2019). Of most relevance to BPD, two studies show psilocybin reduces anxious attachment and rejection sensitivity (Stauffer et al. 2020; Preller et al. 2015) and another study found psilocybin helped people re-connect with close others who had wronged them (Watts et al. 2017). Psilocybin also increases feelings of empathy, and trait openness while decreasing trait neuroticism (Carhart et al. 2018; Roseman et al. 2018). In conjunction with results showing psilocybin induces decreased amygdala reactivity to negative faces (Roseman et al. 2018), these findings raise the possibility that psilocybin could influence mechanisms central to the relational symptoms of BPD such as fear of abandonment, which might have downstream effects on behavioral efforts to avoid this outcome. Finally, psilocybin and related compounds have been shown to actually decrease suicide-related behaviors (see review Zeifman et al. 2021; Ross et al. 2021), hinting at a therapeutic potential for this common BPD symptom. Given the prevalence of self-directed violence in BPD, a critical future consideration is whether psilocybin and related compounds should be integrated with existing EBTs like Dialectical Behavior Therapy (Zeifman and Wagner 2020).

7 Precautions and Possible Contraindications

Given the absence of psilocybin therapy trials for PTSD, the safety and tolerability of this treatment for this population remains unknown. Three of the most obvious potential adverse effects and contraindications include dissociative episodes, concomitant medications, and self-directed violence. Dissociative features are a subtype of PTSD symptoms and are either common or are central to other trauma-related disorders (e.g., BPD, dissociative identity disorder). In the scant studies examining classic psychedelics, no data on baseline or subsequent dissociative episodes has been reported. In the small psilocybin trial by Anderson et al. (2020), one person experienced a flashback a few days after the dosing session. Interestingly, participants in some other psilocybin trials (e.g., Watts et al. 2017) have reported *more* embodiment, not less, possibly suggesting psilocybin could help trauma-related dissociation. Critical lines of future research include the general safety profile of psilocybin-assisted therapy for dissociative subtypes of PTSD and related phenomenology (i.e., flashbacks), BPD, and dissociative disorders. We also need to determine whether people with dissociative features are more likely to experience dissociation during psilocybin sessions, whether that is associated with adverse or *positive* acute and long-term outcomes (e.g., Roseman et al. 2018), and whether psilocybin increases subsequent dissociation frequency.

An alternative approach may be to consider using psycholytic doses, or low doses that provide that serve to lubricate the therapeutic process and socialize users to the effects (Garcia-Romeu and Richards 2018). In theory, psycholytic doses may provide an opportunity for mild relaxation of ego defenses, which could be leveraged to deepen psychotherapeutic processes (Majic et al. 2015). Those with a high propensity for dissociation or re-experiencing symptoms, or who are more apprehensive about psychedelics may also particularly benefit from such a graded approach. Similar to starting any medication, however, using the "start low, go slow" approach will likely be safest. Research comparing the efficacy of macrodosing (i.e., full dose), psycholytic, and microdosing will greatly improve our understanding of how best to use these compounds to treat PTSD. The basic components of preparation sessions for PTSD patients need not necessarily be altered from modern psychedelic protocols (i.e., review safety procedures, what ifs, agreed upon touch, rescue procedures), but clinical judgment should always be used. Regarding concerns about potentially intense exposure experiences, further study is needed to understand tolerability of psilocybin in PTSD. Thus far, psychedelic therapies for PTSD are associated with high ratings of acceptability, satisfaction, and openness to further therapy and low dropout (e.g., Barone et al. 2019; Davis et al. 2020; Feder et al. 2021). However, it is critical to recognize the potential for bias in these findings particularly given that participants in early studies may have unusually positive expectations for treatment.

Another concern is that little is known about possible interactions between psilocybin and psychotropics typically used to treat PTSD. Anecdotal evidence suggests that chronic use of SSRIs, serotonin-norepinephrine reuptake inhibitors

(SNRIs), and antipsychotics all attenuate the psychedelic effects of psilocybin and related compounds (e.g., Bonson et al. 1996). There is also theoretical risk of inducing serotonin syndrome by combining classic psychedelics with other serotonergic agents, which can be life-threatening. However, high quality evidence is lacking. Because these risks are not well-understood, all modern clinical trials have required patients to abstain from most psychotropics and other medications that may influence psilocybin metabolism and/or precipitate adverse effects. Future trials should explore which whether SSRIs, the most common PTSD pharmacotherapy, and other concomitant medications are safe and appropriate to continue during psilocybin-therapy. Regarding risk of self-directed violence, two large population studies reported psilocybin use is associated with *reduced* SI, planning, and attempt (Johansen and Krebs 2015; Krebs and Johansen 2013). This same pattern of findings was also found in a longitudinal study of women sex workers with high trauma exposure (Argento et al. 2017). Psilocybin and ayahuasca have also been associated with reduced SI in clinical trials for depression (e.g., Carhart-Harris et al. 2018; Zeifman et al. 2021). Though this early evidence suggests psilocybin may confer a protective effect (for review Zeifman et al. 2021), research examining changes in self-directed violence in people with trauma-related disorders specifically is essential.

8 Conclusions

Trauma exposure is ubiquitous and the downstream effects on mental and physical health, overall functioning, and quality of life can be devastating. Psilocybin and other classic psychedelics may offer unique value for healing trauma-related disorders through dynamic neuronal and neuromodulation changes across large-scale networks throughout the whole brain. Although there is preliminary support, there is a clear need for rigorous clinical studies that specifically test the efficacy of these compounds in trauma-related disorder samples. Regardless of clinical population, future psychedelic-assisted therapy studies would greatly benefit from measuring trauma exposure, including those falling outside the DSM Criterion A (e.g., racial trauma), PTSD symptoms, and pre- and post-treatment SI and related behaviors. Progress in this field will also require careful investigation of potential adverse effects and contraindications. Future studies that compare the efficacy of different psychedelic-assisted therapy approaches, evaluate dose and sequencing options, determine personalized medicine guidelines, and assess scalability are needed. Notwithstanding the early stage of this work, evidence to date supports further investigation of PAP as a radically new approach for treating PTSD.

References

Agin-Liebes G, Haas TF, Lancelotta R, Uthaug MV, Davis JGRAK (2021) Naturalistic use of mescaline is associated with self-reported psychiatric improvements and enduring positive life changes. ACS Pharmacol Trans Sci 4(2):543–552. https://doi.org/10.1021/acsptsci.1c00018

Akiki TJ, Averill CL, Abdallah CG (2017) A network-based neurobiological model of PTSD: evidence from structural and functional neuroimaging studies. Curr Psychiatry Rep 19(11):81

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders: DSM-5, 5th edn. American Psychiatric Publishing, Washington

Anderson BT, Danforth A, Daroff R et al (2020) Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: an open-label safety and feasibility pilot study. EClinicalMedicine 27:100538

Argento E, Strathdee SA, Tupper K et al (2017) Does psychedelic drug use reduce risk of suicidality? Evidence from a longitudinal community-based cohort of marginalised women in a Canadian setting. BMJ Open 7(9):e016025

Barone W, Beck J, Mitsunaga-Whitten M et al (2019) Perceived benefits of MDMA-assisted psychotherapy beyond symptom reduction: qualitative follow-up study of a clinical trial for individuals with treatment-resistant PTSD. J Psychoactive Drugs 51(2):199–208

Barrett FS, Johnson MW, Griffiths RR (2015) Validation of the revised mystical experience questionnaire in experimental sessions with psilocybin. J Psychopharmacol 29:1182–1190

Baumeister D, Barnes G, Giaroli G, Tracy D (2014) Classical hallucinogens as antidepressants? a review of pharmacodynamics and putative clinical roles. Ther Adv Psychopharmacol 4(4):156–169. https://doi.org/10.1177/2045125314527985

Benjet C, Bromet E, Karam EG et al (2016) The epidemiology of traumatic event exposure worldwide: results from the world mental health survey consortium. Psychol Med 46(2): 327–343

Berntsen D, Rubin DC (2006) The centrality of event scale: a measure of integrating a trauma into one's identity and its relation to post-traumatic stress disorder symptoms. Behav Res Ther 44(2): 219–231

Bogenschutz MP, Ross S (2016) Therapeutic applications of classic hallucinogens. In: Halberstadt AL, Vollenweider FX, Nichols DE (eds) Behavioral neurobiology of psychedelic drugs, vol 36. Springer, Berlin, pp 361–391

Bonson K, Buckholtz JW, Murphy DL (1996) Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans. Neuropsychopharmacology 14(6): 425–436

Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, Kaelen M, Giribaldi B, Bloomfield M, Pilling S, Rickard JA, Forbes B, Feilding A, Taylor D, Curran HV, Nutt DJ (2018) Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology 235(2):399–408. https://doi.org/10.1007/s00213-017-4771-x

Carhart-Harris RL, Erritzoe D, Williams T et al (2012) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc Natl Acad Sci U S A 109:2138–2143

Catlow BJ, Song S, Paredes DA et al (2013) Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning. Exp Brain Res 228(4):481–491

Chen LP, Murad MH, Paras ML et al (2010) Sexual abuse and lifetime diagnosis of psychiatric disorders: systematic review and meta-analysis. Mayo Clin Proc 85(7):618–629

Cloitre M, Stolbach BC, Herman JL et al (2009) A developmental approach to complex PTSD: childhood and adult cumulative trauma as predictors of symptom complexity. J Trauma Stress 22(5):399–408

Cloitre M, Garvert DW, Brewin CR et al (2013) Evidence for proposed ICD-11 PTSD and complex PTSD: a latent profile analysis. Eur J Psychotraumatol 4:1–12

de Castro-Neto EF, da Cunha RH, da Silveira DX, Yonamine M, Gouveia TLF, Cavalheiro EA, Amado D, da Graça Naffah-Mazzacoratti M (2013) Changes in aminoacidergic and

monoaminergic neurotransmission in the hippocampus and amygdala of rats after ayahuasca ingestion. World J Biol Chem 4(4):141. https://doi.org/10.4331/wjbc.v4.i4.141
Davis AK, Barsuglia JP, Lancelotta R, Grant RM, Renn E (2018) The epidemiology of 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption. J Psychopharmacol 32(7):779–792. https://doi.org/10.1177/0269881118769063
Davis AK, Averill LA, Sepeda ND et al (2020) Psychedelic treatment for trauma-related psychological and cognitive impairment among US special operations forces veterans. Chron Stress 4: 2470547020939564
Davis AK, Xin Y, Sepeda ND, Garcia-Romeu A, Williams MT (2021) Increases in psychological flexibility mediate relationship between acute psychedelic effects and decreases in racial trauma symptoms among people of color. Chron Stress 5:247054702110356. https://doi.org/10.1177/24705470211035607
Dolder PC, Schmid Y, Müller F et al (2016) LSD acutely impairs fear recognition and enhances emotional empathy and sociality. Neuropsychopharmacology 41:2638–2646
Ehlers A, Clark DM (2008) Post-traumatic stress disorder: the development of effective psychological treatments. Nord J Psychiatry 62(Suppl 47):11–18
Ehring T, Quack D (2010) Emotion regulation difficulties in trauma survivors: the role of trauma type and PTSD symptom severity. Behav Ther 41:587–598
Feder A, Costi S, Rutter SB et al (2021) A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. Am J Psychiatry 178(2):193–202
Foa EB, Kozak MJ (1986) Emotional processing of fear: exposure to corrective information. Psychol Bull 99:20–35
Fulton JJ, Calhoun PS, Wagner HR et al (2015) The prevalence of posttraumatic stress disorder in operation enduring freedom/operation Iraqi freedom (OEF/OIF) veterans: a meta-analysis. J Anxiety Disord 31:98–107
Galvão-Coelho NL, Marx W, Gonzalez M et al (2021) Classic serotonergic psychedelics for mood and depressive symptoms: a meta-analysis of mood disorder patients and healthy participants. Psychopharmacology (Berl) 238:341–354
Garcia-Romeu A, Richards WA (2018) Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions. Int Rev Psychiatry 30(4):291–316. https://doi.org/10.1080/09540261.2018.1486289
Gasser P, Holstein D, Michel Y et al (2014) Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis 202:513–520
Gasser P, Kirchner K, Passie T (2015) LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. J Psychopharmacol 29(1):57–68. https://doi.org/10.1177/0269881114555249
Gehrt TB, Berntsen D, Hoyle RH et al (2018) Psychological and clinical correlates of the centrality of event scale: a systematic review. Clin Psychol Rev 65:57–80
Goetter EM, Bui E, Ojserkis RA et al (2015) A systematic review of dropout from psychotherapy for posttraumatic stress disorder among Iraq and Afghanistan combat veterans. J Trauma Stress 28(5):401–409
González D, Carvalho M, Cantillo J et al (2017) Potential use of ayahuasca in grief therapy. Omega (Westport) 1:30222817710879
González D, Cantillo J, Pérez I et al (2020) Therapeutic potential of ayahuasca in grief: a prospective, observational study. Psychopharmacology (Berl) 237:1171–1182
Halberstadt AL, Geyer MA (2011) Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens. Neuropharmacology 61(3):364–381
Herzog R, Mediano PAM, Rosas FE et al (2020) A mechanistic model of the neural entropy increase elicited by psychedelic drugs. Sci Rep 10:17725
Johansen PØ, Krebs TS (2015) Psychedelics not linked to mental health problems or suicidal behavior: a population study. J Psychopharmacol 29(3):270–279

Karam EG, Friedman MG, Hill ED et al (2014) Cumulative traumas and risk thresholds: 12 month PTSD in the world mental health (WMH) surveys. Depress Anxiety 31(2):130–142

Kelley DP, Venable K, Destouni A, Bilac G, Ebenezer P, Stadler K, Nichols C, Barker S, Francis J (2022) Pharmahuasca and DMT rescue ROS production and differentially expressed genes observed after predator and psychosocial stress: relevance to human PTSD. ACS Chem Neurosci 13(2):257–274. https://doi.org/10.1021/acschemneuro.1c00660

Kessler RC, Aguilar-Gaxiola S, Alonso J et al (2017) Trauma and PTSD in the WHO world mental health surveys. Eur J Psychotraumatol 8(sup5):1353383

Kometer M, Vollenweider FX (2018) Serotonergic hallucinogen-induced visual perceptual alterations. Curr Top Behav Neurosci 36:257–282

Kraehenmann R, Preller KH, Scheidegger M, Pokorny T, Bosch OG, Seifritz E, Vollenweider FX (2015) Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. Biol Psychiatry 78(8):572–581. https://doi.org/10.1016/j.biopsych.2014.04.010

Krebs TS, Johansen PØ (2013) Psychedelics and mental health: a population study. PLoS One 8:e63972

Krediet E, Bostoen T, Breeksema J, van Schagen A, Passie T, Vermetten E (2020) Reviewing the potential of psychedelics for the treatment of PTSD. Int J Neuropsychopharmacol 23(6):385–400

Krystal JH, Abdallah CG, Averill LA et al (2017) Synaptic loss and the pathophysiology of PTSD: implications for ketamine as a prototype novel therapeutic. Curr Psychiatry Rep 19(10):74

Liberzon I, Abelson JL (2016) Context processing and the neurobiology of post-traumatic stress disorder. Neuron 92(1):14–30. https://doi.org/10.1016/j.neuron.2016.09.039

Litz BT, Stein N, Delaney E et al (2009) Moral injury and moral repair in war veterans: a preliminary model and intervention strategy. Clin Psychol Rev 29(8):695–706

Ly C, Greb AC, Cameron LP et al (2018) Psychedelics promote structural and functional neural plasticity. Cell Rep 23(11):3170–3182

Majic T, Schmidt TT, Gallinat J (2015) Peak experiences and the afterglow phenomenon: when and how do therapeutic effects of hallucinogens depend on psychedelic experiences? J Psychopharmacol 29(3):241–253

Malone TC, Mennenga SE, Guss J, Podrebarac SK, Owens LT, Bossis AP, Belser AB, Agin-Liebes G, Bogenschutz MP, Ross S (2018) Individual experiences in four cancer patients following psilocybin-assisted psychotherapy. Front Pharmacol 9:256. https://doi.org/10.3389/fphar.2018.00256

Markowitz JC, Petkova E, Neria Y et al (2015) Is exposure necessary? A randomized clinical trial of interpersonal psychotherapy for PTSD. Am J Psychiatry 172(5):430–440

Merz J, Schwarzer G, Gerger H (2019) Comparative efficacy and acceptability of pharmacological, psychotherapeutic, and combination treatments in adults with posttraumatic stress disorder: a network meta-analysis. JAMA Psychiat 76(9):904–913

Mithoefer MC, Mithoefer AT, Feduccia AA et al (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

Nardou R, Lewis EM, Rothhaas R et al (2019) Oxytocin-dependent reopening of a social reward learning critical period with MDMA. Nature 569:116–120

Nemeroff CB (2004) Neurobiological consequences of childhood trauma. J Clin Psychiatry 65:18–28

Nielson JL, Megler JD (2014) Ayahuasca as a candidate therapy for PTSD. In: The therapeutic use of ayahuasca, vol 9783642404269. Springer, pp 41–58

Nöthling J, Malan-Müller S, Abrahams N et al (2020) Epigenetic alterations associated with childhood trauma and adult mental health outcomes: a systematic review. World J Biol Psychiatry 21(7):493–512

O'Donovan A, Cohen BE, Seal KH et al (2015) Elevated risk for autoimmune disorders in Iraq and Afghanistan veterans with posttraumatic stress disorder. Biol Psychiatry 77(4):365–374
Osório FL, Sanches RF, Macedo LR et al (2015) Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. Br J Psychiatry 37:13–20
Ostacher MJ, Cifu AS (2019) Management of posttraumatic stress disorder. JAMA 321(2):200–201
Palhano-Fontes F, Barreto D, Onias H et al (2019) Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychol Med 49(4):655–663
Petri G, Expert P, Turkheimer F et al (2014) Homological scaffolds of brain functional networks. J R Soc Interface 11:20140873
Preller K, Pokorny T, Krähenmann R et al (2015) The effect of 5-HT2A/1a agonist treatment on social cognition, empathy, and social decision-making. Eur Psychiatry 30(S1):1–1
Raval NR, Johansen A, Donovan LL et al (2021) A single dose of psilocybin increases synaptic density and decreases 5-HT_{2A} receptor density in the pig brain. Int J Mol Sci 22:835
Riba J, Romero S, Grasa E et al (2006) Increased frontal and paralimbic activation following ayahuasca, the pan-amazonian inebriant. Psychopharmacology (Berl) 186(1):93–98
Rodriguez P, Holowka DW, Marx BP (2012) Assessment of posttraumatic stress disorder-related functional impairment: a review. J Rehabil Res Dev 49:649–666
Romano AG, Quinn JL, Li L, Dave KD, Schindler EA, Harvey VJAJA (2010) Intrahippocampal LSD accelerates learning and desensitizes the 5-HT2A receptor in the rabbit Romano et al. Psychopharmacology 212(3):441–448. https://doi.org/10.1007/s00213-010-2004-7
Roseman L, Nutt DJ, Carhart-Harris RL (2018) Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Front Pharmacol 8:974
Ross S, Agin-Liebes G, Lo S, Zeifman RJ, Ghazal L, Benville J, Corso SF, Real CB, Guss J, Bossis A, Mennenga SE (2021) Acute and sustained reductions in loss of meaning and suicidal ideation following psilocybin-assisted psychotherapy for psychiatric and existential distress in life-threatening cancer. ACS Pharmacol Trans Sci 4(2):553–562. https://doi.org/10.1021/acsptsci.1c00020
Sareen J, Cox BJ, Stein MB et al (2007) Physical and mental comorbidity, disability, and suicidal behavior associated with posttraumatic stress disorder in a large community sample. Psychosom Med 69(3):242–248
Schindler EAD, Wallace RM, Sloshower JA et al (2018) Neuroendocrine associations underlying the persistent therapeutic effects of classic serotonergic psychedelics. Front Pharmacol 1(9):177
Schmid Y, Liechti ME (2018) Long-lasting subjective effects of LSD in normal subjects. Psychopharmacology (Berl) 235(2):535–545
Seligowski AV, Lee DJ, Bardeen JR et al (2015) Emotion regulation and posttraumatic stress symptoms: a meta-analysis. Cogn BehavTher 44(2):87–102
Shalev AY, Freedman S, Peri T et al (1998) Prospective study of posttraumatic stress disorder and depression following trauma. Am J Psychiatry 155(5):630–637
Stauffer CS, Anderson BT, Ortigo KM et al (2020) Psilocybin-assisted group therapy and attachment: observed reduction in attachment anxiety and influences of attachment insecurity on the psilocybin experience. ACS Pharmacol Transl Sci 4(2):526–532
Steenkamp MM, Litz BT, Hoge CW et al (2015) Psychotherapy for military-related PTSD: a review of randomized clinical trials. JAMA 314(5):489–500
Steenkamp MM, Litz BT, Marmar CR (2020) First-line psychotherapies for military-related PTSD. JAMA 323(7):656–657
Tylš F, Páleníček T, Horáček J (2014) Psilocybin – summary of knowledge and new perspectives. Eur Neuropsychopharmacol 24(3):342–356
van Amsterdam J, Opperhuizen A, van den Brink W (2011) Harm potential of magic mushroom use: a review. Regul Toxicol Pharmacol 59(3):423–429
Vollenweider FX, Preller KH (2020) Psychedelic drugs: neurobiology and potential for treatment of psychiatric disorders. Nat Rev Neurosci:1–14

Wasson RG (1980) The wondrous mushroom. Mycolatry in Mesoamerica. Ethnomycoloical studies no. 7. McGraw-Hill Book Company, New York

Watts BV, Schnurr PP, Mayo L et al (2013) Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. J Clin Psychiatry 74(6):e541–e550

Watts R, Day C, Krzanowski J et al (2017) Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. J Humanist Psychol 57(5): 520–564

Williams MT, Metzger IW, Leins C et al (2018) Assessing racial trauma within a DSM–5 framework: the UConn racial/ethnic stress & trauma survey. Pract Innov 3(4):242–260

Williams MT, Davis AK, Xin Y et al (2021) People of color in North America report improvements in racial trauma and mental health symptoms following psychedelic experiences. Drugs 28(3): 215–226

Woodhouse S, Ayers S, Field AP (2015) The relationship between adult attachment style and post-traumatic stress symptoms: a meta-analysis. J Anxiety Disord 35:103–117

Zeifman RJ, Wagner AC (2020) Exploring the case for research on incorporating psychedelics within interventions for borderline personality disorder. J Contextual Behav Sci 15:1–11

Zeifman RJ, Wagner AC, Watts R et al (2020) Post-psychedelic reductions in experiential avoidance are associated with decreases in depression severity and suicidal ideation. Front Psych 11: 782

Zeifman RJ, Singhal B et al (2021) On the relationship between classic psychedelics and suicidality: a systematic review. ACS Pharmacol Transl Sci 4(2):436–451