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Psilocybin and MDMA for the treatment of trauma-related psychopathology

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ABSTRACT
This review examines the role of trauma in psychiatric morbidity and analogous psychoneurobiological changes. Trauma is a necessary criterion for Post-Traumatic Stress Disorder (PTSD), however, trauma history is highly correlated with a variety of psychiatric conditions. Some evidence suggests that Major Depressive Disorder (MDD) is the most common psychiatric condition that arises following trauma. Approximately 50% of PTSD cases present with co-morbid MDD. Overlapping symptomatology and neurobiology between these conditions underlie the debate over whether these phenomena result from problematic nosology or whether comorbid MDD + PTSD is a distinct phenotype of trauma-related psychopathology. Regardless, similar treatment approaches have been employed historically, with varying success. The drug-assisted psychotherapy treatment model, which combines pharmacological and psychotherapeutic approaches, is currently being trialled as a novel treatment approach in psychiatry. Both psilocybin- and 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy have received Food and Drug Administration ‘breakthrough therapy’ designation for the treatment of resistant MDD and PTSD, respectively. This paper reviews the therapeutic rationale of both psilocybin and MDMA for treating both trauma-related MDD and PTSD.

Drug-assisted psychotherapy: psilocybin and 3,4-methylenedioxymethamphetamine (MDMA)

Classical psychedelic drugs include phosphoryloxy-N,N-dimethyltryptamine (psilocybin), dimethyltryptamine (DMT), d-lysergic acid diethylamide (LSD) and mescaline. They are agonists at serotonin receptors, with the subjective psychoactive effects dependent on partial agonism of the type 2A serotonin receptor (Vollenweider & Kometer, 2010), which is predominantly expressed on layer V pyramidal neurons in the prefrontal cortex (Hall et al., 2000; Saulin et al., 2012). Historical and present-day recreational, medicinal and religious use of plant-based psychedelics by different, geographically isolated human societies has been observed (El-Seedi et al., 2005; Nichols, 2020; Tupper, 2009). Some reports date this use extending back thousands of years, although this timeline is still debated. Subsequent to the serendipitous discovery and marketing of LSD in the Western world, from 1950 to the early 1970s, more than 1,000 clinical papers were published about the treatment of thousands of patients with psychedelics. Whilst these trials were suboptimal in many respects, a recent review of the pre-1970s literature concluded that they were likely to be safe when delivered in medically controlled settings and deserved further investigation with the benefit of modern paradigms of trial design (Rucker et al., 2018).

The Controlled Substance Act (CSA), 1970, in the US (and the largely synonymous Misuse of Drugs Act, 1971, and associated regulations in the UK) severely restricted the use of psychedelics in research and prohibited all routine clinical use. However, in 1992, the National Institute on Drug Abuse and the FDA reached an agreement that facilitated the resumption of clinical research with classical psychedelics (Nichols, 2014).

Since then, modern pilot and feasibility trials have demonstrated encouraging preliminary safety and efficacy data for psilocybin as a treatment for anxiety and depression in end-of-life care (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), OCD (Moreno et al., 2006), alcohol dependence (Bogenschutz et al., 2015), tobacco addiction (Johnson et al., 2014), major depression (Carhart-Harris et al., 2014).
The drug development process with psilocybin is now accelerating. More recently, a large randomized placebo-controlled phase 1 trial compared the safety profile between a single dosing session of a placebo, 10 mg and 25 mg of psilocybin in 89 healthy volunteers (Rucker et al., 2019). There were no serious adverse events recorded and no adverse events led to withdrawal from the study. The adverse event profile was of the expected ‘psychadelic’ nature, with the vast majority of ‘mood altered’ adverse events judged (post-hoc) to be positive in nature (Rucker et al., 2019). This trial concluded that psilocybin was safe and well-tolerated when given to up to 6 healthy volunteers, simultaneously, in a controlled setting. It should be noted that the results from this trial have yet to be published in a peer-reviewed journal.

Numerous phase 2 multi-site clinical trials with psilocybin in the treatment of the major depressive disorder (MDD) and treatment-resistant depression (TRD) are now ongoing (ClinicalTrials.gov Identifiers: NCT03775200; NCT04433858; NCT03866174). The most notable of these from a medical regulatory perspective is a large multicentre randomized controlled phase 2b trial of single doses of psilocybin given to participants with treatment-resistant depression, taking place across Europe and North America. Results are expected in 2022.

MDMA was first synthesized by Merck in 1912 (Passie, 2018). Following the discovery of its psychoactive properties, MDMA was used as an adjunct for both individual and couples psychotherapy between 1977 and 1985 by an estimated 4000 psychiatrists and psychologists (Eisner, 1989; Holland, 2001). Similar to psilocybin and the other classical psychedelics, MDMA became a controlled substance and was placed in Schedule 1 of the CSA in 1985 after becoming popular for recreational use (‘ecstasy’). It remains in this most restrictive category today. MDMA is an amphetamine derivative (Elliott & Beveridge, 2005) and stimulates the release of monoamines (serotonin, dopamine, norepinephrine), hormones (cortisol, oxytocin) and downstream signalling molecules (including brain-derived neurotropic factor (BDNF)), which (amongst other things) may act to modulate neural circuitry implicated in the processing of traumatic memories (Dumont et al., 2009; Feduccia & Duvachelle, 2008; Feduccia & Mithoefer, 2018; Nash & Brodkin, 1991).

MDMA elicits a wide range of subjective effects, including increased feelings of empathy, affiliation and interpersonal trust (Feduccia & Mithoefer, 2018; Johansen & Krebs, 2009). MDMA is often categorized as an ‘entactogen’ (literally: ‘to produce touch within’) (Mithoefer et al., 2016). Since 2000, MDMA-assisted psychotherapy has been under clinical investigation for the treatment of PTSD (Mithoefer et al., 2019), social anxiety in autistic adults (Danforth et al., 2018) and alcohol use disorder (Sessa et al., 2019). A pooled analysis of six randomized, double-blind controlled clinical trials investigating MDMA-assisted psychotherapy for the treatment of PTSD found significantly greater reductions in PTSD symptoms (measured by The Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV)) (Mithoefer et al., 2019). Following two-drug treatment sessions with either active doses of MDMA (75–125 mg) or placebo/control doses (0–40 mg), 54.2% of participants in the active group no longer met CAPS-IV diagnostic scores for PTSD in comparison to 22.6% in control groups (Mithoefer et al., 2019).

There is no evidence from ongoing clinical trials with MDMA that suggest clinical neurotoxicity at the doses used (Mithoefer et al., 2016). MDMA has been well-tolerated in modern clinical trials (Mithoefer et al., 2019). Acutely, the physical effects of MDMA include mildly increased heart rate and blood pressure. A typical clinical ‘therapeutic’ dose is 125 mg, with effects lasting around 4–8 h (Johansen & Krebs, 2009; Krediet et al., 2020). The majority of deaths following recreational MDMA use have been linked either to polydrug use (Jones et al., 2011; Kaye et al., 2009) or as a result of drug use plus risky behaviours and environment, for example of dehydration/over-exertion at raves or due to brain oedemas following over-hydration (Mithoefer et al., 2016). More granular systematic reviews have reconfirmed these findings and further investigated adverse event data, concluding that MDMA at these doses is a relatively safe treatment when given in a controlled environment (Illingworth et al., 2020).

Treatment models of psilocybin- and MDMA-assisted psychotherapy overlap (Krediet et al., 2020), with both drugs used to facilitate salutary psychological change within a safe, comfortable, trusting and non-judgmental set and setting. Dosing sessions with MDMA and psilocybin take place in a comfortable, quiet, neutrally furnished room, with relaxing music and a supportive relationship with at least one therapist, which is thought to ‘deepen’ the therapeutic process (Krediet et al., 2020; Mithoefer et al., 2016). The psychotherapeutic approach to dosing is supportive but non-directive. ‘Preparation’ sessions are given
Psilocybin therapy has been designated in the same category for both the treatment of MDD and TRD (COMPASS Pathways, 2018; Feduccia et al., 2015; McQuaid et al., 2001). The ‘breakthrough therapy’ designation from the FDA, assigning priority in the regulatory drug development process. In 2017, MDMA was granted this designation for its use in psilocybin therapy for the treatment of PTSD. As of September 2020, the Multidisciplinary Association for Psychedelic Studies (MAPS) have completed one of two planned phase 3 randomized, double-blind, placebo-controlled, multi-site clinical trials to assess the safety and efficacy of MDMA-assisted psychotherapy in participants with PTSD (Mitchell et al., 2021; Multidisciplinary Association for Psychedelic Research, 2020).

Psilocybin therapy has been designated in the same ‘breakthrough’ category for both the treatment of MDD and TRD (COMPASS Pathways, 2018; Feduccia et al., 2019; Nichols, 2020). Given the status of current research and drug development efforts, PTSD and MDD seem likely to be the first psychiatric conditions to be treated with licenced MDMA or psilocybin outside of a research setting. In the present article, the role of trauma in psychiatric morbidity, and corresponding neurobiological changes in PTSD and MDD, are reviewed. Whilst PTSD and MDD are distinct disorders, they often co-occur and demonstrate a significant degree of clinical overlap. Furthermore, trauma exposure is a common driving factor underlying both conditions. Given the positions of psilocybin and MDMA in the drug development process, the potential mechanisms by which they may exert their therapeutic effects in both trauma-related MDD and PTSD are discussed. A practical point of interest is whether psilocybin before MDMA or MDMA before psilocybin might be, respectively, better for MDD and PTSD subtypes of trauma-related mental health problems.

**Trauma & psychopathology**

Exposure to traumatic events, including serious accidents, physical or sexual abuse, war-related incidents and life-threatening illness (to oneself or loved ones), is a universal risk factor in the development of psychopathology (de Vries & Olff, 2009; Kessler et al., 2017). The World Health Organization’s World Mental Health (WMH) Survey (n = 68,894 in 24 countries) found 70.4% of responders had experienced lifetime trauma of the above description, with the mean number of exposures reported at 4.6 (Kessler et al., 2017). Reactions to traumatic events include low mood, anxiety, exhaustion, dissociation, heightened physical arousal, agitation and numbness (Kessler et al., 2017), amongst others. Most can manage this stress response to regain optimal functioning, and not all who experience a traumatic event will subsequently meet the criteria for a mental health condition (Atwoli et al., 2015; McQuaid et al., 2001). The ‘Trauma- and Stressor-Related Disorders’ outlined in The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) include Posttraumatic Stress Disorder (PTSD) and Acute Stress Disorder (ASD). Both cite trauma as a necessary diagnostic criterion (American Psychiatric Association, 2013). As ASD requires symptoms to resolve less than 1 month in the aftermath of the trauma, PTSD is the diagnosis that is most likely to represent a chronic or lifelong condition (Howlett & Stein, 2016; Kessler, 2000) and a lifetime diagnosis occurs in around 4% of the global population (Koenen et al., 2017). PTSD is characterized by recurring symptoms of depressive and negative thoughts...
and feelings (self-blame, isolation), hyperarousal (irritability, aggression, elevated startle response), re-experiencing (intrusive upsetting memories, flashbacks, nightmares) and avoidance of distressing memories, feelings, thoughts or external reminders of the event. DSM-5 includes a PTSD dissociative subtype that includes experiences of depersonalization, derealization and feeling detached (American Psychiatric Association, 2013). Severity can also be observed through the degree of functional impairment as a result of these symptoms, possibly contributing to an increased risk of suicidality (Mauritz et al., 2013). The International Classification of Disease, 11th Revision (ICD-11; World Health Organization, 2018) includes complex posttraumatic stress disorder (CPTSD), where all diagnostic requirements for PTSD must be met along with additional problems including affect regulation, beliefs about oneself (self-blame, worthlessness) and difficulties in sustaining relationships (World Health Organization, 2018). The trauma definition under CPTSD is slightly less categorical than that of PTSD, defining distressing events that are usually prolonged or repetitive in nature and where escape is difficult or impossible (prolonged domestic abuse, childhood sexual or physical abuse, discrimination, torture, slavery) (World Health Organization, 2018).

Trauma exposure has also been linked to the development and severity of various other psychiatric conditions including major depressive disorder (MDD), dysthymia, bipolar disorder, substance abuse disorders and anxiety disorders (Hammen et al., 1992; Koenen et al., 2008; Laugharne et al., 2010; Mueser et al., 1998; Ompad et al., 2005), where trauma presents as an external risk factor. MDD may be the most common condition following trauma (Center for Substance Abuse Treatment, 2014; Foa et al., 2006; Laugharne et al., 2010) and there is an overlapping cluster of symptoms shared between MDD and PTSD diagnoses (see Figure 1). The relationship between trauma exposure and MDD is complex and not well understood, where both depression and trauma

Figure 1. Overlapping symptomatology of MDD and PTSD.
exposure are heritable traits (Coleman et al., 2020; Kendler et al., 1999; Kendler & Karkowski-Shuman, 1997). However, robust correlations between childhood adversity (e.g. physical and sexual abuse, family violence and neglect) and increased vulnerabilities to adverse adult mental health outcomes, including PTSD, MDD and anxiety have been demonstrated (Baldwin et al., 2019; Collishaw et al., 2007, Felitti et al., 1998; McLaughlin et al., 2010).

The severity and impact of a stress reaction, and the lasting psychoneurobiological changes, represent risk factors contributing to adverse outcomes, including the subsequent development and/or diagnosis of a psychiatric condition (Agorastos et al., 2019; Center for Substance Abuse Treatment, 2014). Underlying genetic vulnerabilities affect outcomes following trauma exposure (Coleman et al., 2020; Daskalakis et al., 2018). Furthermore, there are a variety of factors that influence outcomes following traumatic experiences (Grant et al., 2011). The nature and severity of the trauma (e.g. assaultive vs. non-assaultive) can influence the occurrence and presentation of resulting psychopathology (McQuaid et al., 2001). Gender, race, sexual orientation and previous exposure to trauma are some of the factors that can increase the incidence of trauma exposure (Roberts et al., 2011; Van der Kolk, 2000; Wise et al., 2001).

**PTSD and MDD: comorbidity and treatment**

It is estimated that 62–92% of PTSD cases demonstrate comorbidity (Gros et al., 2012; Keane et al., 2007; Perkonigg et al., 2000). MDD is the most common co-morbid condition in those with a diagnosis of PTSD (Center for Substance Abuse Treatment, 2014), with co-occurring PTSD + MDD present in around half of those with PTSD (Elhai et al., 2005; Flory & Yehuda, 2015; Rojas et al., 2014). A US-based report from 1997/8 showed that comorbid PTSD and depression was the most common psychiatric diagnosis (Macy, 1998 cit. Van der Kolk, 2000). Furthermore, the disorders share associated risk factors, symptoms and treatments (Carlson & Rosser-Hogan, 1991; Grant et al., 2008; Gros et al., 2012; Levitan et al., 1998; Singer et al., 1995).

The co-occurrence of PTSD and MDD is associated with increased burden, greater functional impairment and increased suicidal behaviours when compared to individuals with non-comorbid MDD and PTSD (Center for Substance Abuse Treatment, 2014; Frayne et al., 2004; Gros et al., 2012; Oquendo et al., 2003). Gros et al. (2012) demonstrated that participants with comorbid MDD-PTSD had significantly higher scores on PTSD symptoms scales (using the PTSD Checklist – Civilian Version (Weathers et al., 1994)) compared to those with MDD-only or PTSD-only diagnoses ($t > 2.8; ps < 0.01$).

MDD is a heterogeneous and aetiologically complex condition with depressed mood and anhedonia being central to the condition. Anhedonia, concentration difficulties/memory impairment, sleep disturbances, guilt and distorted cognition are symptoms that overlap between PTSD and MDD (Flory & Yehuda, 2015) (see Figure 1). Comparable levels of PTSD symptoms have been found in both participants with MDD-only and PTSD-only, and more severe PTSD symptoms have been reported in participants with comorbid MDD and PTSD (Gros et al., 2010, 2012). A history of MDD has shown to be predictive of PTSD following exposure to trauma (Foa et al., 2006) and PTSD has also been found to increase the risk for the first onset of MDD (Breslau et al., 1998).

Overall, PTSD and MDD in response to trauma may be best represented as two distinct, yet strongly related constructs (Post et al., 2016). The high comorbidity rates between PTSD and MDD may be due to imprecisions in the classification of symptoms. An alternative explanation is that comorbid MDD and PTSD represent a trauma-related phenotype that is separate from MDD, where comorbidity of these two conditions indicates an underlying degree of risk for psychopathology following trauma (Flory & Yehuda, 2015; Grant et al., 2008).

The conceptualization of co-morbidity between PTSD and MDD has implications for treatment, specifically in determining whether treatments for PTSD can be effective in treating MDD and vice versa, or for those who present with symptoms of both conditions.

**The neurobiology of the trauma response**

The collection of symptoms and behaviours that are captured within PTSD descriptions likely reflect underlying changes in neurobiological and endocrine functions in response to stress. Dysregulation of brain circuitry involved in the stress response can lead to alterations to the limbic system (which includes the amygdala, hypothalamus and hippocampus), the hypothalamic-pituitary-adrenal (HPA) axis and key monoamine neurotransmitter systems associated with traumatic experience(s) (Heim & Nemeroff, 2009; Van der Kolk, 2000; Weiss, 2007). Some structural and functional differences may represent more general
risk factors rather than changes resulting from trauma per se. Whilst not all depression involves a history of childhood trauma, it has been suggested that there may be biologically distinct subtypes of depression, with a basis in the neurobiological changes associated with severe childhood trauma (Heim et al., 2008). An in-depth description of neurobiological effects of trauma is out of the scope of this manuscript (see Heim & Nemeroff, 2009; Weiss, 2007), however a basic outline of these changes and how they relate to behavioural symptoms of PTSD follows. Selected brain changes seen in MDD are also outlined.

**The limbic system**

The limbic system receives sensory input via the thalamus, and its subcomponents (the amygdala, hypothalamus and the hippocampus) co-operate to mediate balanced behavioural and affective responses to external stimuli. Those who are trauma-exposed may display impaired relay of information from the thalamus to the cortex under stressful conditions (Kimble & Kaufman, 2004).

The executive functions of the cortex filter out irrelevant information and inhibit responses to sensory stimuli, coordinating a complex, moderated response to any given situation. PTSD patients exhibit decreased volumes in cortical areas including the prefrontal cortex and the anterior cingulate cortex (Bremner, 2002; Heim & Nemeroff, 2009, Weiss, 2007; Yamasue et al., 2003). Neglect and stress during childhood are associated with cortical atrophy, including loss of neurons, dendrites and synaptic connections in these areas (Perry, 2002; Weiss, 2007). In PTSD, these structural changes contribute to hypoactivation in these areas which, in turn, can impair extinction of fear responses and top-down mechanisms involved in inhibiting reactivity to emotional stimuli (Etkin & Wager, 2007; Sherin & Nemeroff, 2011; Yang et al., 2004).

The amygdala is a key limbic structure that is involved in the mediation of fear responses and emotional processing (Heim & Nemeroff, 2009). The amygdala generates an emotional valence that is sent to subcortical motor structures and the brain stem to determine an appropriate motor response or reflex (e.g. facial expression, startle reaction). In PTSD, the amygdala displays a heightened response to neutral and emotional stimuli, contributing to irritability, aggression and overall hypervigilance (Sherin & Nemeroff, 2011; Shin et al., 2006). Increased amygdala activity, particularly in response to emotional faces has also been observed in MDD (Drevets et al., 1992; Siegle et al., 2002). Grant et al. (2011) demonstrated that the degree of heightened amygdala response in depression may be a risk factor dependent on exposure to childhood trauma. Using fMRI, they found a strong positive correlation between childhood physical abuse and amygdala response, where this relationship was much weaker in those with non-violent forms of abuse like neglect, suggesting that depression is mediated by heightened amygdala response, but differs by trauma type. Greater bilateral amygdala responses to sad faces than happy faces were observed in depressed patients using fMRI (Stuhrmann et al., 2013), where healthy controls had greater amygdala responses to happy than sad faces. In the depressed group, reduced right amygdala response to happy faces was associated with increased physical anhedonia scores, which the authors suggest may result from ‘reduced salience attribution to positive information’ (Stuhrmann et al., 2013).

The hippocampus works to integrate control of contextual aspects of fear conditions, fear conditioning and the control of stress response. Neuroimaging studies have shown decreased activation and lower levels of metabolism in the hippocampi of trauma-exposed people, which may be associated with reduced hippocampal volume that, in turn, is relative to the length and severity of trauma experience (Bremner et al., 1995, 1997; Gurvits et al., 1996; Heim & Nemeroff, 2009; Stein et al., 1997). These changes in volume and activity may underlie the occurrence of avoidance and numbing, memory loss of the trauma, as well as dissociation experiences (Weiss, 2007). Similarly, early life trauma in MDD patients (particularly childhood abuse), is associated with reduced hippocampal volume (Vythilingam et al., 2002).

**The HPA axis**

The HPA axis operates as the main neuroendocrine stress response system (McEwen, 2004). Acute stress stimulates a hormonal cascade via this axis. The hypothalamus is a part of the HPA axis, secreting corticotropin-releasing hormone (CRH) following trauma and other stress. CRH stimulates the production and release of adrenocorticotropic (ACTH), which subsequently stimulates the release of glucocorticoids (cortisol in humans) from the adrenal cortex (Heim & Nemeroff, 2009). The hypothalamus receives emotional information from the amygdala, and the HPA axis is modulated by inhibitory activity from the PFC.
and hippocampus. The release of cortisol from the adrenal cortex activates the sympathetic nervous system and, normally, suppresses further CRH release.

Whilst uniform changes to cortisol levels in PTSD have not been observed (see Yehuda (2006) for review), decreased cortisol in response to chronic stress is often observed in individuals with PTSD leading to a dysregulation of the negative feedback loop between HPA axis and cortisol production. This is hypothesized to lead to abnormal stress encoding and fear processing (Sherin & Nemeroff, 2011).

A sustained, increased level of CRH as a result of HPA dysregulation may contribute to hippocampal atrophy and a desensitized ACTH response to CRH stimulation.

Hyperactivity of the HPA axis is observed in MDD, with increased cortisol levels observed in patients experiencing a depressive episode (Posener et al., 2000; Young et al., 2001).

The mechanisms discussed most probably influence monoaminergic neurotransmitter turnover and subsequent neuromodulation. Current pharmacological treatments recommended for PTSD are all antidepressants (i.e. they were not developed to specifically address PTSD symptoms) that specifically target the serotonin transporter (SERT). The poor efficacy of treatments (such as sertraline) that influence SERT in PTSD suggests that pharmacologically targeting SERT is insufficient. In addition, revisiting traumatic memories with the required emotional engagement via talking therapy alone is sufficiently challenging for some patients that it introduces the risk of worsening the condition (Feduccia et al., 2018).

It is in this context that promising results from MDMA-assisted psychotherapy for PTSD are interesting. MDMA, as well as being a SERT inhibitor, stimulates the release of serotonin into the synaptic cleft by binding to vesicular transport proteins within the synapse. This leads to an acute surge of extracellular serotonin and a clinical state of interpersonal tenderness, empathy and warmth. It seems that these pharmacologically induced changes provide an opportunity to ‘engage’ with trauma-related material during psychotherapy in a way that is more likely to lead to positive reappraisal. Put another way, the effects of MDMA are sufficiently different to more classical SERT inhibitors that it may render the brain biologically ‘ready’ for psychological change, particularly within a safe, supportive psychotherapeutic setting.

It seems there is an overlapping clinical and neurobiological phenotype between depression and PTSD. This means that the pharmaco-/psycho-therapy combination model with psilocybin and MDMA is theoretically applicable and useful for the treatment of PTSD and/or trauma-related MDD.

**MDD and PTSD: current treatments**

**PTSD**

In the UK, the only licenced drugs for the treatment of PTSD are the antidepressant drugs sertraline and paroxetine (Hoskins et al., 2015; National Institute for Health & Care Excellence, 2018). Both sertraline and paroxetine are also the only antidepressants with FDA approval for the treatment of PTSD in the United States (American Psychiatric Association, 2017). Other SSRIs and SNRIs including fluoxetine, venlafaxine and mirtazapine are sometimes used off-label in the treatment of PTSD in both countries (American Psychiatric Association, 2017; Baldwin et al., 2014; National Institute for Health and Care Excellence, 2018). A meta-analysis of 37 randomized placebo-controlled trials found that only paroxetine, sertraline and venlafaxine were better at treating PTSD symptoms than placebo (Ippser & Stein, 2012). While approximately 60% of patients respond to SSRI treatment, only 20–30% of patients achieve remission (Alexander, 2012). The use of benzodiazepines can negatively impact treatment outcomes in PTSD and are not recommended as a first-line pharmacological treatment (Van Minnen et al., 2002). Thus, pharmacological interventions for PTSD have been classified as ‘low effect’ treatments (Hamblen et al., 2019). Current UK treatment guidelines recommend psychological interventions as the first-line therapy for the treatment of PTSD (National Institute for Health and Care Excellence, 2018). Although it is worth noting that the comparative efficacy of pharmacological and psychological treatments for PTSD is not yet established. The British Association for Psychopharmacology guidelines recommend pharmacological (paroxetine, sertraline or venlafaxine) or psychological (trauma focused CBT or EMDR) for the acute treatment of PTSD, highlighting that the comparative efficacy of psychological versus pharmacological treatment for PTSD has yet to be established (Baldwin et al., 2014).

NICE recommends trauma-focused, exposure-based psychotherapies for PTSD: cognitive processing therapy (CPT), cognitive therapy for PTSD (t-CBT), narrative exposure therapy (NET), prolonged exposure therapy (PET), and Eye Movement Desensitisation and Reprocessing (EMDR). Trauma-focused CBT and Eye Movement Desensitisation and Reprocessing (EMDR) therapy are favoured as evidence-based therapies (Baldwin et al., 2014). Trauma-
focused psychotherapies aim to facilitate reductions in PTSD symptoms by encouraging re-exposure and re-processing of emotionally charged memories (Bradley et al., 2005; Kline et al., 2018). However, non-response to initial treatment with pharmacological and psychological treatments is high with PTSD (Baldwin et al., 2014). Around 40–60% of patients do not achieve significant clinical improvement (Haagen et al., 2015; Steenkap et al., 2017; Watkins et al., 2018). Those with dissociative symptoms, severe affect dysregulation, increased suicidal ideation and disturbances in learning, memory, attention, and concentration may struggle to engage in trauma-focused therapies (Bisson et al., 2013; Laniu et al., 2010; Raines et al., 2017). Psychosocial problems such as unemployment, homelessness and substance misuse may further undermine efforts at therapeutic engagement (Davidson et al., 1991; Jakupcak et al., 2009; Marshall et al., 2001; Sareen et al., 2007). Dropout rates between 25 and 30% have been reported and one-third to one-half of patients completing treatment still report symptoms and ongoing impairment (Bradley et al., 2005).

**Depression**

Treatment approaches for MDD vary in intensity depending on the severity of and the individual’s history with depression. Psychological therapies are favoured for milder forms, with antidepressants and combination treatments recommended for moderate to severe forms (Cleare et al., 2015; NICE; Maudsley Prescribing Guidelines (Taylor et al., 2018)). The first-line treatment for moderate-severe depression is a selective serotonin reuptake inhibitor (SSRI, for example; sertraline, citalopram, fluoxetine, paroxetine). Other pharmacological antidepressant treatments include serotonin-noradrenaline reuptake inhibitors (SNRIs; duloxetine, venlafaxine), noradrenaline and specific serotonergic antidepressants (NASSAs; mirtazapine), tricyclic antidepressants (TCAs; amitriptyline, clomipramine, imipramine) and monoamine oxidase inhibitors (MAOIs; tranylcypromine, phenelzine and isocarboxazid). Antidepressants can be used in cases of mild depression, particularly when there is a history of moderate-severe recurrent depression, or the depression persists for 2–3 months (Cleare et al., 2015). Cognitive behavioural therapy (CBT), behavioural activation and interpersonal psychotherapy are some of the talking therapies recommended for mild-severe depression. Psychological therapy alone is not recommended in severe cases of depression and combination therapy of an antidepressant and talking therapy may be more efficacious than either alone (Cleare et al., 2015). Roughly 50–60% of people will see an improvement following antidepressant treatment, compared to 25–30% of those taking placebo (Anderson et al., 2008; Royal College of Psychiatrists, 2019).

Treatment-resistant depression (TRD), defined as those who do not improve despite (usually) at least two established treatments (Strawbridge et al., 2019), develops in approximately 1/3 of those with a diagnosis of depression (Crown et al., 2002). Medical strategies for treatment-resistant depression include dose increase, augmentation with a second antidepressant, lithium or an antipsychotic (Cleare et al., 2015; Taylor et al., 2018). In TRD, the risk of suicide increases, and patients are more likely to require hospitalization and less likely to respond to subsequent treatments (Bergfeld et al., 2018). People with TRD are more likely to be economically inactive and psychosocially disabled, often leading to increased carer burden (Crown et al., 2002; Fava, 2003).

**Novel treatment approaches**

Despite these treatment gaps, there has been little progress in pharmacological treatments for MDD or PTSD since the approval of SSRIs in the 1980s, with pharmaceutical companies reducing the focus on psychiatric drug treatments or ceasing this effort altogether (Hyman, 2013). However, more recently esketamine, an N-methyl-d-aspartate (NMDA) receptor antagonist, has been licenced as a treatment for MDD given in combination with an SSRI, demonstrating rapid and sustained antidepressant effects within hours of intranasal administration (Daly et al., 2019; Fedgchin et al., 2019; Murrough et al., 2013; Ochs-Ross et al., 2018; Popova et al., 2019; Wilkinson et al., 2018). The rapid action of esketamine highlights the delayed therapeutic onset seen with SSRIs and other available pharmacotherapies. (R,S)ketamine, as an adjunct to psychotherapy, has also been investigated for the treatment of PTSD, with encouraging preliminary results (Pradhan et al., 2017, 2018).

The development of esketamine, whilst it reflects a new target mechanism of action, nonetheless is an old drug with a new indication. Racemic ketamine was developed as an anaesthetic to replace phencyclidine in 1962, with its antidepressant properties not investigated until the 1990s. Similarly, since the late 1990s, there has been a slow yet steady resurgence of research into the antidepressant and anxiolytic properties of psilocybin and methylenedioxymethamphetamine (MDMA). Although it should be noted that
the current model for the treatment of depression with ketamine does not involve an element of psychotherapy. The reasons for researchers ‘looking to history for inspiration’ are complex, but likely reflect a general failure to develop truly novel pharmacological treatments in psychiatry and slow relaxation of the sociopolitical opprobrium that surrounded drugs such as MDMA and psilocybin.

The following section outlines the therapeutic utility of treating trauma-related MDD and PTSD with both psilocybin and MDMA. Based on existing evidence about their potential in eliciting salutary psychological change, potential mechanisms of action in MDD and PTSD symptom reduction are discussed.

**MDMA and psilocybin-assisted psychotherapy: transdiagnostic uses**

**Mood effects and emotional processing**

Both psilocybin and MDMA can alter the processing of affective information. In a randomized, double-blind study, comparing the effects of psilocybin, ketanserin (a 5-HT2 receptor antagonist) or psilocybin + ketanserin, Kometer et al. (2012) found that psilocybin reduced recognition of negative facial expression and enhanced positive mood. The ketanserin-only group displayed no effects on emotional tasks but psilocybin-induced mood improvements were obstructed and the recognition of negative emotional stimuli was attenuated, demonstrating the central role of the 5-HT2A receptor in these processes. Correspondingly, Schmidt et al. (2013) observed that psilocybin impaired the subjective discrimination between fearful and neutral faces and reduced the encoding of fearful faces. In TRD, improved emotion recognition was shown to persist 1-month post-treatment with psilocybin (Stroud et al., 2018)

As previously mentioned, hyperactivity of the amygdala and reduced pre-frontal control of the region underlies a heightened fear response to emotional stimuli following trauma and has been observed in both MDD and PTSD populations. In fMRI studies in healthy volunteers, psilocybin attenuates amygdala reactivity to negative and neutral stimuli (Kraehenmann et al., 2015). This was associated with observed increases in positive mood states following psilocybin administration (Kraehenmann et al., 2015). Reduced amygdala reactivity in response to affective stimuli and associated negative affect was decreased 1-week post psilocybin administration in healthy volunteers (Barrett et al., 2020). However, in contrast, an increase in amygdala reactivity to fearful faces has been observed in participants with TRD 1-day post psilocybin session (Roseman et al., 2018), where the authors hypothesized that psilocybin facilitated the processing of negative memories/experiences acutely, allowing patients to ‘reconnect’ with their emotions post drug effect. In the same sample of patients, Mertens et al. (2020) observed decreased functional connectivity between the ventromedial prefrontal cortex and the amygdala post-treatment with psilocybin. It is worth noting that these scans were conducted before psychological integration had occurred with the assigned therapists, which may be required to achieve lasting benefits in the balanced processing of negative emotions (Vollenweider & Preller, 2020). Further studies may elucidate the effects of psilocybin on the amygdala and the relevance of these changes to clinical outcomes. Kraehenmann et al. (2016) demonstrated via fMRI connectivity analyses that psilocybin reduced threat-induced modulation of connectivity from the amygdala to the primary visual cortex, suggesting a mechanism for decreased threat sensitivity following psilocybin. Furthermore, animal studies have shown that psilocybin facilitates fear extinction in mice (Catlow et al., 2013) as well as promoting functional and structural neural plasticity in the PFC in vivo and in vitro (Ly et al., 2018). Together, changes in neurogenesis, synaptogenesis and spinogenesis have been postulated to contribute to antidepressant and anxiolytic effects of psilocybin (Ly et al., 2018).

The above findings suggest that the effects of psilocybin on emotional processing may have therapeutic utility in addressing negative cognitive and emotional biases seen in depression. It is possible that dampened processing of emotional responses and increased affinity to positive mood states occurring following psilocybin is regulated by amygdala connectivity. In PTSD, psilocybin may also inhibit fear responses during the revisiting of traumatic material. Depressive and negative thoughts are also present within PTSD diagnoses, and the potential for psilocybin to augment positive mood states may also have therapeutic utility in this population.

There has been historic use of classical psychedelics, mainly LSD (and psilocybin and ketamine to a lesser extent), in the treatment of ‘concentration camp syndrome’ (Bastiaans, 1983; Krediet et al., 2020). The therapy aimed to allow patients to re-experience traumatic material within a supportive environment. However, this treatment occurred prior to the addition of PTSD as a psychiatric diagnosis, and no clinical research into the utility of psilocybin for the
Acutely, MDMA induces a rapid, dose-dependent release of monoamines from pre-synaptic vesicles (5-HT). MDMA also competes with synaptic monoamines for reuptake into the neuron. The net effect is an acute increase in monoamine concentration in the synaptic cleft, however, MDMA has 10-fold more affinity for the 5-HT transporter in comparison to either noradrenaline or dopamine, leading to a relative surge in 5-HT concentration. Mice deficient in the serotonin transporter do not respond to MDMA (Fox et al., 2007) and SSRIs act to attenuate the effects of MDMA, suggesting antagonistic competition to SERT in both animal and human models (Liechti & Vollenweider, 2000; Schmidt & Taylor, 1987). This mechanism suggests MDMA may be a suitable candidate for antidepressant treatment under a similar pharmacological rationale to the therapeutic use of SSRIs (Patel & Titheradge, 2015; White et al., 2008). Post-mortem brain tissue analysis, as well as measurements using cerebrospinal fluid in animal models, have demonstrated 5-HT depletion following acute, MDMA-induced 5-HT release (Schmidt et al., 1986; Taffe et al., 2003). However, the dosing regimens employed in these studies employed doses over 10 times the average recreational dose used, with multiple dosing sessions sometimes given in rapid succession. This response is unlikely with the lower doses used in modern clinical research (Patel & Titheradge, 2015).

Given the current understanding of the role of the 5-HT system in modulating mood in anxiety and depression, MDMA-assisted therapy may enhance positive mood states and facilitate the therapeutic processing of traumatic memories in PTSD (Feduccia et al., 2018) and perhaps in trauma-related MDD.

There is indirect evidence for the antidepressant effects of MDMA-assisted psychotherapy from secondary outcomes in completed clinical trials. An open-label, proof of concept, phase I trial investigating MDMA-assisted psychotherapy for alcohol use disorder (AUD) (Sessa et al., 2019, 2021) demonstrated significant decreases in depressive symptoms as measured by the Patient Health Questionnaire-9 (PHQ-9). Improvements in self-compassion, mindfulness and quality of life were also observed, although the final results for these measures have yet to be published. A randomized, double-blind, dose-response phase II trial investigating MDMA-assisted psychotherapy for chronic PTSD, where participants were randomized to receive 30 mg (active control), 75 mg or 125 mg over two sessions, employed the Beck Depression Inventory-II (BDI-II) as a secondary
outcome. Depressive symptoms were significantly reduced in the 125 mg group compared with the 30 mg group (mean change of BDI-II score of −24.6 vs −4.6; \( p = 0.0003 \)) at 1 month follow up. Comparisons between the 75 mg and 30 mg groups were non-significant, although the 75 mg group demonstrated a larger average drop from baseline (Mithoefer et al., 2019). A pooled analysis of four phase 2 RCTs investigating MDMA for PTSD (Mithoefer et al., 2019), including the above study demonstrated that improvement in depression symptoms (as measured by the BDI-II) only trended towards significant group differences but was greatest for the active group compared to the control group (Mithoefer et al., 2019). The therapy delivered in these trials followed a manual specifically designed for the treatment of PTSD (Mithoefer et al., 2016). A meta-analysis of four RCTs investigating MDMA-assisted psychotherapy for treatment of PTSD observed a significant decrease in BDI scores in the 75 mg group only, in comparison to placebo (Illingworth et al., 2020). Although the persistence and/or emergence of depressive symptoms may be part of the therapeutic process involved in the processing of previously avoided traumatic memories (Illingworth et al., 2020). Alternatively, it may be that (subtle) changes in depressive symptomatology are not well captured by operationalised measures designed to quantify. Qualitative analyses may be useful in capturing these characteristic changes in quality. However, it is worth noting that in Mithoefer et al.’s MDMA for PTSD trials, changes in depressive symptoms were a secondary outcome measure. The self-report BDI scale, the outcome measure used in these trials, is not a blinded outcome measure thus expectancy effects are more likely to have contributed to findings. A recent, phase 3 RCT investigating MDMA therapy for PTSD by the same group demonstrated MDMA therapy was effective in reducing depressive mood symptoms (as measured by the BDI-II) (Mitchell et al., 2021).

Social cognition
Impaired social cognition and empathic abilities contribute to negative social interactions and impact the ability to perceive and process socially relevant information (Weightman et al., 2014). Improved therapeutic alliance and emotional empathy are outcomes central to the hypothesized social processing improvements following both MDMA and psilocybin-assisted therapy.

Increased emotional empathy (Kuypers et al., 2017), subjective ratings of closeness to others and increased feelings of trust (Schmid et al., 2014) have been seen following MDMA. Increased feelings of openness and closeness towards others have also been reported (Schmid et al., 2014). Oxytocin levels increase as a result of 5-HT efflux, following MDMA, which has been hypothesised to contribute to subjective increases in feelings of trust (Hysek et al., 2014; Vizeli & Liechti, 2018). Thompson et al. (2007) suggest MDMA-stimulated oxytocin may be central to prosocial effects of MDMA. However, the exact role of oxytocin released following MDMA is still unclear.

Oxytocin modulates neural circuitry related to the neurobiological response to trauma, including the amygdala and the PFC, and has been shown to reduce activity in the amygdala (Eckstein et al., 2015) This is a potential underlying mechanism of the attenuation of amygdala activity observed (Carhart-Harris et al., 2015; Feduccia et al., 2018; Gamma et al., 2000). Furthermore, the use of oxytocin as an adjunct to psychotherapy has been investigated due to its purported ability to enhance prosocial behaviour (MacDonald et al., 2013). However, the apparent relatedness of improved emotional empathy following MDMA, and peripheral oxytocin levels, has not been observed consistently (Kuypers et al., 2014, 2017).

Psilocybin has been shown to increase emotional empathy, without affecting cognitive empathy (Pokorny et al., 2017), as well as decrease feelings of social exclusion and rejection processing in the anterior cingulate cortex (Preller et al., 2016) These effects may contribute to improved patient-therapist relationships and reduce social withdrawal (Vollenweider & Preller, 2020). In depression, participants reported increased feelings of connection (from self, others and the world) and reduced feelings of avoidance following psilocybin-assisted psychotherapy (Watts et al., 2017). Qualitative analysis of participant accounts in a pilot trial investigating the use of psilocybin for smoking cessation, participants reported feelings of reconnection of their environment, as well as increased prosocial behaviour and altruism (Noorani et al., 2018). Charuvastra and Cloitre (2008) found that positive outcomes in PTSD therapy show a firm relationship with the strength of the therapeutic alliance. Empathy as an essential component of the therapeutic alliance across psychotherapeutic modalities has been suggested (Feller & Cottone, 2003). Psilocybin may help in reducing treatment drop-out rates and improve psychotherapeutic efficacy by supporting the
development of a strong therapeutic alliance via the promotion of empathy in PTSD.

**Conclusion**

Existing evidence that may support the use of psilocybin-assisted psychotherapy for the treatment of trauma-related symptomatology, and MDMA-assisted psychotherapy for the treatment of depressive symptomatology, has been outlined above. Whilst depression is a complex psychosocial condition with a multitude of triggers, there is robust evidence to suggest that it can arise as a result of traumatic experiences, particularly in early life. When comorbid with PTSD, a multifaceted approach to treatment is required. The combination of psychotherapy and pharmacology as is presented in drug-assisted psychotherapy models seems to be a valuable approach in treating both depression and PTSD, especially in those who have not responded to available treatments. The occasional persistence of depressive symptoms following MDMA may be an artefact or a key mechanism in the processing of traumatic memories. A potential treatment course could be to administer MDMA-assisted psychotherapy in the first instance and then offer psilocybin-assisted psychotherapy in those for whom depressive symptoms still persist. It has been suggested that this course may allow the patient to be more accustomed to the heightened arousal experienced under psilocybin after experiencing more ‘present’ altered states of consciousness under MDMA (Krediet et al., 2020). The ‘trust enhancing’ qualities of MDMA may prove useful in strengthening therapeutic alliance in the first instance to allow for a ‘deeper’ subsequent acute psilocybin experience. Proof of concept studies is required in order to directly investigate the potential transdiagnostic uses of psilocybin- and MDMA-assisted psychotherapy for comorbid and non-comorbid PTSD and depression.

**Disclosure statement**

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