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Name of Journal: *World Journal of Psychiatry*

Manuscript NO: 83375

Manuscript Type: MINIREVIEWS

**Therapeutic role of psilocybin and 3,4-methylenedioxymethamphetamine in trauma:
a literature review**

Role of psilocybin and MDMA

Lakshan N Fonseka, Benjamin K.P. Woo

Abstract

With the FDA designation in 2017 of 3,4-methylenedioxymethamphetamine (MDMA) as a breakthrough therapy in post-traumatic stress disorder and psilocybin in treatment-resistant depression, psychedelic drugs have continued to garner the attention of researchers and clinicians for their promise of unmatched, rapid improvement in a multitude of psychiatric conditions. Classic psychedelic drugs including psilocybin, LSD, and ayahuasca, as well as non-classic drugs such as MDMA and ketamine, are currently being investigated for a potential therapeutic role in trauma, depressive disorders, and other psychopathologies. However, psilocybin and MDMA each have a functional profile well-suited for integration with psychotherapy. The present review focuses on psilocybin and MDMA in psychedelic-assisted therapy (PAT), as these studies compose most of the literature pool. A literature search for ((psilocybin) OR (MDMA)) AND (trauma) was conducted on PubMed database and Reference Citation Analysis. The aim of this review is to summarize the literature on psychedelic drugs, with an emphasis on the role of MDMA and psilocybin in PAT in the setting of trauma and related comorbidities from 2020 to 2022, bridging the gap from Reiff *et al.*'s review encompassing articles from 2007 to 2019 on the efficacy of psychedelic drugs across multiple psychiatric disorders. The article concludes with

thoughts for future research, such as incorporating wearables and standardization of symptom scales, therapy styles, and assessment of adverse drug reactions.

Key Words: Psychedelics; trauma; depression; methylenedioxymethamphetamine; ecstasy; psilocybin

Fonseka LN, Woo BK. Therapeutic role of psilocybin and 3,4-methylenedioxymethamphetamine in trauma: a literature review. *World J Psychiatry* 2023; In press

Core Tip: Psychedelic-assisted therapy with psilocybin or MDMA is strongly supportive across psychiatric conditions, especially trauma and related comorbidities, as demonstrated through a pattern of rapid and sustained symptom relief. Both treatments seem to have benefits beyond the FDA breakthrough designations of treatment-resistant depression for psilocybin and PTSD for MDMA.

INTRODUCTION

The psychedelic renaissance of modern psychiatry can trace its resurgence to 2017-2018, when the FDA designated breakthrough therapy status to psilocybin in treatment-resistant depression and 3,4-methylenedioxymethamphetamine (MDMA) in post-traumatic stress disorder (PTSD). Psychedelics can be broadly categorized as classic psychedelics that act as agonists at the 5-HT_{2A} receptor (i.e., psilocybin, lysergic acid diethylamide, ayahuasca/dimethyltryptamine), empathogens that increase serotonin levels (i.e., MDMA), antagonists at N-methyl-D-aspartate receptors (i.e., ketamine), and atypical hallucinogens with effects across neurotransmitter systems^[1-2]. Psychedelic-assisted psychotherapy (PAT) involving MDMA or psilocybin composes most of the literature pool, though studies involving other psychopathologies and compounds have also been investigated to a lesser extent. The predominance of both psilocybin and

MDMA in the literature may be attributed to the properties that make each an ideal adjunct to psychotherapy.

Psilocybin and its active metabolite psilocin are derived from psychoactive mushroom species originally used in ceremonial settings to facilitate spiritual experiences in Central and South America, later introduced to Western culture in the 1950s^[1, 3]. As a classic psychedelic, psilocybin is a 5-HT_{2A} receptor agonist that was found to produce rapid yet enduring improvement in treatment-resistant depression and major depressive disorder^[4-6]. More recently, psilocybin was compared to escitalopram in a double-blind trial. Both treatments were found to have similar efficacy in depression, which will be discussed in more detail in the present article^[7].

Psilocybin further enhances its synergism with psychotherapy by evoking a sense of unity, ego-dissolution, and awe through “mystical” experiences^[8-10]. As described by Vaid *et al.* (2022), PAT may enable the processing of emotional experiences that were previously inaccessible due to trauma blocks. This promotes reconnection with the self and “foundational identity deficit repair,” a re-stabilization of the core ideas that together represent the conscious identity, self-esteem, and other aspects of the self^[11]. As will be described later in this article, patients in recent studies report significant reductions in symptom rating scales, with benefits partly attributed to this mystical component—experiences of oneness or ego-dissolution, connection to self-essence, and a broadened perspective beyond self-imposed limits on thought processes and rigid mental frameworks that may once have been adaptive responses to life events^[12-13].

MDMA was initially developed by Merck & Co. for hemostasis in 1912, and its psychoactive effects were not published until 1978. After becoming popularized as recreational drug “ecstasy” in the 1980s^[1,14-15], the Drug Enforcement Agency cited concerns of abuse potential and neurotoxicity and assigned schedule I status to MDMA in 1985. MDMA is part of a class of psychedelics, termed empathogens or enactogens,

that increase empathy and social connection. Its effects are primarily mediated by serotonergic activity, including serotonin/norepinephrine transporter reuptake inhibition and partial agonism of serotonin receptors (5-HT_{2A}, 5-HT_{1A}, 5-HT_{2C})^[1]. By far, MDMA studies formed most of the research elicited by the PubMed search terms. The reasons for the clear bias in the literature and its consequences are varied and discussed in the future directions section. Nevertheless, the research has yielded promising results across psychopathologies, though most research aligns with its FDA designation for PTSD. A recent double-blind, phase 3 clinical trial found that 67% of participants receiving MDMA-assisted psychotherapy no longer met PTSD criteria after 2 mo^[16]. These improvements are attributed to several downstream changes in cognition that further complement psychotherapy.

MDMA has been previously shown to decrease amygdala response when patients are presented with angry faces, as well as increase ventral striatum response when viewing happy faces, further supporting that MDMA reduces threat response, enhances reward, and facilitates positive social interactions^[1, 17-18]. MDMA has the reputation of generating feelings of closeness, connection, and emotional empathy, although similar features also exist in classic psychedelics^[19-20]. However, MDMA uniquely offers augmentation of the therapeutic alliance, easefully lowering barriers and enabling the patient to process traumatic memories without feeling overwhelmed^[1, 21].

MDMA, psilocybin, and other psychedelics appear to induce a temporary period of increased neuroplasticity with associated changes in psychological flexibility^[21,22]. Psilocybin studies have demonstrated increased neurogenesis, spinogenesis, and synaptogenesis that facilitate the reconditioning of fear memory and the reversal of stress-induced changes to the prefrontal cortex^[23-25]. The plasticity counters the deficits in fear memory extinction seen in PTSD, alleviating distress from the cycle of avoidance and flashbacks associated with persistent traumatic memories^[26-28]. Kéri *et al.* suggest that psychedelic-induced serotonin-glutamate interactions affect memory pathways

responsible for memory destabilization and reconsolidation^[29]. The neuroplastic and fear memory changes enrich the benefits drawn from combination with psychotherapy.

The present focus is on psychedelics involved in psychedelic-assisted therapy (PAT), namely MDMA and psilocybin as these studies compose much of the literature pool. A literature review was conducted through PubMed database search of ((psilocybin) OR (MDMA)) AND (trauma). The search was also performed on Reference Citation Analysis (<https://www.referencecitationanalysis.com/>). The aim is to summarize the literature on psychedelic drugs, with an emphasis on the role of MDMA and psilocybin in PAT in the setting of trauma and related depressive disorders, from 2020 to 2022, bridging the gap from Reiff *et al.*'s review encompassing articles from 2007 to 2019 on the efficacy of psychedelic drugs across multiple psychiatric disorders. The article concludes with thoughts for future research, such as incorporating wearables and standardization of symptom scales, therapy styles, and assessment of adverse drug reactions.

PSILOCYBIN

With its FDA designation for treatment-resistant depression, it follows to begin the discussion of psilocybin with updates in depression, a common comorbidity in trauma-related conditions. Carhart-Harris *et al.* published a clinical trial comparing psilocybin *vs* escitalopram in 59 patients with major depressive disorder (MDD)^[7]. The psilocybin group ($n = 30$) received 25 mg of psilocybin at the start and a second dose at 3 wk, all while receiving 6 wk of daily placebo. The escitalopram group ($n = 29$) received 1 mg of psilocybin at the start and a second dose of 1 mg at 3 wk, with daily oral escitalopram 10 mg throughout the 6-week study. The primary outcome measure was changes from baseline scores (range 0 to 27) on the ¹Quick Inventory of Depressive Symptomatology (QIDS-SR-16), with a response defined as reduction in score of at least 50% and remission defined as a score of 5 or less.

A response occurred in 70% of the psilocybin group and ²48% of the escitalopram group, while remission occurred in 57% of the psilocybin group and 28% of the escitalopram group. Although these differences do not reach significance, it is notable that both psilocybin and escitalopram appear, at a minimum, to have equivalent impacts. The lack of control group prevents the comparison of each treatment to a baseline population, but it is promising that the efficacy is similar between psilocybin and escitalopram. The authors report that while the initial trial design included a placebo group, this became too practically complex and expensive. Other limitations of the study include the duration, as escitalopram may require more time to display its full efficacy. Additionally, the patients in the trial were not from varying socioeconomic or ethnic backgrounds, limiting external validity. The study also included many secondary outcomes, including scores on other symptom scales, but these were not considered useful as the data were unadjusted for multiple comparisons.

Further analysis of the study was conducted by Murphy *et al.* regarding the influence of therapeutic alliance. It was found that increased strength of therapeutic alliance led to greater emotional breakthrough and mystical experiences across two PAT sessions^[30]. Interestingly, the ⁵average symptom severity scores at baseline were in the range for moderate depression^[7], highlighting an additional application for psilocybin beyond treatment-resistant depression.

In a patient population with moderate to severe MDD, Davis *et al.*^[31] performed an 8-week intervention consisting of two psilocybin dosing sessions less than two weeks apart with supportive psychotherapy. Exclusion criteria illustrate the reduced the severity of depression within the sample population: selected patients were screened to avoid current antidepressant use, past diagnosis with a psychotic disorder, serious suicide attempts, or prior psychiatric hospitalization. However, enrolled patients required a score of at least 17 on the GRID-Hamilton Depression Rating Scale (GRID-HAMD), the scale used to evaluate outcomes in this study at weeks 1 and 4 post-

1
treatment with psilocybin. A total of 27 patients were selected and randomized into an immediate-treatment group (weeks 1-4, $n = 14$) and delayed-treatment group (weeks 5-8, $n = 12$), which served as a waiting list control condition that later received PATas well. At baseline, the mean GRID-HAMD score was 22.8 with standard deviation (SD) 3.9. Patients receiving immediate treatment showed significant reductions at weeks 1 and 4, with mean scores returning at 8.0 (SD 7.1) during week 1 and 8.5 (SD 5.7) at week 4. Overall, 17 patients demonstrated reductions in GRID-HAMD scores of at least 50%, 14 patients went into remission, and 3 patients dropped out before completing the intervention. Although preliminary, the effect sizes seen with psilocybin in this trial are several times larger than that seen in psychotherapy or antidepressant monotherapy^[31-33].

The efficacy of psilocybin seen in depression studies likely offers benefits in a trauma-centered approach, due to the widespread comorbidity of trauma with depressive disorders. The role of psilocybin continues to expand outside its FDA designation for treatment-resistant depression. Khan *et al.*^[34] reported on an open-label study that provided psilocybin-assisted therapy in traumatized AIDS survivors. The authors noted reductions in PTSD symptoms, attachment anxiety, and demoralization. The intent underlying psychedelic use appears to be important. One survey demonstrated that therapeutic intent behind past psychedelic use in patients with history of child maltreatment showed significant reductions in complex trauma symptoms and internalized shame^[35]. This further suggests that psilocybin's benefits extend beyond depression and into trauma-related pathologies. Though outside the scope of the present article, psilocybin is being explored across several domains including substance use disorders, neurodegenerative diseases such as Alzheimer's disease^[36].

Adverse reactions

In the psilocybin and escitalopram study, the escitalopram group had a higher prevalence of anxiety, dry mouth, sexual dysfunction, and reduced emotional

responsiveness. Due to these side effects, four patients self-discontinued the medication and one patient modified regimen to half a daily dose. No patients in the psilocybin group requested dose adjustment or discontinuation^[7]. In the trial by Davis *et al.*, participants reported mild-to-moderate headache, as well as difficult emotions during in-session time only. No serious adverse events were reported or observed^[31].

MDMA

In 2021, Mitchell *et al.* reported data from a double-blind, phase 3 clinical trial found that 67% of participants receiving MDMA-assisted psychotherapy ceased to meet PTSD criteria after 2 mo.^[16] The MDMA-treated group ($n = 46$) showed significant decreases on Clinician-Administered PTSD Scale for DSM-5 (CAPS-V) compared to inactive placebo with therapy ($n = 44$). Participants attended three experimental sessions, spaced four weeks apart. The first session started with 80 mg MDMA and the option for a supplemental half-dose of 40 mg, 1.5-2.5 h later. For the next two sessions, the initial dose was increased to 120 mg with supplemental half-dose of 60 mg. No tolerability issues led to participants being withheld the supplemental doses.

MDMA-assisted therapy led to increases in posttraumatic growth, encompassing increased positivity towards self-perception, relationships, or philosophy of life^[37]. Scores from 60 participants, pooled from three phase 2 clinical studies meeting PTSD criteria, were assigned to treatment with 75-125 mg MDMA ($n = 45$) or active control (0-40 mg MDMA, $n = 15$). The MDMA group had significantly improved scores on the posttraumatic growth inventory (PTGI) and greater reduction in PTSD symptom severity at 12 mo, and 67% of participants no longer met criteria for PTSD. MDMA may promote adaptive stress responses in PTSD that lead to the downstream benefits seen in recent research, such as reduced ratings of PTSD symptom severity by clinicians^[38-39].

MDMA has also been studied in the setting of couples therapy, in which one partner has a current diagnosis of PTSD. One study included 6 romantic dyads, in which both

partners received MDMA followed by couples' cognitive behavioral therapy. This led to improved happiness and significant reductions across PTSD symptoms, as unanimously rated by patient, partner, and clinician^[40]. Further analysis of this study found enduring improvements in post-traumatic growth, social intimacy, and relational support at 6-month follow up^[41].

These benefits extend to common comorbidities seen in PTSD such as depression^[42], substance use^[43] and sleep disorders^[44], with improvements in Pittsburgh Sleep Quality Index scores that remained significant at one-year follow up. MDMA also shows promise in various other psychopathologies including eating disorders^[45] and end of life anxiety associated with life-threatening illness ^[46], in which patients reported increased ability to cope as they faced illness and existential fears, as well as overall improved quality of life. See Table 1 for a summary of relevant articles discussed in the above psilocybin and MDMA sections.

Adverse reactions

Mitchell *et al.* concluded that MDMA was safe and well-tolerated and note that the treatment did not induce abuse potential, suicidality, or QT prolongation^[16]. Other studies show that risk factors for developing hyperthermia may include adolescent age and increased alcohol consumption^[47-49]. Hyperthermia and rhabdomyolysis are likely context-dependent, occurring at lower frequency when used with therapeutic intent rather than recreational use in the setting of other risk factors^[47, 50]. Likewise, the "come downs" previously associated following MDMA use may be due to research confounds related to environment and drug sourcing, as clinically administered MDMA has noticeably lacked this side effect^[51]. Other reports in the literature include hepatotoxicity that improved with vitamin E^[52], and a case of spinal cord injury suspected to be due to the serotonin surge induced by MDMA, as the vasoconstrictive properties of serotonin may have induced ischemia^[53].

FUTURE DIRECTIONS

Dual therapy

As the evidence for each treatment builds independently, the future may include the integration of both treatments in sequence. In this scenario, MDMA would likely be used first as it has a larger influence on building therapeutic alliance. The augmented therapeutic alliance would allow for a potentially improved psilocybin experience upon switching at next session, aligning with previously discussed research that strong therapeutic alliances are associated with greater mystical experiences and emotional breakthroughs. Treatment with MDMA has been associated with persistent depressive symptoms, and the antidepressant effects of psilocybin may alleviate this following administration^[42]. In a model described by Oehen and Gasser^[54], MDMA tended to be used in the first phase to build the therapeutic alliance and increase the patient's openness to change, leading to enhanced resilience and lowered stress levels. Once further changes were noticed, such as improved self-regulation, less negative self-perception, and increased tolerance to trauma exposure, lysergic acid diethylamide was introduced to assist psychotherapy. The deepening of the therapeutic process led to improvement per clinical judgment, without adverse events.

Standardization

Although variation in research methodology is needed to enrich the literature pool, standardization in several aspects may allow for more informed comparisons between treatment modalities. Symptom rating scales for depression (i.e, QIDS-SR, GRID-HAMD) and PTSD (i.e, CAPS-IV, CAPS-V) varied, with some studies using subjective reports of PTSD diagnostic criteria. Similarly, the therapy modalities that accompanied psychedelic administration were diverse, including uniquely developed forms of therapy as in the Accept-Connect-Embody manualized therapy developed in a psilocybin trial^[7, 30], supportive therapy^[31], and couples' cognitive behavioral therapy^[40]. The future may look more like the manualized MDMA-assisted therapy provided through public benefit corporation Multidisciplinary Association for

Psychedelic Studies (MAPS). MAPS also has an ethics code, a vital addition to future protocols as patients are placed in a state of increased suggestibility and affective instability during and after the treatment^[55]. This critical period requires a trauma-informed approach to care, with support for transgender and gender diverse patients.^[56] Lastly, the method of eliciting adverse drug reactions may benefit from standardization. Studies varied in terms of asking open-ended questions, prompting for specific symptoms, and documenting clinical observations. It is comforting that current studies have not shown any serious adverse events, and future studies may benefit by drawing upon a standardized set of common symptoms.

Wearables

Wearable technology has previously demonstrated efficacy as a bridge between patients and providers in mental health, such as in MDD, dementia, schizophrenia^[57-59]. Wearables are likewise being used in non-psychiatric contexts, including medical monitoring in oncology and gastroenterology^[60-61]. It follows that wearables may have clinical utility in monitoring patient symptoms during and after psychedelic-assisted therapy. Daily functioning, including wearable-derived sleep and activity data, is incorporated in a protocol examining the effects of microdosed psychedelics and may be a useful metric to track long term changes following psychedelic treatment^[62].

CONCLUSION

The literature on PAT using psilocybin or MDMA is strongly supportive across psychiatric conditions, especially trauma and related comorbidities. Both treatments seem to have benefits beyond the FDA breakthrough designations of treatment-resistant depression for psilocybin and PTSD for MDMA. As adjuncts to psychotherapy, psilocybin and MDMA show a pattern of rapid and sustained symptom relief. Future studies may consider the advantages of a standardized approach to symptom rating scales, therapy styles, and assessment of adverse drug reactions. Wearables may also offer additional metrics to examine the long-term trends in activity and sleep. As

clinical trials continue to show positive results, providers and patients become closer to seeing the effects translate to the clinic and the community.

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