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The Emerging Role of Psilocybin and MDMA in the Treatment of Mental Illness

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Abstract

Introduction: Mental illness has a chronic course of illness with a number of clinical manifestations. Affected individuals experience significant functional, emotional, cognitive and/or behavioral impairments. The growing prevalence of mental illness has been associated with significant social and economic costs. Indeed, the economic burden of mental illness is estimated to exceed $1.8 trillion USD over the next 30 years. A significant number of individuals affected by mental illness fail to respond to first-line treatment options. Therefore, there remains an unmet need for rapidly attenuating therapeutic options for mental health disorders with minimal social and economic burden.

Areas covered: The paucity of novel treatment options warrants a renewed investigation of psychedelic-based psychotherapy. Herein, the authors will evaluate the therapeutic potential of traditional psychedelics, psilocybin and MDMA, in the treatment of mental illness with a narrative review of available literature.

Expert opinion: Psychedelics, such as psilocybin and MDMA, offer an alternative avenue of therapy for many mental health disorders. Available evidence indicates that psychedelics may offer a single-dose, rapid effect model that have robust effects with treatment-resistant mental disorders and a unique advantage as a possible monotherapy for mental illness. Novel clinical trials that evaluate the safety, tolerability and efficacy in clinically representative populations are warranted.

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Key words: psilocybin, MDMA, major depressive disorder, anxiety, post-traumatic stress disorder, psychiatric disorders, mood disorders

Article highlights

- There is a significant unmet need for single-dose, rapidly attenuating therapeutic options for mental illness.
- Psychedelics, such as psilocybin and MDMA, may offer an alternative treatment option for mental health disorders.
- Herein, the therapeutic potential of psilocybin and MDMA for the treatment of major depressive disorder, post-traumatic stress disorder and anxiety is evaluated.
- Psilocybin- and MDMA-based psychotherapy options should be explored as a possible monotherapy for mental health disorders.
- Dose-response studies in placebo-controlled settings with a real-world clinical population are required as an important next step.

1. Introduction

Mental illness has many different clinical manifestations and presentations. Generally, any mental health disorder is defined as a mental, emotional or behavioural disorder with impairments observed in a person's thoughts, emotions and/or behaviour [1,2]. Data from the 2017 National Survey on Drug Use and Health (NSDUH) reported 46.1 million Americans were diagnosed with a mental illness and 19.8 million adults received mental health treatment [2]. The growing prevalence of mental illness has been associated with significant social and economic costs. Indeed, the economic burden of mental illness is estimated to exceed over $1.8 trillion USD over the next 30 years [3]. However, current underlying etiology and pathophysiology of many mental illnesses remain unclear. Treatment-resistance and poor treatment responses are prevalent issues for many mental health disorders [4–7]. As such, patients fail to achieve societal and patient-desired outcomes; the need for treatments that improve

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patient-reported outcomes provides the impetus for developing novel treatments that provide multi-dimensional symptom relief.

The paucity of novel treatment options that provide sustained symptom relief and improve quality of life has renewed interest in psychedelic-based psychotherapy for mental illness. Psychedelics have been used for spiritual, religious and healing practices that date back more than 2000 years [8]. The suggestion that psychedelics, such as psilocybin, may be a beneficial treatment for major depressive disorder (MDD), anxiety, and other mental health disorders sparked clinical interest in the 1950s [9]. Psychedelic research continued to grow over a period of nearly 15 years following its emergence in the 1950s. However, following growing health and safety concerns, government restrictions made it increasingly difficult for novel psychedelic psychotherapy trials to develop and influence psychiatric research [10].

A growing appreciation for the therapeutic potential of psychedelic drugs foresaw the re-emergence of psychedelic-based psychotherapy in the 1990s. In particular, the classic psychedelics psilocybin and 3,4-methylenedioxymethamphetamine (MDMA) have offered promising new models for the treatment of mental illness in the 'second wave' of psychedelic research. Psilocybin is a classic psychedelic and a naturally occurring alkaloid that may have antidepressant properties [11,12]. For example, a study by Vollenweider et al. demonstrated psilocybin's ability to induce schizophrenia-like psychosis in humans by way of the serotonin pathway. They highlighted the effects of psilocybin on serotonin-2A receptor activation, independent of the dopaminergic pathway [13]. The effects of psilocybin on the serotonin pathway led researchers to investigate the therapeutic potential of psychedelics in the treatment of other mental

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health disorders, such as MDD [10]. For example, a pilot trial assessing the safety and efficacy of psilocybin in MDD found reduced depressive symptoms one week and three months following psilocybin-based psychotherapy [14]. Importantly, the participants reported no adverse physical or psychological side effects.

Similarly, MDMA, the active component of ecstasy, was synthesized at the beginning of the 20th century; the effects of MDMA were discovered later on as euphoric and stimulatory. MDMA, an amphetamine derivative, is a complex drug with significant effects on a wide range of neurotransmitters, with profound effects on the serotonergic system, specifically the 5-HTT and SERT serotonin transporters [15]. The first trial of MDMA as a psychotomimetic in humans was completed in 1978 [16]. Later in 1986, a placebo-controlled trial found that MDMA presented positive effects on treating anxiety, post-traumatic stress disorder (PTSD), and other psychiatric disorders with few reported adverse effects [17]. Extant findings from clinical and preclinical trials suggest MDMA psychotherapy-induced mood changes are mediated by 5-HT_2 receptors and transcriptional activity of the serotonin transporter gene (*SLC6A4*) [18–20]. However, the connection between MDMA use, serotonergic receptor activation, and mood affect in psychiatric populations remains unclear.

Growing evidence indicates the possibility of implementing psilocybin- and MDMA-based psychotherapy for the treatment of psychiatric disorders. However, there is a paucity of clinical research assessing the tolerability and efficacy of psilocybin and MDMA in psychiatric disorders and the potential mechanisms responsible for the observed effects remain largely unclear. Herein, we will review the extant literature of

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psilocybin- and MDMA-based psychotherapy for the treatment of psychiatric disorders, as well as potential avenues for future research.

2. Proposed mechanisms of action in mental illness

2.1 Mechanism of action for psilocybin

Psilocybin, a naturally occurring alkaloid, has been classified, along with its active metabolite psilocin, as a tryptamine. When ingested, psilocybin is metabolised by intestinal alkaline phosphatases and esterases, which rapidly dephosphorylate the alkaloid into psilocin [21]. The putative target of psilocin and psilocybin is the agonism of the $5HT_2$ receptor class; however, studies have confirmed that there is also affinity for $5HT_1$, $5HT_4$, $5HT_5$, $5HT_6$, $5HT_7$, D1, and D3 receptors [22,23].

Psilocybin- and psilocin-mediated effects on serotonergic and glutamatergic neurons are believed to produce antidepressant and anxiolytic responses in humans. Converging lines of evidence suggest that $5HT_2$ receptor activation leads to neuroplastic changes that desensitize and downregulate the receptor density, which may exert antidepressant and anxiolytic effects [24–26]. For example, a $5HT_{2A}$ receptor knockout rat model exhibited decreased anxiety- and depression-like behaviours [27]. Moreover, when the receptor signaling was rescued, the anxiety behaviours were normalized, suggesting that the $5HT_{2A}$ receptor mediates a critical role in anxiety and depression pathophysiology [27]. It has been further postulated that $5HT_{2A}$ receptor agonism increases extracellular glutamatergic concentrations in the prefrontal cortex [28,29]. Subsequent glutamatergic modulation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors on cortical pyramidal cells exerts downstream upregulation of neurotrophin (i.e., brain

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derived neurotrophic factor) expression [30]. Other medications that modulate the glutamatergic system, such as ketamine, have robust efficacy in reducing depressive symptomatology, including but not limited to suicidal ideation [31]. Indeed, positron emission tomography studies with ^{18}flurodeoxyglucose suggest that S-ketamine and psilocybin affect similar prefrontal and limbic networks [28]. However, further research is needed to investigate the potential therapeutic effects of psilocybin in other mental illnesses (i.e., PTSD) [32]. Similarly, dose-response studies in placebo-controlled settings with a real-world clinical population are required. For example, a recent meta-analysis of psilocybin clinical trials observed that many studies were proof-of-concept open-label trials with a limited sample size, thus underscoring the need for additional randomized, double-blind placebo controlled trials that evaluate the safety, tolerability and efficacy of psychedelics in real-world clinical settings [33,34].

2.2 Mechanism of action for MDMA

The methamphetamine derivative, MDMA, is structurally different from amphetamine and methamphetamine due to the addition of a methylenedioxy (-O-CH_2-O-) group to the aromatic ring. Notably, MDMA is a metabolically active molecule which is readily absorbed by intestinal mucosa, producing sympathomimetic effects, and crosses the blood-brain barrier [35]. Given its rapid absorption rate, the peak plasma concentration is reached within 2-3 hours, allowing for rapid onset effects which remain a significant unmet need in the treatment of psychiatric disorders [36].

The principal mechanism of action of MDMA in treating mental illness is through reuptake inhibition of the monoamines (i.e., serotonin, norepinephrine, and dopamine) [36]. MDMA has the highest affinity for serotonin reuptake transporter (SERT), as its

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affinity for the norepinephrine and dopamine transporters are eight-fold less [37]. It is therefore hypothesized that MDMA may exhibit similar effects as the antidepressant selective serotonin reuptake inhibitor (SSRI) drug class by increasing functionally available cerebral serotonin (5-hydroxytryptamine, 5-HT) [38]. Indeed, Liechti and Vollenweider reported that co-administration of MDMA with the SSRI citalopram led to significantly attenuated cardiovascular responses suggesting competition for serotonin-binding sites [39]. However, current trials with MDMA have been limited to proof-of-concept studies with a small sample size [40].

3. Safety and tolerability

3.1 Safety and tolerability of psilocybin

Numerous studies have investigated the safety and tolerability of psilocybin. In an open-label feasibility study by Carhart-Harris et al. (2016), 12 patients with moderate to severe TRD reported no serious adverse effects. Transient adverse effects experienced include anxiety during drug onset (n=12), confusion or thought disorder (n=9), and mild nausea (n=4) [14]. Other common short term adverse effects include tiredness, headaches, paranoia, and non-clinically severe increase in blood pressure and heart rate [14,41–43]. Psychological effects include perceptual changes, such as visual distortions, synesthesia across sensory modalities, and intensified emotions. Individuals may also experience cognitive changes, including altered perception of time, altered sense of self, and an increased introspective focus [44].

Moreover, studies investigating the abuse potential of psilocybin report no cases of physical dependence or withdrawal. There have been no documented adverse effects following discontinuation of the drug [45–47]. Psilocybin is also low in chronic

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toxicity, and moderate in acute toxicity. Thus, it carries little risk of overdose toxicity due to cardiovascular events or respiratory depression. However, despite the low risk of addiction and dependence, there remains a potential for abuse due to potential dose-dependent adverse effects. These effects include panic reactions, and long lasting psychiatric conditions or visual perceptual disturbances [44]. As such, psilocybin should be administered under controlled clinical conditions only and further investigation regarding the safety and tolerability profile of psilocybin in specific subpopulations (i.e., TRD patients) is highly recommended.

3.2 Safety and tolerability of MDMA

The safety and tolerability of MDMA-based psychotherapy in clinical trials has been previously investigated [48,49]. For example, Mithoefer et al. (2011) found loss of appetite, nausea and dizziness were among the most common reported side effects. Following a week of treatment, loss of appetite and irritability were the most common reported side effects in the MDMA group [48]. However, there were no serious drug related neurocognitive effects. It should be noted, however, that growing evidence suggests that MDMA administration can lead to marked cerebrospinal serotonin depletion and lower SERT expression [36,50,51]. Preclinical data suggest an association between MDMA use and structural damage to serotonin neuronal axons and synaptic terminals [52,53]. In addition, without careful monitoring, the drug's sympathomimetic effects may portend cardiac arrhythmia, malignant hypertension, or risk of hemorrhage [54]. Taken together, MDMA may attenuate depressive and PTSD symptomatology via modulation of the monoamine system. However, studies need to carefully consider the drug's therapeutic index and safety profile.

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Moreover, recreational use of MDMA is associated with hyper-activation of the sympathomimetic system [55]. Hyperactivity, hyperthermia, heightened heart-rate, increased blood pressure and trismus are common side-effects associated with the recreational use of MDMA [56,57]. Furthermore, a placebo-controlled trial illustrated that MDMA may cause a significant increase in body temperature [58]. According to epidemiological data, deaths following MDMA use were more common than deaths following amphetamine/methamphetamine [59]. Euphoria and elevated mood states are some of the most common acute mood effects produced by MDMA use [57,60,61]. However, MDMA may also heighten negative emotional states [62,63]. External influences and internal expectations can affect the patterns of mood experienced when taking MDMA [64]. As such, the safety and tolerability profile of MDMA requires careful attention and monitoring and should only be administered in a closed clinical setting.

4. Major depressive disorder

Major depressive disorder is a major cause of morbidity and mortality around the world. It has a chronic course of illness, with up to 50% of patients reporting recurrent depressive episodes [65]. Currently, SSRIs and serotonin and NE reuptake inhibitors (SNRIs) are first-line treatment options for MDD [66]. However, approximately 50% of patients fail to respond to the first-line treatment options [67]. Poor response to first-line antidepressant options often leads to patient frustration and poor patient reported outcomes [68]. This provides the impetus for alternative treatment options that help decrease the economic and social burden associated with failed MDD therapy.

4.1 MDMA-assisted therapy for the treatment of major depressive disorder

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The postulate for MDMA therapy for the treatment of depression is based on the monoamine hypothesis for depression [69]. MDMA commonly exerts its effects on the serotonergic system, similar to the action of many commonly prescribed antidepressants. Preclinical trials have demonstrated potential antidepressive effects of MDMA-based therapy [70]. Meanwhile, early clinical trials have focused on the effects of recreational MDMA use on depressive symptomatology. Win et al. assessed the short- and long-term impacts (the criteria for short- and long-term use was not specified) of MDMA on mood using a sample of moderate, heavy, and former heavy MDMA users. In addition, the interaction between changes in mood due to MDMA and dose, gender, and 5-HT neurotoxicity were explored. While the prevalence of mood disorders was not significantly different between groups, when compared to MDMA-naïve controls, former heavy MDMA users reported significantly higher scores on the Beck Depression Inventory (BDI; p=.045). A higher BDI score indicates an increased severity of depression symptoms. There were no significant associations between mood and 5-HT neurotoxicity or gender [71].

A separate randomized-control trial investigated the role of regular MDMA use on self-reported depression and associated help-seeking behaviour. Twenty-three percent of MDMA users (n=200) reported depressive symptoms preceding a six-month follow-up interview and a significant positive correlation was determined between Center for Epidemiological Studies Depression Scale (CES-D) scores and Kessler Psychological Distress Scale (K10) scores ($r = 0.812$, $p < 0.01$). Therefore, MDMA-related drug use was associated with greater prevalence of depressive symptoms (23%) than the general population [72]. In contrast, Majumder et al. evaluated the antidepressant

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effects of MDMA in participants predisposed to depression, as determined by the Brief Symptom Inventory (BSI). Participants taking MDMA reported a significant reduction in depressive symptoms compared to the drug-free group (p=.596) [73]. Further research is required to assess the sustainability of antidepressant effects as depressive symptoms may return after acute antidepressant effects diminish [74].

The promising results from early preclinical and clinical trials investigating the effects of recreational ecstasy use have provided the impetus for MDMA-based psychotherapy for the treatment of MDD. Future trials are required to evaluate the tolerability, efficacy, and dose-response of MDMA-assisted psychotherapy for the treatment of MDD.

4.2 Psilocybin-assisted psychotherapy for the treatment of major depressive disorder

Historically, psilocybin has been used in preliminary trials in the 1950s to 1970s in conjunction with lysergic acid diethylamide (LSD) to assess their therapeutic potential in psychiatric disorders [75]. As a non-selective serotonin 2A receptor (5-HT_{2AR}) agonist, psilocybin's potential for use in psychiatric treatment lies in its ability to modulate these receptors, as the downregulation of 5-HT_{2A} receptors produces antidepressant and anxiolytic effects, which are evident in more commonly used antidepressants and atypical antipsychotics [76]. Extant literature investigating the use of psychedelic drugs such as psilocybin focuses on the delivery of these drugs under controlled and optimal conditions in order to produce therapeutic effects. These studies hope to harness the psychospiritual experiences that may be induced by drugs such as psilocybin and direct them into therapeutic experiences for individuals with disorders that may be difficult to

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treat [75,76]. The proposed mechanism of action for psilocybin in mitigating depressive symptomatology is highlighted in **Figure 1**.

As such, Carhart-Haris et al. assessed the feasibility, efficacy, and safety of psilocybin in a sample of 12 participants with unipolar TRD. Participants received 10 mg and 25 mg of psilocybin seven days apart. Results indicated that psychedelic effects peaked two to three hours following dosing and subsided after six hours. Depressive symptoms were reduced significantly one week following treatment (p= .002). Improvements in anxiety and anhedonia were also observed [14]. Similarly, Roseman et al. reported significant improvements in Quick Inventory of Depressive Symptoms (QIDS-SR16) scores following two therapy sessions where participants were administered 10 mg and 25 mg of psilocybin, respectively (n=20) [77]

In a follow-up neuroimaging trial, Carthart-Harris et al. investigated the physiological response invoked by psilocybin when used to treat individuals with TRD. The findings demonstrated that a decrease in cerebral blood flow to the amygdala correlated with a reduction in depressed mood in patients who were resistant to standard treatments [75]. A *post-hoc* analysis of psilocybin treatment indicated that a 'mystical' experience during a high-dose psilocybin session was predictive of treatment response, further supporting the notion that psilocybin-assisted psychotherapy may effectively improve depressive symptomatology in individuals who have not responded to more traditional forms of therapy [75]. Therefore, early clinical and neuroimaging trials underscore the potential therapeutic use of psilocybin in patients with chronic or TRD.

5. Anxiety disorders

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Anxiety disorders are common and debilitating conditions that are highly comorbid with MDD. An estimated 41.6% of individuals with MDD report a comorbid anxiety disorder [78]. Individuals with anxiety disorders report significant functional impairments across many social domains (i.e., work, school, and social life) [79]. The relevance of anxiety disorders in the mood disorder population is highlighted by increased suicidality and poor psychosocial outcomes [4,80]. As such, this underscores the importance of addressing symptoms of anxiety in comorbid mood disorder populations.

5.1 Psilocybin-assisted psychotherapy for the treatment of anxiety disorders

There are few studies that have assessed the tolerability and efficacy of psilocybin-assisted psychotherapy for comorbid anxiety disorders. One double-blind, placebo-controlled pilot study assessed the efficacy of psilocybin treatment for anxiety in advanced-stage cancer patients (n=12). There were significant improvements in trait anxiety at three months (p= .03) and depressive symptoms after six months (p= .03) following a moderate dose of psilocybin (0.2 mg/kg) [41]. A separate study by Ross et al. assessed psilocybin treatment for anxiety and depression in 29 participants. Participants reported sustained antidepressant and anxiolytic effects six and a half months following 0.3mg/kg psilocybin-assisted psychotherapy [42]. Therefore, early findings from clinical trials suggest psilocybin-based psychotherapy may also induce anxiolytic effects. Future studies should expand on these findings in real-world clinical settings with anxiety as a primary outcome measure.

6. Post-traumatic stress disorder

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Post-traumatic stress disorder is a disabling mental disorder that results from exposure to a traumatic event and is highly comorbid with other psychiatric disorders such as MDD and anxiety disorders [7,81]. According to the US National Comorbidity Survey Replication (NCS-R), 3.6% of American adults reported PTSD in the previous year and 6.8% reported a life-time prevalence of PTSD [82]. There are high rates of treatment drop out and poor treatment response. As such, treatment resistance is high among PTSD patients [83]. Consequently, the need for adjunct psychotherapy to alleviate many of the core features of PTSD (i.e., hypervigilance, fear, avoidance, and affective dysregulation) is an important unmet need.

6.1 MDMA assisted-psychotherapy for the treatment of PTSD

The psychopharmacological profile of MDMA offers promise as a potential adjunct therapy for PTSD [84,85]. The effects of MDMA (i.e., euphoria and heightened social interaction) may reduce fear and awareness of traumatic memories [86,87]. A pilot trial evaluating the safety and efficacy of MDMA therapy in PTSD populations reported significant improvements in PTSD symptoms (p= .015) with no serious adverse effects [48]. In a follow-up study, Mithoefer et al. demonstrated that MDMA-assisted psychotherapy provided persistent symptomatic relief for chronic, treatment-resistant PTSD. They observed no statistically significant difference in the mean Clinician-Administered PTSD Scale (CAPS) score when comparing results from study completion and in a long-term follow-up (p = .91). Therefore, participants maintained statistically significant symptomatic relief [88]. Similarly, Ot'alora et al. assessed MDMA treatment with psychotherapy in 28 individuals with chronic PTSD. In this double-blind clinical trial, the participants received either two active doses of MDMA (100 and 125 mg) or one low

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dose of MDMA (40 mg) during an eight hour psychotherapy session. The MDMA treatment reduced PTSD symptoms significantly. Participants receiving an active dose of 125 mg of MDMA showed the greatest reduction in PTSD symptoms ($p=0.03$). In a 12-month follow-up, PTSD symptoms remained lower than baseline values ($p<0.001$) [89].

Moreover, a double-blind clinical trial evaluated the safety and efficacy of varying doses of MDMA in a sample of six women with treatment-resistant PTSD. Two participants were randomly assigned to receive placebo, three received 50mg of MDMA, while one received 75mg. Psychological and physiological safety was demonstrated with both 50 mg and 75 mg doses of MDMA. The subject receiving 75 mg performed better on outcome measures compared to the 50 mg group, while the 50 mg group outperformed the control group. Due to the small sample size, between-group statistical analysis was not possible [90]. Furthermore, in a dose-response phase two clinical trial, veterans and first responders diagnosed with PTSD received 30 mg (n=7), 75 mg (n=7), or 125 mg (n=12) of MDMA-assisted psychotherapy. One month following treatment, the 75mg and 125mg groups (n=19) reported significant reduction in PTSD symptoms ($p= .001$). These improvements were sustained after a 12-month follow-up assessment [91]. In the latest series of clinical trials, Gorman et al. assessed the effects of MDMA-assisted psychotherapy on PTSD and posttraumatic growth (PTG) using active (75-125mg, n=45) and control doses (0-49mg, n=15) of MDMA. The largest improvement was observed in the active MDMA group ($p<0.001$). Moreover, after unblinding, participants that received 0-75 mg doses of MDMA were randomized to receive three open-label psychotherapy sessions with 100-125 mg of MDMA. A 12-

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month follow-up of participants that received at least one active dose of MDMA (n=57) revealed significant reductions in PTG and PTSD symptoms (both $p<0.001$) [92]. Therefore, early randomized placebo-controlled clinical trials indicate effective and significant improvements in PTSD symptoms following MDMA-assisted psychotherapy.

7. Expert opinion

Despite the recent interest in MDMA for the treatment of PTSD, there remains a lack of research regarding other comorbid psychiatric conditions. For example, research regarding the effects of MDMA on cognition is mainly limited to samples of healthy individuals. Several studies have shown pro-cognitive effects of MDMA therapy including improved mood and social connectedness, increased emotional sensitivity, responsiveness, and heightened openness [93,94]). However, some studies also demonstrate anti-cognitive effects of MDMA in samples of healthy individuals. For example, Croft et al. (2001) examined the relationship between cannabis and MDMA in cognitive impairment. Participants that were cannabis but not MDMA users (n=18), and participants who used both MDMA and cannabis (n=11) were compared to a control group of participants who used neither drug (n=31) [95]. A battery of neuropsychological tests indicated that the MDMA/cannabis and cannabis-only groups did not differ in results. However, both experimental groups performed poorly when compared to the control group in tests of manual dexterity, word fluency, learning, speed of processing, and memory. While most cognitive factors correlated more strongly with cannabis use, reduced speed of processing was predicted by higher MDMA use [95]. Furthermore, Krystal et al. assessed MDMA users for impairments in cognition and depressive

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symptomatology (n=9). Mild to moderate cognitive impairments were observed. In particular, MDMA use was associated with impairments in memory and attention ($0.05<p<0.1$) [96]. In a developmental comparison of the neurobehavioural effects of MDMA, Piper (2007) noted that MDMA is consistently found to have sustained behavioural consequences, including deficits in learning and memory. Forebrain structures are particularly sensitive to MDMA, and changes in the serotonin system in these regions promote such deficits [97]. This highlights the need for research further elucidating the relationship between cognition and MDMA in individuals with mental illness.

Similarly, obsessive compulsive disorder (OCD) is highly comorbid with both anxiety and depression and has a lifetime prevalence of 2.5%. Serotonin is believed to play a role in the manifestation of OCD symptoms, and the regulation of 5-HT may be effective in reducing obsessive ideation and behaviour [98]. Thus, psilocybin's serotonergic properties indicate its potential therapeutic use in OCD patients. For example, Moreno et al. (2006) assessed the safety tolerability and efficacy of psilocybin in OCD patients (n=9) in a single arm, within-subject, variable dose study. All participants reported improvements within 24 hours (p=.046). However, there was no correlation between psilocybin dose and symptom improvement [99]. Therefore, early single-dose findings underscore the potential application of psilocybin for OCD patients. However, studies with repeat-dose and larger real-world clinical samples are required to translate preliminary findings into a clinically viable option.

Moreover, predicting treatment response remains one of the primary challenges for psychiatric disorders. Kuypers et al. assessed the role of 5-HTTLPR polymorphism

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in modulating MDMA-induced mood effects and found that participants homozygous for the *l*-allele demonstrated increased ratings of anxiety, independent of sex or treatment condition. They also found that the effects of MDMA in reducing depressive feelings depend on sex and genotype [100]. In particular, females homozygous for the *l*-allele demonstrated reduced depressive mood ratings. However, it is important to note that the effect size of this interaction was small (p= .02), and the sample size of females homozygous for the *l*-allele was less than 10 [100]. Therefore, there is a need for future research examining the modulating factors that influence subjective experiences in response to MDMA and psilocybin for the treatment of psychiatric disorders.

Furthermore, psychedelics offer a unique advantage as a possible monotherapy for TRD. Antidepressant prescription has increased 5% in the past decade and 25% of individuals continue to rely on antidepressant medications for a decade or more [101]. As such, many depressed individuals struggle with daily prescription of pills that contribute to poor quality of life outcomes. Indeed, 42% of patients discontinue antidepressant treatment within the first 30 days and 72% of patients discontinue taking antidepressants within the first three months.

While other treatments are typically used to augment current antidepressant prescriptions, psychedelics (i.e., psilocybin) offer a one-dose treatment option [102,103]. Therefore, future research should continue the renewed focus on single-dose monotherapy options for the treatment of mood disorders and other mental health disorders. The development of psychedelic research in psychiatry has offered a novel avenue of potential treatment options that are worth exploring [104]. A summary of

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active and/or currently recruiting trials evaluating the efficacy of MDMA/psilocybin-based treatment in mental illness is provided in **Table 3.**

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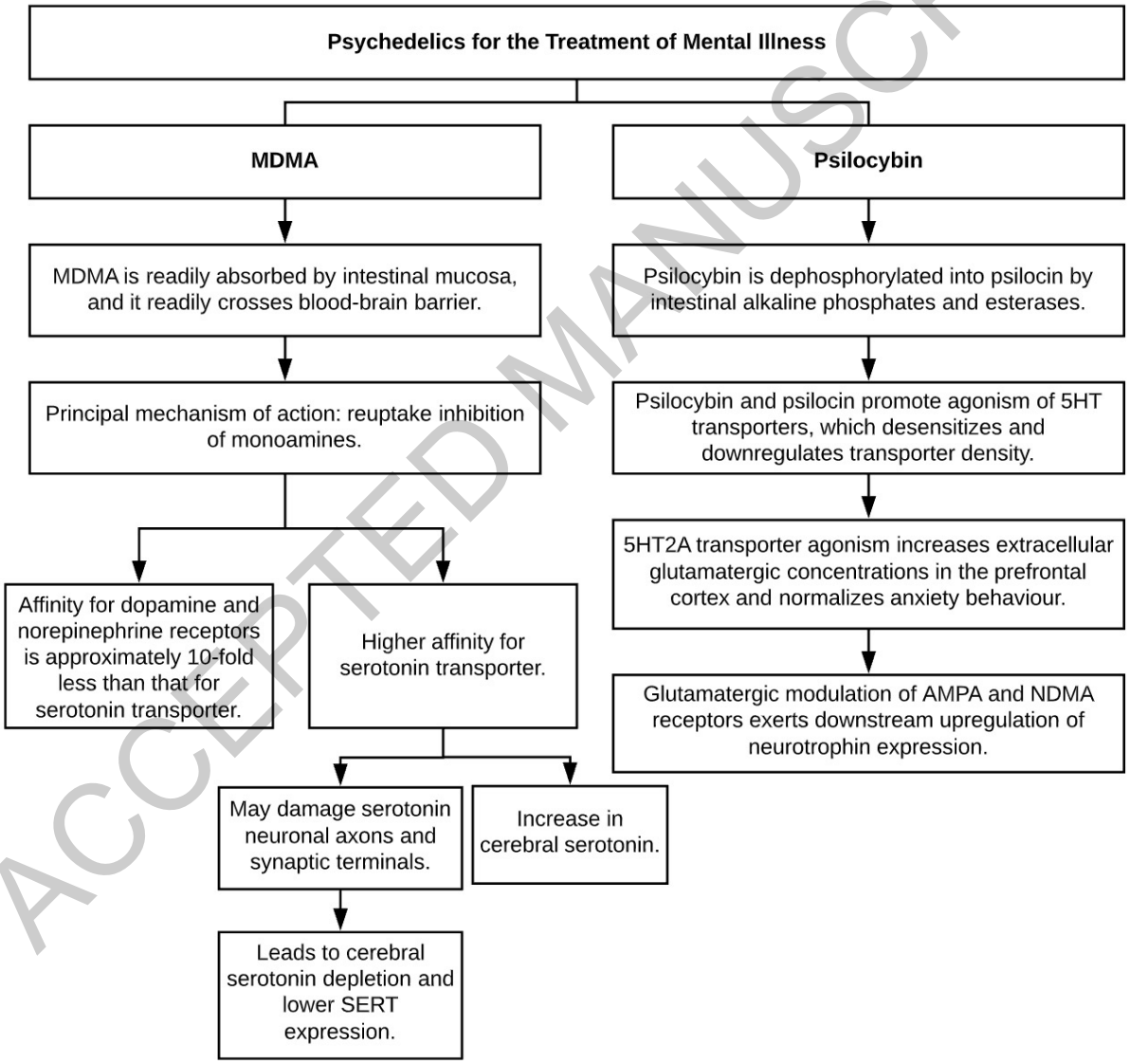

Figure 1: Proposed mechanism of action for Psilocybin and MDMA in the treatment of mental illness

Table 1: Table illustrating the characteristics of studies evaluating the effects of psilocybin and MDMA in psychiatric populations

Source	Sample Size	Gender (No. %)	Mean Age (SD)	Psilocybin or MDMA	Mental Illness	Psychiatric Assessment	Study Design
Carhart-Harris et al., 2016 [14]	12	F: 50%; M: 50%	42.7	Psilocybin	TRD	21-item HAM-D, MADRS, 16-item QIDS, BDI	Open-label feasibility study; no control
Matthews and Bruno, 2010 [53]	100	F: 46% M: 54%	23	MDMA	Depression	CES-D	RCT
Grob et al., 2011 [62]	12	F: 83%, M: 17%	40.2	Psilocybin	Depression and anxiety	BDI, STAI	Double-blind, placebo controlled RCT
Mithoefer et al., 2011 [71]	12	F: 85%, M: 15%	40.2	MDMA	PTSD	CAPS	Double-blind RCT
Mithoefer et al., 2013 [72]	19	F: 84.2%, M: 15.8%	41.01	MDMA	PTSD	CAPS	Double-blind, crossover study

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Oehen et al., 2013 [68]	12	F: 83.3% M:16.7 %	41.4 (11.2)	MDMA	PTSD	CAPS	RCT
Win et al., 2004 [52]	38			MDMA	Depression	BDI	RCT
Krystal et al., 1992 [80]	9	F: 22.2%, M: 77.8%	34 ± 7	MDMA	Depression	Hamilton depression scale, BDI	RCT
Gorman et al., 2020 [76]	60	F=48% M=52%		MDMA	PTSD	PTGI, CAPS-IV	RCT
Moreno et al., 2006 [83]	9	F=22.2 % M=78.8 %	40.9	Psilocybin	OCD	DSM-IV	Double-blinded RCT
Bouso et al., 2008 [74]	6	F=100% M=0%	29-49	MDMA	PTSD	CAPS	RCT
Ot'alora et al., 2018 [73]	28	F: 67.9%, M:32.1 %	42	MDMA	PTSD	BDI-II	RCT
Roseman et al., 2017 [58]	20	F: 30% M: 70%	44.1	Psilocybin	TRD	QIDS-SR16, BDI, HAM-D, SHAPS	Open-label clinical trial
Mithoefer et al., 2018 [75]	26	F: 27% M: 73%	37.2 (10.3)	MDMA	PTSD	CAPS-IV	Randomized, double-blind, dose response trial
Ross et al., 2016 [63]	29	F: 62.1% M: 37.9%	56.28	Psilocybin	Anxiety, depression	HADS, BDI	Randomized, double-blind, placebo-controlled crossover trial

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Majumder et al., 2012 [54]	20	F: 65% M: 35%	18.5 (0.4)	MDMA	Depression	BDI	RCT
Carhart-Harris et al., 2017 [56]	16	F: 25% M: 75%	42.8	Psilocybin	TRD	QIDS-SR16	Open-label clinical trial (no control)

Abbreviations: M=male, F=female, SD=standard deviation, TRD=treatment resistant depression, RCT=randomized control trial, CAPS=clinically administered-PTSD scale, QIDS-SR16=quick inventory of depressive symptomatology (self-report) (16-item), BDI-II=Beck depression inventory-II, HADS=hospital anxiety and depression scale, MADRS= Montgomery–Åsberg Depression Rating Scale, HAM-D=Hamilton depression rating scale, SHAPS=Snaith-Hamilton pleasure scale, PTGI=Posttraumatic Growth Inventory

Table 2: Table illustrating study outcomes and findings for the effects of psilocybin and MDMA on mental illness.

Source	Study Outcomes	Primary Findings
Carhart-Harris et al., 2016 [14]	The feasibility, efficacy and safety of psilocybin assessed in unipolar TRD participants. Participants received 10mg and 25mg of psilocybin 7 days apart.	Psychedelic effects peaked two-three hours following dosing and subsided after six hours. Depressive symptoms significantly reduced one week following treatments. Similarly, improvements observed in anxiety and anhedonia.
Matthews and Bruno, 2010 [53]	The incidence of self-reported depression and help seeking was assessed in a sample of 100 regular ecstasy users.	23% of participants reported recent experience of depression, while one-third of these participants consulted a health professional about their depression.

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Grob et al., 2011 [62]	The efficacy and safety of 0.2mg/kg of psilocybin in patients with reactive anxiety and advanced-stage cancer.	No clinically significant adverse effects were reported after psilocybin use. Significant reductions in anxiety were observed one, three, and six months following treatment with psilocybin.
Mithoefer et al., 2011 [71]	Evaluating therapeutic efficacy of MDMA in 20 participants with chronic PTSD. Twelve participants received MDMA intervention and eight were allocated to placebo non-drug therapy.	Significantly greater improvements in PTSD scores observed in MDMA group compared to controls at all time points. No adverse events were reported for the MDMA therapy group.
Mithoefer et al., 2013 [72]	Evaluating the long-term tolerability and efficacy of MDMA in PTSD patients. Follow-up clinical trial with 16 of 20 original participants completing a long-term follow-up.	Majority of participants maintained statistically-significant favourable long-term improvements in PTSD symptoms. Two subjects reported relapse. No participants reported adverse effects from their participation in the study.
Oehen et al., 2013 [68]	Evaluating the safety and efficacy of MDMA-assisted psychotherapy in 12 PTSD patients. Patients were administered either low-dose (25mg) or high-dose (125mg) MDMA.	No adverse effects were reported following therapy. No significant reductions in CAPS score were observed after initial assessment. However, they improved after 1 year and three treatment sessions were more effective than two.
Win et al., 2004 [52]	The short and long term effects of MDMA on mood, and its association with dose, gender, and 5-HT neurotoxicity in samples of moderate, heavy, and former heavy ecstasy users compared to ecstasy-naive controls.	According to the CIDI, prevalence of mood disorders was not significantly different between groups. BDI scores were higher in former heavy ecstasy users, compared to ecstasy-naive controls (P=0.045). There were no significant associations between BDI or CIDI scores and 5-HT transporter density or gender.
Krystal et al., 1992 [80]	Nine MDMA users were assessed for impairments in cognition and depressive symptomatology.	Mild to moderate impairments in cognition (memory and attention assessed by WMS) were associated with MDMA use. There was an absence of clinical depression present in this sample.
Gorman et al., 2020 [76]	The effects of MDMA assisted psychotherapy on PTG in PTSD patients. Participants meeting criteria for PTSD were assessed for PTG and symptom reduction.	After a 12-month follow-up, there were significant PTSD symptom reduction and PTG in the MDMA group compared to active controls. Two thirds of participants no longer met criteria for PTSD.
Moreno et al., 2006 [83]	The safety, tolerability, and clinical efficacy of up to four single doses of psilocybin was assessed in nine participants with OCD. The doses ranged from sub-hallucinogenic to frankly hallucinogenic.	Psilocybin was associated with transient symptomatic reduction of OCD symptoms in subjects with treatment-resistant OCD. There was no significant effect of dose, or interaction of time and dose.

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Bouso et al., 2008 [74]	Evaluate the efficacy of varying doses of MDMA in a sample of six women with treatment-resistant PTSD.	Psychological and physiological safety was demonstrated by low doses of MDMA between 50 and 75mg.
Ot'alora et al., 2018 [73]	Evaluate the safety and efficacy of MDMA-assisted psychotherapy in a sample of 28 participants with PTSD using two active doses (100mg and 125mg) and one low dose (40mg) of MDMA.	The active groups demonstrated the largest reduction in CAPS-IV score. 12 months following baseline measures, PTSD symptoms remained below baseline with 76% of participants failing to meet PTSD criteria.
Roseman et al., 2017 [58]	Assess the therapeutic efficacy of psilocybin in a sample of 20 participants with TRD.	High OBN and low DED indicated the clinical efficacy of psilocybin in TRD.
Mithoefer et al., 2018 [75]	A randomised, double-blind phase two trial evaluating the dose response of 30mg, 75mg, and 125mg of MDMA-assisted psychotherapy in 26 veterans and first-responders	Participants receiving 75mg (n=7) and 125mg (n=12) of MDMA reported significant improvements in PTSD symptoms after 1 month. These improvements were sustained after a 12-month follow-up assessment.
Ross et al., 2016 [63]	Assess the effects of 0.3mg/kg of psilocybin on a sample of 29 patients with cancer-related anxiety and depression.	Participants receiving psilocybin demonstrated significant and sustained improvements in anxiety and depression. 6.5 months following treatment, 60-80% of participants continued demonstrating clinically significant reductions in anxiety and depression.
Majumder et al., 2012 [54]	Evaluate the effects of MDMA in ecstasy users that are predisposed to depression.	Individuals predisposed to depression reported significant reduction of depressive symptoms when under the influence of MDMA compared to when drug-free.
Carhart-Harris et al., 2017 [56]	Assess the relationship between decreases in depressive symptoms following treatment with psilocybin and functional neuroimaging data in a sample of nineteen patients with TRD.	All participants demonstrated reduced depressive symptomatology one week post-treatment, while 47% met response criteria five weeks post-treatment. Whole brain analysis revealed reduced CBF in the amygdala. Increased vmPFC-ilPC RSFC was predictive of treatment response at five weeks.

Abbreviations: PTSD= post-traumatic stress disorder; WMS=Wechsler Memory scale, CIDI=composite international diagnostic interview, PTG= posttraumatic growth, TRD=treatment resistant depression, OBN=Oceanic Boundlessness, DED=dread of ego dissolution, CBF=cerebral blood flow, vmPFC-ilPC=ventromedial prefrontal cortex-

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bilateral inferior lateral parietal cortex, RSFC=resting state functional connectivity; CAPS= The Clinician-Administered PTSD Scale

Table 3: Table illustrating the characteristics of active and/or recruiting clinical trials evaluating the effects of psilocybin and MDMA in psychiatric populations

NCT Number	Estimated/ Completed Enrollment	Psilocybin or MDMA	Mental Illness	Primary Outcome Measure	Study Design
NCT04030169	40	MDMA	PTSD	CAPS-5	Open-label Phase 3 RCT
NCT03752918	20	MDMA	PTSD	CAPS-5	Double-blind placebo-controlled RCT
NCT03554174	18	Psilocybin	MDD	EEG	Double-blind placebo-controlled RCT
NCT03537014	100	MDMA	PTSD	CAPS-5	Double-blind placebo-controlled RCT
NCT03866174	80	Psilocybin	Depression	MADRS	Double-blind placebo-controlled RCT
NCT04264026	10	MDMA	PTSD	CAPS-5	Open-label phase 2 clinical trial
NCT04077437	100	MDMA	PTSD	CAPS-5	Double-blind placebo-controlled RCT

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NCT04123314	20	Psilocybin	Depression	CSDD	Open-label clinical trial
NCT03300947	15	Psilocybin	OCD	Y-BOCS	Double-blind, placebo-controlled RCT
NCT03429075	59	Psilocybin	MDD	fMRI	Double-blind, placebo-controlled RCT
NCT03356483	30	Psilocybin	OCD	Y-BOCS	Double-blind, placebo-controlled RCT
NCT03380442	60	Psilocybin	MDD	MADRS, HDRS	Double-blind, placebo-controlled RCT
NCT03181529	24	Psilocybin	MDD	GRID-HAMD	RCT
NCT03715127	60	Psilocybin	MDD	MADRS, BDI	Double-blind, placebo-controlled RCT
NCT03775200	216	Psilocybin	TRD	MADRS	RCT
NCT04353921	80	Psilocybin	Depression	MADRS	Observational
NCT04353921	80	Psilocybin	Depression	MADRS	Observational

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Abbreviations: RCT=randomized control trial, TRD=treatment resistant depression, EEG= Electroencephalography, fMRI= Functional magnetic resonance imaging, CAPS=clinically administered-PTSD scale, BDI=Beck depression inventory, HAM-

D=Hamilton depression rating scale, MADRS= Montgomery–Åsberg Depression Rating Scale, HDRS= Hamilton Depression Rating Scale, Y-BCOS= Yale-Brown Obsessive Compulsive Scale, CSDD= Cornell Scale for Depression in Dementia, LSAS= Liebowitz Social Anxiety Scale

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