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# Psychedelics for post-traumatic stress disorder: A systematic review and meta-analysis

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***ABSTRACT:***

***Objective:*** *Post-Traumatic Stress Disorder (PTSD) is a devastating psychiatric illness with few effective pharmacologic treatment options. Recently, psychedelic and hallucinogenic drugs have been explored as treatments in conjunction with psychotherapy. The objective of this systematic review and meta-analysis was to examine the efficacy of psychedelic drugs for the treatment of PTSD. methylene dioxymethamphet amine (MDMA), ketamine, lysergic acid diethylamide (LSD), or psilocybin, and with clearly presented clinician-administered PSTD scale (CAPS) pre and post treatment. To find these studies, literature searches in PubMed, Embase, PsycInfo, the Cochrane Library, and PTSDpubs were performed. Oxford quality score was used to assess individual studies. A meta-analysis was performed using a metameter of the mean difference between pre and post-treatment CAPS scores.*

***Results:*** *Ultimately, 9 studies were included, with a total of 205 subjects. Only studies of MDMA and ketamine met our inclusion criteria. Meta-analysis was favorable towards treatment, with an effect size of -2.76 (95% CI -3.41,-2.10). Limitations in this analysis included small samples sizes in the studies and heterogeneity amongst the studies. Despite these limitations, our results do offer support for the efficacy of MDMA and ketamine in the treatment of PTSD.*

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***Conclusions****: Despite these limitations, our results do offer support for the efficacy of MDMA and ketamine in the treatment of PTSD.*

**Keywords:** Post traumatic stress disorder, Psychedelics, MDMA, Ketamine.

## INTRODUCTION

Post-Traumatic Stress Disorder (PTSD) is a psychiatric disorder involving extreme distress and disruption of daily living that happens in relation to exposure of a traumatic event. The DSM-5 criteria for PTSD include, first, direct or indirect exposure to traumatic event, followed by symptoms in four categorized: intrusion, avoidance, negative changes in thoughts and mood, and changes in arousal and reactivity.

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Barone W CS et, 2018).The DSM-5 criteria also include that the symptoms must last for at least 1 month, cause considerable distress and/or interfere with life, and not caused by another medical condition or by substance use (Figure 1). The yearly prevalence of PTSD is up to 3.5% in US adults (American Psychiatric Association). PTSD prevalence is significantly higher in high trauma exposure jobs, such as militarypersonnel and veterans as well as first responders (Barone W et, 2019).

Psychedelics (also known as hallucinogens) are a class of psychoactive substances that produce changes in perception, mood and cognitive processes. Psychedelics affect all the senses, altering a person's thinking, sense of time and emotions. They can also produce visual and auditory hallucinations (Garcia-Romeu A et, 2016).

The most common known psychedelics are mescaline, LSD, psilocybin, and MDMA.

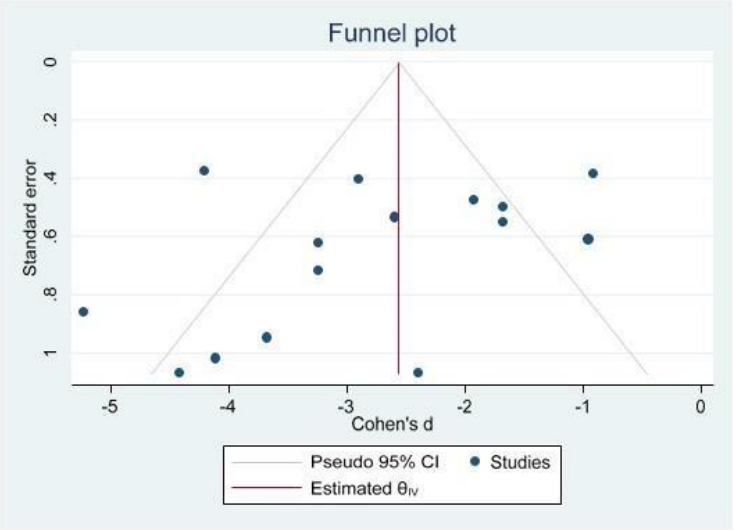


**Figure 1.** Egger's test for small-study effects displayed small-study effects with a statistically significant p- value of 0.0006. In addition, Begg's test also demonstrated a p-value of 0.1376, which is higher than the 0.05 level of significance. These results confirm the existence of mild small-study effects in our meta-analysis since Beggs and Egger tests didn't produce the same results.

Subgrouping by treatment intervention indicated that studies including ketamine had an I2 of 74.06, compared to 73.11 for studies that included MDMA. These findings suggest that studies with ketamine as the treatment intervention had a higher level of heterogeneity gen erally when compared to MDMA. (Figure 5).

**RATIONALE:** PTSD has been labeled as a "pharmacotherapy crisis" (Abdallah, et al, 2019) due to limited treatment options. For example, a 2015 review found that 60-72% of patients treated with standard therapies alone did not achieve lasting improvement in symptoms (Steenkamp, et al, 2015). Recent research has sought to find an answer for treatment-resistant PTSD, leading to a rise in studies examining the possible roles of standard pharmaco- and/or psychotherapies augmented with psychedelic or hallucinogenic drugs (Garcia -Romeu et al, 2016). Psychedelic, hallucinogenic, and other recreational drugs, such as MDMA, had previously been used for assisted psychotherapy for a variety of conditions, including PTSD due to their dissociative and/or consciousness-altering properties, but they fell out of favor in recent decades (Nutt et al, 2019). now we are seeing a resurgence of interest due to the prevalence of treatment-resistant PTSD. Psychedelics could transform the treatment paradigm for mental health disorders (David Nutt, 2021). However, trial design considerations, regulatory hurdles, and economics still pose problems for psychedelic-assisted therapies (Figure 2).

## METHOD

**ELIGIBILITY CRITERIA:** Our population of interest was adults (> age 18 years) with a diagnosis of PTSD. The intervention of interest was psychedelic drug treatment - specifically ketamine, MDMA, psilocybin, or LSD. Included studies reported pretreatment and post-treatment Clinician-Administered PTSD Scale (CAPS) scores to calculate our metameter: mean difference in score before and after treatment with the study drug. Included studies were published from 2013-present to capture recent studies only (8 years). Included studies were performed in the ambulatory setting only (Jardim AV et.al,1996).Exclusion criteria include pediatric populations, patients with severe PTSD (defined as requiring inpatient care), patients with PTSD comorbid with bipolar disorder or any psychosis, studies reporting results on a scale other than CAPS or without clear pretreatment and post-treatment measurements, and studies prior to 2013 (Figure 3). Additionally, case reports, ongoing studies, abstract only, unavailable full-text, non-peer-reviewed, and studies with incomplete data were excluded (Mitchell JM et.al.)

**INFORMATION SOURCES:** Searches were conducted in the following databases: PubMed, Embase, PsycInfo, the Cochrane Library, and PTSDpubs. All searches were conducted on Aug 3, 2021, and studies published up to that date were eligible for inclusion (Monson CM et.al, 2018) (Table 1).

**SEARCH STRATEGY:** The following searches were employed, each capturing PTSD + treatment (MDMA, ketamine, LSD, or psilocybin):

**PUBMED:**("Stress Disorders, Post-Traumatic"[Mesh] OR stress disorder*[tiab] OR stress symptom*[tiab] OR stress syndrome*[tiab] OR traumatic stress*[tiab] OR posttraumatic stress*[tiab] OR traumatic psycho*[tiab] OR posttraumatic psycho*[tiab] OR traumatic neurosis[tiab] OR ptsd[tiab]) AND ("Hallucinogens"[Mesh] OR "Psychotropic Drugs"[Mesh] OR psychedelic*[tiab] OR psychotropic drug*[tiab] OR hallucinogen*[tiab] OR ("N-Methyl-3,4-methylenedioxyamphetamine"

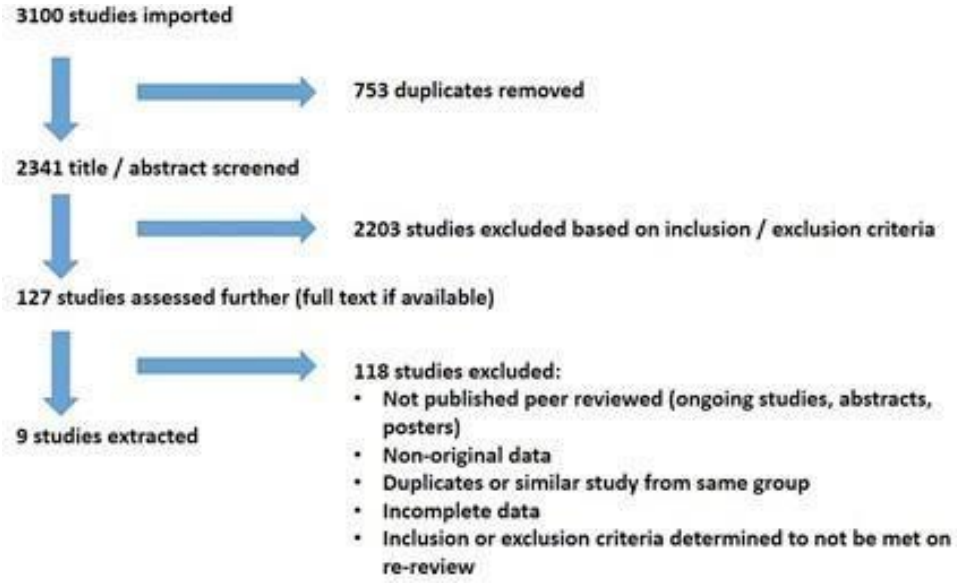


**Figure 2.** PRISMA Flow Diagram for Study selection.

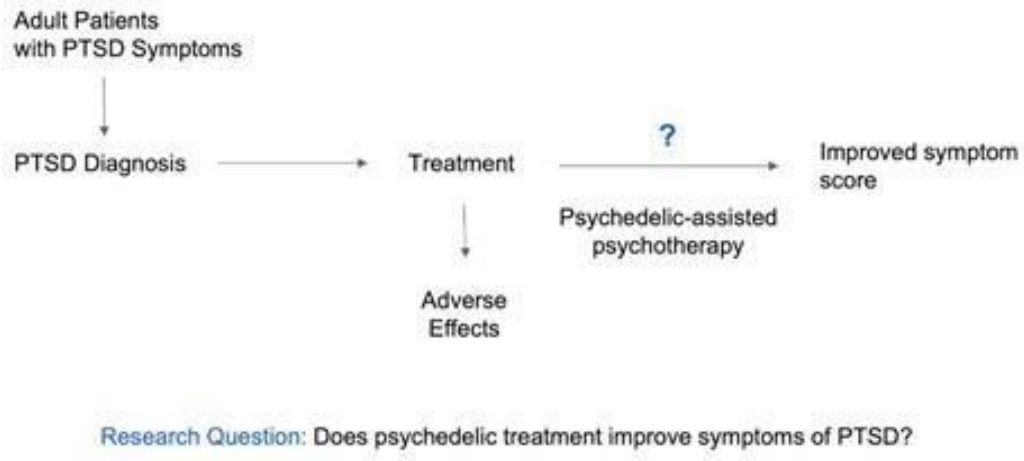


**Figure 3.** Analytic framework.

**Table 1**.

Evidence table: N*=number of subjects that received treatment drug in each study

| Study | Year | N | Weeks | Scoring Tool | Mean (Pre) | SD (Pre) | Mean(Post) | SD(Post) |
|---|---|---|---|---|---|---|---|---|
| **Albott 2018** | 2018 | 15 | 2 | CAPS-5 | 39.7 | 9.3 | 33.3 | 3.4 |
| **Feder 2014** | 2014 | 22 | 1 | CAPS-5 | 82.5 | 4.5 | 73.8 | 12.0561 |
| **Feder 2014** | 2014 | 22 | 2 | CAPS-5 | 82.5 | 4.5 | 69.8 | 4.2 |
| **Feder 2021** | 2021 | 13 | 2 | CAPS-5 | 41.9 | 6.1 | 33.1 | 2.17 |
| **Feder 2021** | 2021 | 13 | 1 | CAPS-5 | 41.9 | 6.1 | 30.02 | 2.14 |
| **Jardim 2021** | 2021 | 3 | 3 | CAPS-4 | 80 | 9.165 | 32 | 26.851 |
| **Mitchell 2021** | 2021 | 46 | 18 | CAPS-5 | 44 | 6.01 | 19.6 | 5.59 |
| **Mithoefer 2018** | 2018 | 12 | 4.3 | CAPS-4 | 89.7 | 8.82653 | 45.3 | 17.2449 |
| **Mithoefer 2018** | 2018 | 12 | 52 | CAPS-4 | 89.7 | 8.82653 | 37.8 | 10.9184 |
| **Monson 2020** | 2020 | 6 | 7 | CAPS-5 | 41.42 | 2.93878 | 19.37 | 6.9949 |
| **Monson 2020** | 2020 | 6 | 12.9 | CAPS-5 | 41.42 | 2.93878 | 17.43 | 8.7449 |
| **Monson 2020** | 2020 | 6 | 25.8 | CAPS-5 | 41.42 | 2.93878 | 15.52 | 7.76531 |
| **Ot'alora 2018** | 2018 | 11 | 4.3 | CAPS-4 | 91.6 | 20 | 65.3 | 9.5 |
| **Ot'alora 2018** | 2018 | 9 | 4.3 | CAPS-4 | 94.4 | 20.2 | 70 | 4 |
| **Shiroma 2020** | 2020 | 9 | 10 | CAPS-5 | 42.56 | 9.54 | 13.11 | 8.609 |

[Mesh] OR methylenedioxyamphetamine[tiab]OR Methylenedioxymethamphetamine[tiab] OR mdma[tiab] OR ecstasy[tiab] OR molly[tiab]) OR ("Ketamine"[Mesh] OR "Esketamine"[nm] OR ketamine[tiab] OR ketalar[tiab] OR esketamine[tiab]) OR "Psilocybin"[Mesh] OR "Lysergic Acid Diethylamide"[Mesh] OR psilocybin[tiab] OR lsd[tiab])

**EMBASE:**(' Posttraumatic stress disorder'/exp OR 'posttraumatic stress disorder':ab,ti,kw OR 'stress disorder*':ab,ti,kw OR 'posttraumatic stress*':ab,ti,kw OR 'ptsd':ab,ti,kw) AND ('psychedelic agent'/exp OR 'psychedelic agent':ab,ti,kw OR 'midomafetamine'/exp OR 'midomafetamine':ab,ti,kw OR 'mdma':ab,ti,kw OR 'methylenedioxyamphetamine':ab,ti,kw OR 'ecstasy':ab,ti,kw OR 'lysergide'/exp OR 'lysergide':ab,ti,kw OR 'lsd':ab,ti,kw OR 'psilocybine'/exp OR 'psilocybin*':ab,ti,kw)

**PSYCHINFO:** DE ("Posttraumatic Stress Disorder" OR "Complex PTSD") OR TI ("stress disorder*" OR "stress symptom*" OR "stress syndrome*" OR "traumatic stress*") OR AB ("stress disorder*" OR "stress symptom*" OR "stress syndrome*" OR "traumatic stress*") DE ("Hallucinogenic Drugs" OR "Psychotropic Drugs" OR "Lysergic Acid Diethylamide" OR "Psilocybin" OR "Ketamine" OR "Methylenedioxymethamphetamine")

Additionally "PTSD" + each drug ("ketamine", "MDMA"/" methylenedioxyamphetamine", "LSD"/" lysergic acid diethylamide", "psilocybin") were manually searched in the Cochrane Library and in PTSDpubs (Norbury A et,2021) (Figure 4).

**SELECTION PROCESS:** Covidence software was used to organize the study selection process and to remove duplicates. The initial screen of the title/abstract was done by a single reviewer using the above-stated inclusion and

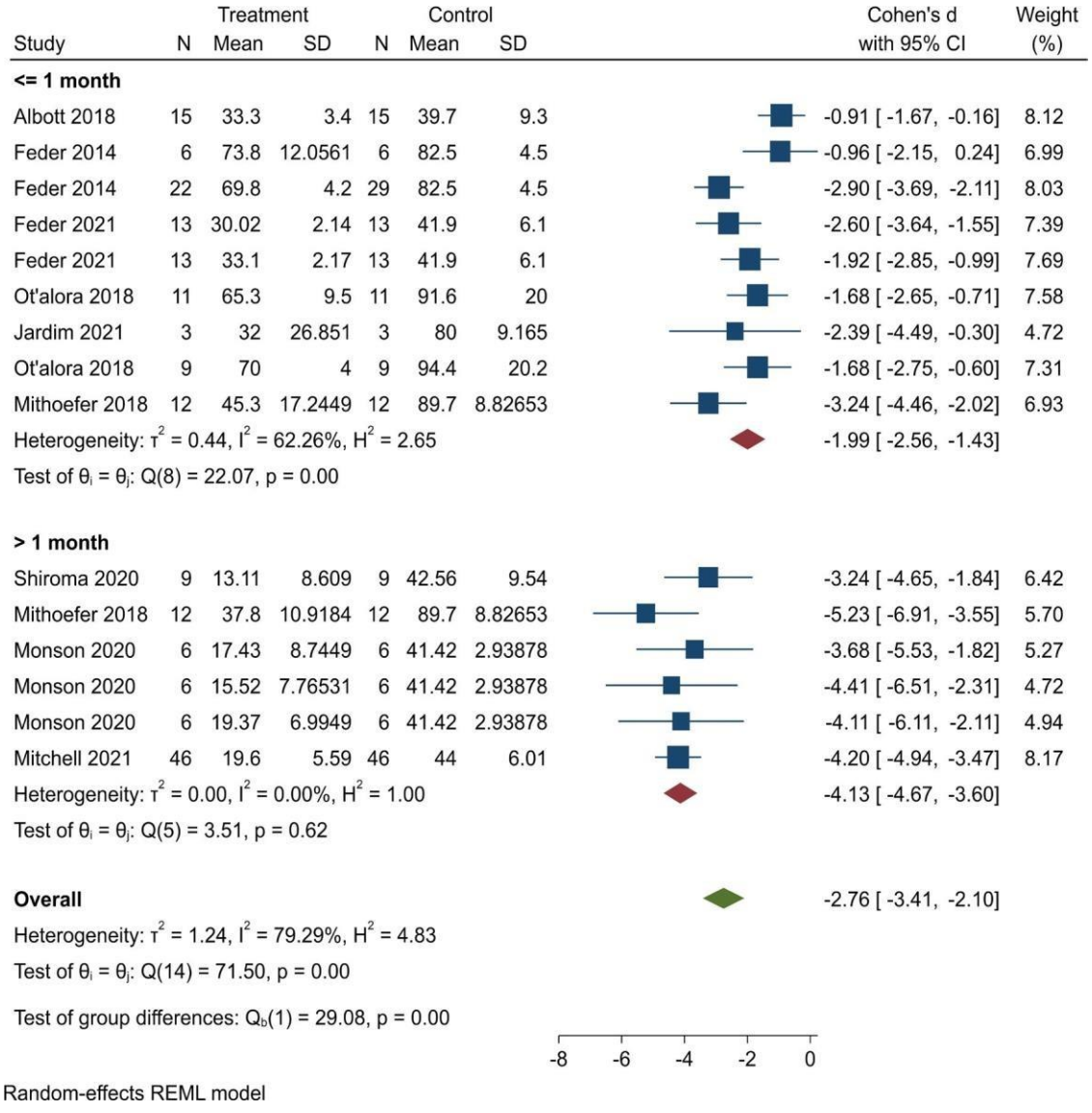


**Figure 4.** Random- effects REML model.

exclusion criteria. Subsequent full-text review of remaining studies was done by two independent reviewers, and discrepancies were resolved by the third, again using the above-stated inclusion and exclusion criteria (Nutt D, 2019).

**DATA COLLECTION PROCESS:** Data were manually extracted from the qualifying manuscripts by a single reviewer and checked by a second reviewer. The following data were extracted: first author, year of publication, number of subjects in the study (treatment arm only if controlled trial), treatment drug, length of follow-up, scoring tool (CAPS-4 or CAPS-5), pretreatment mean score, post-treatment mean score, and/or mean difference in pretreatment and post-treatment measures; these data were used for analyses(Ot'alora G M, et al, 2018). Also, to additionally compare studies and determine other potential sources of heterogeneity, the following data were collected: start date, end date, country/region of study origin, study design, median or mean age of subjects, sex of subjects (number female), subject inclusion criteria, subject exclusion criteria, treatment drug dose and frequency. Studies without clearly presented pre and post-treatment measurements were excluded (Figure 5).

**STUDY RISK OF BIAS ASSESSMENT:** One possible source of bias in this assessment is that, due to a limited number of reviewers, only one reviewer reviewed the title/abstract for initial inclusion. Methods for mitigating bias included our broad search strategy, our method of two independent reviewers assessing each full-text document (with a third arbitrating), and similarly our method of one reviewer extracting data and another checking it. Each study was reviewed and assigned a quality assessment score based on the Oxford scale. (Jadad et al, 1996). Quality of studies can be a major pain point in this field since no many high quality studies exist. A separate forest plot was made to classify studies based on quality (Figure 6).

**EFFECT MEASURES:** Our metameter was the mean difference in CAPS-4 or -5 score pretreatment vs post-treatment. We calculated and reported the effect size in Cohen's d to allow for analysis across two different CAPS scaet al, 2020).

**SYNTHESIS METHODS:** Only studies meeting the inclusion criteria above were analyzed. All meta-analysis was performed using Stata statistical software package version 17. Studies were analyzed first as a comprehensive group and then divided into subgroups by treatment drug given. Studies were additionally synthesized by the length of follow-up. In studies that did not report the mean difference, this was calculated using the pretreatment and

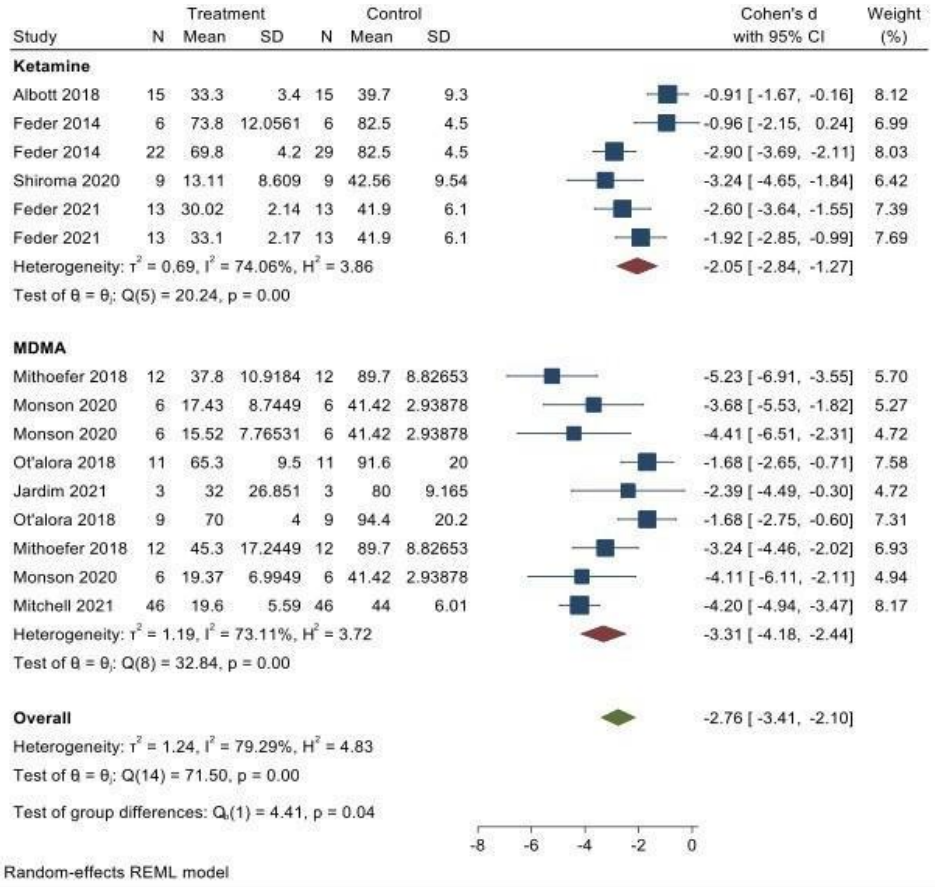


**Figure 5.** Forest Plot of All Studies, Grouped by Treatment Drug.

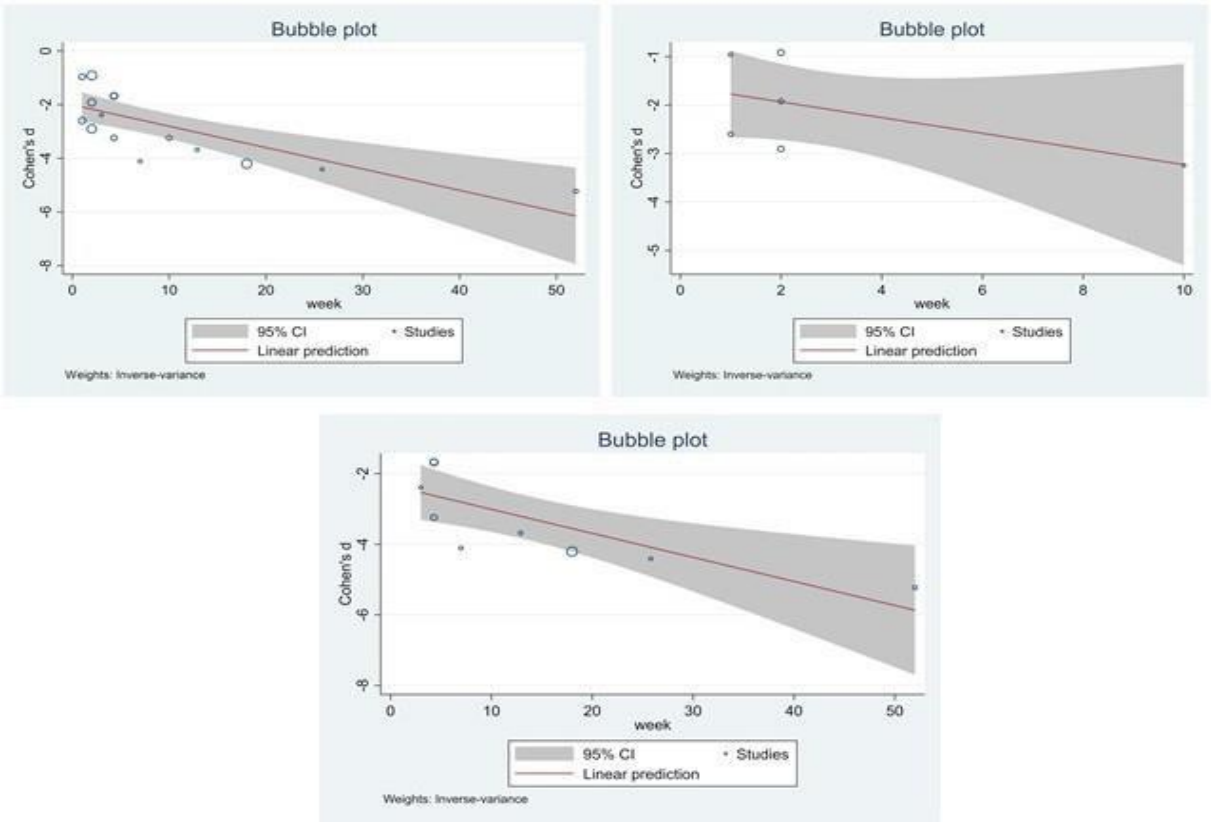


**Figure 6.** Meta-Regression ( Ketamine and MDMA).

post-treatment raw score data. Confidence intervals were determined from mean and standard deviation (Figure 7). We chose Cohen's d as our metric of effect size to present a homogeneous analysis of different reported outcomes (CAPS-4 or -5). We derived Cohen's d from the available pre and post-treatment data means, sample size, and standard error of the mean using the equations: Cohen's di = (mposti – mprei)/sdi and SD(di) = √[Ni/npreinposti + di2/2(Ni-2)] . Results were presented in a forest plot. A random-effects model for meta-analysis was performed (Hake, H. S. et al.)To explore causes of heterogeneity, we performed a combination of subgroup and sensitivity analyses. We then categorized subgroups based on length of time to follow up on the forest plot while observing the overall impact of each subcategory. We classified the data according to the length of intervention to follow up in weeks, intervention type and the scale of evaluation. Additionally, we subgrouped the two treatment interventions (Ketamine or MDMA) to observe possible differences in respective outcomes. Differences were identified in different time intervals to follow-up, and we thought best to highlight these accordingly. The most common time intervals of those demonstrating discernable differences were observed in the timeframe of time to follow-up less than or equal to 2 months, between 2 to 12 months and equal to or greater than 12 months. Sensitivity analysis was selected to best address different scales of evaluation (CAPS-4 or -5). In alignment with our selected random effects model, all plots in the sensitivity analysis were similarly selected using random effects models, particularly since the Q values support the same.

**REPORTING BIAS ASSESSMENT:** Publication bias was graphically demonstrated and assessed visually by funnel plot. Eggers and Beggs tests were performed to assess for bias due to small study effect (Table 2).

**CERTAINTY ASSESSMENT:** Each analysis was reviewed within the GRADE framework for the certainty of recommendations (Guyatt et al, 2008).

## RESULTS

**STUDY SELECTION:** Three thousand one hundred studies resulted from collective searches; 2,341 remained after the removal of duplicates (Covidence). These remaining studies were screened by title and abstract, after which 127 studies underwent full-text review. Ultimately, nine studies met all inclusion and exclusion criteria. In some cases (for example, Norbury 2021), it appeared that the study met our criteria; however it was discovered that data reported in the study were differently-analyzed duplicate data to other studies already included and thus were ultimately excluded from our analysis. Of note, no studies of LSD or psilocybin met our inclusion criteria; therefore, we analyzed only studies of MDMA and ketamine.

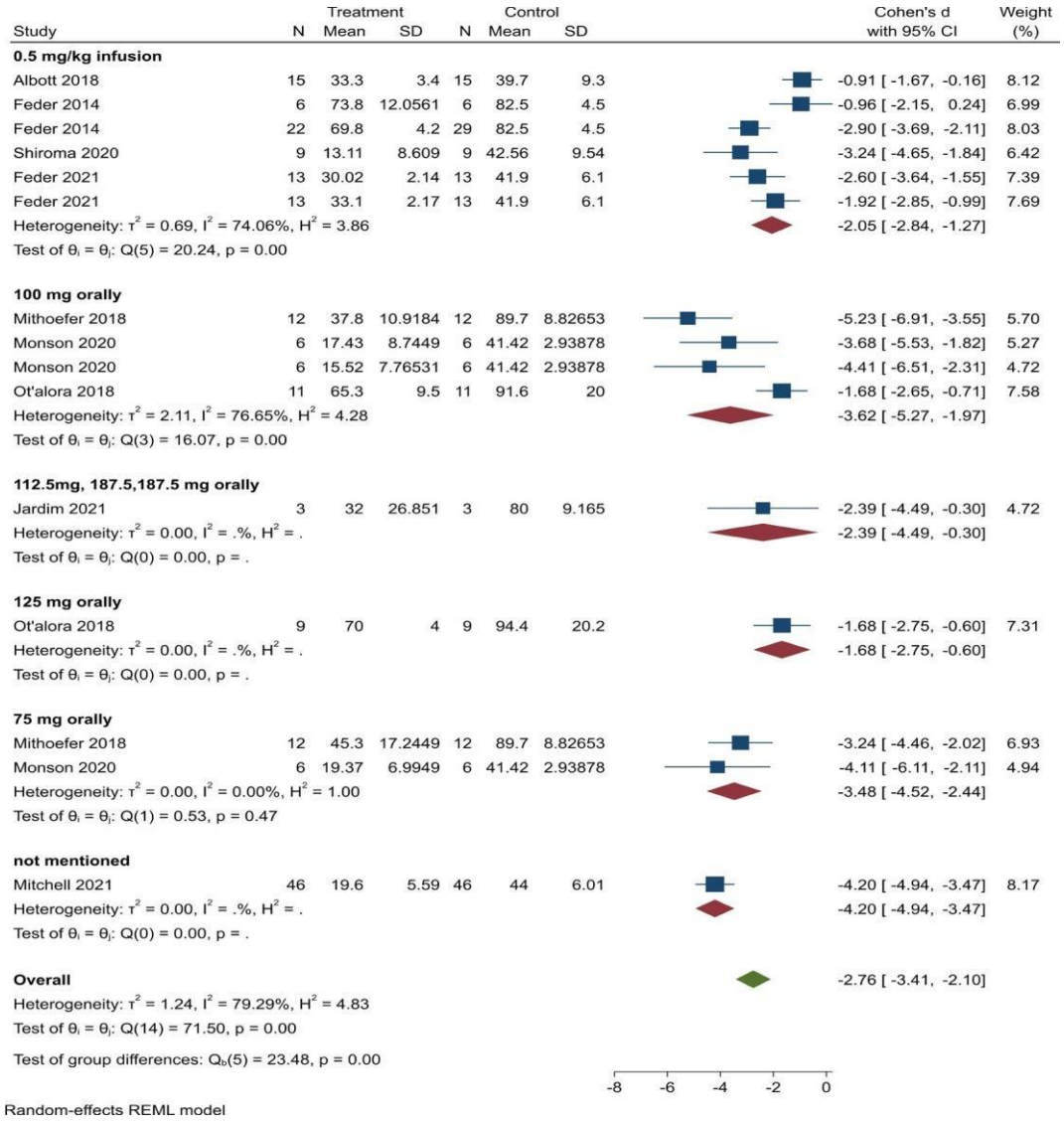


**Figure 7.** Effect size with different dose.

**Table 2**.

GRADE of recommendations

| Participants(number of studies) Time to follow | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication Bias | Overall Quality of Evidence |
|---|---|---|---|---|---|---|
| **Efficacy of psychedelics** | | | | | | |
| **205(9) 1 - 52 weeks** | moderate | serious | No serious risk | No serious risk | moderate | LOW |
| **Efficacy of psychedelics during short-term follow up(up to 4.2 weeks)** | | | | | | |
| **104(7) 1-4.2 weeks** | moderate | serious | No serious risk | No serious | moderate | LOW |
| **Efficacy of psychedelics during long-term follow up (more than 4.2 weeks)** | | | | | | |
| **85 (4) >4.2 weeks** | high | No serious risk | No serious risk | serious | Moderate - high | VERY LOW |
| **Efficacy of ketamine** | | | | | | |
| **78 (4) from 1 to 52 weeks** | moderate | serious | No serious risk | No serious risk | moderate | LOW |
| **Efficacy of MDMA** | | | | | | |
| **111 (6) 1 - 52 weeks** | moderate | serious | No serious risk | No serious risk | moderate | LOW |

## DISCUSSION

Our analyses suggest that both MDMA and Ketamine appear to improve PTSD symptom scores in the short-term as is illustrated by the mean difference in CAPS scores within our small heterogeneous samples. However, Ketamine appears to be a mediating factor in the regression model that combines Ketamine and MDMA since the model is affected by treatment duration. Nonetheless, comparison of the individual models along with a review of the effect size reveals that patients on the MDMA-assisted psychotherapy branches have enhanced improvement in symptoms with an extended treatment period and a higher dose that does not exceed 100mg. Ketamine, on the other hand, appears to be better than all control medication in studies and provides a higher reduction in CAPS score. The quality and bias of the evidence provided was ranked by the GRADE system that revealed mostly low-quality evidence with moderate publication bias. Below we proceed to highlight the information we have obtained thus far with each agent and its associated medical use.

MDMA; 3-4methylenedioxymethamphetamine is a substituted amphetamine. It remains a Schedule 1 drug according to the federal laws in USA, but the FDA has granted its use in research and treatment for life-threatening illness which led to the "Breakthrough Therapy" designation from the FDA in 2019 (Mithoefer et al, 2021). Some experts even argue that there exists sufficient evidence at present to transfer MDMA from Schedule 1 drug class (no medical use) to Schedule 2 (misused but useful medicine) (Krebs & Johansen, 2013). Its associated street names are Ecstasy, XTC, love drug and Molly. It is known to function on many receptor systems; more specifically, DAT, NET, SERT, TAAR1, VMAT2,5-HT2A & α1- & ß-adrenoceptors (Sitaram et al, 1990). Since its synthesis in 1912, it was not till the 1970s when it was utilized by 'Sasha Shulgin' in "Couples Psychotherapy" and was subsequently banned in the mid-1980s due to its growing recreational use (Shulgin & Shulgin, 1991).

MDMA-assisted psychotherapy for PTSD patients has been circling the arena for some time regarding its ability to improve symptoms of PTSD. In studies, 85% of the participants on MDMA-assisted psychotherapy no longer had a PTSD diagnosis compared to 15% on the placebo arm, In addition, 3.5 years later it appeared that the observed improvement was sustained (Mithoefer et al. (2010), Chabrol,2013). Since best use of MDMA has historically been studied along with psychotherapy, it is sensible that the similar methods are utilized to maintain a state of both theoretical and clinical equipoise but begs the question as to whether the observed difference in effect sizes in MDMA assisted psychotherapy and Ketamine use in our results are so due to the additional or synergistic confounding effects of the associated psychotherapeutic intervention. This appeals to researchers and clinical investigators within the realm of psychedelics to conduct further controlled clinical trials that may perhaps highlight potential differences that may be associated with distinct psychotherapeutic interventions.

The rationale for the improvement of symptoms in PTSD seems to be the effect of MDMA on the hyperactive Amygdala; fear and alertness as part of the fight-flight response. It is also presumed that MDMA deters or avoids emotional or limbic system involvement and facilitates the maintenance of a state at the Prefrontal cortex level [Mithoefer et al, 2011].

Furthermore, MDMA's observed effectiveness is also linked to its action on the hormonal systems. It works to stimulate the release of Oxytocin and Prolactin, which are known for their empathogenic effects along with their ability to foster trust and looseness. This may be associated with the improvement in specific subgroups of symptoms of PTSD- fear associated with hyperarousal. This ties into previous MDMA trial literature that displayed enhanced fear memory extinction and the ability to modulate fear memory reconsolidation along with boosting social behavior – as observed in animal models.(Hake & Nardu 2019). Our MDMA assisted psychotherapy studies focused mainly on the reduction in CAPS score overall but a few Ketamine studies did comment on the subgroups where reductions were observed; namely, intrusion, avoidance and negative mood and cognition yet not with hyperarousal, with ketamine use (Feder et al). This may be a valuable point to consider when administering different psychedelic agents to patients with distinct symptomatology under the umbrella of PTSD.

With respect to its historical value in Military medicine, the Vietnam war had previously been accused of criminalizing psychedelic use for selfish purposes; that is, the fear of the counterculture and opposition of war by the youth (Lee & Shlain, 1992). On the other hand, the more recent Iraq and Afghanistan wars helped bring them back to the scene as many soldiers with PTSD were observed to have a phenomenal suicide rate along with depression (Hoge et al, 2004), where the available FDA approved antidepressants for PTSD had not been found to be an adequate solution (Nardou et al, 2019).

Proponents of MDMA research may state that it is not a risky agent in its pure form and that street versions probably contain less than 50% of the drug. Nonetheless; due to lack of sufficient supporting evidence, healthcare practitioners must exercise caution in its administration and monitoring along with a strict selection profile of patients to administer it to, as it does come with a whole host of side effects that have not been intricately studied in addition to its abuse potential (Nichols DE et al,2017). Adverse side effects include fatal overdoses, high blood pressure, arrhythmias, loss of consciousness and seizures, hyperthermia, electrolyte (sodium) imbalance, fatal swelling of the brain, dehydration (hydration monitoring is vital especially in young people at night clubs where over or under-hydration can be fatal).

It may also cause loss of appetite, mild depersonalization, illogical or disorganized thoughts, sleep disturbances, decreased cognitive function and increased muscle tension leading to jaw clenching and bruxism (Mithoefer MC et al, 2018).

Ketamine is an arylcycloexylmine; a derivative of phencyclidine that was synthesized in the 1950s (Domino et al, 1965). It is a dissociative anesthetic and a glutamate N-methyl-D aspartate (NMDA) receptor antagonist; a neurotransmitter system found in the prefrontal cortex involved in memory and learning (Shulgin A et al,1991). It is FDA-approved as an anesthetic for specific procedures in emergency, combat and veterinary medicine and is widely used for its analgesic purposes. Legally it is a schedule 3 substance in the USA and a controlled medicine globally. Street names include: special K, K, Kit Kat, Cat Valium, Super Acid, Special La Coke, Purple, Jet, and Vitamin K.

The rationale and support for its growing use in psychiatric disorders originates from the theoretical knowledge that Ketamine is presumed to promote the regrowth of neurons in the Prefrontal cortex; which has been found to atrophied in disorders like Schizophrenia, Depression and Anxiety (Li et al, 2010). In addition, Ketamine's mechanism of action differs from that of SSRIs. Ketamine as an NMDA receptor antagonist blocks the action of glutamate, the main excitatory neurotransmitter in the brain (Zanos et al, 2018). This action leads to a rapid increase in synaptic plasticity and the formation of new neural connections, which is believed to be responsible for ketamine's rapid and sustained antidepressant and anti-PTSD effects (Duman et al, 2016). SSRIs, on the other hand, work by blocking the reuptake of serotonin, which increases the amount of serotonin available in the brain (Morrison et al, 2019). The different mechanisms of action suggest that ketamine may be more effective for patients who do not respond to SSRIs or other traditional treatments. Some side effects of ketamine include euphoria and dissociation (a sense of detachment from reality). In small or microdoses it may cause a floating feeling or at times a lack of body perception. In larger doses, it is also known to cause hallucinations and forgetfulness.

The first report demonstrating the rapid antidepressant effect of Ketamine was in 2000 (Berman et al., 2000). However, more recently Intranasal Esketamine; its enantiomer, has been FDA-approved for treatment of Treatment Resistant Depression (TRD) and noticeably beneficial in these patients within 72 h after infusion (Daly et al., 2019). Some side effects of Ketamine include euphoria, nausea, dysgeusia, dizziness and dissociation. In small or microdoses it may cause a floating feeling or at times a lack of body perception. In larger doses, it is also known to cause hallucinations and forgetfulness. More serious adverse effects are the 'Ketamine bladder' or K-bladder. It results in physical damage and inflammation to the bladder wall that can be irreversible, and some patients eventually require surgical removal (Shahani et al, 2007). Another side effect is the "K-hole." This is characterized by intense anxiety, paranoid ideation, and panic attacks, within a dissociated state (Morgan et al, 2004). Despite its potent and encouraging psychoactive properties, limitations of its use include the transient nature of its antidepressant effect and the need for repeated dosing. Healthcare practitioners administering Esketamine should also be wary of the abuse potential and the effects on cognition that this drug poses and exercise caution accordingly. The drug may be heading into an epidemic; similar to the opioid epidemic situation, and this has become more noticeable in countries like China and across Europe; where the powder form of the drug is snorted or injected (EMCDDA, 2019). Healthcare practitioners need also be mindful of the complications associated with Intravenous drug use, such as blood borne diseases; HIV and Hepatitis B&C.

LSD; lysergic acid diethylamide is a classic psychedelic and a potent hallucinogen. Its psychoactive properties were first discovered in 1938 by Albert Hoffman (Stoll A, 1943). It was investigated in the 1980s by Jan Bastiaans in the Netherlands as a therapeutic means, paired with emotional abreaction, for what was called 'Concertation Camp syndrome' at the time (Ossebaard H, 1999). Its resurgence within the realm of psychiatry has remained on the breaks due to limited clinical trials not only exhibiting general inefficacy with most psychiatric disorders; other than alcoholism, but also worsening of symptoms in certain subgroups of psychiatric disorders; perceptual disturbances were worsened in schizophrenia. (Fuentes et al,2020).

Psilocybin is a plant alkaloid that was known to be utilized by indigenous populations during rites and fell out of favor with other psychedelics due to counterculture at the time and the development and advancement of other psychotropic agents (Hudak, 2013). It has only recently been tapped back into due to the reappearance of psychedelics as a class of potential therapeutic agents that can be utilized in more drug resistant settings. Classical psychedelics have shown themselves to be more unstable and unpredictable with a variety of psychiatric disorders when compared to empathogens like MDMA or dissociative hallucinogens such as Ketamine (Mithoefer et al,2021).

What also remains vague is the approach towards the administration of these substances. We have learned that Intranasal Esketamine appears to be beneficial used in combination with psychotropic agents such as SSRIs and others for TRD. However, there remains a significant paucity in the literature and non-existent clinical trials of a head to head nature between isolated SSRI use; first line for PTSD, and isolated psychedelic use on the other arm for the treatment of PTSD. In summary, MDMA-assisted psychotherapy may offer potential advantages over SSRIs in the treatment of PTSD, including enhanced therapeutic alliance, greater emotional processing, and improved long-term outcomes (Hoge et al .2004).

Ketamine; with its rapid onset of action may alleviate symptoms within hours or even minutes, whereas SSRIs may take several weeks to show noticeable improvements (Feder et al, 2014). This quick relief from symptoms can be particularly beneficial for individuals with severe or treatment-resistant PTSD who may be at a higher risk for self-harm or suicide (Sanacora et al, 2017).

## CONCLUSIONS

Through time the pendulum has swung between advocating for liberal use of psychedelic agents to complete prohibition and back to the current repurposing and reintroduction of these agents into clinical research. The work of some great minds has been highlighted in our discussion regarding historical clinical trials conducted along with potential for future use. On the other hand, it also represents the desperation in facilitating treatment in patients who suffer with PTSD of a more chronic and/or resistant nature.

**LIMITATIONS:** Of this study include small sample sizes within the individual studies and heterogeneity of the studies. Additionally, even though we aimed to broadly evaluate the effectiveness of psychedelic-assisted therapy for PTSD symptoms, there were no studies using LSD or Psilocybin that met our inclusion criteria. Therefore, this meta-analysis only includes studies of MDMA assisted psychotherapy and Ketamine.

In conclusion, our meta-analysis and systematic review demonstrates that psychedelics could prove to be beneficial in people who are suffering from disabling mental disorders like chronic PTSD, where traditional psychotropic agents have reached their maximum effect. It is important to note that thus far, clinical trials have illustrated inherent difficulties; namely, small sample sizes, unaccounted for placebo effect, high uncertainty regarding associated adverse side effects and a non-negligible potential for abuse of these agents. Further and more rigorous study on specific groups of patients in unison with specific treatment protocols are required before this association can be utilized to guide clinical practice; however, the results of our meta-analysis appear promising. We do acknowledge that studies of psychedelic agents are challenging to fund economically, difficult to blind, and may face extensive regulatory hurdles. Notwithstanding, we call upon the field to persevere in exploring these treatment options.

Last but not least, from a pharmaceutical and economic standpoint, even if clinical trials do yield positive results, there may be different obstacles in disseminating these agents due to their profitability trajectory, since these pharmacological agents are unlikely to be re-patented.

## CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

**Footnotes AA:**

- Classic psychedelic drugs" – psilocybin, mescaline, LSD
- "Dissociative hallucinogens" – ketamine, dextromethorphan
- "Entactogens" or "empathogens" – MDMA

## REFERENCES


Abdallah, CG., Averill, LA., Akiki, TJ., Raza, M., Averill, CL., Gomaa, H., et al.(2019).The neurobiology and pharmacotherapy of posttraumatic stress disorder. *Annu Rev Pharmacol Toxicol*. 59:171-89.

Albott, CS., Lim, KO., Forbes, MK., Erbes, C., Tye, SJ., Grabowski, JG., et al.(2018).Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. *J Clin Psychiatry*. 79(3):17462.

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

Feder, A., Costi, S., Rutter, SB., Collins, AB., Govindarajulu, U., Jha, MK., et al.(2021). A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. *Am J Psychiatry*. 178(2):193-202.

Feder, A., Parides, MK., Murrough, JW., Perez, AM., Morgan, JE., Saxena, S., et al.(2014). Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. 71(6):681-8.

Garcia-Romeu, A., Kersgaard, B., Addy, PH.(2016). Clinical applications of hallucinogens: A review. *Exp Clin Psychopharmacol*. 24(4):229.

Guyatt, GH., Oxman, AD., Kunz, R., Jaeschke, R., Helfand, M., Liberati, A., et al.(2008). Incorporating considerations of resources use into grading recommendations. *BMJ*. 336(7654):1170-3.

Jadad, AR., Moore, RA., Carroll, D., Jenkinson, C., Reynolds, DJ., Gavaghan, DJ., et al.(1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Control Clin Trials*. 17(1):1-2.

Jardim, AV., Jardim, DV., Chaves, BR., Steglich, M., Ot'alora, G M., Mithoefer, MC., et al.(2020). 3, 4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for victims of sexual abuse with severe post-traumatic stress disorder: an open label pilot study in Brazil. *Braz J Psychiatry*.43:181-5.

Mitchell JM, Bogenschutz M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., et al. (2021). MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med*. 27(6):1025-33.

Mithoefer, MC., Mithoefer, AT., Feduccia, AA., Jerome, L., Wagner, M., Wymer, J., et al.(2018). 3,

4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapyfor post-traumaticstressdisorder in militaryveterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry*. 5(6):486-97.

Monson, CM., Fredman, SJ., Adair, KC.(2008). Cognitive–behavioral conjoint therapy for posttraumatic stress disorder: Application to Operation Enduring and Iraqi Freedom veterans. *J Clin Psychol*. 64(8):958-71.

Norbury, A., Rutter, SB., Collins, AB., Costi, S., Jha, MK., Horn, SR., et al.(2021). Neuroimaging correlates and predictors of response to repeated-dose intravenous ketamine in PTSD: preliminaryevidence. *Neuropsychopharmacology*.46(13):2266-77.

Nutt D. Psychedelic drugs—a new era in psychiatry? *Dialogues Clin Neurosci*. 2022 Apr 1.

Mithoefer, MC., Feduccia, AA., Jerome, L., Mithoefer, A., Wagner, M., Walsh, Z., et al.(2019). MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *J Psychopharmacol*.236:2735-45.

Shiroma, PR., Thuras, P., Wels, J., Erbes, C., Kehle-Forbes, S., Polusny, M.(2020). A proof-of-concept study of subanesthetic intravenous ketamine combined with prolonged exposure therapy among veterans with posttraumatic stress disorder. *J Clin Psychiatry*. 81(6):10118.

Steenkamp, MM., Litz, BT., Hoge, CW., Marmar, CR. (2015). Psychotherapy for military-related PTSD: A review of randomized clinical trials. *JAMA*. 314(5):489-500.

Hake, HS., Davis, JK., Wood, RR., Tanner, MK., Loetz, EC., Sanchez, A., et al.(2019). 3, 4-methylenedioxymethamphetamine (MDMA) impairs the extinction and reconsolidation of fear memory in rats. *Physiol Behav*.199:343-50.

Nardou, R., Lewis, EM., Rothhaas, R., Xu, R., Yang, A., Boyden, E., et al.(2019). Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature*. 569(7754):116-20.

Stoll, A., Hofmann, A.(1943). Ergot alkaloids. VI. Partial synthesis of ergobasine type alkaloids. *Helv Chim Acta*.26:944-65.

Fuentes, JJ., Fonseca, F., Elices, M., Farré, M., Torrens, M.(2020). Therapeutic use of LSD in psychiatry: a systematic review of randomized-controlled clinical trials. *Frontiers in psychiatry*. 943.

Nichols, DE., Johnson, MW., Nichols, CD.(2017). Psychedelics as medicines: an emerging new paradigm. *Clin Pharm*. 101(2):209-19.

Hudak, R., & Gannon, J. M. (2022). Post-traumatic Stress Disorder. In *Handbook of Psychiatric Disorders in Adults in the Primary Care Setting* (pp. 169-182).

Cham: Springer International Publishing.Krebs, T. S., & Johansen, P. Ø. (2013). Psychedelics and mental health: a population study. PLoS One, 8(8), e63972.

Shulgin, AT., Shulgin, A.(1991). PIHKAL: a chemical love story. Berkeley, CA: Transform Press; 1991 Oct.

Schmidt, CJ., Levin, JA., Lovenberg, W. (1987). In vitro and in vivo neurochemical effects of methylenedioxymethamphetamine on striatal monoaminergic systems in the rat brain. *Biochem Pharmacol*. 36(5):747-55.

Berman, RM., Cappiello, A., Anand, A., Oren, DA., Heninger, GR., Charney, DS., et al. (2000). Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 47(4):351-4.

Domino, EF., Chodoff, P., Corssen, G. (1965). Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. *Clin Pharm*. 6(3):279-91.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). (2019).

European Drug West R. European monitoring centre of drugs and drug addiction (EMCDDA), insights. models of addiction. EMCDDA. Luxembourg: Publications Office of the European Union, Lisbon, Portugal. 2013.

Hoge, CW., Castro, CA., Messer, SC., McGurk, D., Cotting, DI., Koffman, RL. (2004). Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *New England journal of medicine*. 351(1):13-22.

Lee MA, Shlain B. Acid dreams: The complete social history of LSD: The CIA, the sixties, and beyond. Grove Press; 1992.

Li, N., Lee, B., Liu, RJ., Banasr, M., Dwyer, JM., Iwata, M., et al.(2010). mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Sci*. 329(5994):959-64.

Morgan, C. J., Muetzelfeldt, L., Curran, H. V., & Dillon, J. (2004). The K-hole: a 3D-model of the subjective effects of ketamine. *Psychedelic Sci*. 96, 27.

Morrison, P. D., Murray, R. M., & McGuire, P. K. (2019). From the ketamine model of schizophrenia to the development of novel therapeutics. In Neuropsychopharmacology (pp. 265-282). Springer, Cham.

Shahani, R., Streutker, C., Dickson, B., Stewart, RJ.(2007). Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology*. 69(5):810-2.

Zanos, P., Moaddel, R., Morris, PJ., Riggs, LM., Highland ,JN., Georgiou, P., et al.(2018). Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. *Pharmacol Rev*. 70(3):621-60.

Duman, RS., Aghajanian, GK., Sanacora, G., Krystal, JH.(2016). Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med*. 22(3):238-49.

Mithoefer, MC., Wagner, MT., Mithoefer, AT., Jerome ,L., Doblin, R.(2011). The safety and efficacy of±3, 4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Clin Psychopharmacol*. 25(4):439-52.