VOLUME 35/NO. 4 • ISSN: 1050-1835 • 2024

National Center for PTSD
POSTTRAUMATIC STRESS DISORDER

PTSD Research Quarterly

ADVANCING SCIENCE AND PROMOTING UNDERSTANDING OF TRAUMATIC STRESS

Published by:
National Center for PTSD
VA Medical Center (116D)
215 North Main Street
White River Junction
Vermont 05009-0001 USA

(802) 296-5132
FAX (802) 296-5135
Email: ncptsd@va.gov

All issues of the PTSD Research Quarterly are available online at:
www.ptsd.va.gov

U.S. Department of Veterans Affairs

Update on Novel Psychedelic Treatments for PTSD

Stephanie L. Haft, PhD
Department of Psychiatry and Behavioral Sciences, University of California San Francisco

Ellen Bradley, MD
Parkinson's Disease Research, Education, & Clinical Center, San Francisco Veterans Affairs Medical Center
Department of Psychiatry and Behavioral Sciences, University of California San Francisco

Aoife O'Donovan, PhD
San Francisco Veteran's Affairs Medical Center
Department of Psychiatry and Behavioral Sciences, University of California San Francisco

Josh Woolley, MD/PhD
San Francisco VA Healthcare System
Department of Psychiatry and Behavioral Sciences, Weill Institute of Neuroscience, University of California San Francisco

After nearly 25 years without a new FDA-approved treatment for posttraumatic stress disorder (PTSD), there is a growing consensus that new therapies are urgently needed. Recently, there has been a large upswell in academic, industry, and patient interest and focus on psychedelic treatments for mental health conditions, including PTSD. This issue of the *Research Quarterly* reviews key articles and updates on the evidence regarding various psychedelic treatments (3,4-methylenedioxymethamphetamine (MDMA), psilocybin, ibogaine, and 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT)) as well as updates about recent regulatory agency actions regarding these treatments. The discussion concludes with methodological and ethical considerations that should be incorporated to foster continued innovation, rigor, and safety in psychedelic therapy for PTSD.

Randomized controlled trials (RCTs) for psychedelic therapy have thus far involved administration of a psychedelic drug under supervision with psychotherapeutic support. Paradigms implemented in extant trials have typically included two to four psychotherapy sessions before the drug is administered, the drug administration session(s) itself, and then another two to four psychotherapy sessions. The therapeutic effects of psychedelics are not yet well understood, though preclinical literature has implicated multiple possible mechanisms including modulation of numerous neurotransmitter systems, anti-inflammatory effects, upregulation of neurotrophic factors, and enhancement of synaptic plasticity. It is hypothesized that these drug-induced changes, in combination with psychotherapy, may provide a window of opportunity for new learning and behavioral change that leads to clinical improvement. Particularly relevant for PTSD, psychedelics may help to reduce fear responses and enhance engagement with trauma-related content. Each psychedelic compound has a distinct pharmacological profile with different neurochemical effects, which may significantly impact clinical application.

MDMA-Assisted Psychotherapy for PTSD

MDMA is a methamphetamine derivative that is a potent stimulator of norepinephrine and dopamine as well as serotonin through activity at 5-HT2A

Continued on page 2

Author Addresses: **Stephanie L. Haft, PhD** is affiliated with the Department of Psychiatry and Behavioral Sciences, University of California San Francisco, 675 18th St, San Francisco, CA 94107. **Ellen Bradley, MD** is affiliated with Parkinson's Disease Research, Education, and Clinical Center, San Francisco Veterans Affairs Medical Center, 4150 Clement St, San Francisco, CA 94121, and with the Department of Psychiatry and Behavioral Sciences, University of California San Francisco, 675 18th St, San Francisco, CA 94107. **Aoife O'Donovan, PhD** is affiliated with the Department of Psychiatry and Behavioral Sciences, University of California San Francisco, 675 18th St, SF, CA 94107, and with San Francisco Veteran's Affairs Medical Center, 4150 Clement St. San Francisco, CA 94121. **Josh Woolley, MD/PhD** is affiliated with San Francisco Veteran's Affairs Medical Center, 4150 Clement St. San Francisco, CA 94121, and with the Department of Psychiatry and Behavioral Sciences, Weill Institute of Neuroscience, University of California San Francisco, 675 18th St. San Francisco, CA 94107. Author Email: Stephanie.Haft@ucsf.edu; ellen.bradley@ucsf.edu; aoife.odonovan@ucsf.edu; josh.woolley@ucsf.edu.

Continued from cover

and 5-HT1A receptors. These actions lead to acute effects lasting 2 to 4 hours, including mood elevation and a heightened sense of emotional connection and empathy. In healthy individuals, MDMA reduces amygdala activity while increasing prefrontal cortex activity (Feduccia & Mithoefer, 2018), which may help PTSD patients process traumatic memories without feeling overwhelmed. MDMA-assisted therapy (MDMA-AT) is currently the most researched psychedelic treatment for PTSD. Compelling results from phase 2 RCTs led the FDA to designate MDMA-AT as a "breakthrough therapy" in 2017, prompting expansion into phase 3 trials.

The first published phase 3 RCT of MDMA-AT included 90 participants with severe PTSD from the US, Canada, and Israel (Mitchell et al., 2021). The study design mirrored earlier phase 2 trials, with participants randomized to either three administrations (spaced 1 month apart) of MDMA or placebo combined with ~50 hours of psychotherapy (with two therapists present). The MDMA-AT group had significantly greater reductions in PTSD symptoms compared to the placebo group after treatment, yielding a large between-group effect size (Cohen's $d = 0.91$). Participants in the MDMA-AT group were twice as likely to recover from their PTSD diagnosis and showed greater reductions in clinician-rated functional impairment ($d = 0.43$). The second phase 3 RCT included 104 participants with moderate to severe PTSD in the US and Israel (Mitchell et al., 2023) and used the same study design; again, the MDMA-AT group had significantly larger reductions in PTSD symptoms ($d = 0.70$) and functional impairment compared to the control group (d = 0.40). To make the results more generalizable, this trial included a demographically diverse sample, with 61% of participants identifying as belonging to racial or ethnic minoritized groups. This diversity addresses a common criticism of psychedelic therapy studies, which often underrepresent these populations despite their higher rates of PTSD. There were no reported serious adverse events in either RCT.

MDMA's effectiveness for treating PTSD may reflect enhanced emotional processing and increased openness, possibly mediated by the drug's serotonergic, dopaminergic, and oxytocinergic effects. For example, a secondary analysis of Mitchell et al. (2021) found that the MDMA-AT group showed significantly greater gains in self-compassion and reductions in alexithymia post-treatment compared to the control group (van der Kolk et al., 2024). This study is one of the few to investigate potential change mechanisms in MDMA-AT—however, formal mediational analysis is needed to establish causal links, and these associational findings do not preclude other mechanisms of action. Future research investigating the precise mechanisms of MDMA-AT is needed to optimize the intervention and determine which patients are most likely to benefit.

FDA Response to MDMA-Assisted Therapy

Findings from the two-phase 3 trials of MDMA-AT for PTSD supported a new drug application to the FDA in December 2023 by Lykos Therapeutics (formerly the Public Benefit Corporation of the Multidisciplinary Association for Psychedelic Studies, MAPS). However, the Institute for Clinical and Economic Review (ICER) raised concerns about the safety and efficacy of MDMA-AT, particularly long-term safety, ineffective masking, and the influence of expectancy effects. The subjective effects of MDMA, including its euphoric and empathogenic properties, make effective masking difficult. Indeed, in the Mitchell et al. (2023) study, 85% of participants correctly guessed their treatment allocation, with only one person in the MDMA group believing they received a placebo. Ineffective masking may have led participants in the MDMA group to expect positive changes, and those in the placebo group to expect negative outcomes related to disappointment. It is difficult to determine the influence of these expectancy effects on treatment outcomes. Additionally, ICER highlighted concerns about the generalizability of the results, as the phase 3 trials were conducted under highly controlled conditions that may not reflect typical clinical settings. The report also disclosed ethical concerns with the RCTs, including reports of substantial boundary violations by study therapists, questions about incomplete reporting of adverse events, and biases regarding who was allowed into the long-term follow-up period. Overall, the report concluded that "currently publicly available evidence for MDMA-AT is insufficient" (p. ES2).

In June 2024, an FDA advisory panel voted against approving MDMA-AT for PTSD, citing similar concerns as the ICER report. The FDA followed this recommendation, formally denying approval in August 2024. The rejection came as a surprise to many, given the apparently compelling data from the phase 3 trials (Beachy et al., 2024). This decision underscores the need for more rigorous research on the safety and efficacy of psychedelic treatments.

Psilocybin-Assisted Therapy for PTSD

Psilocybin, the active ingredient in hallucinogenic mushrooms, is a serotonergic agonist predominantly at the 5HT-2A receptor that produces potent psychedelic effects (Garcia-Romeu et al., 2016). In healthy individuals, single administrations of psilocybin increase optimism and introspection and reduce negative mood (Garcia-Romeu et al., 2016). While no published RCTs have directly examined psilocybin for PTSD, several studies highlight its safety and potential efficacy in addressing mental health issues often comorbid with PTSD, including depression and anxiety (Khan et al., 2022). Moreover, it is possible that psilocybin could directly impact mechanisms of PTSD development and maintenance. A recent preclinical study found that psilocybin administration enhanced fear extinction, with a specific dose showing lasting effects on fear renewal (Woodburn et al., 2024). Psilocybin was effective only when administered concurrently with extinction exposure, suggesting that simultaneous behavior modification may be necessary to produce enhancement of fear extinction.

Two large-scale RCTs have examined psilocybin therapy for the treatment of depression, which has overlapping symptoms and is highly comorbid with PTSD. An international phase 2b trial (Goodwin et al., 2022) randomized people with treatment-resistant depression (TRD) to receive psilocybin 25 mg, 10 mg, or 1 mg (considered placebo), each paired with psychotherapy. Nearly a third of participants in the 25 mg arm experienced rapid remission—a response rate much higher than the typical 10-20% observed in TRD-given standard treatments. Similarly, a 2023 multisite study found that participants with major depressive disorder (MDD) had rapid and sustained reductions in depressive symptoms after a 25 mg dose of psilocybin with psychotherapy (Raison et al., 2023). Given psilocybin's promise in treating mood symptoms, several clinical trials are currently recruiting to test its efficacy for PTSD (e.g., Davis et al., 2023).

An open-label pilot study of psilocybin-assisted group therapy in 18 long-term AIDS survivors (Anderson et al., 2020) found substantial reductions in the primary outcome of demoralization (η_p^2 = 0.47). Results also indicated reductions in PTSD symptoms (9-point drop in PTSD Checklist-5 (PCL-5) scores; clinically significant change threshold = 10 points). Effect sizes were medium to large (d = 0.72 post-treatment; d = 0.51 at 3-month follow-up) despite only three study participants having PCL-5 scores above the clinical threshold for PTSD. These findings offer preliminary support for the feasibility, safety, and potential efficacy of psilocybin-assisted therapy for individuals facing significant traumatic loss.

Ibogaine and 5-MeO-DMT Therapy for PTSD

Ibogaine and 5-MeO-DMT are "atypical" psychedelics that are emerging as potential psychiatric treatments. The neuropharmacology of the alkaloid ibogaine is not completely understood, although its NMDA receptor antagonism and opiate receptor-mediated signaling are thought to contribute to its antiaddiction effects (Garcia-Romeu et al., 2016). Ibogaine's subjective effects include vivid hallucinations (4 to 8 hours), a period of deep introspection (8 to 20 hours), and a residual phase of heightened awareness (up to 72 hours). In contrast to this longer timeframe, the indolealkylamine 5-MeO-DMT is typically inhaled or insufflated and produces rapid and intense effects typically lasting only 5 to 20 minutes. 5-MeO-DMT acts primarily on serotonin receptors, leading to mystical experiences such as increased awe and loss of awareness of time and space (Davis et al., 2018).

Two observational Ibogaine studies found positive effects for substance use disorders and mood, prompting interest in its use for PTSD. One study involved 30 Special Operations Forces (SOF) Veterans with traumatic brain injuries, 77% of whom met PTSD criteria (Cherian et al., 2024). After group preparatory and ceremonial activities at a retreat center in Mexico, participants received an ibogaine dose (with magnesium supplementation for cardioprotection) alongside monitoring support and follow-up integration activities the next day. Participants experienced immediate, significant reductions in PTSD symptoms (d = 2.54), functional impairment (d = 0.74), and suicidal ideation—a key finding given the high suicide rates among Veterans with PTSD. Another observational study involved 86 trauma-exposed SOF Veterans who received ibogaine followed by 5-MeO-DMT at a residential clinic in Mexico (Davis, Xin, et al., 2023). Therapeutic support included group and individual preparation and integration sessions, with monitoring during dosing. Improvements in PTSD symptoms (d = 0.41), depression (d = 0.28), anxiety (d = 0.28), and life satisfaction (d = 0.37) were noted 3 days after treatment, with benefits lasting 6 months. Both studies highlight ibogaine's and 5-MeO-DMT's rapid effects on PTSD symptoms, a stark contrast to conventional treatments that often take weeks or months to show results. However, the observational design of these studies and significant extra-pharmacological treatment components limit our ability to draw conclusions about the efficacy of either drug. Prospective RCTs with standardized protocols are an essential next step.

Ethical Considerations and Future Directions

The recent FDA decision to reject MDMA for treating PTSD likely represents a delay, rather than the end, of psychedelic treatments for mental health conditions including PTSD. The rejection may provide an impetus for investigators to improve psychedelic study designs, allowing for more robust comparisons of psychedelic therapy to extant evidence-based treatments for PTSD. Indeed, future studies will likely benefit from Lykos Therapeutics' experience, applying lessons learned to enhance rigor.

A recently published viewpoint co-authored by a patient abused in an MDMA-AT trial (McNamee et al., 2023) emphasized the need for future psychedelic therapy research to incorporate more rigorous measurements of adverse events and potential harms experienced by study participants. Specifically, the authors recommended using phenomenological research to understand possible harm arising from the psychotherapy component of psychedelic therapy, which can involve heightened suggestibility and dependence on the therapist. The article's suggestion to further clarify the role of the psychotherapeutic component in psychedelic therapy is especially salient, given that this was a point of contention in the FDA's rejection. The article also echoed commonly discussed concerns about masking and expectancy effects, which will continue to be challenges that the field of psychedelic therapy must grapple with and solve. By upholding rigorous methods and stringent ethics in psychedelic therapy treatment trials, researchers can ensure that safe and increasingly more effective treatments are available for the millions affected by PTSD.

Featured Articles

Anderson, B. T., Danforth, A., Daroff, R., Stauffer, C., Ekman, E., Agin-Liebes, G., Trope, A., Boden, M. T., Dilley, J., Mitchell, J., & Woolley, J. (2020). **Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study.** *EClinicalMedicine, 27,*100538. doi:10.1016/j.eclinm.2020.100538 *Background:* Psilocybin therapy has shown promise as a rapid-acting treatment for depression, anxiety, and demoralization in patients with serious medical illness (e.g., cancer) when paired with individual psychotherapy. This study assessed the safety and feasibility of psilocybin-assisted group therapy for demoralization in older long-term AIDS survivor (OLTAS) men, a population with a high degree of demoralization and traumatic loss. *Methods:* Self-identified gay men OLTAS with moderate-to-severe demoralization (Demoralization Scale-II ≥8) were recruited from the community of a major US city for a single-site open-label study of psilocybin-assisted group therapy comprising 8-10 group therapy visits and one psilocybin administration visit (0·3-0·36 mg/kg po). Primary outcomes were rate and severity of adverse events, and participant recruitment and retention. The primary clinical outcome was change in mean demoralization from baseline to end-of-treatment and to 3-month follow-up assessed with a two-way repeated measures ANOVA. Trial registration: Clinicaltrials.gov (NCT02950467). *Findings:* From 17 July 2017 to 16 January 2019, 18 participants (mean age 59·2 years (SD 4·4)) were enrolled, administered group therapy and psilocybin, and included in intent-to-treat analyses. We detected zero serious adverse reactions and two unexpected adverse reactions to psilocybin; seven participants experienced self-limited, severe expected adverse reactions. We detected a clinically meaningful change in demoralization from baseline to 3-month follow-up (mean difference -5·78 [SD 6·01], ηp 2 = 0·47, 90% CI 0·21-0·60). *Interpretation:* We demonstrated the feasibility, relative safety, and potential efficacy of psilocybin-assisted group

therapy for demoralization in OLTAS. Groups may be an effective and efficient means of delivering psychotherapy pre- and post-psilocybin to patients with complex medical and psychiatric needs.

Cherian, K. N., Keynan, J. N., Anker, L., Faerman, A., Brown, R. E., Shamma, A., Keynan, O., Coetzee, J. P., Batail, J.-M., & Phillips, A., Bassano N. J., Sahlem, G. L., Inzunza, J., Millar, T., Dickinson, J., Rolle, C. E., Keller, J., Adamson, M., Kratter, I. H., & Williams, N. R. (2024). **Magnesium–ibogaine therapy in veterans with traumatic brain injuries.** *Nature Medicine, 30*(2), 373–381. doi:10.1038/s41591-023-02705-w Traumatic brain injury (TBI) is a leading cause of disability. Sequelae can include functional impairments and psychiatric syndromes such as post-traumatic stress disorder (PTSD), depression and anxiety. Special Operations Forces (SOF) Veterans (SOVs) may be at an elevated risk for these complications, leading some to seek underexplored treatment alternatives such as the oneirogen ibogaine, a plant-derived compound known to interact with multiple neurotransmitter systems that has been studied primarily as a treatment for substance use disorders. Ibogaine has been associated with instances of fatal cardiac arrhythmia, but coadministration of magnesium may mitigate this concern. In the present study, we report a prospective observational study of the Magnesium-Ibogaine: the Stanford Traumatic Injury to the CNS protocol (MISTIC), provided together with complementary treatment modalities, in 30 male SOVs with predominantly mild TBI. We assessed changes in the World Health Organization Disability Assessment Schedule from baseline to immediately (primary outcome) and 1 month (secondary outcome) after treatment. Additional secondary outcomes included changes in PTSD (Clinician-Administered PTSD Scale for *DSM-5*), depression (Montgomery-Åsberg Depression Rating Scale) and anxiety (Hamilton Anxiety Rating Scale). MISTIC resulted in significant improvements in functioning both immediately ($P_{corrected} < 0.001$, Cohen's $d = 0.74$) and 1 month ($P_{corrected} < 0.001$, $d = 2.20$) after treatment and in PTSD (Pcorrected < 0.001, $d = 2.54$), depression ($P_{corrected} < 0.001$, $d = 2.80$) and anxiety ($P_{corrected} < 0.001$, $d = 2.13$) at 1 month after treatment. There were no unexpected or serious adverse events. Controlled clinical trials to assess safety and efficacy are needed to validate these initial open-label findings.

Davis, A. K., Xin, Y., Sepeda, N., & Averill, L. A. (2023a). **Open-label study of consecutive ibogaine and 5-MeO-DMT assisted-therapy for trauma-exposed male Special Operations Forces Veterans: Prospective data from a clinical program in Mexico.** *The American Journal of Drug and Alcohol Abuse, 49*(5), 587–596. doi:10.1080/00952990.2023.2220874 *Background:* Research in psychedelic medicine has focused primarily on civilian populations. Further study is needed to understand whether these treatments are effective for Veteran populations. Objectives: Here, we examine the effectiveness of psychedelic-assisted therapy among trauma-exposed Special Operations Forces Veterans (SOFV) seeking treatment for cognitive and mental health problems in Mexico. *Methods:* Data were collected from an ibogaine and 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) clinical treatment program for SOFV with a history of trauma exposure. This clinical program collects prospective clinical program evaluation data, such as background characteristics, symptom severity, functioning (e.g., satisfaction with life, posttraumatic stress disorder symptoms, depression symptoms, anxiety symptoms, sleep disturbance, psychological flexibility, disability in functioning, cognitive functioning, neurobehavioral symptoms, anger, suicidal ideation), and substance persisting/enduring effects through online surveys at four timepoints (baseline/pre-treatment, 1-, 3-, and 6 months after treatment). *Results:* The majority of the sample ($n = 86$; Mean Age = 42.88, SD = 7.88) were Caucasian (87.2%), non-Hispanic (89.5%), and males (100%). There were significant and large improvements in self-reported PTSD symptoms ($p < .001$, $d = 0.414$), depression ($p < 0.001$, $d = 0.275$), anxiety ($p < 0.001$, $d = 0.276$), insomnia severity ($p < 0.001$, $d = 0.351$), and post-concussive symptoms ($p < .001$, $d = 0.389$) as well as self-reported satisfaction with life ($p < 0.001$, $d = 0.371$), psychological flexibility ($p < 0.001$, $d = 0.313$) and cognitive functioning ($p < 0.001$, $d = 0.265$) from baseline to 1-month follow-up. *Conclusions:* Data suggest combined ibogaine and 5-MeO-DMT assisted therapy has the potential to provide rapid and robust changes in mental health functioning with a signal of durable therapeutic effects up to 6 months. Future research in controlled settings is warranted.

Goodwin, G. M., Aaronson, S. T., Alvarez, O., Arden, P. C., Baker, A., Bennett, J. C., Bird, C., Blom, R. E., Brennan, C., Brusch, D., Burke, L., Campbell-Coker, K., Carhart-Harris, R., Cattell, J., Daniel, A., DeBattista, C., Dunlop, B. W., Eisen, K., Feifel, D., … Malievskaia, E. (2022). **Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression.** *The New England Journal of Medicine, 387*(18), 1637–1648. doi:10.1056/NEJMoa2206443 *Background:* Psilocybin is being studied for use in treatment-resistant depression. *Methods:* In this phase 2 double-blind trial, we randomly assigned adults with treatment-resistant depression to receive a single dose of a proprietary, synthetic formulation of psilocybin at a dose of 25 mg, 10 mg, or 1 mg (control), along with psychological support. The primary end point was the change from baseline to week 3 in the total score on the Montgomery–Åsberg Depression Rating Scale (MADRS; range, 0 to 60, with higher scores indicating more severe depression). Secondary end points included response at week 3 (≥ 50% decrease from baseline in the MADRS total score), remission at week 3 (MADRS total score ≤ 10), and sustained response at 12 weeks (meeting response criteria at week 3 and all subsequent visits). *Results:* A total of 79 participants were in the 25-mg group, 75 in the 10-mg group, and 79 in the 1-mg group. The mean MADRS total score at baseline was 32 or 33 in each group. Least-squares mean changes from baseline to week 3 in the score were −12.0 for 25 mg, −7.9 for 10 mg, and −5.4 for 1 mg; the difference between the 25-mg group and 1-mg group was −6.6 (95% confidence interval [CI], −10.2 to −2.9; $P < 0.001$) and between the 10-mg group and 1-mg group was −2.5 (95% CI, −6.2 to 1.2; $P = 0.18$). In the 25-mg group, the incidences of response and remission at 3 weeks, but not sustained response at 12 weeks, were generally supportive of the primary results. Adverse events occurred in 179 of 233 participants (77%) and included headache, nausea, and dizziness. Suicidal ideation or behavior or self-injury occurred in all dose groups. *Conclusions:* In this phase 2 trial involving participants with treatment-resistant depression, psilocybin at a single dose of 25 mg, but not 10 mg, reduced depression scores significantly more than a 1-mg dose over a period of 3 weeks but was associated with adverse effects. Larger and longer

trials, including comparison with existing treatments, are required to determine the efficacy and safety of psilocybin for this disorder.

McNamee, S., Devenot, N., & Buisson, M. (2023). **Studying harms is key to improving psychedelic-assisted therapy—participants call for changes to research landscape.** *JAMA Psychiatry, 80*(5), 411–412. doi:10.1001/jamapsychiatry.2023.0099 Although psychedelic drugs generally have good safety profiles, a recent systematic review concluded that adverse events in psychedelic trials are poorly defined, not systematically assessed, and likely underreported. In the past year there have been multiple reports of serious adverse events (SAEs), and long-lasting harms to participants in clinical trials of psychedelic-assisted therapy (PAT) have emerged. We draw attention to a unique and overlooked category of risk in PAT stemming from the interactions between therapists and patients receiving high doses of psychedelics. In our view, the understudied therapeutic component of PAT presents the most serious risks. Addressing it requires interdisciplinary approaches by researchers free from conflicts of interests. [Adapted]

Mitchell, J. M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., Ot'alora G, M., Garas, W., Paleos, C., Gorman, I., Nicholas, C., Mithoefer, M., Carlin, S., Poulter, B., Mithoefer, A., Quevedo, S., Wells, G., Klaire, S. S., van der Kolk, B., … Doblin, R. (2021). **MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study.** *Nature Medicine, 27*(6), 1025–1033. doi:10.1038/s41591-021-01336-3 Post-traumatic stress disorder (PTSD) presents a major public health problem for which currently available treatments are modestly effective. We report the findings of a randomized, double-blind, placebo-controlled, multi-site phase 3 clinical trial (NCT03537014) to test the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for the treatment of patients with severe PTSD, including those with common comorbidities such as dissociation, depression, a history of alcohol and substance use disorders, and childhood trauma. After psychiatric medication washout, participants (n = 90) were randomized 1:1 to receive manualized therapy with MDMA or with placebo, combined with three preparatory and nine integrative therapy sessions. PTSD symptoms, measured with the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5, the primary endpoint), and functional impairment, measured with the Sheehan Disability Scale (SDS, the secondary endpoint) were assessed at baseline and at 2 months after the last experimental session. Adverse events and suicidality were tracked throughout the study. MDMA was found to induce significant and robust attenuation in CAPS-5 score compared with placebo ($P < 0.0001$, $d = 0.91$) and to significantly decrease the SDS total score ($P = 0.0116$, $d = 0.43$). The mean change in CAPS-5 scores in participants completing treatment was –24.4 (s.d. 11.6) in the MDMA group and –13.9 (s.d. 11.5) in the placebo group. MDMA did not induce adverse events of abuse potential, suicidality or QT prolongation. These data indicate that, compared with manualized therapy with inactive placebo, MDMA-assisted therapy is highly efficacious in individuals with severe PTSD, and treatment is safe and well-tolerated, even in those with comorbidities. We conclude that MDMA-assisted therapy represents a potential breakthrough treatment that merits expedited clinical evaluation.

Mitchell, J. M., Ot'alora G, M., van der Kolk, B., Shannon, S., Bogenschutz, M., Gelfand, Y., Paleos, C., Nicholas, C. R., Quevedo, S., & Balliett, B. (2023). **MDMA-assisted therapy for moderate to severe PTSD: A randomized, placebo-controlled phase 3 trial.** *Nature Medicine, 29*(10), 2473–2480. doi:10.1038/s41591-023-02565-4 This multi-site, randomized, double-blind, confirmatory phase 3 study evaluated the efficacy and safety of 3,4-methylenedioxymethamphetamine-assisted therapy (MDMA-AT) versus placebo with identical therapy in participants with moderate to severe post-traumatic stress disorder (PTSD). Changes in Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) total severity score (primary endpoint) and Sheehan Disability Scale (SDS) functional impairment score (key secondary endpoint) were assessed by blinded independent assessors. Participants were randomized to MDMA-AT ($n = 53$) or placebo with therapy ($n = 51$). Overall, 26.9% (28/104) of participants had moderate PTSD, and 73.1% (76/104) of participants had severe PTSD. Participants were ethnoracially diverse: 28 of 104 (26.9%) identified as Hispanic/Latino, and 35 of 104 (33.7%) identified as other than White. Least squares (LS) mean change in CAPS-5 score (95% confidence interval (CI)) was -23.7 (-26.94, -20.44) for MDMA-AT versus -14.8 (-18.28, -11.28) for placebo with therapy ($P < 0.001$, $d = 0.7$). LS mean change in SDS score (95% CI) was -3.3 (-4.03, -2.60) for MDMA-AT versus -2.1 (-2.89, -1.33) for placebo with therapy ($P = 0.03$, $d = 0.4$). Seven participants had a severe treatment emergent adverse event (TEAE) (MDMA-AT, $n = 5$ (9.4%); placebo with therapy, $n = 2$ (3.9%)). There were no deaths or serious TEAEs. These data suggest that MDMA-AT reduced PTSD symptoms and functional impairment in a diverse population with moderate to severe PTSD and was generally well tolerated.

Raison, C. L., Sanacora, G., Woolley, J., Heinzerling, K., Dunlop, B. W., Brown, R. T., Kakar, R., Hassman, M., Trivedi, R. P., Robison, R., Gukasyan, N., Nayak, S. M., Hu, X., O'Donnell, K. C., Kelmendi, B., Sloshower, J., Penn, A. D., Bradley, E., Kelly, D. F., … Griffiths, R. R. (2023). **Single-dose psilocybin treatment for major depressive disorder: A randomized clinical trial.** *JAMA, 330*(9), 843–853. doi:10.1001/jama.2023.14530 *Importance:* Psilocybin shows promise as a treatment for major depressive disorder (MDD). *Objective:* To evaluate the magnitude, timing, and durability of antidepressant effects and safety of a single dose of psilocybin in patients with MDD. Design, Setting, and Participants: In this phase 2 trial conducted between December 2019 and June 2022 at 11 research sites in the US, participants were randomized in a 1:1 ratio to receive a single dose of psilocybin vs niacin placebo administered with psychological support. Participants were adults aged 21 to 65 years with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition diagnosis of MDD of at least 60 days' duration and moderate or greater symptom severity. Exclusion criteria included history of psychosis or mania, active substance use disorder, and active suicidal ideation with intent. Participants taking psychotropic agents who otherwise met inclusion/exclusion criteria were eligible following medication taper. Primary and secondary outcomes and adverse events (AEs) were assessed at baseline (conducted within 7 days before dosing) and at 2, 8, 15, 29, and 43 days after dosing. Interventions: Interventions were a 25-mg dose of synthetic psilocybin or a 100-mg dose of niacin in identical-appearing capsules, each administered with psychological support.

Main Outcomes and Measures: The primary outcome was change in central rater–assessed Montgomery-Asberg Depression Rating Scale (MADRS) score (range, 0-60; higher scores indicate more severe depression) from baseline to day 43. The key secondary outcome measure was change in MADRS score from baseline to day 8. Other secondary outcomes were change in Sheehan Disability Scale score from baseline to day 43 and MADRS-defined sustained response and remission. Participants, study site personnel, study sponsor, outcome assessors (raters), and statisticians were blinded to treatment assignment. *Results:* A total of 104 participants (mean [SD] age, 41.1 [11.3] years; 52 [50%] women) were randomized (51 to the psilocybin group and 53 to the niacin group). Psilocybin treatment was associated with significantly reduced MADRS scores compared with niacin from baseline to day 43 (mean difference,–12.3 [95% CI, –17.5 to –7.2]; $P < .001$) and from baseline to day 8 (mean difference, –12.0 [95% CI, –16.6 to –7.4]; $P < .001$). Psilocybin treatment was also associated with significantly reduced Sheehan Disability Scale scores compared with niacin (mean difference, –2.31 [95% CI, –3.50 to –1.11]; $P < .001$) from baseline to day 43. More participants receiving psilocybin had sustained response (but not remission) than those receiving niacin. There were no serious treatment-emergent AEs; however, psilocybin treatment was associated with a higher rate of overall AEs and a higher rate of severe AEs. *Conclusions and Relevance:* Psilocybin treatment was associated with a clinically significant sustained reduction in depressive symptoms and functional disability, without serious adverse events. These findings add to increasing evidence that psilocybin—when administered with psychological support—may hold promise as a novel intervention for MDD.

van der Kolk, B. A., Wang, J. B., Yehuda, R., Bedrosian, L., Coker, A. R., Harrison, C., Mithoefer, M., Yazar-Klosinki, B., Emerson, A., & Doblin, R. (2024). **Effects of MDMA-assisted therapy for PTSD on self-experience.** *PLoS One, 19*(1), e0295926. doi:10.1371/journal.pone.0295926 *Introduction:* There is a resurgence of interest in the therapeutic potential of psychedelic substances such as 3,4-methylenedioxymethamphetamine (MDMA). Primary findings from our randomized, double-blind, placebo-controlled, multi-site Phase 3 clinical trial of participants with severe PTSD (NCT03537014) showed that MDMA-assisted therapy induced significant attenuation in the Clinician-Administered PTSD Scale for DSM-5 compared to Therapy with placebo. Deficits in emotional coping skills and altered self-capacities constitute major obstacles to successful completion of available treatments. The current analysis evaluated the differential effects of MDMA-assisted therapy and Therapy with placebo on 3 transdiagnostic outcome measures and explored the contribution of changes in self-experience to improvement in PTSD scores. *Methods:* Participants were randomized to receive manualized therapy with either MDMA or placebo during 3 experimental sessions in combination with 3 preparation and 9 integration therapy visits. Symptoms were measured at baseline and 2 months after the last experimental session using the 20-item Toronto Alexithymia Scale (TAS-20), the 26-item Self Compassion Scale (SCS), and the 63-item Inventory of Altered Self-Capacities (IASC). *Results:* 90 participants were randomized and dosed (MDMA-assisted therapy, $n = 46$; Therapy with placebo, $n = 44$); 84.4% (76/90) had histories of developmental trauma, and 87.8% (79/90) had suffered multiple traumas. MDMA-assisted therapy facilitated statistically significant greater improvement on the TAS-20, the SCS, and most IASC factors of interpersonal conflicts; idealization disillusionment; abandonment concerns; identity impairment; self-awareness; susceptibility to influence; affect dysregulation; affect instability; affect skill deficit; tension reduction activities; the only exception was identity diffusion. *Conclusion:* Compared with Therapy with placebo, MDMA-assisted therapy had significant positive effects on transdiagnostic mental processes of self-experience which are often associated with poor treatment outcome. This provides a possible window into understanding the psychological capacities facilitated by psychedelic agents that may result in significant improvements in PTSD symptomatology.

Woodburn, S. C., Levitt, C. M., Koester, A. M., & Kwan, A. C. (2024). **Psilocybin facilitates fear extinction: Importance of dose, context, and serotonin receptors.** *ACS Chemical Neuroscience, 15*(16), 3034–3043. doi:10.1021/acschemneuro.4c00279 A variety of classic psychedelics and MDMA have been shown to enhance fear extinction in rodent models. This has translational significance because a standard treatment for post-traumatic stress disorder (PTSD) is prolonged exposure therapy. However, few studies have investigated psilocybin's potential effect on fear learning paradigms. More specifically, the extents to which dose, timing of administration, and serotonin receptors may influence psilocybin's effect on fear extinction are not understood. In this study, we used a delay fear conditioning paradigm to determine the effects of psilocybin on fear extinction, extinction retention, and fear renewal in male and female mice. Psilocybin robustly enhances fear extinction when given acutely prior to testing for all doses tested. Psilocybin also exerts long-term effects to elevate extinction retention and suppress fear renewal in a novel context, although these changes were sensitive to dose. Analysis of sex differences showed that females may respond to a narrower range of doses than males. Administration of psilocybin prior to fear learning or immediately after extinction yielded no change in behavior, indicating that concurrent extinction experience is necessary for the drug's effects. Cotreatment with a 5-HT2A receptor antagonist blocked psilocybin's effects for extinction, extinction retention, and fear renewal, whereas 5-HT1A receptor antagonism attenuated only the effect on fear renewal. Collectively, these results highlight dose, context, and serotonin receptors as crucial factors in psilocybin's ability to facilitate fear extinction. The study provides preclinical evidence to support investigating psilocybin as a pharmacological adjunct for extinction-based therapy for PTSD.

References (* indicates 14 featured in article)

*Anderson, B. T., Danforth, A., Daroff, R., Stauffer, C., Ekman, E., Agin-Liebes, G., Trope, A., Boden, M. T., Dilley, J., Mitchell, J., & Woolley, J. (2020). **Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study.** *EClinicalMedicine, 27,*100538. doi:10.1016/j.eclinm.2020.100538

*Cherian, K. N., Keynan, J. N., Anker, L., Faerman, A., Brown, R. E., Shamma, A., Keynan, O., Coetzee, J. P., Batail, J.-M., & Phillips, A., Bassano N. J., Sahlem, G. L., Inzunza, J., Millar, T., Dickinson, J., Rolle, C. E., Keller, J., Adamson, M.,

REFERENCES *continued*

Kratter, I. H., & Williams, N. R. (2024). **Magnesium–ibogaine therapy in veterans with traumatic brain injuries.** *Nature Medicine, 30*(2), 373–381. doi:10.1038/s41591-023-02705-w

*Davis, A. K., Barsuglia, J. P., Lancelotta, R., Grant, R. M., & Renn, E. (2018). **The epidemiology of 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) use: Benefits, consequences, patterns of use, subjective effects, and reasons for consumption.** *Journal of Psychopharmacology, 32*(7), 779-792. doi:10.1177/0269881118769063

Davis, A. K., Levin, A. W., Nagib, P. B., Armstrong, S. B., & Lancelotta, R. L. (2023a). **Study protocol of an open-label proof-of-concept trial examining the safety and clinical efficacy of psilocybin-assisted therapy for veterans with PTSD.** *BMJ Open, 13*(5), e068884. doi:10.1136/bmjopen-2022-068884

*Davis, A. K., Xin, Y., Sepeda, N., & Averill, L. A. (2023b). **Open-label study of consecutive ibogaine and 5-MeO-DMT assisted-therapy for trauma-exposed male Special Operations Forces Veterans: Prospective data from a clinical program in Mexico.** *The American Journal of Drug and Alcohol Abuse, 49*(5), 587–596. doi:10.1080/00952990.2023.2220874

*Feduccia, A. A., & Mithoefer, M. C. (2018). MDMA-assisted psychotherapy for PTSD: **Are memory reconsolidation and fear extinction underlying mechanisms?** *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 84*(Pt A), 221–228. doi:10.1016/j.pnpbp.2018.03.003

*Garcia-Romeu, A., Kersgaard, B., & Addy, P. H. (2016). **Clinical applications of hallucinogens: A review.** *Experimental and Clinical Psychopharmacology, 24*(4), 229–268. doi:10.1037/pha0000084

*Goodwin, G. M., Aaronson, S. T., Alvarez, O., Arden, P. C., Baker, A., Bennett, J. C., Bird, C., Blom, R. E., Brennan, C., Brusch, D., Burke, L., Campbell-Coker, K., Carhart-Harris, R., Cattell, J., Daniel, A., DeBattista, C., Dunlop, B. W., Eisen, K., Feifel, D., … Malievskaia, E. (2022). **Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression.** *The New England Journal of Medicine, 387*(18), 1637–1648. doi:10.1056/NEJMoa2206443

*Khan, A. J., Bradley, E., O'Donovan, A., & Woolley, J. (2022). **Psilocybin for trauma-related disorders.** *Disruptive Psychopharmacology,* 319–332. doi:10.1007/7854_2022_366

*McNamee, S., Devenot, N., & Buisson, M. (2023). **Studying harms is key to improving psychedelic-assisted therapy—participants call for changes to research landscape.** *JAMA Psychiatry, 80*(5), 411–412. doi:10.1001/jamapsychiatry.2023.0099

*Mitchell, J. M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., Ot'alora G, M., Garas, W., Paleos, C., Gorman, I., Nicholas, C., Mithoefer, M., Carlin, S., Poulter, B., Mithoefer, A., Quevedo, S., Wells, G., Klaire, S. S., van der Kolk, B., … Doblin, R. (2021). **MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study.** *Nature Medicine, 27*(6), 1025–1033. doi:10.1038/s41591-021-01336-3

*Mitchell, J. M., Ot'alora G, M., van der Kolk, B., Shannon, S., Bogenschutz, M., Gelfand, Y., Paleos, C., Nicholas, C. R., Quevedo, S., & Balliett, B. (2023). **MDMA-assisted therapy for moderate to severe PTSD: A randomized, placebo-controlled phase 3 trial.** *Nature Medicine, 29*(10), 2473–2480. doi:10.1038/s41591-023-02565-4

*Raison, C. L., Sanacora, G., Woolley, J., Heinzerling, K., Dunlop, B. W., Brown, R. T., Kakar, R., Hassman, M., Trivedi, R. P., Robison, R., Gukasyan, N., Nayak, S. M., Hu, X., O'Donnell, K. C., Kelmendi, B., Sloshower, J., Penn, A. D., Bradley, E., Kelly, D. F., … Griffiths, R. R. (2023). **Single-dose psilocybin treatment for major depressive disorder: A randomized clinical trial.** *JAMA, 330*(9), 843–853. doi:10.1001/jama.2023.14530

*van der Kolk, B. A., Wang, J. B., Yehuda, R., Bedrosian, L., Coker, A. R., Harrison, C., Mithoefer, M., Yazar-Klosinki, B., Emerson, A., & Doblin, R. (2024). **Effects of MDMA-assisted therapy for PTSD on self-experience.** *PLoS One, 19*(1), e0295926. doi:10.1371/journal.pone.0295926

*Woodburn, S. C., Levitt, C. M., Koester, A. M., & Kwan, A. C. (2024). **Psilocybin facilitates fear extinction: Importance of dose, context, and serotonin receptors.** *ACS Chemical Neuroscience, 15*(16), 3034–3043. doi:10.1021/acschemneuro.4c00279