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How and why could MDMA-assisted psychotherapy treat PTSD?

DATE PUBLISHED

3 September 2021



> *The Idea Of Enhancing Psychological Treatment Of Ptsd Pharmacologically To Improve Effectiveness, Increase Tolerability, Or Reduce Dropout Is Not New. However, Results From Previous Pharmacological Approaches, Including D-Cycloserine, Propranolol, And Ssri Augmentation, Have Been Mixed And Overall Disappointing.*

MDMA-assisted psychotherapy is currently undergoing international trials to treat posttraumatic stress disorder (PTSD). Results are encouraging – using MDMA as an add-on to psychotherapy may be helpful for many patients, even those who have suffered from severe PTSD symptoms for decades and for whom other treatments have failed.1,2 Understanding how therapeutic interventions lead to desired outcomes can help us optimize and further develop them, train clinicians to deliver them optimally, and identify patient characteristics on which their effectiveness may depend.3 This is also the case for MDMA-assisted psychotherapy.

Below, I outline what we know and still need to learn about how and why MDMA-assisted psychotherapy might be an effective treatment for PTSD. I argue that with this novel treatment, more patients may be able to adequately process their trauma. While much of its efficacy might be attributable to mechanisms of change shared with other PTSD treatments, such as adaptive changes in trauma-affected beliefs and improved inhibition of unhelpful fear reactions, combining MDMA administration and psychotherapy may also tap into unique recovery processes.

Current strategies to treat PTSD

The best evidence currently suggests that trauma-focused psychological therapies are most effective for treating PTSD. For instance, some commonly used therapies are prolonged exposure, cognitive processing

therapy, narrative exposure therapy, and eye movement desensitization and reprocessing therapy.4 These are typically short, manual-based, broadly cognitive-behavioral interventions. All of them involve engaging with and processing traumatic memories in some way through methods such as imagining and describing the memory or identifying and evaluating problematic thoughts and beliefs related to it. Clinical research demonstrates that these treatments are safe and quite effective, even for people with repeated traumatic experiences or those with more complex symptoms.5-8

Still, existing trauma-focused treatments are far from perfect. Around 10–30 % of patients who intend to start treatment either never start it or drop out before completing it.9,10 A further one third or so experience no meaningful respite from their symptoms despite completing treatment.10 The idea of enhancing psychological treatment of PTSD pharmacologically to improve effectiveness, increase tolerability, or reduce dropout is not new. However, results from previous pharmacological approaches, including d-cycloserine, propranolol, and SSRI augmentation, have been mixed and overall disappointing.11,12 As quite a different approach to pharmacological augmentation, making use of the acute effects of MDMA in psychotherapy appears much more promising.1,2

How and why might MDMA-assisted psychotherapy be a particularly effective treatment for PTSD? First, the unique psychological effects of MDMA may allow more trauma survivors to undergo psychotherapy in the first place and to engage in it intensely enough for it to be helpful. Second, while this MDMA-augmented psychotherapy may promote recovery from PTSD through mechanisms shared with other forms of treatment, it may do so more effectively. Third, it may work through some unique mechanisms of change that other treatments are not able to tap into.

Promoting ability to engage

Based on clinical observations, MDMA seems to reduce avoidance and enable patients to engage in imaginal exposure, wherein they revisit their traumatic memory in their imagination. This may allow them to process traumatic memories which they otherwise feel unable to revisit.13 This could be because MDMA helps patients tolerate the negative emotional reactions associated with the memory better or because it attenuates such reactions in the first place. MDMA tends to reduce anxiety and stress reactivity,14,15 and the ability to detect and process negative emotional information15 – all while promoting an overall happier, more receptive, and open mood.15,16 The stimulating effects of MDMA, on the other hand, elevate levels of arousal, which may increase motivation to engage and make avoidance, withdrawal, or dissociation less likely.15 This combination of effects has led to descriptions of MDMA as providing an “optimal state of engagement for effectively processing traumatic memories”.17 MDMA-induced increases in emotional empathy, trust, and closeness16 are additional factors that may increase willingness and ability to deal with traumatic material, especially as they promote a stronger therapeutic alliance.

Interested in interdisciplinary research investigating how MDMA may foster the therapeutic alliance and how this can contribute to PTSD recovery? Check out this interview with Prof. Gül Dölen about how MDMA and classic psychedelic can modify social learning.

Mechanisms of action shared with other treatments

Provided patients can revisit or re-evaluate their traumatic memories with the help of MDMA, how could this then lead to reduced symptoms and suffering? The most established mechanism of change in recovery from PTSD are changes in maladaptive or dysfunctional posttraumatic appraisals and beliefs.18 Studies have found that positive change in problematic beliefs about the self, others, and the world appears to drive PTSD symptom improvement in many effective treatments.18,19

Clinical research on MDMA-assisted psychotherapy has so far not included typical self-report measures of changes in trauma-affected cognitions, yet there are reasons to believe that it could profoundly affect them. First, the capacity of MDMA to induce empathy and compassion towards oneself may help correct problematic self-related thoughts and feelings such as shame and self-blame. Qualitative research on MDMA-assisted therapy provides examples of such positive re-evaluation of one's own role in the traumatic event and felt blame.20,21 Second, the strong therapeutic alliance and connection to the therapists could act as a corrective experience for re-assessing trauma-affected beliefs about what one can expect from other people. In addition, reduced reactions to social rejection or threat22 and increased experiences of connectedness and closeness15,16 could help patients re-evaluate their relationships with other people, both in relation to their trauma and beyond. Finally, reduced fear, distress, and need for vigilance when recalling the trauma may disprove trauma-induced beliefs about the world, such as that it is a totally unpredictable and dangerous place.

Researchers and treatment developers have suggested that changes in the qualities of the traumatic memories themselves, such as better organization and coherence, less sensory-laden nature, or clearer temporal and spatial context, could be another mechanism behind the effectiveness of trauma-focused treatments,23,24 though empirical evidence is limited.18 Again, while the effects of MDMA-assisted psychotherapy on traumatic memories have not yet been studied with typical measures in humans, animal research and basic research into the neurobiology of memory suggest that MDMA may make traumatic memories more labile and subject to change.25 This could be useful for altering both the qualities of these memories and the emotionally charged meanings and reactions associated with them. At least healthy participants also appear to experience reduced negative mood when thinking about a difficult memory under the influence of MDMA.26 Since memory is a reconstructive process, one's current emotional state greatly influences what we recall about events. Hence, a less negative mood paired with increased empathy and open-mindedness could lead participants to focus on different parts of their traumatic experiences. They could notice perspectives and elements they have previously missed when recalling the event under great distress. The result could be a more complete, balanced memory. For the moment, this is quite speculative, however. Given that MDMA also impairs some aspects of memory function,27 how patients' memories of their traumatic experiences change as a result of recalling and re-evaluating them under the influence of MDMA is an important area for future research.

A third mechanism that MDMA-assisted psychotherapy may share with other treatments concerns how patients learn to inhibit their excessive and unhelpful fear reactions when faced with traumatic memories or their triggers. Previously, methods like imaginal exposure were thought to be therapeutic mainly because links between triggers and fear reactions would gradually weaken through habituation.28 However, more recent research suggests that exposure supports so-called inhibitory learning, where new, overriding connections form between triggers and feelings of safety or at least the lack of danger.29,30 Here, the MDMA state may again be useful. As it lets patients access traumatic memories under feelings of psychological safety and even empathy and love, strong overriding connections may form that function to inhibit the earlier links to a sense of ongoing danger and threat.25 The massive mismatch between what was expected to happen if traumatic

memories are triggered (fear, uncontrollable reactions, panic) and what actually occurred (nothing bad, feeling safe, able to consider the memory from many different perspectives) helps such inhibitory learning.30

Possible unique mechanisms of MDMA-assisted psychotherapy

MDMA-assisted psychotherapy could, of course, have some other, unique psychological mechanisms of action that other treatments do not employ. For one, reduction in PTSD symptoms after giving MDMA in psychotherapy has been found to co-occur with increases in the personality domain 'openness'.31 It is not yet clear, however, whether the increased openness leads to recovery from PTSD, or is better understood as a side-effect of the treatment or even a result of recovery itself.

Surprising insights or revelations about one's life and thinking may constitute another mechanism of change that could be particularly involved in MDMA-assisted psychotherapy.25 Again, the available qualitative research provides examples of such breakthroughs and insights.20,21 Breakthroughs or sudden changes in thought and perspective can certainly occur in other forms of therapy, but they are rare, sought-after events. If this augmented psychotherapy regularly results in meaningful insights or truly fresh perspectives on one's life, this could be an important factor in its effectiveness in treating PTSD as well as other conditions.

Conclusions

In sum, the power of using MDMA as an adjunct to psychotherapy for PTSD may lie in three directions: First, it may help patients to engage in trauma-focused work, both by reducing treatment dropout and by inviting in patients who may be reluctant to engage in treatment because they find confronting their trauma too challenging; second, it may enhance recovery through established therapeutic processes such as adaptive changes in trauma-affected beliefs and improved inhibition of unhelpful fear reactions; and third, its distinctive characteristics may set in motion unique recovery processes, perhaps beyond the resolution of PTSD symptoms.

What should come next? Trials comparing MDMA-assisted psychotherapy to evidence-based psychological treatments would be highly informative both for assessing relative effectiveness and for understanding how mechanisms of action may differ. In addition, future trials would do well to include explicit analyses of psychological mechanisms of change and recovery, using existing, validated measures.

Increased understanding of the mechanisms of change underlying MDMA-assisted psychotherapy can be highly informative for further developing even more effective treatments. Given the evidence for the efficacy of trauma-focused treatments, I am most enthusiastic to see treatment modalities developed and tested that would explicitly focus on processing traumatic memories with the assistance of MDMA. Fortunately, several distinct models of how to use MDMA in psychotherapy are currently being trialed,32,33 and in the longer term, a range of MDMA-assisted psychotherapies could develop.

References:

1. Jerome L, Feduccia AA, Wang JB, Hamilton S, Yazar-Klosinski B, Emerson A, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. Psychopharmacology. 2020 Aug;237(8):2485–97.
2. Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med [Internet]. 2021 May 10 [cited 2021 Jun 8]; Available from: http://www.nature.com/articles/s41591-021-01336-3
3.

Kazdin AE. Mediators and Mechanisms of Change in Psychotherapy Research. Annu Rev Clin Psychol. 2007 Apr;3(1):1–27.

4. Cusack K, Jonas DE, Forneris CA, Wines C, Sonis J, Middleton JC, et al. Psychological treatments for adults with posttraumatic stress disorder: A systematic review and meta-analysis. Clinical Psychology Review. 2016 Feb;43:128–41.
5. Hendriks L, Kleine RA de, Broekman TG, Hendriks G-J, Minnen A van. Intensive prolonged exposure therapy for chronic PTSD patients following multiple trauma and multiple treatment attempts. European Journal of Psychotraumatology. 2018 Jan;9(1):1425574.
6. Karatzias T, Murphy P, Cloitre M, Bisson J, Roberts N, Shevlin M, et al. Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. Psychol Med. 2019 Aug;49(11):1761–75.
7. Van Woudenberg C, Voorendonk EM, Bongaerts H, Zoet HA, Verhagen M, Lee CW, et al. of an intensive treatment programme combining prolonged exposure and eye movement desensitization and reprocessing for severe post-traumatic stress disorder. European Journal of Psychotraumatology. 2018 Jan;9(1):1487225.
8. Zoet HA, Wagenmans A, van Minnen A, de Jongh A. Presence of the dissociative subtype of PTSD does not moderate the outcome of intensive trauma-focused treatment for PTSD. European Journal of Psychotraumatology. 2018 Jan;9(1):1468707.
9. Imel ZE, Laska K, Jakupcak M, Simpson TL. Meta-analysis of dropout in treatments for posttraumatic stress disorder. Journal of Consulting and Clinical Psychology. 2013;81(3):394–404.
10. Lewis C, Roberts NP, Gibson S, Bisson JI. Dropout from psychological therapies for post-traumatic stress disorder (PTSD) in adults: systematic review and meta-analysis. European Journal of Psychotraumatology. 2020 Dec 31;11(1):1709709.
11. Bryant RA. Post traumatic stress disorder: a state of the art review of evidence and challenges. World Psychiatry. 2019 Oct;18(3):259–69.
12. Hoskins MD, Sinnerton R, Nakamura A, Underwood JFG, Slater A, Lewis C, et al. Pharmacological-assisted Psychotherapy for Post-Traumatic Stress Disorder: a systematic review and meta-analysis. European Journal of Psychotraumatology. 2021 Jan 1;12(1):1853379.
13. Mithoefer MC, Grob CS, Brewerton TD. Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. The Lancet Psychiatry. 2016 May;3(5):481–8.
14. Gamma A. 3,4-Methylenedioxymethamphetamine (MDMA) Modulates Cortical and Limbic Brain Activity as Measured by [H215O]-PET in Healthy Humans. Neuropsychopharmacology. 2000 Oct;23(4):388–95.
15. Dolder PC, Müller F, Schmid Y, Borgwardt SJ, Liechti ME. Direct comparison of the acute subjective, emotional, autonomic, and endocrine effects of MDMA, methylphenidate, and modafinil in healthy subjects. Psychopharmacology. 2018 Feb;235(2):467–79.
16. Hysek CM, Schmid Y, Simmler LD, Domes G, Heinrichs M, Eisenegger C, et al. MDMA enhances emotional empathy and prosocial behavior. Soc Cogn Affect Neurosci. 2014 Nov;9(11):1645–52.
17. Ot'alora G M, Grigsby J, Poulter B, Van Derveer JW, Giron SG, Jerome L, et al. 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial. J Psychopharmacol. 2018 Dec;32(12):1295–307.
18. Kangaslampi S, Peltonen K. Mechanisms of change in psychological interventions for posttraumatic stress symptoms: A systematic review with recommendations. Curr Psychol [Internet]. 2019 Dec 10 [cited 2020 Aug 12]; Available from: http://link.springer.com/10.1007/s12144-019-00478-5

19. Sripada RK, Rauch SAM, Liberzon I. Psychological Mechanisms of PTSD and Its Treatment. Curr Psychiatry Rep. 2016 Nov;18(11):99.
20. Barone W, Beck J, Mitsunaga-Whitten M, Perl P. Perceived Benefits of MDMA-Assisted Psychotherapy beyond Symptom Reduction: Qualitative Follow-Up Study of a Clinical Trial for Individuals with Treatment-Resistant PTSD. Journal of Psychoactive Drugs. 2019 Mar 15;51(2):199–208.
21. Sola EM. MDMA-Assisted Psychotherapy for PTSD: A Thematic Analysis of Transformation in Combat Veterans [dissertation on the Internet]. San Francisco, CA: California Institute of Integral Studies; 2017 [cited 2021 May 05]. Available from: https://www.proquest.com/docview/2054006157
22. Frye CG, Wardle MC, Norman GJ, de Wit H. MDMA decreases the effects of simulated social rejection. Pharmacology Biochemistry and Behavior. 2014 Feb;117:1–6.
23. Brewin CR. Memory and Forgetting. Curr Psychiatry Rep. 2018 Oct;20(10):87.
24. Schauer M, Neuner F, Elber, T. Narrative Exposure Therapy: A short-term treatment for traumatic stress disorders. 2nd ed. Göttingen: Hogrefe.
25. Feduccia AA, Mithoefer MC. MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms? Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018 Jun;84:221–8.
26. Carhart-Harris RL, Wall MB, Erritzoe D, Kaelen M, Ferguson B, De Meer I, et al. The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. Int J Neuropsychopharm. 2014 Apr;17(04):527–40.
27. Doss MK, Weafer J, Gallo DA, de Wit H. MDMA Impairs Both the Encoding and Retrieval of Emotional Recollections. Neuropsychopharmacol. 2018 Mar;43(4):791–800.
28. Foa EB, Kozak MJ. Emotional Processing of Fear: Exposure to Corrective Information. Psychological Bulletin. 1986;99(1):20–35.
29. Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A. Optimizing inhibitory learning during exposure therapy. Behaviour Research and Therapy. 2008 Jan;46(1):5–27.
30. Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. Maximizing exposure therapy: An inhibitory learning approach. Behaviour Research and Therapy. 2014 Jul;58:10–23.
31. Wagner MT, Mithoefer MC, Mithoefer AT, MacAulay RK, Jerome L, Yazar-Klosinski B, et al. Therapeutic effect of increased openness: Investigating mechanism of action in MDMA-assisted psychotherapy. J Psychopharmacol. 2017 Aug;31(8):967–74.
32. Multidisciplinary Association for Psychedelic Studies Canada. Overview of CPT+MDMA Pilot Study [Internet]. [cited 2021 May 04]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6695343/
33. Monson CM, Wagner AC, Mithoefer AT, Liebman RE, Feduccia AA, Jerome L, et al. MDMA-facilitated cognitive-behavioural conjoint therapy for posttraumatic stress disorder: an uncontrolled trial. European Journal of Psychotraumatology. 2020 Dec 31;11(1):1840123.