

COMMENTARY

Defending MDMA as a Treatment for PTSD

Michael C. Mithoefer, MD; Allison Feduccia, PhD; Lisa Jerome, PhD; Rick Doblin, PhD

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MAPS' Rebuttal

We are writing in response to the recent Medscape video presentation by Dr Jeffrey A. Lieberman, [Misplaced Ecstasy? Questioning the Role of Psychedelics as Therapy](#). In this commentary, Lieberman expresses concern over a perceived, "movement to reintroduce or reevaluate the potential use of psychedelic drugs, MDMA included."

We firmly agree that, like any other treatment, MDMA should be investigated with rigor and care, and its acceptance based on results from randomized, controlled clinical trials. Most of Lieberman's concern is directed toward the use of MDMA, because it can produce euphoria and, thus, has some abuse liability. However, his statements do not accurately reflect findings from phase 1 and 2 studies of MDMA in clinical settings, nor its proposed mechanism of action as an adjunct to therapy.

They also do not describe the research paradigm followed by the Multidisciplinary Association for Psychedelic Studies (MAPS). Phase 2 clinical trials of MDMA-assisted psychotherapy for treatment of posttraumatic stress disorder (PTSD) have shown promising safety and efficacy outcomes, leading the US Food and Drug Administration (FDA) to grant "breakthrough therapy" designation for this investigational treatment in August 2017.

Assisting Therapy, not Producing Euphoria

The hypothesized mechanisms underlying the effectiveness of MDMA-assisted psychotherapy to treat PTSD are not based on its producing euphoria, but rather on its capacity to make confronting trauma-related thoughts, feelings, and memories more tolerable during therapeutic processing with support of a co-therapy team. MDMA is a monoamine releaser, but unlike stimulants, it preferentially releases serotonin, followed by norepinephrine and dopamine.^[1-3] This difference matters, because it fundamentally changes the nature of the drug's effects. MDMA increases positive mood, but it also shares some effects with the classic psychedelics, such as changing the perceived meaning of thoughts and experiences.^[4,5] Most important, MDMA increases empathy for the self and others^[6,7] and the tolerability of facing emotionally distressing memories or experiences, such as one's "worst" memories or social rejection.^[8,9]

Neuroimaging studies in healthy individuals have demonstrated that MDMA reduces amygdala activity,^[10] a possible contributor to greater ease in facing emotionally upsetting material. MDMA increases levels of the affiliative neurohormone oxytocin, a finding also not shared with stimulants.^[11,12] This specific type of "feeling into" or "staying with" painful emotions and memories is a key element in established psychotherapies for PTSD, including prolonged exposure therapy. Although such treatments as prolonged exposure can be successful on their own, they also have high drop-out rates and many individuals fail to adequately respond.^[13-17]

It is also notable that healthy controls and people with PTSD report both increased and decreased anxiety after MDMA.^[5,18-20] This suggests that like many other psychoactive substances, the effects of MDMA are at least partially dependent on the situation of use and the user's mindset—or set and setting.

Clinical observations and participant reports from clinical trials of MDMA-assisted psychotherapy are contrary to Lieberman's suggestion that MDMA used in therapy is "more likely to produce either euphoria or other types of analgesic-type activity than a genuine therapeutic effect at whatever the underlying pathophysiology of the illness is." MDMA ingested in the context of an 8-hour psychotherapy session is not going to produce the same extent or type of euphoria that might occur at a party or nightclub, because the person is undergoing nondirected processing of traumatic experiences. In fact, many patients feel no euphoria at all; one clinical trial participant who had good therapeutic responses to MDMA-assisted psychotherapy nonetheless said, "I don't know why they call this 'ecstasy.'"

MDMA-assisted therapy consists of administering the drug a small number of times, often no more than three, during extended psychotherapy sessions occurring at approximately 1-month intervals.^[21-24] Participants are screened for contraindicated medical and psychiatric disorders before enrollment, and MDMA is not given as a take-home dose and never administered daily. For these reasons, the risk for dependence and tolerance with MDMA therapy in controlled settings is low. Published findings^[21] from MAPS-sponsored studies indicate that very few participants have sought out "ecstasy" beyond the confines of the psychotherapeutic setting, and no one reported adverse events related to ecstasy use or abuse. This suggests that worries over

tolerance and addiction of MDMA used in medical contexts are unsupported. Our continued examination of data collected from phase 2 studies suggests that the risk for problematic use of "ecstasy" after study participation is very low.

A Bias Toward a Beneficial Treatment

Bias is hardly unique to research with psychoactive substances, and is addressed by a willingness to share data and findings. It is entirely expected that an organization investing the additional time and money needed to study the most restrictively regulated substances will hold a bias in favor of the treatment; why else go through trouble to address multiple regulatory agencies and additional hurdles to support and conduct these studies?

MAPS believes that MDMA has potential to help people with PTSD, in part on the basis of narrative accounts of the use of MDMA in therapy sessions before its designation as schedule 1 in 1985. MAPS follows FDA and good clinical practice guidelines for drug development programs in the same manner as all pharmaceutical drug trial sponsors. MAPS-sponsored trials are carried out at independent sites, either clinics or university laboratories. Bias is minimized by blinding of participants and therapy teams to treatment group assignment, and also by having independent raters not present during therapy sessions administer outcome measures. Findings from six phase 2 studies showed that the beneficial effects of treatment were attained across multiple sites within and outside of the United States, therapy teams, and PTSD from different types of traumatic experiences. Publications featuring results from these six studies are being prepared for peer-reviewed journal articles.

Unlike most pharmaceutical companies, MAPS is a nonprofit organization that relies entirely on private donations for trials of MDMA, cannabis, and other psychedelic agents. If MDMA becomes an FDA-approved medication in the future, MAPS Public Benefit Corporation will be responsible for the sale of the drug to trained providers. As with all public benefit corporations, decisions on drug pricing and company directives will be based first on societal and environmental impact, not solely on company profits. All financial reports are currently posted on maps.org. Transparency will continue for MAPS and its fully owned subsidiary, MAPS Public Benefit Corporation.

We fully agree with Dr Lieberman's call for further rigorous investigations to define the safety and therapeutic potential of MDMA and other psychedelic substances across large samples. Multisite phase 3 trials of MDMA-assisted psychotherapy have been cleared by the FDA through a Special Protocol Assessment program and will commence in spring 2018. If safety and efficacy results are replicated, MDMA therapy could be a new treatment option by 2021.

When assessing the use of any drugs, the risk/benefit profile for clinical use must be evaluated separately from risks associated with consumption of substances of unknown purity by unscreened individuals in nonmedical settings. Drug policy discussions addressing the criminalization of "feel-good substances," as Dr Lieberman describes recreational use of psychoactives, are completely independent of clinical investigations and should not be confused with the pursuit to understand the potential therapeutic application for life-threatening disorders, such as PTSD.

References

1. Han DD, Gu HH. Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. *BMC Pharmacol.* 2006;6:6.
2. Liechti ME, Vollenweider FX. Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. *Hum Psychopharmacol.* 2001;16:589-598. [Abstract](#)
3. Simmler LD, Rickli A, Hoener MC, Liechti ME. Monoamine transporter and receptor interaction profiles of a new series of designer cathinones. *Neuropharmacology.* 2014;79:152-160. [Abstract](#)
4. Kirkpatrick MG, Baggott MJ, Mendelson JE, et al. MDMA effects consistent across laboratories. *Psychopharmacology (Berl).* 2014;231:3899-3905. [Abstract](#)
5. Liechti ME, Gamma A, Vollenweider FX. Gender differences in the subjective effects of MDMA. *Psychopharmacology (Berl).* 2001;154:161-168. [Abstract](#)
6. Hysek CM, Schmid Y, Simmler LD, et al. MDMA enhances emotional empathy and prosocial behavior. *Soc Cogn Affect Neurosci.* 2014;9:1645-1652. [Abstract](#)
7. Bedi G, Phan KL, Angstadt M, de Wit H. Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology (Berl).* 2009;207:73-83. [Abstract](#)
8. Carhart-Harris RL, Wall MB, Erritzoe D, et al. The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. *Int J Neuropsychopharmacol.* 2014;17:527-540. [Abstract](#)
9. Frye CG, Wardle MC, Norman GJ, de Wit H. MDMA decreases the effects of simulated social rejection. *Pharmacol Biochem Behav.* 2014;117:1-6. [Abstract](#)

10. Gamma A, Buck A, Berthold T, Liechti ME, Vollenweider FX. 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H(2)(15)O]-PET in healthy humans. *Neuropsychopharmacology*. 2000;23:388-395. [Abstract](#)
11. Bershad AK, Kirkpatrick MG, Seiden JA, de Wit H. Effects of acute doses of prosocial drugs methamphetamine and alcohol on plasma oxytocin levels. *J Clin Psychopharmacol*. 2015;35:308-312. [Abstract](#)
12. Dumont GJ, Sweep FC, van der Steen R, et al. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci*. 2009;4:359-366. [Abstract](#)
13. Goetter EM, Bui E, Ojserkis RA, Zakarian RJ, Brendel RW, Simon NM. A systematic review of dropout from psychotherapy for posttraumatic stress disorder among Iraq and Afghanistan combat veterans. *J Trauma Stress*. 2015;28:401-409. [Abstract](#)
14. Miles SR, Smith TL, Maieritsch KP, Ahearn EP. Fear of losing emotional control is associated with cognitive processing therapy outcomes in U.S. veterans of Afghanistan and Iraq. *J Trauma Stress*. 2015;28:475-479. [Abstract](#)
15. Eftekhari A, Ruzek JI, Crowley JJ, Rosen CS, Greenbaum MA, Karlin BE. Effectiveness of national implementation of prolonged exposure therapy in Veterans Affairs care. *JAMA Psychiatry*. 2013;70:949-955. [Abstract](#)
16. McLean CP, Asnaani A, Foa EB. Prolonged exposure therapy. In: Schnyder U, Cloitre M, eds. *Evidence Based Treatments for Trauma-Related Psychological Disorders*. Basel, Switzerland: Springer; 2015:143-159.
17. Mott JM, Mondragon S, Hundt NE, Beason-Smith M, Grady RH, Teng EJ. Characteristics of U.S. veterans who begin and complete prolonged exposure and cognitive processing therapy for PTSD. *J Trauma Stress*. 2014;27:265-273. [Abstract](#)
18. Tancer M, Johanson CE. The effects of fluoxetine on the subjective and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology (Berl)*. 2007;189:565-573. [Abstract](#)
19. Harris DS, Baggott M, Mendelson JH, Mendelson JE, Jones RT. Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology (Berl)*. 2002;162:396-405. [Abstract](#)
20. Cami J, Farre M, Mas M, et al. Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. *J Clin Psychopharmacol*. 2000;20:455-466. [Abstract](#)
21. Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (+/- 3,4-methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorder (PTSD). *J Psychopharmacol*. 2013;27:40-52. [Abstract](#)
22. Mithoefer MC, Grob CS, Brewerton TD. Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA. *Lancet Psychiatry*. 2016;3:481-488. [Abstract](#)
23. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. 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 Psychopharmacol*. 2011;25:439-452. [Abstract](#)
24. Mithoefer MC, Wagner MT, Mithoefer AT, et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *J Psychopharmacol*. 2013;27:28-39. [Abstract](#)

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