Psychotherapy-supported MDMA treatment for PTSD

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The first Phase III randomized controlled trial of 3,4-methylenedioxymethamphetamine (MDMA) provided compelling evidence supporting the efficacy of this drug for the treatment of posttraumatic stress disorder (PTSD) (Mitchell et al., 2021). This was an 18-week study of 90 patients (MDMA n=46, Placebo n=44) involving three drug administration sessions combined with a supportive psychotherapy. From a baseline PTSD severity score of approximately 44 on the Clinician Administered PTSD Scale for DSM5, MDMA was associated with a 24.4-point (55.5%) reduction in PTSD severity, which was significantly greater than that seen with placebo (13.9 points, 31.5% reduction). By the end of the study, 14 of 42 (33%) patients in the MDMA group and 2 of 37 (5%) patients in the placebo group were in remission from their PTSD. The effect size of MDMA relative to placebo was large (d>0.9). MDMA also produced significant improvements relative to placebo in depression severity and social disability. Overall, these were impressive results.

How does MDMA produce this clinical improvement? We have remarkably little insight into the answer to this question as the development of MDMA as a treatment for PTSD emerged from clinical observations. Animal studies suggest that blockade of serotonin transporters by MDMA is essential for its ability to facilitate fear extinction (Young et al., 2017). However, promotion of fear extinction does not seem to fully capture the clinical responses in the current study for many reasons including: 1) the current study did not employ explicit exposure/extinction procedures, 2) blockade of serotonin transporters by antidepressants (SSRI) does not seem adequate to produce these types of clinical improvement, 3) history of prior SSRI responses were not related to clinical outcomes in the current study, and 4) clinical improvements were seen in clinical domains beyond fear.

Clinical research findings with MDMA might serve to guide mechanistic research pursuing the neurobiology of its therapeutic effects, particularly in the domain of social cognition. The efficacy of MDMA combined with psychotherapy for PTSD, as reported in this and other MDMA studies may involve alterations in the inferences drawn about oneself and others. MDMA may augment the response to reactivating positive autobiographical memories, diminish the response to negative autobiographical memories, and promote self-compassion (Carhart-Harris et al., 2014; Kamboj et al., 2018). Perhaps consistent with these effects, in mice, MDMA attenuates fear reconsolidation (Hake et al., 2019). MDMA also produces prosocial effects in animals (Curry et al., 2018) that may be related to prosocial MDMA effects in humans. For example, MDMA increases trust, increases responsiveness to positive stimuli and social cues, diminishes responses to negative stimuli and negative social cues, enhances one's perception of empathy in others, promotes one's empathy for others, facilitates the sharing of sensitive personal information with others, and enhances the response to social touch, among other effects (Bershad et al., 2019; Bershad et al., 2016). Given these prosocial effects, it is not surprising that MDMA is being tested to promote the efficacy of couples therapy (Monson et al., 2020) and perhaps other group treatments.

Confidence in the newly reported findings is increased by prior positive pilot studies, however, questions remain. First, while a Phase III study, this was still a relatively small study. There were 37 completers in the placebo group and 42 completers in the MDMA group. Thus, this was the

size of a typical Phase II psychiatry study (~50/group) as opposed to the size of a typical Phase III study (>200/group). The small size is justified by the large expected effect size for MDMA versus placebo. However, the statistical problem of the "winners curse" has plagued psychiatric drug development, i.e., many encouraging results from small studies were not replicated in larger studies. Thus, replication of the current findings, preferably in a larger trial, will be important. A second concern is whether placebo is the appropriate comparator for MDMA. The subjective effects of MDMA are robust and not difficult to differentiate from placebo, potentially unblinding the study and influencing clinical assessments. One wonders whether dexamphetamine or methylphenidate, drugs with relatively low affinity for serotonin transporters, would be appropriate comparator drugs to control for the stimulant-like effects of MDMA. The use of an active comparator would be consistent with the use of midazolam as a comparator for Esketamine in Janssen's Phase III trials. A third concern is related to MDMA safety. The side effects of MDMA in this trial were not serious and included muscle tightness, reduced appetite, excessive sweating, feeling cold, and pupil dilation. However, this study did not address the two primary concerns related to MDMA safety: neurotoxicity and addiction liability. We are not aware of evidence that a limited series of widely spaced MDMA therapeutic dosing, as used in this study, produces persisting cognitive impairment or other clear evidence of neurotoxicity in humans. However, MDMA recreational use does appear to produce circuit dysfunction and cognitive impairments in some individuals (Aguilar et al., 2020). Similarly, MDMA is a drug of abuse. Limiting exposure to MDMA to clinic settings is likely to reduce its abuse liability. However, it will be important to include measures related to addiction (MDMA craving, MDMA liking, willingness to spend money to obtain MDMA outside of the clinic, etc.) in future clinical trials.

If MDMA is to be an important new treatment for PTSD, then it will be important for agencies responsible for funding mental health research to support this work as well. The current study, like many prior studies, was supported by the Multidisciplinary Association for Psychedelic Studies (MAPS). To the credit of its leader, Rick Doblin, this study is the product of a sustained effort over more than 30 years to bring MDMA forward as a treatment for psychiatric disorders. MAPS, along with the Heffter Research Institute, a few other research foundations, and an active group of philanthropic individuals also has invested in developing psilocybin. It would be important for the U.S. National Institute of Mental Health, the U.S. Department of Veterans Affairs, the Wellcome Trust, Medical Research Council, and other agencies to expand their support of MDMA research in order to ensure that future clinical trials are informed by peer review, that neuroscience studies provide a foundation for understanding MDMA safety and efficacy, to develop well-trained experts in this area of research, and to see that the implementation of MDMA treatment is optimized, should it continue to generate positive results in Phase III.

In closing, there is tremendous need for new treatments for PTSD. It is a common and commonly disabling disorder that increases the risk for many bad outcomes, including comorbid substance use disorders and suicide. Currently, there are only two medications approved for PTSD pharmacotherapy and both are SSRIs. Proportionate to the prevalence and impact of PTSD, there are very few novel pharmacotherapeutic mechanisms under evaluation.

The study by Mitchell and colleagues published in *Nature Medicine* suggests that MDMA may be an important new source of hope for people with PTSD and healthcare systems responsible for their care.

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Patents and Inventions
1. Seibyl JP, Krystal JH, Charney DS. Dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia. US Patent #:5,447,948, September 5, 1995.
2. Vladimir, Coric, Krystal, John H, Sanacora, Gerard – Glutamate Modulating Agents in the Treatment of Mental Disorders. US Patent No. 8,778,979 B2 Patent Issue Date: July 15, 2014. US Patent Application No. 15/695,164: Filing Date: 09/05/2017.
3. Charney D, Krystal JH, Manji H, Matthew S, Zarate C., Intranasal Administration of Ketamine to Treat Depression United States Patent Number: 9592207, Issue date: 3/14/2017. Licensed to Janssen Research & Development.
4. Zarate, C, Charney, DS, Manji, HK, Mathew, Sanjay J, Krystal, JH, Yale University "Methods for Treating Suicidal Ideation", Patent Application No. 15/379,013 filed on December 14, 2016 by Yale University Office of Cooperative Research.

5. Arias A, Petrakis I, Krystal JH. – Composition and methods to treat addiction. Provisional Use Patent Application no.61/973/961. April 2, 2014. Filed by Yale University Office of Cooperative Research.
6. Chekroud, A., Gueorguieva, R., & Krystal, JH. "Treatment Selection for Major Depressive Disorder" [filing date 3rd June 2016, USPTO docket number Y0087.70116US00]. Provisional patent submission by Yale University.
7. Gihyun, Yoon, Petrakis I, Krystal JH – Compounds, Compositions and Methods for Treating or Preventing Depression and Other Diseases. U. S. Provisional Patent Application No. 62/444,552, filed on January10, 2017 by Yale University Office of Cooperative Research OCR 7088 US01.
8. Abdallah, C, Krystal, JH, Duman, R, Sanacora, G. Combination Therapy for Treating or Preventing Depression or Other Mood Diseases. U.S. Provisional Patent Application No. 62/719,935 filed on August 20, 2018 by Yale University Office of Cooperative Research OCR 7451 US01
9. John Krystal, Godfrey Pearlson, Stephanie O'Malley, Marc Potenza, Fabrizio Gasparini, Baltazar Gomez-Mancilla, Vincent Malaterre. Mavoglurant in treating gambling and gaming disorders. U.S. Provisional Patent Application No. 63/125,181filed on December 14, 2020 by Yale University Office of Cooperative Research OCR 8065 US00.

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References

Aguilar, M.A., García-Pardo, M.P., and Parrott, A.C. (2020). Of mice and men on MDMA: A translational comparison of the neuropsychobiological effects of 3,4-methylenedioxymethamphetamine ('Ecstasy'). Brain Res *1727*, 146556.
Bershad, A.K., Mayo, L.M., Van Hedger, K., McGlone, F., Walker, S.C., and de Wit, H. (2019). Effects of MDMA on attention to positive social cues and pleasantness of affective touch. Neuropsychopharmacology *44*, 1698-1705.
Bershad, A.K., Miller, M.A., Baggott, M.J., and de Wit, H. (2016). The effects of MDMA on socio-emotional processing: Does MDMA differ from other stimulants? J Psychopharmacol *30*, 1248-1258.
Carhart-Harris, R.L., Wall, M.B., Erritzoe, D., Kaelen, M., Ferguson, B., De Meer, I., Tanner, M., Bloomfield, M., Williams, T.M., Bolstridge, M.*, et al.* (2014). The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. Int J Neuropsychopharmacol *17*, 527-540.
Curry, D.W., Young, M.B., Tran, A.N., Daoud, G.E., and Howell, L.L. (2018). Separating the agony from ecstasy: R(-)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice. Neuropharmacology *128*, 196-206.
Hake, H.S., Davis, J.K.P., Wood, R.R., Tanner, M.K., Loetz, E.C., Sanchez, A., Ostrovskyy, M., Oleson, E.B., Grigsby, J., Doblin, R.*, et al.* (2019). 3,4-methylenedioxymethamphetamine

(MDMA) impairs the extinction and reconsolidation of fear memory in rats. Physiol Behav *199*, 343-350.
Kamboj, S.K., Walldén, Y.S.E., Falconer, C.J., Alotaibi, M.R., Blagbrough, I.S., Husbands, S.M., and Freeman, T.P. (2018). Additive Effects of 3,4-Methylenedioxymethamphetamine (MDMA) and Compassionate Imagery on Self-Compassion in Recreational Users of Ecstasy. Mindfulness (N Y) *9*, 1134-1145.
Mitchell, J.M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., Ot'alora, G.M., Garas, W., Paleos, C., Gorman, I.*, et al.* (2021). MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med *27*, 1025-1033.
Monson, C.M., Wagner, A.C., Mithoefer, A.T., Liebman, R.E., Feduccia, A.A., Jerome, L., Yazar-Klosinski, B., Emerson, A., Doblin, R., and Mithoefer, M.C. (2020). MDMA-facilitated cognitive-behavioural conjoint therapy for posttraumatic stress disorder: an uncontrolled trial. European journal of psychotraumatology *11*, 1840123.
Young, M.B., Norrholm, S.D., Khoury, L.M., Jovanovic, T., Rauch, S.A.M., Reiff, C.M., Dunlop, B.W., Rothbaum, B.O., and Howell, L.L. (2017). Inhibition of serotonin transporters disrupts the enhancement of fear memory extinction by 3,4-methylenedioxymethamphetamine (MDMA). Psychopharmacology (Berl) *234*, 2883-2895.