Cell Reports Medicine

CellPress
OPEN ACCESS

Preview

Psychotherapy-supported MDMA treatment for PTSD

John H. Krystal,[1,2,*] Benjamin Kelmendi,[1,2] and Ismene L. Petrakis[1,2]
[1]Department of Psychiatry, Yale School of Medicine, New Haven, CT 06525, USA
[2]Clinical Neuroscience Division, National Center for PTSD, VA Connecticut Healthcare System, West Haven, CT 06525, USA
*Correspondence: john.krystal@yale.edu
https://doi.org/10.1016/j.xcrm.2021.100378

A promising new Phase III study of MDMA plus psychotherapy for PTSD treatment by Mitchell and colleagues that appeared in *Nature Medicine* raises important new questions about the biology and optimal treatment of this disorder.

The first Phase III randomized controlled trial of 3,4-methyl enedioxy methamphetamine (MDMA) supported the efficacy of this drug for the treatment of posttraumatic stress disorder (PTSD).[1] This 18-week study (MDMA n = 46, Placebo n = 44) involved 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 produced 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). At study end, 14 of 42 (33%) patients in the MDMA group and 2 of 37 (5%) patients in the placebo group were in PTSD remission. The MDMA effect size 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.

We have little insight into how MDMA alleviates PTSD symptoms. Animal studies suggest that blockade of serotonin transporters is essential for its ability to facilitate fear extinction.[2] However, this effect does not seem to fully capture clinical responses in the current study: (1) it did not employ explicit exposure/extinction procedures, (2) blockade of serotonin transporters by antidepressants (SSRI) does not produce the spectrum of effects observed in this study, and (3) history of prior SSRI responses were not related to clinical outcomes in the current study.

Clinical research findings with MDMA might guide mechanistic research pursuing the neurobiology of its therapeutic effects (see Table 1). MDMA efficacy in combination with psychotherapy in PTSD may involve alterations in the inferences drawn about oneself and others. MDMA augments the response to reactivating positive autobiographical memories, diminishes the response to negative autobiographical memories, and promotes self-compassion.[3,4] Perhaps consistent with these effects, MDMA attenuates fear reconsolidation[5] and produces prosocial effects in animals.[6] In humans, MDMA increases trust, increases responsiveness to positive stimuli and social cues, diminishes responses to negative stimuli and social cues, enhances empathy, facilitates the sharing of sensitive personal information with others, and enhances the response to social touch, among other effects.[7,8]

Confidence in these new findings is increased by prior positive pilot studies; however, questions remain. First, this was a small Phase III study (Placebo n = 37 completers; MDMA n = 42 completers). Thus, this study was the size of a typical Phase II psychiatry study (~50 patients/group) as opposed to the size of a typical Phase III study (>200 patients/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 are not replicated in larger studies. Thus, replication of the current findings in larger trials 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 patients and influencing clinical assessments. One wonders whether methylphenidate, a stimulant with relatively low affinity for serotonin transporters would be an appropriate comparator for 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. MDMA side effects were not serious and included muscle tightness, reduced appetite, excessive sweating, feeling cold, and pupil dilation. However, this study did not address 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 signs of neurotoxicity in humans. However, MDMA recreational use does appear to produce circuit dysfunction and cognitive impairments in some individuals.[9] 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.

It will be important for funding agencies to support this research. This study 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 30-year effort to bring MDMA forward as a treatment for psychiatric disorders. It would be important for the U.S. National Institute of Mental Health and other agencies to expand their support of MDMA research in order to ensure that future clinical trials are informed by peer

Table 1. Description of the principal targets, expected effects, and possible benefits of MDMA for patients diagnosed with PTSD

Targets	MDMA effects	Potential benefits for PTSD patients
Serotonin transporter	augmented responses to positive non-social stimuli, social stimuli, autobiographical memories	reduce exaggerated expectations of threats from others; reducing hyperarousal, defensiveness, and mistrust
Dopamine transporter	diminished responses to negative non-social stimuli, social stimuli, autobiographical memories	enhanced self-forgiveness; reductions in shame and guilt
Norepinephrine transporter	promotes self-compassion	reduced social withdrawal; increased capacity for intimacy; greater capacity to engage in social activities and psychotherapy
Vesicular transporter	increases trust	reduction in depression-like symptoms (anergia, anhedonia, negative expectances)
Trace amine-associated receptor 1 (TAAR1)	increases empathy	reduced preoccupation with trauma memories; reduced reactivity to trauma reminders; reduced avoidance of trauma reminders
	increases openness (promotes disclosure)	
	promotes response to social touch	
	euphoria, positive arousal	
	promotes fear extinction and reduces fear reconsolidation in animals	

Table presents the primary targets, effects, and potential therapeutic benefits of MDMA for PTSD patients. References are cited in the text. The row demarcations are not intended to convey links in the information presented across columns (i.e., the information presented in each columns is independent from the information presented in the other columns).

review, to ensure 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.

There is tremendous need for new PTSD treatments, a distressing and commonly disabling disorder that increases the risk for suicide. Currently, there are only two SSRI medications approved for PTSD pharmacotherapy. Despite the need, there are also few novel pharmacotherapeutic mechanisms under evaluation. The study by Mitchell and colleagues suggests that MDMA may be an important new source of hope for people with PTSD.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrm.2021.100378.

ACKNOWLEDGMENTS

The preparation of this article was supported by the National Center for PTSD, US Department of Veterans Affairs.

DECLARATION OF INTERESTS

Financial disclosures can be found in the supplemental information.

REFERENCES

1. 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.
2. 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.
3. 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.
4. 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.
5. 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., and Greenwood, B.N. (2019). 3,4-methylenedioxymethamphetamine (MDMA) impairs the extinction and reconsolidation of fear memory in rats. Physiol. Behav. *199*, 343–350.
6. 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.
7. 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.
8. 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.
9. 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.

Cell Reports Medicine, Volume *2*

Supplemental information

Psychotherapy-supported MDMA treatment for PTSD

John H. Krystal, Benjamin Kelmendi, and Ismene L. Petrakis

John H. Krystal, M.D. - Financial Disclosures:

The Individual Consultant Agreements listed below are less than $10,000 per year

Aptinyx, Inc., Atai Life Sciences, AstraZeneca Pharmaceuticals, Biogen, Idec, MA, Biomedisyn Corporation, Bionomics, Limited (Australia), Boehringer Ingelheim International, Cadent Therapeutics, Inc., Clexio Bioscience, Ltd., COMPASS Pathways, Limited, United Kingdom, Concert Pharmaceuticals, Inc., Epiodyne, Inc., EpiVario, Inc., Greenwich Biosciences, Inc., Heptares Therapeutics, Limited (UK), Janssen Research & Development, Jazz Pharmaceuticals, Inc., Otsuka America Pharmaceutical, Inc., Perception Neuroscience Holdings, Inc., Spring Care, Inc., Sunovion Pharmaceuticals, Inc., Takeda Industries, Taisho Pharmaceutical Co., Ltd.

Scientific Advisory Board

Biohaven Pharmaceuticals, BioXcel Therapeutics, Inc. (Clinical Advisory Board), Cadent Therapeutics, Inc. (Clinical Advisory Board), Cerevel Therapeutics, LLC., EpiVario, Inc, Eisai, Inc., Jazz Pharmaceuticals, Inc., Lohocla Research Corporation, Novartis Pharmaceuticals Corporation, PsychoGenics, Inc., RBNC Therapeutics, Inc., Tempero Bio, Inc., Terran Biosciences.

Board of Directors

Freedom Biosciences, Inc.

Stock

Biohaven Pharmaceuticals, Sage Pharmaceuticals, Spring Care, Inc.

Stock Options

Biohaven Pharmaceuticals Medical Sciences, EpiVario, Inc., RBNC Therapeutics, Inc., Terran Biosciences, Inc., Tempero Bio, Inc.

Income Greater than $10,000

Editorial Board

Editor - Biological Psychiatry

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.

NON Federal Research Support
AstraZeneca Pharmaceuticals provides the drug, Saracatinib, for research related to NIAAA grant "Center for Translational Neuroscience of Alcoholism [CTNA-4]
Novartis provides the drug, Mavoglurant, for research related to NIAAA grant "Center for Translational Neuroscience of Alcoholism [CTNA-4]

Dr. Benjamin Kelmendi serves as member of the Scientific Advisory Board for Lobe Sciences.