

# MDMA as a Probe and Treatment for Social Behaviors

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**MDMA, better known as the recreational drug “ecstasy,” is well known for stimulating a feeling of closeness and empathy in its users. We advocate that exploring its mechanism of action could lead to new treatments for psychiatric conditions characterized by impairments in social behavior.**

MDMA ( $\pm$ 3,4-methylenedioxymethamphetamine) is a strictly regulated, schedule I drug, which has been used recreationally (and illegally) by millions of individuals over the last few decades, often in highly social situations such as raves. Its best-known and most well-documented effect is the feeling of closeness and empathy it fosters in users, thus giving rise to its classification as an “empathogen.” Because of this powerful prosocial action, there is great excitement among a cadre of clinicians who see its potential as a powerful adjunct to psychotherapy for the treatment of post-traumatic stress disorder (PTSD), as well as a potential primary treatment for the social dysfunction that occurs in a wide range of other neuropsychiatric disorders (Danforth et al., 2016; Mithoefer et al., 2013). Here, we argue for the importance of using all the available tools of modern basic and clinical neuroscience research to map MDMA’s mechanism of action in the brain.

Two reasons for the importance of facilitating the study of MDMA using rigorous scientific methods are as follows: (1) MDMA is a novel and powerful tool for delineating the neural mechanisms underlying prosocial behaviors and empathy. At a time of great hostility and mistrust both nationally in the United States and internationally, what is more important than elucidating the mechanisms in our brains that generate empathy, openness, and the most positive of social experiences? Because the identity and location of their critical molecular targets can be defined, drugs such as MDMA are potentially powerful tools to probe brain functions. Indeed, historically, much has been learned about the brain by studying the mechanisms of action of psychoactive

substances. (2) The drug pipeline for psychiatric disorders is near exhaustion, in large part because of the continued focus on pharmacological mechanisms identified decades ago. Given the enormous burden of psychiatric illness, the research community has a clear mandate to pursue new modes of therapy. Elucidating MDMA’s mechanisms of actions in the context of treatment trials will pave the way for developing new therapeutic agents that target previously unidentified brain mechanisms. Maladaptive social behavior occurs not only in autism spectrum disorders but in a broad array of neuropsychiatric diseases, including depression and schizophrenia. Furthermore, MDMA and the treatments developed from its study may be powerful adjuncts to various forms of psychotherapy that will help ameliorate the suffering of those dealing with illnesses such as PTSD. We believe that there is a need to overcome the sociopolitical stigma surrounding MDMA and perhaps similar drugs in order to see their potential as an important starting point for discovery.

## A History of MDMA

How have we come to a point where we are arguing that a DEA schedule 1 drug (i.e., no accepted medical use) may be among the most promising lead therapies for psychiatric disease and a powerful probe of important brain functions? Since its popularization as a recreational drug in the early 1980s, clubgoers and college students primarily know MDMA as “ecstasy” or “molly,” among other monikers. MDMA was first synthesized, patented, and effectively shelved by Merck in 1912. MDMA’s modern history most likely

began in 1976 when career synthetic chemist Alexander Shulgin, Ph.D., rediscovered the compound, his interest stemming from its structural similarities to both amphetamine and the hallucinogen mescaline. Noting its pleasant effect, he disseminated it among a small community of physicians, therapists, and scientists in northern California (Shulgin, 1990). MDMA quickly earned a reputation as an “empathogen.” Early case series and anecdotal reports reflect this impression, detailing the use of MDMA as an adjunct treatment during therapy for patients with debilitating social anxiety and PTSD (Greer and Tolbert, 1990).

Clinical experience with MDMA was in its infancy when its recreational use skyrocketed, prompting an emergency meeting of the US Drug Enforcement Agency (DEA) in May of 1985. The outcome of this meeting was the immediate placement of MDMA into the Schedule I category, making it subject to the most stringent regulation and penalties for possession, use, and distribution. European authorities quickly followed suit, classifying MDMA as a Schedule 1 controlled substance in the Convention of Psychotropic Substances, effectively freezing any meaningful clinical investigation of MDMA. In 2004, after nearly 20 years of advocacy by a non-governmental organization in the United States, the US Food and Drug Administration (FDA) and DEA approved the first use of MDMA in humans as an Investigational New Drug (IND) for patients suffering from PTSD. The therapeutic model used by the investigators was based on the work performed 25 years prior and targeted a population and disease entity they felt most likely to benefit from MDMA-assisted

therapy. The findings from one recent small clinical trial are described below.

### What Makes It Unique?

Although MDMA is an amphetamine derivative and thus shares some features with psychostimulants such as cocaine, its actions of enhancing positive social interactions and empathy are entirely unique, making it unlike any other known psychoactive substance. These effects have been documented repeatedly in anecdotal reports and human studies (Greer and Tolbert, 1990; Kirkpatrick et al., 2014) and have received increased attention in the context of on-going clinical trials for the treatment of PTSD. Typical PTSD therapy consists of long-term treatment with a serotonin-selective reuptake inhibitor (SSRI) coupled with “re-exposure therapy,” wherein a therapist and patient gradually re-explore the traumatic event in an effort to desensitize its emotional impact. Re-exposure and desensitization have a sound basis in neuroscience, drawing on concepts of learned fear extinction and memory reconsolidation, processes that have been extensively studied in human and animal models. This mode of therapy can be remarkably effective for simple fears, such as a pathological fear of heights, but in the context of PTSD, it is marginally effective, producing an estimated remission rate of only 20%–30% above placebo (Jonas et al., 2013).

In a recent small ( $n = 19$ ), randomized, blinded, placebo-controlled clinical trial, MDMA-assisted psychotherapy produced an approximately 80% response rate in patients already considered “treatment refractory,” having failed two or more courses of conventional therapy (Mithoefer et al., 2013). Even accounting for the low sample size and potential patient selection bias, this degree of stable treatment response over a 4-year follow-up period is exceedingly rare in the psychiatric literature. Two features set MDMA apart from the vast majority of existing psychiatric therapies and present a rare opportunity for “reverse translation”: defining the neural basis for MDMA’s therapeutic success.

First, MDMA’s therapeutic effect was often rapid, happening over the course of hours or only a few short therapeutic

sessions. Second, one or at most two MDMA-assisted psychotherapy sessions could catalyze a years-long-and-counting remission of symptoms. In the words of one patient,

*“I had never before felt what I felt today in terms of loving connection. I’m not sure I can reach it again without MDMA but I’m not without hope that it’s possible. Maybe it’s like having an aerial map so now I know there’s a trail”* (Mithoefer, 2013).

For this patient and others with similar experiences, a compelling hypothesis is that, by enhancing feelings of trust, emotional openness, and empathy, MDMA strengthened the bond between therapist and patient, thereby helping overcome frequently cited obstacles to PTSD therapy, such as extreme anger, emotional numbing, and overwhelming anxiety. No other mode of therapy seems to work this way. The well-defined time window of MDMA’s actions dramatically simplifies the search for an underlying neural mechanism of its prosocial effect. If we can measure MDMA’s most salient therapeutic aspects on this short timescale, we can design experiments that explicitly test the requirements for its mechanism, using tools ideally suited to acute measurement and intervention. Furthermore, while we often attribute therapeutic recovery from mental illnesses to plasticity of synapses and circuits, because most common treatments take weeks or months to provide relief, we can rarely pinpoint exactly *when* that plastic process occurs. The discrete time window, during and immediately after MDMA’s acute effect, is very amenable to mechanistic studies ranging from human neuroimaging to animal models of MDMA-based therapies.

Beyond MDMA’s potential role in treating PTSD, its unique ability to improve the positive qualities of social interaction in humans could have therapeutic implications for many disorders where sociability is impaired, including autism, schizophrenia, social anxiety disorder, and major depressive disorder. Importantly, we have vanishingly few if any methods to selectively enhance a trait or behavior as complex as sociability. Because it is a

drug that can be given to animals and people acutely in highly controlled contexts, we can explore MDMA’s mechanism of promoting prosocial behavior at the level of its molecular targets, the synapses and cells in which these targets are found, and the changes in neural circuit activity that ultimately mediate its psychological and behavioral effects. By probing these mechanisms, we will gain fundamental insight into the biology of some of the most important aspects of prosocial behavior.

### What Do We Know about Its Mechanism?

MDMA is a high-affinity ligand for the serotonin (5-HT) transporter (SERT) and, to a lesser extent, it binds dopamine (DA) and norepinephrine transporters (DAT, NET). MDMA also has reported direct effects on several 5-HT receptor subtypes (Kamilar-Britt and Bedi, 2015). Via SERT, MDMA stimulates 5-HT efflux from synaptic terminals, most likely via a reverse-transport mechanism. Serotonin-selective reuptake inhibitors (SSRIs) effectively block MDMA’s ability in vitro to bind SERT and stimulate 5-HT release. Across species, MDMA’s interaction with SERT appears to be necessary for several of its behavioral effects. For example, SSRIs significantly attenuate MDMA’s empathogenic properties in humans, and (in rats) MDMA-induced prosocial behavior and locomotor activation (Kamilar-Britt and Bedi, 2015). In mice, SSRIs or genetic deletion of SERT abolished MDMA-induced locomotor activation and self-administration. However, in neither animals nor humans do SSRIs generate the prosocial, empathogenic effects of MDMA. This result suggests that MDMA’s actions may involve interactions with molecular targets in addition to SERT.

Perhaps because MDMA first achieved mass recognition as a public health threat, the bulk of early research efforts focused on its neurotoxicity and abuse potential. The most dire health warnings came from a highly publicized study demonstrating that human-relevant doses given to non-human primates produced not only 5-HT neurotoxicity but DA neurotoxicity as well, accompanied by a 20% mortality of their test subjects (Ricaurte et al., 2002). Echoing the very

real threat of MPTP-linked Parkinsonism in the early 1980s, there were concerns that MDMA's neurotoxicity might be linked to early-onset Parkinsonism. The former study was ultimately retracted when it was discovered that test subjects had mistakenly received methamphetamine (a less strictly controlled US DEA Schedule 2 drug), not MDMA. Moreover, the epidemiological threat of early-onset Parkinsonism linked to MDMA use has failed to materialize in the 30 years since its introduction to public awareness. Nonetheless, the publication fed into an institutional predisposition to see MDMA as a toxin, which has undoubtedly slowed investigation into its potential therapeutic properties.

This is not to understate the risks of MDMA use: a large body of evidence shows that MDMA, especially at high or repeated doses, is associated with profound neurotoxicity at 5-HT nerve terminals in rodent brain. Translating the relevance of multiple high-dose MDMA injections in rodents to meaningful clinical sequelae has proven challenging. In moderate to heavy MDMA users, clinical neuroimaging studies using PET/SPECT have found decreased binding of SERT radioligands (a proxy for 5-HT terminal density), changes that appear to reverse after a period of abstinence (Roberts et al., 2016). Not surprisingly, neurocognitive testing of moderate-to-heavy MDMA users (in addition to other recreational drugs) revealed mild deficits in several domains (Zakzanis et al., 2007). The relevance of these findings to patients undergoing MDMA-assisted therapy using one or two doses has been questioned since the available evidence suggests a minimal risk of neurotoxicity (Green et al., 2012).

As an amphetamine derivative, MDMA does have well-established abuse potential, and therefore, like many powerful therapies in other medical fields, the therapeutic window for MDMA is likely narrow. Thus, it is legitimate to have significant safety concerns both for individuals and for public health with the use of MDMA. Rather than deterring research on MDMA, however, these factors should compel us to understand in great detail the neural mechanisms of its prosocial, empathogenic effect and determine whether these mechanisms can be dis-

ciated from those mediating its abuse potential.

Research efforts in this direction are underway, although cumbersome regulatory hurdles for obtaining research quantities of MDMA have no doubt greatly slowed progress. Much of this work has focused on the role of the neuropeptide oxytocin, which, in a wide range of species, including humans and rodents, has been implicated in affiliative and maternal behaviors (Insel, 2010). Studies in humans suggest that MDMA stimulates oxytocin release but have been equivocal on the requirement of oxytocin for MDMA's empathogenic effect (Kamilar-Britt and Bedi, 2015). Studies in rat, where prosocial effects of MDMA have been more extensively documented than in mice, support the notion that MDMA stimulates oxytocin release in the central nervous system and that oxytocin and its receptors are required for MDMA's prosocial effect (Carson et al., 2013). Some studies also suggest that a closely related neuropeptide, arginine vasopressin (AVP), may play a role in MDMA's prosocial effect through the vasopressin 1a receptor (V1AR) (Carson et al., 2013). This work suggests several promising directions forward for separating the mechanisms underlying MDMA's prosocial effects from those that mediate its abuse liability. The cells and circuits producing and influenced by oxytocin are genetically tractable and thus highly amenable to rigorous manipulation using the many tools available for modern neuroscience research.

### Future Directions

Conventional ideas about what constitutes therapy for mental illnesses are changing with the advent of modalities like deep brain stimulation and repetitive transcranial magnetic stimulation, as well as the repurposing of well-known drugs, like the anesthetic ketamine for use as a rapid-acting antidepressant. The early data on MDMA suggest that it belongs in this class of paradigm-shifting therapies. At its heart, healing a patient starts with a relationship between two people. In psychiatry, the importance of an open, trusting bond between clinician and patient is crucial for successful therapy and is strongly linked to better patient outcomes. In many cases, the greatest bar-

rier to therapy is an inability to establish that first connection (Martin et al., 2000). At this early stage, the weight of evidence suggests that MDMA helps forge this very bond. Of course, it will be important to perform empirical clinical research on all aspects of the use of MDMA as an adjunct to psychotherapy or a primary treatment for dysfunctional social behaviors. There is much we need to know about the benefit and harm MDMA can generate before it could be considered a standard treatment. However, irrational barriers to its study based on poor understanding of its actions need to be minimized so that appropriate clinical studies can be performed.

While such pragmatic clinical studies will certainly be important, we are equally excited about the utility of MDMA as a unique and relatively simple manipulation that can be used to probe the neural basis of prosocial behaviors in a wide range of species. What combination of molecular targets are required for MDMA to exert its powerful prosocial effect? We know that interaction with SERT alone is unlikely to be sufficient. What synapses and cells in the brain are the critical targets of MDMA's effects? How do these effects influence critical circuits that mediate prosocial and antisocial behaviors? The answers to these questions can be obtained using the tools of modern neuroscience research and will provide important insights into some of the most positive and beneficial aspects of human interaction. The answers will also allow us to decrease the abuse liability of MDMA and facilitate the development of new agents that will mimic the potential therapeutic actions of MDMA.

More and more results are accumulating to support the proposition that listing MDMA as a schedule I drug with no accepted medical use is no longer a rational societal policy. By no means would we suggest that its recreational use is appropriate. But, its use as an object of rigorous scientific study should be encouraged and perhaps facilitated. As a probe of brain function, it is a remarkably simple but powerful tool that can be used to advance our understanding of the neural basis of empathy, social reward, and related prosocial behaviors. Such understanding can only benefit individuals and the human interactions in

which they engage. The world's populations need more compassion and empathy for one another. The study of MDMA provides one small but potentially important step toward reaching that goal.

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#### REFERENCES

- Carson, D.S., Guastella, A.J., Taylor, E.R., and McGregor, I.S. (2013). *J. Psychopharmacol. (Oxford)* 27, 231–247.
- Danforth, A.L., Struble, C.M., Yazar-Klosinski, B., and Grob, C.S. (2016). *Prog. Neuropsychopharmacol. Biol. Psychiatry* 64, 237–249.
- Green, A.R., King, M.V., Shortall, S.E., and Fone, K.C.F. (2012). *Br. J. Pharmacol.* 166, 1523–1536.
- Greer, G.R., and Tolbert, R. (1990). The therapeutic use of MDMA. In *Ecstasy: The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA*, S.J. Peroutka, ed. (Springer), pp. 21–35.
- Insel, T.R. (2010). *Neuron* 65, 768–779.
- Jonas, D.E., Cusack, K., Forneris, C.A., Wilkins, T.M., Sonis, J., Middleton, J.C., et al. (2013). Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD). Comparative Effectiveness Reviews, No. 92, Report No. 13-EHC011-EF.
- Kamilar-Britt, P., and Bedi, G. (2015). *Neurosci. Biobehav. Rev.* 57, 433–446.
- Kirkpatrick, M.G., Baggott, M.J., Mendelson, J.E., Galloway, G.P., Liechti, M.E., Hysek, C.M., and de Wit, H. (2014). *Psychopharmacology (Berl.)* 231, 3899–3905.
- Martin, D.J., Garske, J.P., and Davis, M.K. (2000). *J. Consult. Clin. Psychol.* 68, 438–450.
- Mithoefer, M. (2013). MDMA-assisted psychotherapy: how different is it from other psychotherapy? *MAPS News-Letters* 23, 10–14. [http://www.maps.org/news-letters/v23n1/v23n1\\_p10-14.pdf](http://www.maps.org/news-letters/v23n1/v23n1_p10-14.pdf).
- Mithoefer, M.C., Wagner, M.T., Mithoefer, A.T., Jerome, L., Martin, S.F., Yazar-Klosinski, B., Michel, Y., Brewerton, T.D., and Doblin, R. (2013). *J. Psychopharmacol. (Oxford)* 27, 28–39.
- Ricaurte, G.A., Yuan, J., Hatzidimitriou, G., Cord, B.J., and McCann, U.D. (2002). Retraction. *Science* 297, 2260–2263.
- Roberts, C.A., Jones, A., and Montgomery, C. (2016). *Neurosci. Biobehav. Rev.* 63, 158–167.
- Shulgin, A.T. (1990). History of MDMA. In *Ecstasy: The Clinical, Pharmacological and Neurotoxicological Effects of the Drug MDMA*, S.J. Peroutka, ed. (Springer), pp. 1–20.
- Zakzanis, K.K., Campbell, Z., and Jovanovski, D. (2007). *Hum. Psychopharmacol.* 22, 427–435.