American Journal of Therapeutics 31, e141–e154 (2024)

Psychedelic Therapy: A Primer for Primary Care Clinicians—3,4-Methylenedioxy-methamphetamine (MDMA)

Kenneth Shinozuka, BA,[1,2,*] Burton J. Tabaac, MD, FAHA,[3,4] Alejandro Arenas, MD,[5] Bryce D. Beutler, MD,[6] Kirsten Cherian, PhD,[7] Viviana D. Evans, BA,[8] Chelsey Fasano, BA,[9] and Owen S. Muir, MD, DFAACAP[10,11]

Background: After becoming notorious for its use as a party drug in the 1980s, 3,4-methylenedioxy-methampetamine (MDMA), also known by its street names "molly" and "ecstasy," has emerged as a powerful treatment for post-traumatic stress disorder (PTSD).

Areas of Uncertainty: There are extensive data about the risk profile of MDMA. However, the literature is significantly biased. Animal models demonstrating neurotoxic or adverse effects used doses well beyond the range that would be expected in humans (up to 40 mg/kg in rats compared with roughly 1–2 mg/kg in humans). Furthermore, human samples often comprise recreational users who took other substances in addition to MDMA, in uncontrolled settings.

Therapeutic Advances: Phase III clinical trials led by the Multidisciplinary Association for Psychedelic Studies (MAPS) have shown that MDMA-assisted psychotherapy has an effect size of $d = 0.7$–0.91, up to 2–3 times higher than the effect sizes of existing antidepressant treatments. 67%–71% of patients who undergo MDMA-assisted psychotherapy no longer meet the diagnostic criteria for PTSD within 18 weeks. We also describe other promising applications of MDMA-assisted psychotherapy for treating alcohol use disorder, social anxiety, and other psychiatric conditions.

Limitations: Thus far, almost all clinical trials on MDMA have been sponsored by a single organization, MAPS. More work is needed to determine whether MDMA-assisted therapy is more effective than existing nonpharmacological treatments such as cognitive behavioral therapy.

Conclusions: Phase III trials suggest that MDMA is superior to antidepressant medications for treating PTSD. Now that MAPS has officially requested the Food and Drug Administration to approve MDMA as a treatment for PTSD, legal MDMA-assisted therapy may become available as soon as 2024.

Keywords: MDMA, psychedelics, PTSD, serotonin, psychedelic assisted psychotherapy

[1]*Centre for Eudaimonia and Human Flourishing, University of Oxford, Oxford, United Kingdom;* [2]*Department of Psychiatry, University of Oxford, Oxford, United Kingdom;* [3]*University of Nevada, Reno School of Medicine, Reno, NV;* [4]*Department of Neurology, Carson Tahoe Health, Carson City, NV;* [5]*Department of Anesthesiology, University of Washington School of Medicine, Seattle, WA;* [6]*University of Southern California, Keck School of Medicine, Los Angeles, CA;* [7]*Department of Psychiatry & Behavioral Sciences, Stanford University, Palo Alto, CA;* [8]*Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY;* [9]*Teachers College, Columbia University, New York, NY;* [10]*Fermata Health, Brooklyn, NY; and* [11]*Acacia Clinics, Sunnyvale, CA.*

The authors have no conflicts of interest to declare.

**Address for correspondence: Kenneth Shinozuka, BA, Centre for Eudaimonia and Human Flourishing, 7 Stoke Place, Headington, Oxford OX3 9BX, United Kingdom. E-mail: kenneth.shinozuka@psych.ox.ac.uk*

CLINICAL CASE

A 32-year-old man with a history of treatment-resistant post-traumatic stress disorder (PTSD) presents for evaluation at a specialized clinic for service-connected disabled veterans. He had been an Air Force combat reconnaissance photographer in his military service, under the Joint Special Operations Command, and although he declines to provide a detailed description on initial evaluation of his myriad deployments, he identifies a number of Category A trauma events over his 15 years of military service. Prior treatments include prolonged exposure psychotherapy, venlafaxine (up to 225 mg), prazosin (up to 25 mg), and quetiapine (up to 600 mg QHS), which is the only medication he is continuing to take at this time. He presents to this specialized setting in the context of insufficient relief from his disabling nightmares, flashbacks, and irritable outbursts which have led to filing for divorce from his spouse of 12 years. On physical examination, he is 280 pounds. He is notably hypervigilant on mental status evaluation, but he evidences no other problems from his neurological or physical examination, although he reports that his urination has become more frequent on his current regimen, compared with when he was on prazosin. His hemoglobin A1C is 7.3 on pre-evaluation bloodwork, and his total cholesterol is 214, with a low-density lipoprotein cholesterol of 143. Absent successful treatment with prior attempts, he was willing to present for MDMA treatment evaluation in this specialized setting, noting "some of my buddies were in the trial for this, and they told me it was worth checking out."

BACKGROUND

History

MDMA, also known by the street names ecstasy, E, molly, mandy, pills, and pinger, was created and patented by Merck, a German pharmaceutical company, in 1912, out of a desire to develop a novel precursor for the synthesis of a chemical that prevents blood clotting.[1] However, MDMA did not gain widespread recognition until famed chemist Alexander Shulgin synthesized it himself and introduced it to psychotherapists in America,[2] who took interest in the drug because it seemed to be less toxic than chemically similar yet therapeutically promising substances.[3] While therapists were using MDMA for couples therapy and as a tool for treating psychosis, PTSD, cancer, and other illnesses in the 1970s and 80s,[3] MDMA started to become widely available as a club drug. Its popularity grew in tandem with rave culture; MDMA fueled the rise of house and techno music. These genres of music, in clubs and similar settings, were experienced as synergistic with the subjective experience of the drug. However, MDMA's use as a "party drug" led the Drug Enforcement Administration (DEA) to classify it as a Schedule I substance in 1985.

Before the federal ban on MDMA, American activist Rick Doblin petitioned the DEA to maintain the legality of MDMA-assisted therapy. When his efforts proved unsuccessful, Doblin founded the nonprofit Multidisciplinary Association for Psychedelic Studies (MAPS) in 1986 to fund research on MDMA (see 4 for a review on the history of MAPS). After funding some initial studies on the safety of MDMA use in dogs and rats,[5] MAPS applied for the Food and Drug Administration (FDA) to grant Investigational New Drug (IND) status to MDMA for the treatment of pain, anxiety, and depression in patients with cancer. In 1994, the FDA conducted a phase I study on MDMA to establish the dose–response safety of MDMA, which established that changes in body temperature and heart rate on MDMA were transient and that MDMA use was well-tolerated in healthy participants.[6]

Chemistry and mechanism of action

Unlike LSD, N,N-dimethyltryptamine (DMT), and psilocybin, MDMA is not a classic psychedelic; it is an amphetamine derivative. However, because MDMA, unlike amphetamines, has a functional group (methylenedioxy) attached to its aromatic ring, its chemical structure resembles that of mescaline.[7] Thus, MDMA is often grouped together with psychedelic drugs. Another characteristic that distinguishes MDMA from amphetamines is the profound feeling of euphoria, compassion, and trust that MDMA elicits. It has historically been referred to as the "love drug." MDMA promotes empathy, and in therapeutic contexts, it enables users to access and heal from traumatic memories.[8]

Because MDMA is not a classic psychedelic, its psychoactive effects are not primarily mediated by the serotonin-2A (5-HT_{2A}) receptor. (That being said, its interaction with 5-HT_{2A} does have a secondary effect on its hallucinogenic[9,10] and therapeutic properties, as discussed below.) Instead, MDMA acts on the serotonin transport systems, of which there are 2 types in the brain.[11,12] In the first, the serotonin transporter (SERT or 5-HTT) brings serotonin across the plasma membrane of a neuron, mediating the reuptake of serotonin from the synaptic cleft.[13] The other transporter, the vesicular monoamine transporter 2 (VMAT2), takes intracellular serotonin from the cytosol and stores it into vesicles, such that they will later be released into

the synaptic cleft.[14] Early research demonstrated that, by binding to SERT, MDMA not only prevents serotonin from entering the plasma membrane but also reverses the normal direction of serotonin flow, causing serotonin to leave the membrane and flood the synapse.[15] Furthermore, by inhibiting VMAT2, MDMA also blocks serotonin from getting stored into vesicles, massively increasing the concentration of serotonin inside the neuron. This further facilitates the outflow of serotonin into the synapse.[16]

MDMA's mechanism of action is not entirely different from that of SSRIs, which similarly prevent the reuptake of serotonin by binding to SERT.[17] However, unlike SSRIs, MDMA additionally releases large amounts of serotonin into the synapse.[18] The subsequent increase in the concentration of extracellular serotonin is potentially much more substantial and rapid on MDMA than on SSRIs.[19] However, owing to the shared mechanism of action at the SERT transporter, taking SSRIs together with MDMA mitigates the subjective intensity and physiological effects, such as increased blood pressure and heart rate, of MDMA.[20]

In addition to inhibiting SERT, MDMA also binds directly to serotonin receptors, such as 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C}.[9] 5-HT_{1B} and 5-HT_{2A} fully and dose-dependently mediate the heightened motor behavior that occurs on MDMA, respectively,[21–24] whereas 5-HT_{2C} inhibits this hyperactivity.[25,26] In addition to regulating motor behavior on MDMA, 5-HT_{2A} also moderates the emotional response to MDMA. Blocking 5-HT_{2A} with the antagonist ketanserin diminishes the emotional excitation caused by MDMA, as well as some hallucinogenic effects.[27] Ketanserin also diminishes the elevated mood induced by MDMA.[28]

MDMA's interaction with both SERT and 5-HT_{2A} may mediate its therapeutic effects by promoting "fear extinction," or the loss of a fearful response to an adverse stimulus[29] conditioned mice to fear-inducing stimuli by pairing a neutral stimulus (i.e. an auditory tone) with an aversive stimulus (i.e. a footshock). To investigate the hypothesis that MDMA's action at SERT is necessary for fear extinction, the authors then treated mice with a SERT inhibitor, a 5-HT_{2A} antagonist, or placebo. Then, they administered MDMA and exposed the mice to extinction training, in which the neutral stimulus was played without the aversive stimulus. MDMA enhanced fear extinction, and this effect was blocked by both SERT and the 5-HT_{2A} antagonist. (However, a subsequent study found that administering MDMA before fear extinction training actually augmented subsequent fear responses, but MDMA treatment during the reconsolidation phase, i.e., immediately after reactivation of the fear-inducing memory, successfully reduced the fear response.[30])

An earlier study by the authors of[31] with a similar protocol, albeit without the 5-HT_{2A} antagonist, demonstrated that MDMA enhanced the expression of brain-derived neurotrophic factor (BDNF),[31] which is known to play a key role in neuroplasticity; dysregulation of BDNF is associated with maladaptive neuroplasticity in depression.[32,33] The study only observed increases in BDNF within the amygdala, a region in the brain that is involved in regulating fear.[34] Meanwhile, neuroimaging studies on humans have discovered that MDMA decreases cerebral blood flow, a measure of brain activity, in the amygdala.[35] In addition, MDMA elevates functional connectivity between the amygdala and hippocampus[35,36] (note that the second study only found a trend-level effect), a region that supports the encoding and retrieval of memories.[37] Taken together, these findings from both humans and rodents seem to be consistent with the clinical observation that MDMA-assisted therapy facilitates access to traumatic memories that were previously repressed. By upregulating BDNF, MDMA may stimulate neuroplasticity and restore impaired synaptic connections within the amygdala, and enhanced connectivity with the hippocampus may then "unlock" the memory of the trauma.[38] Furthermore, reduced blood flow in the amygdala may correspond to a decrease in anxiety,[35,39] enabling recipients of MDMA-assisted therapy to face the traumatic memory with less fear.

Aside from serotonin, MDMA releases 2 other neurotransmitters: norepinephrine and, to a lesser extent, dopamine. While antagonizing dopamine receptors or deleting dopamine receptor genes has little effect on the behavioral response to MDMA,[40,41] MDMA actually binds with higher affinity to the norepinephrine transporter (NET) than to the serotonin and dopamine transporters.[42,43] Furthermore, blocking NET reduces the intensity of the MDMA high, as well as physiological effects of MDMA like elevations in blood pressure and heart rate.[44] NET inhibition lowered subjective ratings of stimulation in response to MDMA, whereas SERT inhibition more strongly suppressed positive mood ratings,[20] suggesting that norepinephrine mediates the stimulant-like effects of MDMA.

In addition, MDMA stimulates the hormone oxytocin, which plays a vital role in parent–infant bonding[45] and social affinity.[46] Thus, MDMA's interaction with oxytocin underlies not only the general empathogenic qualities of MDMA[47] but also the strong sense of trust that MDMA promotes between the therapist and the patient, which is believed to contribute to its uniquely powerful therapeutic effects.[48] Furthermore, oxytocin

receptors in the nucleus accumbens may mediate the "critical period" of synaptic plasticity that MDMA reopens, thereby facilitating social reward learning.[49]

AREAS OF UNCERTAINTY

Ever since the seminal study of Schmidt and colleagues in 1986,[50] the first to report the persistent depletion of serotonin and its metabolite, 5-hydroxyindoleactic acid (5-HIAA), in rat brains for up to a week after a high-dose injection of MDMA, numerous studies have provided apparent evidence that MDMA has neurotoxic effects (see ref. 51 for a comprehensive review). Much of the early research on rats focused on long-term reductions in the concentration of serotonin, 5-HIAA, and tryptophan hydroxylase, an enzyme that facilitates the synthesis of serotonin; damage to axon terminals that take up serotonin; and loss of 5-HTT binding sites.[52–60] MDMA dose-dependently depleted serotonin by anywhere between 16% and 75% in the rat cortex.[61,62] Serotonin concentration declines in the first 3 hours after dosing, recovers between 6 and 24 hours later, and gradually decreases again between 1 and 7 days later.[63] However, many of these studies administered very high, "binge-like" doses of MDMA to rats; for example, the study that reported a 75% reduction in serotonin gave four 10 mg/kg doses to rats, whereas a therapeutic dose of MDMA in humans is considered to be no higher than <2 mg/kg followed by one <1 mg/kg supplemental dose, assuming an average human weight of >60 kg[64] (note: In this study, the administered dose of MDMA did not depend on weight). Other studies on neurotoxicity administered MDMA doses that were nearly 100 times the standard recreational or therapeutic dose of MDMA.[65]

Furthermore, measured declines in serotonin levels do not reliably correlate with damage to brain tissue. MDMA-induced serotonin depletion does not always lead to loss of serotonin axon terminals.[66] These data suggest that reductions in serotonin constitute an adaptive, counteractive response to the effects of MDMA, rather than leading to damage of serotonin terminals.[67] In addition, serotonin concentrations recover between 6 months and 1 year after MDMA exposure, though not always in all brain regions.[62,68] While initial histological research directly revealed degenerating axon terminals, dendrites, and cell bodies in striatal slices of rats that were administered extremely high doses of MDMA (up to 40 mg/kg),[56,57,65,69] a reappraisal of the early research found no evidence for cell death.[67] In particular, several of the studies that used histological stains found evidence of neurodegeneration in nonserotonergic neurons.[65,69,70] Thus, it seems unlikely that serotonin-specific pathways were related to the neurotoxicity observed in those studies. Moreover, because of the very high doses of MDMA that were administered, adverse effects like hyperthermia—excessive heating of the body, which is known to scale with the dose of MDMA[71]—may have been the primary causes of neurotoxicity. Indeed, in one of these histological studies,[70] MDMA-induced neurodegeneration only occurred in rats that experienced hyperthermia of >41°C.

MDMA also does not seem to elicit the so-called "universal reaction to brain injury," reactive gliosis, in which the cell bodies of astrocytes grow excessively.[72] A tell-tale sign of reactive gliosis is the increased synthesis of glial fibrillary acidic protein (GFAP).[73] While an old study found that GFAP was significantly elevated in rats that received extremely high doses of MDMA (75–150 mg/kg), changes in GFAP were not related to levels of serotonin depletion.[74] Two more recent studies demonstrated that MDMA did not affect GFAP expression.[75,76]

However, one mechanism that does seem to contribute to MDMA-induced neurotoxicity is oxidative stress.[77,78] Oxidative stress occurs when mitochondria produce too many reactive oxygen species (ROS), such as hydroxyl "free radicals" (-OH), which are metabolic byproducts of biological processes like protein phosphorylation.[79] If their concentrations are not kept in check, free radicals will excessively oxidize lipids, proteins, and other macromolecules, leading to cancer and cardiovascular disease.[80] MDMA is metabolized into organic compounds known as quinones, which lead to the formation of free radicals[81,82] that in turn may impair the healthy functioning of mitochondria.[83,84] Multiple studies have claimed that the quinone metabolites of MDMA, rather than the MDMA itself, are the source of the drug's neurotoxicity,[85–87] especially since direct injection of the MDMA into local brain regions (without metabolization in the liver) does not cause much neurotoxicity.[88] However, several MDMA metabolites that get oxidized into quinones are not neurotoxic,[89,90, p. 199] and some have claimed that the deamination (breakdown of amino acids) and oxidation of *dopamine* released by MDMA may play a more pivotal role in MDMA-induced neurotoxicity than the metabolites themselves.[91] One metabolite in particular facilitates the uptake of dopamine into serotonergic neurons; the subsequent oxidation of dopamine, not MDMA, produces reactive and toxic quinones.[92]

Thankfully, there is an abundance of evidence that the oxidative stress induced by MDMA can be prevented by antioxidant supplements, which inactivate free radicals. When administered before MDMA, the antioxidant alpha-lipoic acid was found

to block serotonin depletion and changes in GFAP expression,[93] and the antioxidant ascorbate, more commonly known as vitamin C, achieves similar effects.[94,95] Nutrients like acetyl-L-carnitine are not directly antioxidative, but they seem to strengthen the cell membranes of mitochondria, thus preserving the expression of mitochondrial complexes that are otherwise impaired by MDMA.[83] Based on the scientific evidence, recreational users of MDMA have compiled "supplement packs" (e.g. rollsafe.org), consisting of nutrients and antioxidants to take alongside MDMA to avert the neurotoxic effects. That being said, none of these supplement packs, as far as we are aware, have been examined in peer-reviewed research.

So far, this section has covered research on cell and mouse models of MDMA. Next, we evaluate direct evidence for the neurotoxic effects of MDMA on humans. A multitude of PET and SPECT studies have demonstrated reduced SERT density in human users of MDMA.[96–105] Furthermore, MDMA use has been associated with cognitive impairment, in particular deficiencies in sustained or complex attention; short-term and working verbal, spatial, and visual memory; semantic recognition; and verbal reasoning, as well as exacerbation of unfavorable personality traits like hostility and impulsivity.[98,100,105–113] However, 12 of the 18 studies mentioned above do not control for polydrug use. As revealed by the studies themselves, many MDMA users also consume other illicit substances, such as amphetamines and cocaine, which are known to cause long-term cognitive impairments (for comprehensive reviews, see refs. 114, 115). Therefore, in studies that do not control for polydrug use, it is unclear whether it is the MDMA or the other substances that are contributing to the neurotoxic or adverse cognitive effects. (It is also worth noting that in 2 of these studies, significant differences were only found for heavy MDMA users and not for 'normal' MDMA users.[103,108]) The remaining 6 studies putatively controlled for polydrug use by including a group of control participants who were taking illicit substances but had never consumed MDMA. However, in four of these studies, MDMA users consumed much higher quantities of amphetamines and/or cocaine than the non-MDMA, polydrug users.[105,107,110,113] Finally, a fifth study measured drug-induced neurotoxicity with SERT density, but it found that non-MDMA, polydrug users exhibited *higher* binding of SERT than drug-naive participants.[96] This study calls into question the notion that SERT density is a valid metric of neurotoxicity. Only a single study to date has measured cognitive ability in MDMA users who have minimal exposure to other illicit substances, likely because such users are rather uncommon.[116, p. 201] Based on a battery of 15 cognitive tests, there was little evidence for cognitive impairment. The only significant difference was that MDMA users exhibited increased impulsivity; this could be a common, baseline trait of drug users, who are likely to be more risk-taking than the general population.[117]

Finally, studies of MDMA-induced neurotoxicity in humans are confounded by uncertainty about the authenticity or purity of the MDMA ingested. In all these studies, participants used MDMA that they had purchased illegally, rather than receiving MDMA from a licensed laboratory. MDMA can often be adulterated with other substances, such as synthetic cathinones and fentanyl,[118] which are both harmful.[119–121] Therefore, in uncontrolled recreational use, it is unclear whether the neurotoxic effects of MDMA can be reliably attributed to the compound itself.

Anecdotal reports commonly describe a steep emotional "comedown" as one of the major adverse effects of MDMA. This comedown is often referred to as "Blue Monday" or the "Tuesday Blues" because the comedown sometimes does not occur until 2 days after the MDMA experience.[122] Intriguingly, in a recent study in which MDMA was administered for alcohol use disorder, participants did not report negative changes in mood in the 7 days after the MDMA session.[123] In fact, participants reported an emotional "afterglow," or a consistently elevated mood, after receiving the MDMA treatment. The authors attribute anecdotal accounts of comedowns to the harmful conditions in which MDMA is often taken when consumed recreationally; people who use MDMA at raves tend to exhaust themselves by dancing all night, get poor sleep, and take other drugs simultaneously. However, a critique of this study pointed out that it apparently did not take baseline measurements of mood.[124] Another study that administered MDMA to 166 healthy participants did find significant adverse effects 24 hours after the session, including headache, lack of appetite, lack of energy, and difficulty concentrating, especially in participants who were given a high (125 mg) rather than a medium (75 mg) dose; that being said, there were no differences in depressed mood between the MDMA and placebo groups nor did any "serious" adverse effects occur.[125]

Methodological issues notwithstanding, Sessa's findings are consistent with observations in clinical studies in which MDMA was administered in a controlled, therapeutic setting, unlike recreational contexts. In a recent phase III trial of MDMA for treating PTSD, only one of 46 participants in the MDMA group experienced an adverse event of depressed mood; otherwise, there were no incidences of lowered mood.[64] In

the other phase III trial, there do not seem to be any significant differences in incidences of suicidal ideation between the MDMA and placebo groups.[126]

THERAPEUTIC ADVANCES

Early anecdotal reports of MDMA-assisted psychotherapy suggested that MDMA was potentially useful for treating PTSD because it enabled people to access repressed emotions or memories, such as traumas, while also feeling greater self-compassion.[127] MAPS pivoted toward pursuing MDMA as a treatment for PTSD and released their first protocol for MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD in 2001. Phase II trials commenced in 2004, administering 125 mg of MDMA to 12 participants with PTSD (and placebo to 8 other participants) over 2 sessions. Participants also went through 8 integration sessions with therapists to discuss and process the MDMA session. To assess symptoms of PTSD, clinicians measured scores on the Clinician-Administered PTSD Scale (CAPS) at baseline, 4 days after each session, and 2 months after the second session. Remarkably, 83% of participants exhibited clinical response, defined as a greater than 30% reduction in CAPS scores, whereas the clinical response rate in the control group (placebo with therapy) was only 25% (Table 1).[128] Participants in the placebo group were given the opportunity to receive MDMA therapy at the 2-month follow-up. Among the 7 control participants who crossed over into the MDMA group after failing to respond to the placebo therapy or relapsing into PTSD symptoms, 100% exhibited a clinical response. A long-term follow-up that took place 17–74 months after the second session reported that almost all the participants who received MDMA maintained low CAPS scores.[129] Five subsequent MAPS-sponsored phase II trials, 3 of which were published,[130–132] reported similarly promising results, although one of them found that reductions in CAPS scores from MDMA-assisted therapy did not meet the threshold for statistical significance.[131] Two of these studies also demonstrated that the therapeutic effects of MDMA were dose-dependent; the effect sizes of medium (75–100 mg) and high (125 mg) doses were much greater than that of low (30–40 mg) doses, and participants who crossed over from the low-dose group to the medium-dose or high-dose group exhibited significant improvements in PTSD symptomatology.[130,132] A review of all 6 phase II trials concluded that 54% of participants across all the MDMA groups no longer met the diagnostic criteria for PTSD, compared with only 23% of placebo participants.[133]

The large effect sizes from the phase II trials led MDMA to receive Breakthrough Therapy Designation from the FDA in 2017, and they paved the way for 2 phase III studies. In the first, 46 participants were assigned to receive 3 sessions, spaced 4 weeks apart, of MDMA-assisted therapy across multiple sites in the United States, Canada, and Israel.[64] (Another 44 were randomized to the control group.) The first session consisted of an initial dose of 80 mg and a supplemental half-dose of 40 mg, which was taken 1.5–2.5 hours later. In the second and third sessions, participants were administered 120 mg and a supplemental half-dose of 60 mg. After each session, participants underwent 3 integration sessions, which took place a week apart from one another. Eighteen weeks after baseline, MDMA significantly reduced CAPS scores relative to placebo ($d = 0.91$, $P < 0.0001$); the mean change in CAPS scores was nearly 1.76x higher in the MDMA group (−24.4) than in the placebo group (−13.9), and 67% of the participants in the MDMA group no longer met the diagnostic criteria for PTSD, compared with just 32% of the placebo group. The second confirmatory phase III trial, which enrolled 104 participants and followed the same experimental procedure, produced similarly positive results.[126] Mean change in CAPS scores was 1.6x higher in the MDMA group (−23.7) than in the placebo group (−14.8), and 72% of participants in the MDMA group no longer met the diagnostic criteria for PTSD by the end of the study, compared with just 48% in the placebo group. In December 2023, MAPS officially requested the FDA to approve MDMA-assisted therapy as a treatment for PTSD.[134] Approval is anticipated as early as 2024.

How does MDMA compare with existing treatments for PTSD? At the moment, sertraline and paroxetine, which are both antidepressants of the SSRI (selective serotonin reuptake inhibitor) class, are the only FDA-approved pharmacological treatments. Across all 6 phase II trials, the effect size of MDMA-assisted psychotherapy was nearly 2 times higher than that of paroxetine and 3 times higher than that of sertraline.[135] There are several other advantages that MDMA-assisted therapy has over sertraline or paroxetine. First, sertraline and paroxetine must be taken on a daily basis for anywhere between 2 and 12 weeks to observe any changes in PTSD symptoms, whereas just a single MDMA dose is sufficient to significantly reduce CAPS scores only 3–5 days later.[135] Second, dropout rates are 1.7 times lower for MDMA therapy than for paroxetine and 4.1 times lower than for sertraline, perhaps because of the swift and powerful therapeutic effects of MDMA.[135] However, regarding effect size, MDMA is nearly as effective as or perhaps less effective than trauma-focused psychotherapies, such as eye-movement desensitization

Table 1. Contemporary (21st-century) clinical trials on MDMA.

Study	Type	Dosing	Sample	Findings
128,129	Double-blind, inactive placebo-controlled RCT (phase II)	Stage 1: 2 blinded sessions, each with one dose of 125 mg + optional supplemental dose of 62.5 mg 2–2.5 hours later. Stage 2: Placebo group allowed to cross over into the MDMA group (2 sessions), and the MDMA group were allocated an additional open-label session.	20 patients with PTSD	Stage 1, at 2 months: significant decrease in CAPS scores (MD: −33.6; $P = 0.013$); 83% clinical response rate in MDMA group, compared with 25% in placebo group. Stage 2, at 4–6 weeks: significant decrease in mean CAPS scores for crossover participants (MD: −31.7; $P < 0.05$). At long-term follow-up (mean: 45.4 mo), all participants: decreases in CAPS scores were sustained, except for 2 relapses.
131	Double-blind, active placebo-controlled RCT (phase II)	Stage 1: 3 blinded sessions, each with one of 2 doses: 25 mg (active control) or 125 mg. Optional supplemental dose at half the initial dose. Stage 2: 25 mg group allowed to cross over into 125 mg group (3 sessions). Stage 3: Nonresponders in 125 mg group in Stage 1 were allocated 2 additional open-label sessions.	12 patients with PTSD	Stage 1, at 3 weeks: insignificant decrease in CAPS scores (MD: −15.7, $P = 0.066$), Stage 1, at 2 months: 50% clinical response rate. Stage 2: 100% clinical response rate. Stage 3: no further improvements in CAPS scores. At long-term follow-up (12 mo), all participants: 24-point decrease in CAPS scores relative to baseline for the full-dose group in Stage 1, 35-point decrease for crossover group; 42% of all participants no longer met diagnostic criteria for PTSD.
130	Double-blind, dose-response RCT (phase II)	Stage 1: 2 blinded sessions, each with one of 3 doses: 30 mg (active control), 75 mg, or 125 mg. Optional supplemental dose at half the initial dose. Stage 2: 30 and 75 mg groups allowed to cross over into high-dose group (3 sessions), and 125 mg group were allocated an additional open-label session.	26 veterans and first responders with PTSD	Stage 1, at 1 mo: significant decrease in CAPS-IV scores (MD between 75 mg and 30 mg groups: −46.9, $d = 2.8$, $P = 0.001$; MD between 125 mg and 30 mg groups: −32.9, $d = 1.1$, $P = 0.001$); 58% in 125 mg group, 86% in 75 mg group, and 29% in 30 mg group no longer met PTSD diagnostic criteria. Stage 2, at 1 mo: significant decrease in CAPS-IV scores (MD relative to end of Stage 1: −27.0) for crossover participants; 33% no longer met PTSD diagnostic criteria. At long-term follow-up (12 mo), all participants: significant decrease in CAPS-IV scores relative to baseline (MD: −48.3, $P < 0.0001$); 67% no longer met PTSD diagnostic criteria.
132	Double-blind, dose-response RCT (phase II)	Stage 1: 2 blinded sessions, each with one of 3 doses: 40 mg (active control), 100 mg, or 125 mg. Optional supplemental dose at half the initial dose. Stage 2: 40 mg group allowed to cross over into 100–125 mg groups (3 sessions). 100 and 125 mg groups allocated an additional open-label session.	28 patients with PTSD	Stage 1, at 1 mo: significant decrease in CAPS-IV scores for 125 mg group, per protocol subset (MD relative to 40 mg group: −33.0, $d = 1.12$, $P = 0.01$); insignificant decrease in CAPS-IV scores for 100 mg group, per protocol subset (MD: −20.4, $d = 0.73$, $P = 0.10$); 42% in 125 mg group, 44% in 100 mg group, and 33% in 40 mg group no longer met PTSD diagnostic criteria, intent-to-treat subset. Stage 2, at 2 months: significant decrease in CAPS-IV scores (MD relative to end of Stage 1): −34.7, $P = 0.01$ and 80% no longer met PTSD diagnostic criteria, intent-to-treat subset. At long-term follow-up (12 mo), all participants: significant decrease in CAPS-IV

(*Continued on next page*)

Table 1. (*Continued*) Contemporary (21st-century) clinical trials on MDMA.

Study	Type	Dosing	Sample	Findings
				scores relative to baseline (MD: −61, $P <$ 0.0001) and 76% no longer met PTSD diagnostic criteria, intent-to-treat subset.
64,144,145	Double-blind, inactive placebo-controlled RCT (phase III)	3 blinded sessions: first with 80 mg + supplemental 40 mg half-dose, second and third with 120 mg + supplemental 60 mg half-dose. No crossover.	90 patients with PTSD, 28 of whom met clinical criteria or had high risk for an ED.	At 18 weeks: significant decrease in CAPS-5 scores relative to placebo (MD: −11.9, d = 0.91, $P < 0.0001$); 67% in MDMA group no longer met PTSD diagnostic criteria, compared with 32% in placebo group; significant decrease in AUDIT scores for all participants relative to placebo (MD: −1.42, g = 0.45, P = 0.0436); significant decrease in EAT-26 scores for all participants relative to placebo (MD: −2.36, g = 0.33, P = 0.0335), although RCI values indicated that change from baseline was not reliable.
126	Double-blind, inactive placebo-controlled RCT (phase III)	3 blinded sessions: first with 80 mg + supplemental 40 mg half-dose, second and third with 120 mg + supplemental 60 mg half-dose. No crossover.	104 PTSD patients	At 18 weeks: significant decrease in CAPS-5 scores relative to placebo (MD: −8.9, d = 0.7, $P < 0.001$); 71% in MDMA no longer met PTSD diagnostic criteria, compared with 48% in placebo group.
142	Double-blind, inactive placebo-controlled RCT (pilot)	Stage 1: 2 blinded sessions: first with 75–100 mg and second with 100–125 mg. Stage 2: Placebo group allowed to cross over to MDMA group (2 sessions; data not presented.)	12 people with SAD and autism	Stage 1, at 1 mo: significant decreases in LSAS scores relative to placebo (MD: −24.8, d = 1.4, P = 0.037); clinical response rate of 86% in MDMA group, compared with 50% in placebo group. Stage 1, at 6 mo: significant decrease in LSAS scores relative to placebo (MD: −24.4, d = 1.1, P = 0.036); clinical response rate of 75% in MDMA group, compared with 50% in placebo group
140	Double-blind, inactive placebo-controlled RCT (pilot)	Stage 1: 2 blinded sessions, each with 125 mg + optional supplemental dose of 62.5 mg. Stage 2: Placebo group allowed to cross over to MDMA group (3 sessions). MDMA group allocated an additional open-label session.	18 patients with anxiety from an LTI	Stage 1, at 1 mo: insignificant decreases in STAI-Trait scores relative to placebo (MD: −14.7, g = 1.03, P = 0.0558). Stage 2, at 1 mo after second session: decrease in STAI-Trait scores relative to 1 mo after stage 1 (MD: −4.2). At long-term follow-up (12 mo), all participants: significant decrease in STAI-Trait scores relative to baseline (MD: −26.9, $P < 0.0001$).
143	Open-label	2 sessions, each with 125 mg + supplemental dose of 62.5 mg. MDMA therapy began after completion of detox program.	14 patients with AUD	At 9 months after detox: large decrease in alcohol consumption relative to predetox (MD: −111.9 units/week); abstinence in 64% of participants.

Time points in "findings" column are given relative to the final session in the corresponding stage, unless stated otherwise. MDMA was accompanied by psychotherapy in all trials; typically, 2–3 sessions of psychotherapy occurred alongside each MDMA session. Abbreviations: AUD, Alcohol Use Disorder; AUDIT, Alcohol Use Disorders Identification Test; CAPS(-IV) (−5), Clinician-Administered PTSD Scale (-for DSM IV) (-for DSM 5); EAT-26, Eating Attitudes Test, 26-item; ED, Eating Disorder; LSAS, Liebowitz Social Anxiety Scale; LTI, life-threatening illness; MD, mean difference; PTSD, post-traumatic stress disorder; RCI, Reliable Change Index; RCT, randomized controlled trial; SAD, social anxiety disorder; STAI-Trait, State-Trait Anxiety Inventory, Trait subscale.

reprocessing (EMDR), exposure therapy, cognitive behavioral therapy (CBT), art therapy, and more.[135–138]

MDMA shows promise for treating other conditions, such as anxiety disorders, alcohol use disorder (AUD), substance use disorders, eating disorders (EDs), and more. Just as psilocybin has reduced end-of-life anxiety in terminally ill populations,[139] a MAPS-sponsored phase II trial found that MDMA-assisted therapy

significantly reduced State-Trait Anxiety Inventory scores, although the difference between the MDMA and placebo groups was just under the threshold for statistical significance.[140] Another MAPS-sponsored phase II trial explored the efficacy of MDMA for treating social anxiety in adults with autism, who are at a much greater risk for social anxiety disorder than the general population.[141] MDMA significantly reduced scores on the Leibowitz Social Anxiety Scale for autistic adults who previously had very severe social anxiety.[142]

With regard to addiction, a recent study found that MDMA caused a staggering drop in alcohol consumption, from 130.6 units per week to 18.7 units per week, in a group of 14 participants with AUD.[143] During one phase III trial on MDMA for PTSD, researchers also measured changes in measures of hazardous alcohol and substance use over the course of treatment, and they reported that MDMA-assisted therapy for PTSD led to a concomitant, significant reduction in these measures.[144] A subset of participants (32%) in the phase III trial were also at high risk for EDs, according to baseline measurements of Eating Attitudes Test 26 (EAT-26) scores. MDMA therapy for PTSD significantly reduced EAT-26 scores.[145] These results are expected given that AUD and EDs are comorbidities with PTSD.[146,147] MAPS is now planning a phase II trial on MDMA for anorexia nervosa and binge-eating disorder in a group of 18 participants.[148]

CONCLUSIONS

Preliminary evidence suggests that MDMA in conjunction with psychotherapy may be a highly effective treatment for PTSD, as well as other conditions such as AUD, ED, anxiety, and more. By inhibiting the serotonin transporter, stimulating plasticity in the amygdala, and enhancing connectivity between the amygdala and hippocampus, MDMA enables users to process repressed memories of traumatic events without experiencing the fear that typically arises with them. While MDMA abuse in recreational contexts can lead to cognitive impairments, clinical research has shown that MDMA does not induce any psychological or neurological deficits when it is administered in a controlled, therapeutic context. More trials are needed to confirm the promising effect sizes of MDMA-assisted psychotherapy.

REFERENCES

1. Freudenmann RW, Öxler F, Bernschneider-Reif S. The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents*. *Addiction*. 2006;101:1241–1245.
2. Benzenhöfer U, Passie T. Rediscovering MDMA (ecstasy): the role of the American chemist Alexander T. Shulgin. *Addiction*. 2010;105:1355–1361.
3. Passie T. The early use of MDMA ("Ecstasy") in *psychotherapy* (1977–1985). *Drug Sci Policy L*. 2018;4:205032451876744.
4. Emerson A, Ponté L, Jerome L, et al. History and future of the multidisciplinary association for psychedelic studies (MAPS). *J Psychoactive Drugs*. 2014;46:27–36.
5. Frith CH, Chang LW, Lattin DL, et al. Toxicity of methylenedioxymethamphetamine (MDMA) in the dog and the rat. *Fundam Appl Toxicol*. 1987;9:110–119.
6. Grob CS, Poland RE, Chang L, et al. Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations. *Behav Brain Res*. 1996;73:103–107.
7. Kalant H. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. *CMAJ*. 2001;165:917–928.
8. Nichols DE. Entactogens: how the name for a novel class of psychoactive agents originated. *Front Psychiatry*. 2022;13. Available at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.863088. Accessed May 25, 2023.
9. Bankson MG, Cunningham KA. 3,4-Methylenedioxymethamphetamine (MDMA) as a unique model of serotonin receptor function and serotonin-dopamine interactions. *J Pharmacol Exp Ther*. 2001;297:846–852.
10. Green AR, Cross AJ, Goodwin GM. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy"). *Psychopharmacology (Berl)*. 1995;119:247–260.
11. Rudnick G, Fishkes H, Nelson J, et al. Evidence for two distinct serotonin transport systems in platelets. *J Biol Chem*. 1980;255:3638–3641.
12. Lizarraga LE, Cholanians AB, Phan AV, et al. Vesicular monoamine transporter 2 and the acute and long-term response to 3,4-(±)-methylenedioxymethamphetamine. *Toxicol Sci*. 2015;143:209–219.
13. Yang D, Gouaux E. Illumination of serotonin transporter mechanism and role of the allosteric site. *Sci Adv*. 2021;7:eabl3857.
14. Nickell JR, Siripurapu KB, Vartak A, et al. Chapter two - the vesicular monoamine transporter-2: an important pharmacological target for the discovery of novel therapeutics to treat methamphetamine abuse. In Dwoskin LP, ed. *Advances in Pharmacology*, vol 69, Emerging Targets & Therapeutics in the Treatment of Psychostimulant Abuse, Academic Press, 2014, 71–106.
15. Rudnick G, Wall SC. The molecular mechanism of "ecstasy" [3,4-methylenedioxy-methamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release. *Proc Natl Acad Sci USA*. 1992;89:1817–1821.
16. Schuldiner S, Steiner-Mordoch S, Yelin R, et al. Amphetamine derivatives interact with both plasma membrane and secretory vesicle biogenic amine transporters. *Mol Pharmacol*. 1993;44:1227–1231.
17. Zhou Z, Zhen J, Karpowich NK, et al. Antidepressant specificity of serotonin transporter suggested by three

LeuT-SSRI structures. *Nat Struct Mol Biol*. 2009;16:652–657.
18. Higuchi M, Suzuki Y, Yatani Y, et al. Augmentation of serotonin release by sustained exposure to MDMA and methamphetamine in rat organotypic mesencephalic slice cultures containing raphe serotonergic neurons. *J Neurochem*. 2008;106:2410–2420.
19. Dobry Y, Rice T, Sher L. Ecstasy use and serotonin syndrome: a neglected danger to adolescents and young adults prescribed selective serotonin reuptake inhibitors. *Int J Adolesc Med Health*. 2013;25:193–199.
20. Liechti ME, Vollenweider FX. The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers. *J Psychopharmacol*. 2000;14:269–274.
21. Callaway CW, Rempel N, Peng RY, et al. Serotonin 5-HT1-like receptors mediate hyperactivity in rats induced by 3,4-methylenedioxymethamphetamine. *Neuropsychopharmacology*. 1992;7:113–127.
22. Kehne JH, Ketteler HJ, McCloskey TC, et al. Effects of the selective 5-HT2A receptor antagonist MDL 100,907 on MDMA-induced locomotor stimulation in rats. *Neuropsychopharmacology*. 1996;15:116–124.
23. McCreary AC, Bankson MG, Cunningham KA. Pharmacological studies of the acute and chronic effects of (+)-3,4-methylenedioxymethamphetamine on locomotor activity: role of 5-hydroxytryptamine1a and 5-hydroxytryptamine1B/1D receptors. *J Pharmacol Exp Ther*. 1999;290:965–973.
24. Scearce-Levie K, Viswanathan SS, Hen R. Locomotor response to MDMA is attenuated in knockout mice lacking the 5-HT1B receptor. *Psychopharmacology (Berl)*. 1999;141:154–161.
25. Gleason SD, Shannon HE. Meta-chlorophenylpiperazine induced changes in locomotor activity are mediated by 5-HT1 as well as 5-HT2C receptors in mice. *Eur J Pharmacol*. 1998;341:135–138.
26. Heisler LK, Tecott LH. A paradoxical locomotor response in serotonin 5-HT2C receptor mutant mice. *J Neurosci*. 2000;20:RC71.
27. Liechti ME, Saur MR, Gamma A, et al. Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the 5-HT2 antagonist ketanserin in healthy humans. *Neuropsychopharmacology*. 2000;23:396–404.
28. van Wel JHP, Kuypers KPC, Theunissen EL, et al. Effects of acute MDMA intoxication on mood and impulsivity: role of the 5-HT2 and 5-HT1 receptors. *PLoS ONE*. 2012;7:e40187.
29. Young MB, Norrholm SD, Khoury LM, et al. Inhibition of serotonin transporters disrupts the enhancement of fear memory extinction by 3,4-methylenedioxymethamphetamine (MDMA). *Psychopharmacology (Berl)*. 2017;234:2883–2895.
30. Hake HS, Davis JKP, Wood RR, et al. 3,4-methylenedioxymethamphetamine (MDMA) impairs the extinction and reconsolidation of fear memory in rats. *Physiol Behav*. 2019;199:343–350.
31. Young MB, Andero R, Ressler KJ, et al. 3,4-Methylenedioxymethamphetamine facilitates fear extinction learning. *Transl Psychiatry*. 2015;5:e634.
32. Chakrapani S, Eskander N, De Los Santos LA, et al. Neuroplasticity and the biological role of brain derived neurotrophic factor in the pathophysiology and management of depression. *Cureus*. 2020;12:e11396.
33. Yang T, Nie Z, Shu H, et al. The role of BDNF on neural plasticity in depression. *Front Cell. Neurosci.* 2020;14. Available at: https://www.frontiersin.org/articles/10.3389/fncel.2020.00082. Accessed May 25, 2023.
34. LeDoux J. The emotional brain, fear, and the amygdala. *Cell Mol Neurobiol*. 2003;23:727–738.
35. Carhart-Harris R, Murphy K, Leech R, et al. The effects of acutely administered 3,4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level-dependent resting state functional connectivity. *Biological Psychiatry*. 2014;78:554–562.
36. Singleton SP, Wang JB, Mithoefer M, et al. Altered brain activity and functional connectivity after MDMA-assisted therapy for post-traumatic stress disorder. *Front Psychiatry*. 2022;13:947622.
37. Wiltgen BJ, Zhou M, Cai Y, et al. The hippocampus plays a selective role in the retrieval of detailed contextual memories. *Curr Biol*. 2010;20:1336–1344.
38. Sottile RJ, Vida T. A proposed mechanism for the MDMA-mediated extinction of traumatic memories in PTSD patients treated with MDMA-assisted therapy. *Front Psychiatry*. 2022;13:991753.
39. Engel K, Bandelow B, Gruber O, et al. Neuroimaging in anxiety disorders. *J Neural Transm*. 2009;116:703–716.
40. Risbrough VB, Masten VL, Caldwell S, et al. Differential contributions of dopamine D1, D2, and D3 receptors to MDMA-induced effects on locomotor behavior patterns in mice. *Neuropsychopharmacology*. 2006;31:2349–2358.
41. Liechti ME, Vollenweider FX. Acute psychological and physiological effects of MDMA ("Ecstasy") after haloperidol pretreatment in healthy humans. *Eur Neuropsychopharmacol*. 2000;10:289–295.
42. Han DD, Gu HH. Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. *BMC Pharmacol*. 2006;6:6.
43. Verrico CD, Miller GM, Madras BK. MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced neurotoxicity and treatment. *Psychopharmacology (Berl)*. 2007;189:489–503.
44. Hysek C, Simmler LD, Ineichen M, et al. The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA ("Ecstasy") in humans. *Clin Pharmacol Ther*. 2011;90:246–255.
45. Scatliffe N, Casavant S, Vittner D, et al. Oxytocin and early parent-infant interactions: a systematic review. *Int J Nurs Sci*. 2019;6:445–453.
46. Jones C, Barrera I, Brothers S, et al. Oxytocin and social functioning. *Dialogues Clin Neurosci*. 2017;19:193–201.
47. Kirkpatrick MG, Lee R, Wardle MC, et al. Effects of MDMA and intranasal oxytocin on social and

emotional processing. *Neuropsychopharmacology*. 2014; 39:1654–1663.
48. Thal SB, Lommen MJJ. Current perspective on MDMA-assisted psychotherapy for posttraumatic stress disorder. *J Contemp Psychother*. 2018;48:99–108.
49. Nardou R, Lewis EM, Rothhaas R, et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature*. 2019;569:116–120.
50. Schmidt CJ, Wu L, Lovenberg W. Methylenedioxymethamphetamine: a potentially neurotoxic amphetamine analogue. *Eur J Pharmacol*. 1986;124:175–178.
51. Capela JP, Carmo H, Remião F, et al. Molecular and cellular mechanisms of ecstasy-induced neurotoxicity: an overview. *Mol Neurobiol*. 2009;39:210–271.
52. Battaglia G, Yeh SY, O'Hearn E, et al. 3,4-Methylenedioxymethamphetamine and 3,4-methylenedioxyamphetamine destroy serotonin terminals in rat brain: quantification of neurodegeneration by measurement of [3H]paroxetine-labeled serotonin uptake sites. *J Pharmacol Exp Ther*. 1987;242:911–916.
53. Broening HW, Bowyer JF, Slikker W. Age-dependent sensitivity of rats to the long-term effects of the serotonergic neurotoxicant (+/-)-3,4-methylenedioxymethamphetamine (MDMA) correlates with the magnitude of the MDMA-induced thermal response. *J Pharmacol Exp Ther*. 1995;275:325–333.
54. Colado MI, Murray TK, Green AR. 5-HT loss in rat brain following 3,4-methylenedioxymethamphetamine (MDMA), p-chloroamphetamine and fenfluramine administration and effects of chlormethiazole and dizocilpine. *Br J Pharmacol*. 1993;108:583–589.
55. Fischer C, Hatzidimitriou G, Wlos J, et al. Reorganization of ascending 5-HT axon projections in animals previously exposed to the recreational drug (+/-)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *J Neurosci*. 1995;15:5476–5485.
56. Molliver ME, Berger UV, Mamounas LA, et al. Neurotoxicity of MDMA and related compounds: anatomic studies. Ann NY Acad Sci. 1990;600:649–661; discussion 661-664.
57. O'Hearn E, Battaglia G, De Souza EB, et al. Methylenedioxyamphetamine (MDA) and methylenedioxymethamphetamine (MDMA) cause selective ablation of serotonergic axon terminals in forebrain: immunocytochemical evidence for neurotoxicity. *J Neurosci*. 1988;8: 2788–2803.
58. O'Shea E, Granados R, Esteban B, et al. The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA ('ecstasy'). *Neuropharmacology*. 1998;37:919–926.
59. Schmidt CJ, Taylor VL. Depression of rat brain tryptophan hydroxylase activity following the acute administration of methylenedioxymethamphetamine. *Biochem Pharmacol*. 1987;36:4095–4102.
60. Stone DM, Stahl DC, Hanson GR, et al. The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) on monoaminergic systems in the rat brain. *Eur J Pharmacol*. 1986;128:41–48.
61. Bull EJ, Hutson H, Fone KCF. Reduced social interaction following 3,4-methylenedioxymethamphetamine is not associated with enhanced 5-HT 2C receptor responsivity. *Neuropharmacology*. 2003;44:439–448.
62. Scanzello CR, Hatzidimitriou G, Martello AL, et al. Serotonergic recovery after (+/-)3,4-(methylenedioxy) methamphetamine injury: observations in rats. *J Pharmacol Exp Ther*. 1993;264:1484–1491.
63. Schmidt CJ. Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. *J Pharmacol Exp Ther*. 1987;240:1–7.
64. Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med*. 2021;27:1025–1033.
65. Jensen KF, Olin J, Haykal-Coates N, et al. Mapping toxicant-induced nervous system damage with a cupric silver stain: a quantitative analysis of neural degeneration induced by 3,4-methylenedioxymethamphetamine. *NIDA Res Monogr*. 1993;136:133–149; discussion 150-154.
66. Wang X, Baumann MH, Xu H, et al. 3,4-methylenedioxymethamphetamine (MDMA) administration to rats decreases brain tissue serotonin but not serotonin transporter protein and glial fibrillary acidic protein. *Synapse*. 2004;53:240–248.
67. Baumann MH, Wang X, Rothman RB. 3,4-Methylenedioxymethamphetamine (MDMA) neurotoxicity in rats: a reappraisal of past and present findings. *Psychopharmacology (Berl)*. 2007;189:407–424.
68. Sabol KE, Lew R, Richards JB, et al. Methylenedioxymethamphetamine-induced serotonin deficits are followed by partial recovery over a 52-week period. Part I: synaptosomal uptake and tissue concentrations. *J Pharmacol Exp Ther*. 1996;276:846–854.
69. Commins DL, Vosmer G, Virus RM, et al. Biochemical and histological evidence that methylenedioxymethylamphetamine (MDMA) is toxic to neurons in the rat brain. *J Pharmacol Exp Ther*. 1987;241:338–345.
70. Schmued LC. Demonstration and localization of neuronal degeneration in the rat forebrain following a single exposure to MDMA. *Brain Res*. 2003;974:127–133.
71. Liechti ME. Effects of MDMA on body temperature in humans. *Temperature (Austin)*. 2014;1:192–200.
72. Buffo A, Rite I, Tripathi P, et al. Origin and progeny of reactive gliosis: a source of multipotent cells in the injured brain. *Proc Natl Acad Sci USA*. 2008;105:3581–3586.
73. Yang Z, Wang KKW. Glial Fibrillary acidic protein: from intermediate filament assembly and gliosis to neurobiomarker. *Trends Neurosci*. 2015;38:364–374.
74. O'Callaghan JP, Miller DB. Quantification of reactive gliosis as an approach to neurotoxicity assessment. *NIDA Res Monogr*. 1993;136:188–212.
75. Bai F, Jones DC, Lau SS, et al. Serotonergic neurotoxicity of 3,4-(+/-)-methylenedioxyamphetamine and 3,4-

(+/-)-methylendioxymethamphetamine (ecstasy) is potentiated by inhibition of gamma-glutamyl transpeptidase. *Chem Res Toxicol*. 2001;14:863–870.
76. Pubill D, Canudas AM, Pallàs M, et al. Different glial response to methamphetamine- and methylenedioxymethamphetamine-induced neurotoxicity. *Naunyn Schmiedebergs Arch Pharmacol*. 2003;367:490–499.
77. Baggott MJ, Mendelson J. Does MDMA cause brain damage? In: *Ecstasy, A Complete Guide*. Inner Tradition; 2001:110–145.
78. Song B-J, Moon K-H, Upreti VV, et al. Mechanisms of MDMA (Ecstasy)-Induced oxidative stress, mitochondrial dysfunction, and organ damage. *Curr Pharm Biotechnol*. 2010;11:434–443.
79. Pizzino G, Irrera N, Cucinotta M, et al. Oxidative stress: harms and benefits for human health. *Oxid Med Cell Longev*. 2017;2017:8416763.
80. Lobo V, Patil A, Phatak A, et al. Free radicals, antioxidants and functional foods: impact on human health. *Pharmacogn Rev*. 2010;4:118–126.
81. Carvalho M, Remião F, Milhazes N, et al. The toxicity of N-methyl-alpha-methyldopamine to freshly isolated rat hepatocytes is prevented by ascorbic acid and N-acetylcysteine. *Toxicology*. 2004;200:193–203.
82. de la Torre R, Farré M, Roset PN, et al. Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition. *Ther Drug Monit*. 2004;26:137–144.
83. Alves E, Binienda Z, Carvalho F, et al. Acetyl-L-carnitine provides effective in vivo neuroprotection over 3,4-methylenedioximethamphetamine-induced mitochondrial neurotoxicity in the adolescent rat brain. *Neuroscience*. 2009;158:514–523.
84. Moon K-H, Upreti VV, Yu LR, et al. Mechanism of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy)-mediated mitochondrial dysfunction in rat liver. *Proteomics*. 2008;8:3906–3918.
85. Easton N, Fry J, O'Shea E, et al. Synthesis, in vitro formation, and behavioural effects of glutathione regioisomers of alpha-methyldopamine with relevance to MDA and MDMA (ecstasy). *Brain Res*. 2003;987:144–154.
86. Miller RT, Lau SS, Monks TJ. Effects of intracerebroventricular administration of 5-(glutathion-S-yl)-alpha-methyldopamine on brain dopamine, serotonin, and norepinephrine concentrations in male Sprague-Dawley rats. *Chem Res Toxicol*. 1996;9:457–465.
87. de la Torre R, Farré M. Neurotoxicity of MDMA (ecstasy): the limitations of scaling from animals to humans. *Trends Pharmacol Sci*. 2004;25:505–508.
88. Esteban B, O'Shea E, Camarero J, et al. 3,4-Methylenedioxymethamphetamine induces monoamine release, but not toxicity, when administered centrally at a concentration occurring following a peripherally injected neurotoxic dose. *Psychopharmacology (Berl)*. 2001;154:251–260.
89. Miller RT, Lau SS, Monks TJ. 2,5-Bis-(glutathion-S-yl)-alpha-methyldopamine, a putative metabolite of (+/-)-3,4-methylenedioxyamphetamine, decreases brain serotonin concentrations. *Eur J Pharmacol*. 1997;323:173–180.
90. Zhao ZY, Castagnoli N, Ricaurte GA, et al. Synthesis and neurotoxicological evaluation of putative metabolites of the serotonergic neurotoxin 2-(methylamino)-1-[3,4-(methylenedioxy)phenyl] propane [(methylenedioxy)methamphetamine]. *Chem Res Toxicol*. 1992;5:89–94.
91. Sprague JE, Nichols DE. Neurotoxicity of MDMA (ecstasy): beyond metabolism. *Trends Pharmacol Sci*. 2005;26:59–61; author reply 60-61.
92. Jones DC, Lau SS, Monks TJ. Thioether metabolites of 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine inhibit human serotonin transporter (hSERT) function and simultaneously stimulate dopamine uptake into hSERT-expressing SK-N-MC cells. *J Pharmacol Exp Ther*. 2004;311:298–306.
93. Aguirre N, Barrionuevo M, Ramírez MJ, et al. Alpha-lipoic acid prevents 3,4-methylenedioxy-methamphetamine (MDMA)-induced neurotoxicity. *Neuroreport*. 1999;10:3675–3680.
94. Gudelsky GA. Effect of ascorbate and cysteine on the 3,4-methylenedioxymethamphetamine-induced depletion of brain serotonin. *J Neural Transm (Vienna)*. 1996;103:1397–1404.
95. Shankaran M, Yamamoto BK, Gudelsky GA. Ascorbic acid prevents 3,4-methylenedioxymethamphetamine (MDMA)-induced hydroxyl radical formation and the behavioral and neurochemical consequences of the depletion of brain 5-HT. *Synapse*. 2001;40:55–64.
96. Buchert R, Thomasius R, Nebeling B, et al. Long-term effects of "ecstasy" use on serotonin transporters of the brain investigated by PET. *J Nucl Med*. 2003;44:375–384.
97. Buchert R, Thomasius R, Wilke F, et al. A voxel-based PET investigation of the long-term effects of "Ecstasy" consumption on brain serotonin transporters. *Am J Psychiatry*. 2004;161:1181–1189.
98. McCann UD, Ridenour A, Shaham Y, et al. Serotonin neurotoxicity after (+/-)3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy"): a controlled study in humans. *Neuropsychopharmacology*. 1994;10:129–138.
99. McCann UD, Rf D, Ga R. Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet*. 1998;352:9138.
100. McCann UD, Mertl M, Eligulashvili V, et al. Cognitive performance in (+/-) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. *Psychopharmacology (Berl)*. 1999;143:417–425.
101. McCann UD, Szabo Z, Seckin E, et al. Quantitative PET studies of the serotonin transporter in MDMA users and controls using [11C]McN5652 and [11C]DASB. *Neuropsychopharmacology*. 2005;30:1741–1750.
102. McCann UD, Szabo Z, Vranesic M, et al. Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (+/-)3,4-methylenedioxymethamphetamine ("ecstasy") users: relationship to cognitive performance. *Psychopharmacology (Berl)*. 2008;200:439–450.

103. Reneman L, Booij J, de Bruin K, et al. Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet*. 2001;358:1864–1869.
104. Semple DM, Ebmeier KP, Glabus MF, et al. Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ("ecstasy") users. *Br J Psychiatry*. 1999;175:63–69.
105. Thomasius R, Zapletalova P, Petersen K, et al. Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective. *J Psychopharmacol*. 2006;20:211–225.
106. Bolla KI, McCann UD, Ricaurte GA. Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology*. 1998;51:1532–1537.
107. Fox HC, McLean A, Turner JJD, et al. Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. *Psychopharmacology (Berl)*. 2002;162:203–214.
108. Gouzoulis-Mayfrank E, Thimm B, Rezk M, et al. Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27:819–827.
109. Jacobsen LK, Mencl WE, Pugh KR, et al. Preliminary evidence of hippocampal dysfunction in adolescent MDMA ("ecstasy") users: possible relationship to neurotoxic effects. *Psychopharmacology (Berl)*. 2004;173:383–390.
110. Morgan M, McFie L, Fleetwood H, et al. Ecstasy (MDMA): are the psychological problems associated with its use reversed by prolonged abstinence?. *Psychopharmacology (Berl)*. 2002;159:294–303.
111. Quednow BB, Jessen F, Kuhn K-U, et al. Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction. *J Psychopharmacol*. 2006;20:373–384.
112. Rodgers J. Cognitive performance amongst recreational users of "ecstasy. *Psychopharmacology (Berl)*. 2000;151:19–24.
113. Schilt T, de Win MML, Koeter M, et al. Cognition in novice ecstasy users with minimal exposure to other drugs: a prospective cohort study. *Arch Gen Psychiatry*. 2007;64:728–736.
114. Ersche KD, Sahakian BJ. The neuropsychology of amphetamine and opiate dependence: implications for treatment. *Neuropsychol Rev*. 2007;17:317–336.
115. Spronk DB, van Wel JHP, Ramaekers JG, et al. Characterizing the cognitive effects of cocaine: a comprehensive review. *Neurosci Biobehav Rev*. 2013;37:1838–1859.
116. Halpern JH, Sherwood AR, Hudson JI, et al. Residual neurocognitive features of long-term ecstasy users with minimal exposure to other drugs. *Addiction*. 2011;106:777–786.
117. Butler GKL, Montgomery AMJ. Impulsivity, risk taking and recreational "ecstasy" (MDMA) use. *Drug Alcohol Depend*. 2004;76:55–62.
118. Rushing R, Burgard DA. Utilizing wastewater-based epidemiology to determine temporal trends in illicit stimulant use in Seattle, Washington. *Wastewater-Based Epidemiology: Estimation of Community Consumption of Drugs and Diets, 1319, 0 Vols, in ACS Symposium Series, vol. 1319, 1319*. American Chemical Society; 2019:155–166.
119. Pichini S, Solimini R, Berretta P, et al. Acute intoxications and fatalities from illicit fentanyl and analogues: an update. *Ther Drug Monit*. 2018;40:38–51.
120. Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol*. 2012;8:33–42.
121. Ross EA, Reisfield GM, Watson MC, et al. Psychoactive "bath salts" intoxication with methylenedioxypyrovalerone. *Am J Med*. 2012;125:854–858.
122. Kozera K, Cichoń L, Wilczyński K, et al. Mdma—hopes and fears associated with therapeutic use in mental disorders. *Pharmacother Psychiatry Neurol*. 2020;36:187–204.
123. Sessa B, Aday JS, O'Brien S, et al. Debunking the myth of "Blue Mondays": No evidence of affect drop after taking clinical MDMA. *J Psychopharmacol*. 2022;36:360–367.
124. Flameling J, van der Does F, van Veelen N, et al. Reply to: not too quick on "Debunking the myth of 'Blue Mondays'". *J Psychopharmacol*. 2022;36:1001–1004.
125. Vizeli P, Liechti ME. Safety pharmacology of acute MDMA administration in healthy subjects. *J Psychopharmacol*. 2017;31:576–588.
126. Mitchell JM, Ot'alora G M, van der Kolk B, et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nat Med*. 2023;29:2473–2480.
127. Grinspoon L, Bakalar JB. Can drugs be used to enhance the psychotherapeutic process? *Am J Psychother*. 1986;40:393–404.
128. Mithoefer MC, Wagner MT, Mithoefer AT, et al. 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.
129. 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.
130. Mithoefer MC, Mithoefer AT, Feduccia AA, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry*. 2018;5:486–497.
131. Oehen P, Traber R, Widmer V, et al. 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.
132. Ot'alora G M, Grigsby J, Poulter B, et al. 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for

treatment of chronic posttraumatic stress disorder: a randomized phase 2 controlled trial. *J Psychopharmacol*. 2018;32:1295–1307.
133. Mithoefer MC, Feduccia AA, Jerome L, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology (Berl)*. 2019;236:2735–2745.
134. Gilbert D, Ovalle D. FDA to review MDMA-assisted therapy, a milestone for psychedelics. *Washington Post*. 2023. Available: https://www.washingtonpost.com/business/2023/12/12/mdma-therapy-fda-maps/. Accessed January 12, 2024.
135. Feduccia AA, Jerome L, Yazar-Klosinski B, et al. Breakthrough for trauma treatment: safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline. *Front Psychiatry*. 2019;10:650.
136. Lee DJ, Schnitzlein CW, Wolf JP, et al. Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. *Depress Anxiety*. 2016;33:792–806.
137. Merz J, Schwarzer G, Gerger H. Comparative efficacy and acceptability of pharmacological, psychotherapeutic, and combination treatments in adults with posttraumatic stress disorder: a network meta-analysis. *JAMA Psychiatry*. 2019;76:904–913.
138. Halvorsen JØ, Naudet F, Cristea IA. Challenges with benchmarking of MDMA-assisted psychotherapy. *Nat Med*. 2021;27:1689–1690.
139. Yu C-L, Yang FC, Yang SN, et al. Psilocybin for end-of-life anxiety symptoms: a systematic review and meta-analysis. *Psychiatry Investig*. 2021;18:958–967.
140. Wolfson PE, Andries J, Feduccia AA, et al. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. *Sci Rep*. 2020;10:20442.
141. Bejerot S, Eriksson JM, Mörtberg E. Social anxiety in adult autism spectrum disorder. *Psychiatry Res*. 2014;220:705–707.
142. Danforth AL, Grob CS, Struble C, et al. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology (Berl)*. 2018;235:3137–3148.
143. Sessa B, Higbed L, O'Brien S, et al. First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. *J Psychopharmacol*. 2021;35:375–383.
144. Nicholas CR, Wang JB, Coker A, et al. The effects of MDMA-assisted therapy on alcohol and substance use in a phase 3 trial for treatment of severe PTSD. *Drug Alcohol Depend*. 2022;233:109356.
145. Brewerton TD, Wang JB, Lafrance A, et al. MDMA-assisted therapy significantly reduces eating disorder symptoms in a randomized placebo-controlled trial of adults with severe PTSD. *J Psychiatr Res*. 2022;149:128–135.
146. Brewerton TD, Lafrance A, Mithoefer MC. The potential use of N-methyl-3,4-methylenedioxyamphetamine (MDMA) assisted psychotherapy in the treatment of eating disorders comorbid with PTSD. *Med Hypotheses*. 2021;146:110367.
147. Straus E, Haller M, Lyons RC, et al. Functional and Psychiatric correlates of comorbid post-traumatic stress disorder and alcohol use disorder. *Alcohol Res Curr Rev*. 2018;39:121–129.
148. Multidisciplinary Association for Psychedelic Studies. *An Open-Label, Multi-Site Phase 2 Study of the Safety and Feasibility of MDMA-Assisted Psychotherapy for Eating Disorders. clinicaltrials.gov, Clinical trial registration NCT04454684*; 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT04454684. Accessed May 24, 2023.