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Dark Classics in Chemical Neuroscience: 3,4-Methylenedioxymethamphetamine (MDMA)

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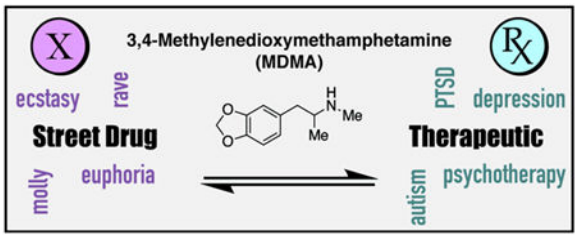
Abstract

Better known as “ecstasy,” 3,4-methylenedioxymethamphetamine (MDMA) is a small molecule that has played a prominent role in defining the ethos of today’s teenagers and young adults, much like lysergic acid diethylamide (LSD) did in the 1960s. Though MDMA possesses structural similarities to compounds like amphetamine and mescaline, it produces subjective effects that are unlike any of the classical psychostimulants or hallucinogens and is one of the few compounds capable of reliably producing prosocial behavioral states. As a result, MDMA has captured the attention of recreational users, the media, artists, psychiatrists, and neuropharmacologists alike. Here, we detail the synthesis of MDMA as well as its pharmacology, metabolism, adverse effects, and potential use in medicine. Finally, we discuss its history and why it is perhaps the most important compound for the future of psychedelic science—having the potential to either facilitate new psychedelic research initiatives, or to usher in a second Dark Age for the field.

Graphical Abstract



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Author Contributions

D.E.O. conceived the structure of the review. L.E.D. and D.E.O. wrote the manuscript with input from A.M.A. All authors edited the manuscript.

Notes

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Keywords

3,4-methylenedioxymethamphetamine; MDMA; psychedelic; entactogen; empathogen

INTRODUCTION

The psychoactive compound MDMA is better known by one of its numerous street names, which include ecstasy, XTC, E, X, MDM, Adam, and EA-1475.[1] Additionally, the term "molly" is often used to refer to MDMA in the United States.[2] Structurally, MDMA possesses a single stereocenter, and due to its small size (freebase MW = 193.24 g/mol) and hydrophobic nature (logP = 2.050),[3] MDMA readily crosses the blood-brain barrier (BBB).[4] Chemically, MDMA is related to amphetamine (**2**), and contains the phenethylamine core structure common to this class of psychostimulants, which also includes methamphetamine (**3**), and methylphenidate (**4**) (Figure 1). The hallucinogens 2,5-dimethoxy-4-iodoamphetamine (DOI, **5**), 2,5-dimethoxy-4-bromophenethylamine (2C-B, **6**), and mescaline (**7**) are also structurally related to MDMA. As such, it is not surprising that MDMA produces effects reminiscent of both psychostimulants and hallucinogens. However, the interoceptive effects of MDMA (i.e., sense of the body's internal state) are distinct from those produced by either of these well-known classes of psychoactive compounds.

In rodent drug discrimination studies, MDMA only partially substitutes for the stimulant *S*-(+)-amphetamine,[5] or the ergoline hallucinogen lysergic acid diethylamide (LSD),[6] and is unable to substitute for the phenethylamine hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM).[7] Furthermore, when rats are trained to discriminate racemic MDMA from saline, incomplete generalization is observed using *S*-(+)-amphetamine, LSD, or DOM.[5] The discriminative stimulus produced by MDMA seems to be modulated by 5-HT1A,[8] 5-HT2A,[8] and oxytocin receptors,[9] with less involvement from D1 receptors.[10] The two enantiomers of MDMA produce relatively similar discriminative stimuli.[11] It should be noted that while MDMA only partially substitutes for *S*-(+)-amphetamine in rats, it completely substitutes for *S*-(+)-amphetamine in rhesus monkeys.[12]

In humans, 75–150 mg of MDMA produces subjective effects that last for several hours.[13,14,15,16,17,18,19] These include context-dependent feelings of closeness with others, reduced social inhibition, positive mood, and increased alertness.[19,20,21,22,23,24] Regarding hallucinations, MDMA is considered to be weakly hallucinogenic.[25] Ingestion of MDMA does not cause auditory hallucinations and only 20% of recreational users have reported experiencing visual hallucinations.[15] The visual hallucinations induced by MDMA do not tend to be well-formed, and instead, are often described as flashes of light in the peripheral visual field.[15] This is in stark contrast to the profound visual disturbances experienced by most people following the administration of classical hallucinogenic agents such as LSD.[26,27] In humans, the weak hallucinogenic effects of MDMA are blocked by ketanserin, a selective 5-HT2A antagonist.[25] The role of 5-HT1A receptors in the subjective effects of MDMA appears to be negligible.[28,29,30] In addition to directly binding to 5-HT2A receptors, albeit with low affinity (vide infra), MDMA can produce subjective effects by increasing the release of monoamines such as serotonin and norepinephrine.[17,31,32,33,34,35] The perceptual

effects of MDMA are more intense in females than in males,[36,37] and have been shown in recent placebo-controlled studies to be clearly distinct from those produced by other psychostimulants.[38,39]

The unique subjective effects of MDMA and related molecules such as 3,4-methylenedioxy-*N*-methyl-α-ethylphenylethylamine (MBDB, **8**) and 5,6-methylenedioxy-2-aminoindane (MDAI, **9**) led to their classification as a separate family of psychoactive compounds, distinct from both stimulants and hallucinogens (Figure 1). Due to their strong propensity to induce empathy and feelings of connectedness, these drugs were originally dubbed "empathogens" in the 1980s—a term favored by Ralph Metzner.[40] David Nichols later highlighted the ambiguous nature of the term empathogen. To avoid any negative connotations associated with "pathos" (i.e., suffering), "pathogen" (i.e., a disease producing agent), or "pathogenesis" (i.e., the development of a disease), Nichols coined the new term "entactogen," which roughly translates from the Greek to mean that which "produces a touching within" (en = within, tactus = touch, gen = to produce).[41] These terms are often used interchangeably. We will use the latter term as it more adequately captures the unique ability of these drugs to promote introspective states—a property that has been proposed to be useful in the context of psychotherapy (vide infra). Though the subjective effects of MDMA appear to be unique compared to those of LSD, both compounds tend to increase openness, promote trust, and enhance emotional empathy.[42,43]

A major point of contention among psychopharmacologists is whether or not MDMA should be classified as a "psychedelic." Because that term can be translated as "mind-manifesting," we propose that MDMA, as well as more potent 5-HT2A agonists like psilocybin, are appropriately placed in this category. Using this classification, psychedelics broadly defined can be subdivided into classical hallucinogens (e.g., psilocybin, LSD, mescaline) and entactogens (e.g., MDMA) on the basis of their distinct subjective effects

The prosocial and stimulant effects of MDMA led to its widespread recreational use and cemented its place in rave (dance party) culture.[44] It is estimated that MDMA has been used by 7% of the population over the age of 12.[45] This is in stark contrast to heroin, which is abused by only 2% of the population.[45] The predominant users of MDMA are teenagers and young adults, with females being more likely to use MDMA than males.[46] In people 12–25 years of age, MDMA accounts for more than 50% of all psychedelic drug use.[45] In recent years, the recreational use of MDMA by people with college degrees has been increasing.[47]

Despite its popularity, MDMA is a controlled substance in the United States and many other countries making its production and sale illegal. The U.S. Drug Enforcement Administration (DEA) has classified MDMA as a Schedule I compound—the most restricted class of chemicals. Schedule I drugs are those deemed to have high abuse potential, do not have an accepted medical use, and lack accepted safety for use under medical supervision. Drugs such as heroin, LSD, gamma hydroxybutyric acid (GHB), and tetrahydrocannabinol (THC) are also classified in Schedule I. Unfortunately, the legal, financial, and political hurdles that accompany Schedule I classification significantly hinder scientific research into the effects of MDMA. As it is one of the few compounds known to reliably produce a prosocial state, MDMA may possess potential as a neurochemical tool for elucidating the mechanisms of

social behaviors and the neural underpinnings of empathy and social bonding.[48] Furthermore, MDMA may possess therapeutic potential for treating disorders associated with disruptions in social interactions such as autism spectrum disorders, social anxiety disorder, schizophrenia, and post-traumatic stress disorder (PTSD).[48]

Despite its relatively simple structure, MDMA elicits robust behavioral responses by binding with high affinity to a number of neuroreceptors and transporters. Below, we discuss the synthesis of MDMA and its pharmacology, metabolism, and adverse effects. Additionally, we review the prosocial and psychoplastogenic (plasticity-promoting) properties of MDMA, the differences between its enantiomers, and its potential use in medicine. Finally, we provide brief historical context for the development of MDMA and conclude by emphasizing the important role that MDMA is expected to play in determining the trajectory of future psychedelic research.

SYNTHESIS

Racemic MDMA—the form used recreationally and in clinical trials—is typically synthesized from safrole (**10**) or piperonal (**13**). The German chemist Anton Köllisch was the first to synthesize MDMA in 1912.[49] His synthetic route began with the hydrobromination of **10** to produce **11**. Displacement of the bromide with methylamine produces MDMA.[50] A similar route was described in the peer-reviewed literature for the first time by Polish chemists Biniecki and Krajewski.[51] Alternatively, MDMA can be synthesized from **10** by Wacker oxidation followed by reductive amination of **12** with methylamine and sodium cyanoborohydride. [52,53] Compound **12** can also be accessed from **10**, following olefin isomerization to produce isosafrole, peracid oxidation to the epoxide, and acid-catalyzed epoxide isomerization to the ketone.[54]

The synthesis of MDMA from piperonal (**13**) is also common, and begins with a Henry reaction between **13** and nitroethane. The key nitrostyrene intermediate formed can then be partially reduced and hydrolyzed to produce ketone **12**, or fully reduced using lithium aluminum hydride to afford 3,4-methylenedioxyamphetamine (MDA, **14**).[55] Conversion of MDA into the carbamate or formamide followed by lithium aluminum hydride reduction yields MDMA. Purification of MDMA is typically achieved following vacuum distillation of the freebase and/or crystallization of the hydrochloride salt.[16] The hydrochloride salt can exist as one of several different hydrated forms.[1]

While the racemate is the most commonly administered form of MDMA, recent research suggests that there are distinct differences in the pharmacology of the two enantiomers. Hence, the development of efficient asymmetric strategies for producing enantiopure MDMA is incredibly important. Traditional resolution via selective crystallization of diastereomeric salt forms has not proven the most effective route for synthesizing MDMA in high enantiomeric excess.[56] Instead, a more successful strategy has relied on the use of removable chiral auxiliaries. The first asymmetric synthesis of MDMA was reported by Nichols and co-workers (Figure 3A).[6] Reductive amination of ketone **12** with (*S*)-α-methylbenzylamine (**15**) produced the (*S,S*) intermediate **16** following crystallization. The use of Raney nickel at 50 psi appears to be crucial for the selectivity of this reaction. In our

hands, Raney nickel catalyzed hydrogenation did not proceed under atmospheric conditions, and the use of hydride reducing agents such as $NaBH_3CN$ yielded an inseparable 1:1 mixture of diastereomers (unpublished results). Palladium-catalyzed hydrogenolysis afforded MDA (**14**), which was converted to MDMA after reduction of the formamide. In 2014, Escubedo and co-workers reported a similar approach using Ellman's sulfonamide as the chiral auxiliary (Figure 3B).[57]

The chiral pool has also been exploited to produce enantiopure MDMA. Using a method developed by Nenajdenko and co-workers,[58] (*S*)-alaninol (**23**) can be protected and converted to the aziridine **24**. Ring opening in the presence of copper(I) iodide using Grignard reagent **25** affords Ts-protected MDA (**26**). Methylation of **26** followed by deprotection yields (*S*)-MDMA.[59] The enantiomeric excess of (*S*)-mDmA produced by Huot and co-workers was not reported, but based on the stereospecific nature of the reactions employed and the fact that the stereocenter is unlikely to epimerize under these conditions, it is assumed that MDMA can be produced as a single enantiomer using this strategy. Nenajdenko and co-workers reported that this is indeed the case for related β-arylalkylamines.[58]

PHARMACODYNAMICS

Effects on Monoamines.

The most well characterized effect of MDMA is its ability to increase brain levels of monoamines such as serotonin, dopamine, and norepinephrine, which is accomplished via complex mechanisms. First, MDMA binds to and inhibits the serotonin transporter (SERT), dopamine transporter (DAT), and norepinephrine transporter (NET), inhibiting monoamine reuptake and leading to increased extracellular levels of these amines.[35,60,61,62,63] Electrophysiology experiments suggest that this inhibition results from MDMA serving as a substrate, rather than a blocker, of these transporters.[64] In contrast to (*S*)-amphetamine, racemic MDMA is a more potent inhibitor of SERT than either DAT or NET (Tables 1 and 2).[65] In addition to inhibiting the uptake of extracellular monoamines, MDMA also prevents transport of monoamines into vesicles. While, MDMA has been shown to inhibit the uptake of serotonin and dopamine into both synaptosomes and vesicles, it does not affect the cellular uptake and/or vesicular packaging of either γ-aminobutyric acid (GABA) or glutamate.[66]

In addition to being a monoamine uptake inhibitor, MDMA is a potent releaser of these neurochemicals, and again, MDMA accomplishes this via several mechanisms. At the cellular membrane, MDMA reverses the flux of monoamines through their transporters, expelling intracellular serotonin, dopamine, and norepinephrine into the extracellular space. Inhibitors of SERT, DAT, and NET completely prevent MDMA-induced monoamine efflux in rat brain slices,[67] and from monoamine transporter-expressing HEK293 cells pre-loaded with radiolabeled monoamines.[35] However, for monoamines to reach sufficiently high cytosolic levels to be reverse transported by membrane transporters, they must first be released from synaptic vesicles into the intracellular space. By directly binding to vesicular amine transporters (VMAT), MDMA reverses the transport of molecules like serotonin.[68,69] Additionally, as a weak base, MDMA passively diffuses across vesicular membranes to

collapse the pH gradient established by VMAT, which is necessary for maintaining high concentrations of monoamines in vesicles.[70,71] Monoamines released from vesicles might be partially protected from degradation due to the ability of MDMA to inhibit both isoforms of monoamine oxidase.[72] Moreover, MDMA may cause SERT internalization,[73] which presumably contributes to increased extracellular serotonin levels. The releasing effects of MDMA are greater for serotonin and norepinephrine, and slightly weaker for dopamine (Tables 2 and 3).[65]

While much of the work elucidating the monoamine-releasing properties of MDMA have employed in vitro and ex vivo models, recently, the DA and 5-HT releasing effects of MDMA have been observed in vivo using microdialysis in the striatum and frontal cortex of rats.[74] There is a general consensus that MDMA increases the release of monoamines, however, there is at least one study using fast-scan cyclic voltammetry (FSCV) in brain slices that suggests that increases in monoamine concentrations following MDMA treatment might be due to inhibition of monoamine reuptake and not release per se.[75]

Direct Effects on Receptors.

In addition to directly interacting with monoamine transporters, MDMA has been shown to bind with modest affinities to a variety of neuroreceptors including adrenergic, serotonergic, histaminergic, and muscarinic receptors.76,77,62 The binding profile of MDMA across much of the recepterome is shown in Table 5. The low micromolar affinities observed support the notion that MDMA induces most of its effects indirectly by modulating monoamine levels. The 5-HT2B receptor is one of the few receptors that MDMA binds to with submicromolar affinity (K_i = 500 nM), though the role of this receptor in the effects of MDMA is unclear. For example, MDMA failed to produce a response in a 5-HT2B functional assay using HEK293 cells.[78] However, it is believed that 5-HT2B agonism is at least partly responsible for the 5-HT releasing effects of MDMA, as pharmacological inhibition or genetic deletion of 5-HT2B receptors block MDMA-induced release of 5-HT.[79] Binding of MDMA to 5-HT2B receptors was studied using a radiolabeled agonist, while many of the other receptor binding assays (e.g., 5-HT2A ad 5-HT2C) utilized radiolabeled antagonists. Therefore, it is possible that the binding affinity of MDMA for many receptors has been underestimated. For example, it is now well established that MDMA binds directly to 5-HT2A receptors, albeit with micromolar affinity, though binding assays performed with ^{3}H-ketanserin do not capture this interaction. Furthermore, MDMA is unable to displace radiolabeled monoamine transporter inhibitors despite exhibiting nM potency in functional assays (Tables 1–4), which is consistent with its proposed role as a monoamine releaser rather than a competitive uptake inhibitor.

Trace Amine-Associated Receptor 1 (TAAR1).

The trace-amine associated receptor (TAAR1) has also been suggested as a key target mediating the effects of MDMA. Bunzow and co-workers demonstrated that MDMA acts as an agonist at rat TAAR1 receptors to increase cAMP production in a TAAR1-expressing HEK293 cell line.[80] Like MDMA, several other hallucinogens and psychostimulants have been shown to bind to and activate TAAR1 to a greater extent than neurotransmitters such as serotonin, dopamine or norepinephrine.[80,81,82] Due to the known modulatory influence of

TAAR1 on monoamine transporter function,[83] it is likely that TAAR1 activation contributes to the effects of MDMA on extracellular monoamine levels. Interestingly, 4-hydroxyamphetamine proved to be a particularly potent agonist of TAAR1 (EC50 = 51 nM). As MdMa is metabolized into 4-hydroxy-substituted compounds, there is the distinct possibility that metabolites of MDMA may potently activate TAAR1. However, to the best of our knowledge, this hypothesis has not been directly tested. Finally, it is unclear if TAAR1 plays any role in the effects of MDMA in humans, as MDMA does not activate human TAAR1 in cellular assays like it does mouse and rat TAAR1.[84]

Sigma-1 Receptor.

Radioligand binding studies have shown that MDMA binds to both sigma-1 and sigma-2 receptors with K_i values in the low micromolar range, which are comparable to the affinities of MDMA for monoamine transporters.[85] Moreover, treatment with BD1063, a selective sigma-1 antagonist, blocked the effects of MDMA on rodent locomotion.[85] The sigma-1 receptor has been proposed to be a novel target for the treatment of depression and anxiety,[86,87,88,89,90] and it is reasonable to hypothesize that this receptor plays some role in the behavioral and clinical effects of MDMA.

Hormonal Effects.

Administration of MDMA to humans leads to robust increases in plasma levels of cortisol, prolactin, dehydroepiandrosterone (DHEA), vasopressin, and oxytocin.[18,38,91,92,93,94,95,96] It is possible that some of these hormonal changes are the result of serotonergic activity,[97,98,99] and it is likely that they modulate some of the effects of MDMA.[100] For example, the rise in plasma DHEA levels was significantly correlated with feelings of euphoria.[18] Furthermore, the effects of MDMA on oxytocin levels are often invoked to explain the drug's prosocial effects. Dumont and co-workers were the first to demonstrate in a controlled laboratory setting that MDMA increases oxytocin levels.[93] They also found that increases in blood oxytocin levels were correlated with the subjective prosocial feelings induced by MDMA more so than blood levels of the drug itself. While numerous other studies have replicated the finding that MDMA elevates oxytocin levels, they have all failed to reproduce a correlation between oxytocin levels and prosocial feelings, calling into question the relevance of this hormone for the prosocial effects of MDMA.[100,101] As such, the role of oxytocin in the effects of MDMA is currently controversial.

Behavioral Effects in Rodents.

Like other serotonergic psychedelics, MDMA produces behavioral effects consistent with serotonin syndrome such as flat body posture, hind limb abduction, and forepaw treading.[102] At lower doses, MDMA produces "amphetamine-like" hyperactivity in the open field. Both of these effects are enhanced following repeated administration of MDMA, demonstrating that MDMA is capable of producing behavioral sensitization.[103] Behavioral sensitization is correlated with the enhanced ability of MDMA to increase monoamine levels (measured via microdialysis) following repeated dosing. [104] The locomotor effects of MDMA are perhaps the best-studied behavioral responses in rodents, and they are modulated by a variety of neuroreceptors including 5-HT1B,[105] 5-HT2A,[106] D1,[107] and D2[107] receptors. Unlike amphetamine, selective serotonin reuptake inhibitors block MDMA-induced increases in

locomotion.[108] Furthermore, MDMA does not produce this behavioral effect in mice genetically lacking SERT, further implicating this monoamine transporter in the hyperlocomotive effects of MDMA.[109]

In rodent models of anxiety, MDMA produces complex effects. At low acute and subchronic doses, MDMA tends to be anxiogenic in the elevated plus maze (EPM).[110,111,112] However, at higher acute and subchronic doses, MDMA produces anxiolytic effects in the EPM. When tested in the light-dark box paradigm, MDMA does not alter preferences of mice for the two compartments.[113]

Some of the rodent behaviors most relevant to potential therapeutic uses of MDMA are related to social behaviors. A 5 mg/kg dose of MDMA decreased aggressive behaviors in rats and increased the time spent engaging in social behaviors such as sniffing, following, crawling under, crawling over, mutual grooming, and adjacent lying.[114] Additionally, MDMA has been shown to induce a social conditioned place preference.[115] Adjacent lying —a behavior in rats where two unfamiliar animals lie passively next to each other—is perhaps one of the more robust prosocial behaviors induced by MDMA in rodents.

In terms of mechanism, systemic MDMA increases plasma levels of oxytocin in rats and activates oxytocinergic neurons in the hypothalamus, as measured by Fos immunohistochemistry.[99] Increases in oxytocin levels and adjacent lying behavior induced by MDMA were abolished by treatment with a 5-HT1A antagonist, while 8-OH-DPAT (a 5-HT1A agonist) produced effects similar to MDMA.[99] This led McGregor and co-workers to propose that MDMA induces oxytocin release via stimulation of 5-HT1A receptors, and that increased adjacent lying resulted from activation of oxytocin receptors. This hypothesis was supported by the fact that intracerebroventricular administration of tocinoic acid, an oxytocin receptor antagonist, blocked MDMA-induced adjacent lying.[99] However, in a follow-up study, McGregor and co-workers could not prevent MDMA-induced adjacent lying using C25,[116] a systemically administered non-peptidic antagonist of oxytocin receptors. In contrast, they were able to prevent this behavior using an antagonist of the vasopressin receptor 1A.[117] There are two possibilities that might explain these contradictory results. First, tocinoic acid could have non-selective antagonistic effects at the vasopressin receptor 1A. Alternatively, C25 might not have been able to cross the blood-brain barrier.

In addition to its prosocial effects, MDMA has been shown by Howell and co-workers to promote fear extinction learning in mice.[118] This seminal study potentially provides a mechanistic explanation for the therapeutic efficacy of MDMA in patients suffering from treatment-resistant PTSD (vide infra). Similar findings have been described for other psychedelics such as psilocybin in mice[119] and *N,N*-dimethyltryptamine (DMT) in rats.[120] The facilitation of fear extinction memory by MDMA appears to be dependent on SeRt.[121]

Plasticity-Promoting Effects.

Like most psychostimulants, MDMA causes robust changes in gene expression and protein levels associated with neural plasticity.[122] Acute treatment with MDMA (10 mg/kg) causes differential gene expression of BDNF in the frontal cortex and hippocampus of rats, with

BDNF levels increasing in the former brain region and decreasing in the latter.[123] The administration of 4 doses over a period of 6 h to rats led to robust increases in *BDNF* transcript levels in several cortical regions both 1 h and 7 h following dosing.[124] The largest effects were seen in the prefrontal cortex with increases in *TrkB* expression observed in that region 24 h after dosing.[124] Here, MDMA produced weaker effects on *NT3* and *TrkC* gene expression.[124] Chronic treatment with MDMA in mice[125] and subchronic administration of large doses (20 mg/kg) in rats[126] led to increases in BDNF transcription and translation in the hippocampus. The latter study also observed a reduced number of dendritic spines in the hippocampus of rats. Finally, MDMA was observed to inhibit neurite outgrowth in PC12 cells,[127] though the relevance of this cell line to studies on neural plasticity is debatable.

To date, most studies assessing the psychoplastogenic (plasticity-promoting) effects of MDMA have observed a reduction in dendritic branching and/or dendritic spine numbers. However, these studies are often conducted using extremely high doses of MDMA administered over extended periods of time, and probably more accurately reflect neurotoxicity resulting from overstimulation of psychoplastogenic receptors. More modest doses would likely yield increases, as opposed to decreases, in dendritic branching and spine density. Recently, we reported that MDMA, and several other psychedelic compounds, significantly increased the complexity of dendritic arbors in cultured cortical neurons[128] Moreover, this phenotype is not produced by all psychostimulants and drugs of abuse, as *S*-(+)-amphetamine had no effect.[128] Future studies should assess the in vivo effects of a single moderate dose of MDMA on dendritic branching and spine density.

METABOLISM AND PHARMACOKINETICS

The primary routes for metabolism of MDMA are *N*-demethylation and loss of the methylene bridge connecting the catechol (Figure 4), both of which are mediated by various cytochrome P450s.[129] The common metabolites of MDMA (**1**) include MDA (**14**), 3,4-dihydroxymethamphetamine (HHMA, **28**), 3,4-dihydroxyamphetamine (HHA, **29**), 4-hydroxy-3-methoxy-methamphetamine (HMMA, **30**), and 4-hydroxy-3-methoxy-amphetamine (HMA, **31**). The major metabolite of MDMA in humans is HMMA, which is mainly excreted as the glucuronic acid conjugate.[130]

Recent genetic findings suggests that a variety of cytrochrome P450s, including CYP2C19, CYP2B6, and CYP1A2, play a role in the demethylation of MDMA.[131,132] Mutations in the CYP2C19 or CYP2B6 genes that reduce enzyme function have been shown to increase the ratio of MDMA/MDA but do not alter HMMA concentrations.[131,132] Subjects with decreased CYP2C19 function also showed greater cardiovascular responses with faster onset times. Mutations in the CYP2B6 gene resulting in decreased enzyme function only influenced metabolism at later time points (i.e., 3–4 h) suggesting that it is a secondary metabolizer of MDMA.[131]

When MDMA is administered to humans at a dose of 100 mg, it has a half-life of approximately 8–9 h and yields plasma C_{max} and t_{max} values of 222.5 ng/ml and 2.3 h, respectively.[133] However, MDMA is known to exhibit nonlinear pharmacokinetics in both humans[131,134,135] and squirrel monkeys.[136] This means that increasing doses of MDMA

prolong its half-life, potentially exacerbating the risk for adverse effects and neurotoxicity. The nonlinear pharmacokinetics observed following administration of MDMA is likely the result of cytochrome P450 inhibition by MDMA and its metabolites.[131,137,138] Additionally, the enantiomers of MDMA are metabolized at different rates, with the R-enantiomer having a longer half-life than the *S*-enantiomer.[139,140, 141]

ADVERSE EFFECTS

Similar to other amphetamines, MDMA produces a number of adverse effects including trismus, tachycardia, bruxism, dry mouth, palpitations, diaphoresis, and insomnia.[15,19,36,142] Rhabdomyolysis, cardiac arrhythmias, hyperthermia, hyponatremia, and acute renal failure are the more severe side-effects and are common causes of death following MDMA intoxication.[143,144] The more severe adverse effects of MDMA are potentially exacerbated by the intense exercise and hot environment characteristic of raves. In Long-Evans rats, slight increases in ambient temperature resulted in excessive brain hyperthermia leading to death at an MDMA dose that is significantly lower than the LD_{50} in rats at room temperature.[145] Similarly, Fantegrossi and co-workers found that MDMA lethality was increased when NIH Swiss mice were housed at high densities (>6 mice per cage), which reduces the ability to dissipate body heat.[146] Risk for serotonin syndrome—a collection of symptoms that include high body temperature, sweating, and tremor (among others)—increases with higher doses of MDMA.[147]

The effects of MDMA on heart function are also significant, with norepinephrine mediating a significant portion of the cardiostimulant effects observed following MDMA administration.[34,35,148,149] In addition to increasing systolic blood pressure,[19,36,92] the drug can induce cardiac arrhythmias and myocarditis.[150] Myocardial infarction can also occur following MDMA use, though this tends to happen less frequently than after cocaine or amphetamine administration.[151,152] In the long-term, MDMA use can result in valvular heart disease,[153] which could be due to oxidative stress[154] or the activation of 5-HT2B receptors by MDMA.[77]

In terms of the addictive potential of MDMA, the data are mixed. Several people have argued that MDMA has lower abuse potential because recreational users have reported that its pleasurable effects diminish with repeated use, but its side effects increase.[15] However, in animal models, MDMA does produce some of the same behavioral effects characteristic of addictive drugs like cocaine and opioids, albeit to a lesser extent. For instance, MDMA is known to produce conditioned place preference in rats[155] and mice,[156,157] and MDMA is self-administered by a variety of species (e.g., rats, mice, non-human primates).[158] Interpretation of self-administration studies using MDMA are complicated by a variety of factors such as dose, timing, and prior exposure of the test animals to other drugs of abuse. For an overview of these issues, we refer the reader to an excellent review by Susan Schenk.[158] Taken together, MDMA does seem to have reinforcing properties, but these appear to be significantly weaker than those of cocaine.

Determining the adverse effects of MDMA in people who consume it recreationally is complicated by the fact that some “MDMA” sold on the street does not contain any MDMA

at all,[159] while other batches of illegally produced “MDMA” are adulterated.[160] Contaminating drugs include, but are not limited to, amphetamine, methamphetamine, MDA, pseudoephedrine, butylone, and caffeine.[161,162] Many recreational MDMA users prefer “molly” as it is believed to be of high purity, however, a recent study employing hair follicle testing revealed that 48% of molly users tested positive for synthetic cathinones despite having reported that they had never used cathinones before.[163] Consuming MDMA as a part of a drug mixture can be extremely dangerous due to drug-drug interactions,[164] and has important implications for evaluating the neurotoxic potential of MDMA in humans.

Certainly, the most controversial aspect of MDMA pharmacology is its potential to induce neurotoxicity. The neurotoxic effects of MDMA have been extensively reviewed by others,[165,166,167,168,169,170,171] and thus, we will focus only on the key studies. Additionally, we will attempt to highlight why this is such a contentious area and why the controversy is not likely to be resolved soon.

People who consume MDMA (particularly those who do so regularly, and in high doses) perform poorly on various tests related to attention, learning, and memory (e.g., working and declarative memory) when compared to MDMA-naïve controls.[172,173,174,175] Those with a history of only moderate MDMA use do not seem to exhibit memory impairments.[176] However, acute MDMA intoxication produces memory deficits.[176] Heavy MDMA users tend to have lower cerebral spinal fluid levels of 5-hydroxyindoleacetic acid (5-HIAA)—the principle metabolite of serotonin—and thus, serotonergic toxicity has been presumed.[177] In general, neuroimaging studies used to assess the effects of MDMA in humans have produced mixed findings, with no clear evidence that MDMA is safe or neurotoxic.[178,179] Finally, when compared with MDMA-naïve controls, MDMA users are more likely to be afflicted with mental illnesses including depression, psychotic disorders, eating disorders, and anxiety disorders.[180]

While retrospective studies on MDMA-using populations are certainly important, there are several confounding factors that limit the interpretability of these data. First, MDMA produced by clandestine laboratories is often contaminated with other drugs of abuse and neurotoxic compounds such as methamphetamine. Second, recreational MDMA users are typically polydrug users.[181] Third, recreational MDMA is often consumed at crowded dance parties (i.e., raves), where excessive activity, high temperatures, and dehydration could exacerbate any inherently neurotoxic effects of the drug. Together, these facts make it difficult, if not impossible, to distinguish the neurotoxic effects induced by MDMA itself versus those caused by impurities, drug-drug interactions, or drug-environment interactions. Furthermore, due to the retrospective nature of many human studies regarding the effects of MDMA, it is unclear if the cognitive impairments and neuropsychiatric disorders observed in groups who have used MDMA reflect a cause or consequence of MDMA use. Prospective studies are incredibly important for answering these questions. One prospective study from The Netherlands found that sensation-seeking, impulsivity, and depression did not predict future MDMA use.[182] However, a much larger study from Germany concluded that MDMA users had significantly higher risk for nearly all DSM-IV mental disorders, and moreover, that the onset of these disorders typically preceded the first use of MDMA.[183]

Because of the many factors that can confound human studies, researchers have turned to well controlled model systems in the laboratory to investigate MDMA neurotoxicity. However, the relevance of these models to human neurotoxicity is often questioned. Capela and co-workers found that MDMA can induce apoptotic cell death in embryonic rat cortical neurons via a 5-HT2A-dependent mechanism.[184] Furthermore, they discovered that the metabolites of MDMA are more potent neurotoxins.[185] Similarly, Stumm and co-workers reported that MDMA and related amphetamines kill cultured rat cortical neurons at comparable concentrations.[186] It is important to note that the concentration of MDMA required to produce substantial neurotoxic effects in these studies is >200 μM, while the maximal brain concentration of MDMA in rats following a 20 mg/kg subcutaneous dose (10x the behaviorally relevant dose) is only circa 100–200 μM.[187] At a more modest concentration (10 μM), our group determined that MDMA produced robust psychoplastogenic effects in embryonic rat cortical cultures without cell death.[128] For comparison, we have observed that several SSRIs and triptans—commonly prescribed medications—are cytotoxic to cultured rat cortical neurons in the range of 10–100 μM (unpublished results).

In addition to studies using cultured neurons, in vivo animal models are frequently used to test the neurotoxic potential of MDMA. While findings dating back to 1987 suggest that MDMA has neurotoxic effects in animals,[188] the relevance of these models to human neurotoxicity is highly debated. Some of the contentious questions the field has to grapple with include, 1) what dosing paradigm most effectively models human use, 2) what species is most relevant, 3) is allometric scaling appropriate, 4) how should the nonlinear human pharmacokinetics of MDMA be factored in, 5) what route of administration should be utilized, and 6) how should “neurotoxicity” be defined/measured (e.g., monoamine levels, neurite degeneration, cell body loss).

In mice, MDMA tends to produce dopaminergic, but not serotonergic, neurotoxicity.[189,190,191] This is in sharp contrast to rats, for which the opposite seems to be true. Two weeks following systemic administration of MDMA to rats (20 mg/kg, subcutaneous, twice daily for 4 d) loss of 5-HT axons (but not catecholamine axons) projecting to the forebrain was observed.[192] Interestingly, axonal degeneration was not accompanied by loss of raphe cell bodies.[192] As a result, serotonergic axons regenerate in rats administered MDMA, however, it is unknown how well these newly sprouted axons function.[193] Additionally, large doses of MDMA produce reductions in levels of 5-HT, 5-HIAA, and SERT.[194,195,196] Levels of 5-HT reuptake sites in rats partially recovered 6 months following MDMA exposure and were fully recovered after 1 year.[194,197] Similarly, 8 doses of MDMA given to rats over 4 days decreased brain 5-HT2 receptor levels by 80% when measured 6 h after the last dose.[198] Receptor levels recovered to 62% after 24 h and were completely normalized after 21 days.[198] The MDMA-induced serotonergic neurotoxicity in rats is exacerbated by increased ambient temperature[199] and can be prevented by blocking SERT with fluoxetine.[200] It should be noted that the doses of MDMA used in rats and mice to induce neurotoxicity are much higher than those often used by humans. Some researchers have justified these large rodent doses on the basis of allometric scaling[201] and the fact that experienced recreational users of MDMA often develop tolerance, leading them to ingest multiple doses in a short period of time to achieve the desired subjective effects of the drug.[202] Others have argued

that MDMA doses used in animals are too high, as MDMA produces behavioral effects at approximately the same dose (1–2 mg/kg) in humans and rats.[167] Finally, it has been posited that species differences in metabolism and neurotoxicity (e.g., dopaminergic toxicity in mice vs. serotonergic toxicity in rats) suggest that the metabolites of MDMA, and not necessarily MDMA itself, are responsible for the neurotoxic effects of MDMA.[168] Therefore, using model systems that more closely recapitulate the pharmacokinetics of MDMA in humans may be more useful.

Like rats, non-human primates experience serotonergic neurotoxicity following administration of large doses of MDMA.[203,204] Unlike rats, these changes seem to be relatively long-lasting in most primate brain regions.[205,206] Abnormal serotonergic innervation patterns were observed 7 years following MDMA exposure in squirrel monkeys, [207] and these patterns seemed to result from axotomy as raphe cell bodies remained intact. [207] In rhesus monkeys, persistent decreases in cerebrospinal fluid levels of 5-HIAA were accompanied by functional changes as measured by electrophysiology.[208] Most of the studies assessing the neurotoxic effects of MDMA in primates administered multiple subcutaneous doses. However, humans typically consume a single oral dose of MDMA either recreationally or during MDMA-assisted psychotherapy (vide infra). To address this discrepancy, Ricaurte and co-workers compared both dose frequency and route of administration in squirrel monkeys. They found that repeated dosing and subcutaneous administration produces greater neurotoxic effects than oral dosing.[209] Importantly, they found that a single, modest (5 mg/kg), oral dose of MDMA still produced serotonin depletion in the thalamus and hypothalamus two weeks after administration.[209]

The mechanism of MDMA-induced neurotoxicity probably involves a combination of mechanisms including glutamate-induced excitotoxicity,[210] increased oxidative stress,[211] hyperthermia,[212] mitochondrial damage, and increased inflammation.[169,171] While the results of the numerous studies investigating MDMA-induced neurotoxicity still leave questions unanswered about the safety of MDMA administered to humans, it is reasonable to conclude that use of MDMA under common recreational conditions (e.g., high doses, multiple doses, polydrug use, high temperatures, prolonged physical activity, dehydration, etc.) is likely to cause adverse effects. However, in controlled studies in the clinic using low doses to assist psychotherapy, MDMA may be safe and well tolerated, as discussed below. When a variety of factors were considered, including physical, social, and economic factors, MDMA consistently ranked as being less harmful than illegal drugs such as heroin, cocaine, and methamphetamine, as well as legal drugs such as alcohol and nicotine.[213,214]

POTENTIAL USE IN MEDICINE

In recent years there has been renewed interest in using psychedelic compounds like psilocybin and MDMA to treat neuropsychiatric disorders.[215,216,217] This should not be surprising because before MDMA was placed on the Schedule I list, it was widely used by some psychiatrists to assist in treating a variety of disorders including anxiety disorders and depression. The benefits of MDMA were believed to result from increased introspection, a decrease in fear response upon accessing painful memories, and the promotion of trust between patients and their therapists.[218,219] However, most of the work conducted during

this period yielded only anecdotal reports, and there were no placebo-controlled clinical trials conducted that adhered to current rigorous standards.

In contrast, recent clinical studies assessing the therapeutic potential of MDMA for treating PTSD are carefully controlled and well documented.[220,221,222] First, patients are screened for medical conditions, including various neuropsychiatric disorders, that might exclude them from the study. Next, they are assessed at baseline using the Clinician-Administered PTSD Scale (CAPS). Patients then receive training sessions to establish rapport with an experienced clinician. The environment is carefully controlled so that it is aesthetically pleasing and resembles a living space rather than a medical facility. Music is often used to facilitate relaxation and/or evoke emotions. Both a male and a female therapist are present for the duration of the treatment session. After the drug is administered, there is limited verbal communication between the therapists and the patient. Instead, the patient is encouraged to explore any feelings that the experience might evoke. The therapists provide nurturing physical contact whenever necessary to help ease tension or distress. After the MDMA-session, the patient receives additional non-drug psychotherapy sessions.

An effective dosing paradigm was established by Oehen and co-workers utilizing low dose MDMA as an active placebo.[221] The use of an active placebo is an important part of the experimental design implemented by Oehen and co-workers. Inactive placebos, such as lactose, fail to produce physiological and psychological responses noticeable to trained clinicians or experienced MDMA users. This raises the question as to whether or not studies utilizing inactive placebos can truly be considered double-blind experiments. Patients in the experimental treatment group received an initial dose of 125 mg of MDMA followed by an additional 62.5 mg after 2.5 h. The active placebo group received an initial dose of 25 mg of MDMA followed by an additional 12.5 mg 2.5 h later. The dose of MDMA used for the active placebo group was chosen to stimulant mild but detectable psychological effects.

The most common use for MDMA in medicine is as an adjunct to psychotherapy for treating anxiety disorders.[223] Of particular note is recent clinical work demonstrating that MDMA can produce beneficial effects in treatment-resistant PTSD patients when it is paired with psychotherapy.[220,221,224,] The beneficial effects of this treatment paradigm seemed to be relatively long-lasting, as demonstrated by follow-up studies conducted several years later.[225] A recent meta-analysis determined that MDMA-assisted psychotherapy produced larger effect sizes in both clinician-observed outcomes and patient self-reports when compared to prolonged exposure therapy.[226] Furthermore, fewer patients in the MDMA-assisted psychotherapy group dropped out of the study.[226] These studies and others have indicated that MDMA was well tolerated when administered in a clinical setting as a single dose in the range of 75–125 mg.[19] Recently, MDMA was granted “breakthrough therapy” status by the FDA for the treatment of PTSD. The phase III clinical trials are estimated to be completed within the next five years, and if the results are positive, it is anticipated that a New Drug Application for MDMA will be submitted to the FDA around 2021.[227]

Recent clinical work to understand the mechanism of MDMA’s therapeutic effects has revealed that this drug impacts the processing of emotionally salient information. Using functional magnetic resonance imaging (fMRI), de Wit and co-workers found that MDMA

attenuated the blood-oxygen-level dependent (BOLD) response to angry faces in the amygdala, while also enhancing the activation of the ventral striatum in response to happy faces.[228] In this study, MDMA also impacted the performance of people during the Reading the Mind in the Eyes Test—a test that has participants attempt to predict what a person is thinking/feeling based on a picture of their face. Specifically, MDMA improved scores when the stimulus had a positive emotional valence. However, when the face had a negative emotional valence, MDMA-treated individuals performed poorly.[229] Moreover, Carhart-Harris and co-workers found that while under the influence of MDMA, participants rated their best and worst memories as being significantly more positive and less negative, respectively.[230] Related to its subjective effects, MDMA increased bilateral blood flow in the ventromedial prefrontal cortex and reduced blood flow in the left amygdala[231]—two brain regions that play important roles in the processing of emotional stimuli and memories. Due to its general tendencies to reduce responses to threatening stimuli while enhancing responses to positive social cues, MDMA is being investigated for treating social anxiety in autistic adults,[232] and it has been suggested that MDMA may prove useful in other conditions with a significant social component.[48]

Finally, MDMA may hold some promise for treating substance use disorders (SUDs).[233,234] Initial reports suggest that MDMA might decrease substance use,[235] and a pilot study conducted by Howell and co-workers demonstrated that *R*-(−)-MDMA decreased response rates during a cocaine self-administration paradigm in squirrel monkeys.[236] Though very few animals were used in the latter study, the results are encouraging. While other psychedelic compounds such as LSD, psilocybin, and ibogaine have been more extensively studied than MDMA with respect to their abilities to treat SUDs, the minimal perceptual disturbances caused by MDMA may offer a distinct advantage over the classical hallucinogens.

S-(+)-MDMA VS *R*-(−)-MDMA

While racemic MDMA is the form used both recreationally and in clinical trials, preclinical work and some human data suggest that there are distinct differences between the *R*- and *S*-enantiomers of MDMA—the non-superposable mirror images of each other.[237] The *R*- and *S*-enantiomers are sometimes referred to as the *l*- and *d*-enantiomers, respectively. An excellent review on this subject was published recently by Howell and coworkers,[236] so we will only cover the highlights here.

Regarding the monoamine releasing and reuptake inhibiting properties of MDMA, there is a general consensus that the *S*-enantiomer is the more potent compound.[59,77,238,239,240,241,242,243,244,245,246] This is consistent with what is known about the effects of *S*-(+)-amphetamine on monoamine levels. However, *R*-(−)-MDMA appears to be a more potent direct binder of 5-HT2A receptors (Table 6),[247,248] which perhaps explains why it has a greater propensity for causing perceptual disturbances. Neither enantiomer is particularly effective at stimulating phosphatidyl inositol turnover in either 5-HT2A or 5-HT2C expressing cells.[249] When rats were trained to discriminate *S*-(+)-amphetamine, LSD, and saline from each other in a 3-lever drug discrimination paradigm, *R*-(−)-MDMA and *S*-(+)-MDMA produced more hallucinogen-like and amphetamine-like discriminative stimuli,

respectively.[250] Furthermore, experiments using mice trained to discriminate either *S*-(+)-MDMA or *R*-(−)-MDMA from vehicle demonstrated that the *S*-enantiomer produced more psychostimulant-like effects while the *R*-enantiomer was more hallucinogen-like.[251]

In terms of their influences on hormone levels, the enantiomers of MDMA also have differential effects. Ex vivo studies utilizing rat hypothalamus tissue demonstrated that *S*-(+)-MDMA is a more potent inducer of oxytocin release than the racemate, while *R*-(−)-MDMA has no effect.[252] However, *R*-(−)-MDMA was more effective at increasing the activation of hypothalamic oxytocinergic neurons, as measured by the number of c-fos positive neurons.[236] Both enantiomers appear to increase vasopressin secretion comparably from the hypothalamus ex vivo.[252] *R*-(−)-MDMA more potently increased plasma prolactin levels in rhesus macaques.[245] Pretreatment with fluoxetine attenuated this effect, but did not block it completely. The selective 5-HT2A antagonist M100907 was required to completely inhibit *R*-(−)-MDMA-induced increases in prolactin, suggesting that indirect effects on 5-HT levels, as well as direct binding to 5-HT2A receptors contribute to the ability of *R*-(−)-MDMA to increase prolactin levels.[246]

Behaviorally, both enantiomers increase affiliative social behaviors in squirrel monkeys, and this effect seems to be dependent on activation of 5-HT2A receptors.[253] In mice, *R*-(−)-MDMA and the racamate (but not *S*-(+)-MDMA) increased social interaction and facilitated fear extinction learning, effects that could be relevant to using MDMA as a therapeutic.[254] Furthermore, the *R*-enantiomer did not increase locomotor activity, a behavioral effect commonly produced by psychostimulants.[254]

As discussed, the primary concern for using MDMA in the clinic is its potential neurotoxicity. Most neurotoxicity studies were performed using the racemate, however, there is some evidence to suggest that the neurotoxic effects of MDMA stem from the *S*-enantiomer, with the *R*-enantiomer being relatively benign. Unlike *R*-(−)-MDMA, *S*-(+)-MDMA increased body temperature and promoted the activation of microglia and astroglia.[255] However, this study employed a relatively low dose of *R*-(−)-MDMA. To more definitely establish a lack of neurotoxicity following *R*-(−)-MDMA administration, Howell and co-workers administered high doses of *R*-(−)-MDMA (four injections of 50 mg/kg given over two days) to mice and compared effects to those produced by the racemic mixture (four injections of 20 mg/kg given over two days).[254] These authors assessed body temperature, mortality, and markers of neurotoxicity. Unlike the racemate, high dose *R*-(−)-MDMA did not influence body temperature or survival. Furthermore, the *R*-enantiomer had no effect on glial fibrillary acidic protein (GFAP) immunoreactivity, DA content, or DAT expression. The racemate significantly increased astrogliosis while decreasing both DA content and DAT expression. This study provides compelling evidence that at least in mice, the *R*-enantiomer of MDMA lacks many of the negative effects associated with the racemate, while still maintaining the ability to promote social interaction and to facilitate fear extinction learning.

Thus, *R*-(−)-MDMA may be an effective pharmaceutical with an acceptable therapeutic index. However, neurotoxicity and other negative effects associated with *S*-(+)-MDMA and racemic MDMA will always be associated with the acryonym “MDMA,” having the potential to bias regulatory bodies, doctors, and patients. Therefore, to identify a term

suitable for common parlance, but devoid of negative connotations, we suggest the use of the alternate terms “armdma,” “esmdma,” and “racmdma” to refer to *R*-(−)-MDMA, *S*-(+)-MDMA, and (±)-MDMA, respectively. These terms are analogous to “arketamine” and “esketamine,” which refer to the *R*- and *S*-enantiomers of the fast-acting antidepressant ketamine, respectively. If armdma proves to be an effective and safe therapeutic in humans, we hope this new terminology will eliminate any potential stigma associated with using a perceived “party-drug” as a medicine.

HISTORY AND IMPORTANCE IN NEUROSCIENCE

Urban legend, rumor, and myth have clouded the true history of MDMA. Several excellent historical accounts of the discovery and development of MDMA have been reported previously,[44,49,256,257] and thus, we only discuss the highlights here (Figure 5). First, it is a common misconception that MDMA was originally designed to be an appetite suppressor or a weight loss drug. Instead, MDMA originated from a campaign by Merck to sidestep a patent on the hemostatic drug hydrastinine held by Bayer, one of Merck’s top rivals. In fact, MDMA was first synthesized in 1912 and subsequently patented, but as it was only intended to be an intermediate en route to the desired compound, its biological activity was not assessed. It was not until 15 years after its initial synthesis that MDMA was actually tested in animal models. Merck was interested in identifying compounds that mimicked the effects of epinephrine,[49] and MDMA was one candidate tested owing to its structural similarities. Unfortunately, the results of these tests could not be found in the Merck archive.[256]

Research on MDMA appeared to stagnate until the 1950s. At that time the US military began using mescalinelike compounds, including MDMA, as part of pharmacologically-assisted interrogation programs.[258] In essence, they were trying to identify so-called “truth drugs”—compounds capable of lowering inhibitions making people more likely to reveal secret information. The chemical warfare code of MDMA was EA-1475.[44] The methylenedioxy-containing entactogens, such as MDA and MDMA, were of particular interest to the military because these compounds tended to encourage people to speak more openly without causing overwhelming perceptual disturbances. The characteristic hallucinations produced by compounds like LSD and mescaline typically disrupted interrogation sessions. In the early 1950s, the military began testing several of these compounds on patients at the New York State Psychiatric Institute. In 1952, a patient named Harold Blauer was administered several compounds over the course of a month before succumbing to a fatal dose of MDA (450 mg).[258] Realizing that safety data on these compounds were woefully lacking, the military contracted a group at the University of Michigan to conduct pharmacokinetic and safety studies in mice, rats, guinea pigs, dogs, and monkeys.[259] After declassification, these data were published in 1973 and revealed that the methylenedioxy compounds were more toxic than their methoxy counterparts.[259]

The first report of the synthesis of MDMA in the peer-reviewed literature was in 1960.[260] Afterwards, MDMA remained relatively unexplored until Alexander Shulgin learned of the unique effects of the compound and tested MDMA on himself in 1976.[261] Thereafter, Shulgin distributed it to friends and psychotherapists in northern California, who began using MDMA to facilitate psychotherapy. Shulgin and Nichols were the first to publish on

the effects of MDMA in humans in 1978.[13,14] Though Shulgin is often credited with the rediscovery of MDMA,[261] the role of David Nichols should also be emphasized as Nichols was a co-author on these first reports of the effects of MDMA in humans. Furthermore, he was largely responsible for reclassifying MDMA and related compounds as entactogens, due to their unique qualities relative to hallucinogens and psychostimulants.[41]

During the period from 1978 to 1985, it is estimated that thousands of patients were treated with MDMA.[216] However, these initial studies did not adhere to the same rigorous standards that we demand of clinical trials today. As a result, the true therapeutic potential of MDMA was not captured in the scientific literature. Furthermore, the properties of MDMA that made it an effective aid to psychotherapy also led to its widespread use in social situations. During this period of time, recreational use of MDMA increased dramatically, and mounting evidence suggested that MDA, a structurally related compound, was neurotoxic. At the time, there was little data on the safety of MDMA, and thus, the DEA decided to place it on the Schedule I list in 1985 largely based on its structural similarity to MDA.[262] This decision was protested by a large number of scientists and therapists, and challenged in court, but ultimately, MDMA was permanently placed on the Schedule I list in 1988.

In a 2002 paper published in *Science*, Ricaurte and co-workers described experiments performed in nonhuman primates demonstrating severe dopaminergic (and to a lesser extent serotonergic) neurotoxicity of MDMA.[263] These authors suggested that MDMA might put users at risk for developing Parkinson's disease. The results of the study were rapidly disseminated by the popular media, leading to the widespread public belief that administration of "recreational doses" of MDMA (3 doses of 2 mg/kg spaced over 6 hours) could have major health consequences. When Ricaurte and co-workers could not reproduce their results, they retracted their *Science* paper a year later.[264] Further analysis revealed that animals used in the original study were likely dosed with methamphetamine, a known dopamine neurotoxin, instead of MDMA, due to a mix-up in the labeling of sample vials.

Despite its retraction, the Ricaurte study had dealt a serious blow to the credibility of MDMA as a safe therapeutic. Heated public debate ensued about the potential dangers of the drug and its government regulation. In 2009, David Nutt published an editorial where he compared the dangers of using ecstasy (1 serious adverse event in 10,000) to those of horseback riding or "equasy" (1 serious adverse event in 350).[265] This editorial highlighted the fact that people in the scientific community felt that government agencies were not using objective criteria for assessing risk when establishing regulations for psychoactive compounds like MDMA. Since the retraction of the Ricaurte study, there have been multiple clinical trials investigating the effects of MDMA, and thus far, all data suggest that MDMA can be administered safely under these conditions.

In 2011, the first completed clinical trial evaluating the potential of MDMA-assisted psychotherapy for alleviating treatment-resistant PTSD was published.[220] The results were positive, and in 2017, MDMA was granted "breakthrough therapy" status by the FDA. This designation helps to expedite the review and potential approval process for promising therapeutics. Phase III clinical trials are currently being planned, and if the results of those trials warrant approval by the FDA, a bona fide accepted medical use for MDMA will have

been established. This would necessitate the removal of MDMA from the Schedule I list, a regulatory change that could have profound implications for the field of psychedelic medicine. Schedule I status has severely hampered access to psychedelics for research purposes. In sum, this trajectory is perhaps why MDMA is the most influential compound for the future of psychedelic research. However, MDMA is also a highly divisive compound having the potential to swing public opinion against general use of psychedelics in medicine.

Since 2012, there has been an upswing in the numbers of songs and pop culture references to “molly,” a trend that parallels that seen for LSD in the 1960s and 1970s. Extensive proselytizing about the non-medical uses of LSD contributed to the creation of the Controlled Substance Act of 1970. This legislation has been a huge barrier to legitimate scientific research on the effects of these drugs and led to the first “Dark Age” for the field —the period of time from roughly 1970 to 1994 when relatively little psychedelic research was conducted. If public discourse on MDMA takes a similar course to that of LSD, we may be doomed to repeat the mistakes of the past. This would be unfortunate as MDMA is an important neurochemical tool for elucidating the neural mechanisms of social behaviors and empathy, and it has the potential to offer real relief to people suffering from PTSD and other anxiety disorders. However, because of its history and neurotoxic potential, MDMA may never achieve clinical and/or societal acceptance. Perhaps the true potential of MDMA lies in its use as a lead structure for the development of safer and more efficacious alternatives.

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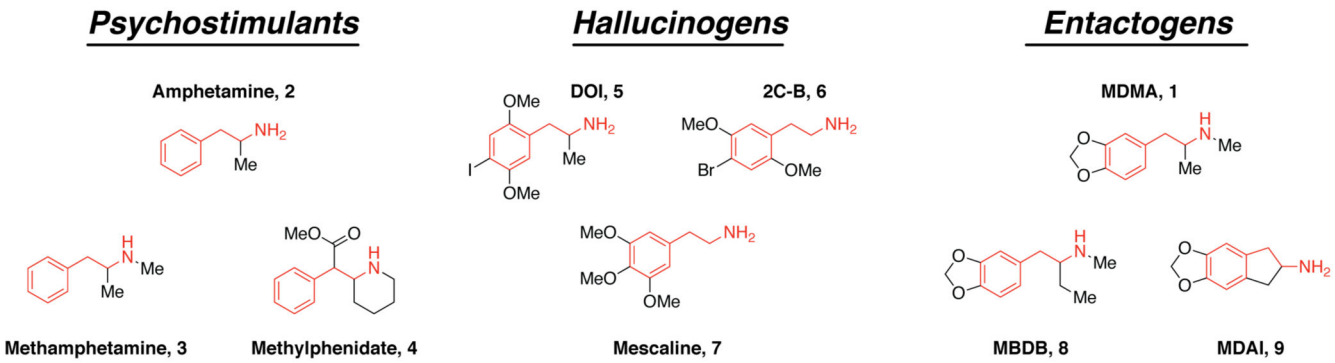

Figure 1.

Structural relationships between MDMA and other psychoactive compounds. The common phenethylamine core is highlighted in red. Compounds are classified as psychostimulants, hallucinogens, or entactogens based on the behavioral responses they produce in experimental animals and their subjective effects in humans.

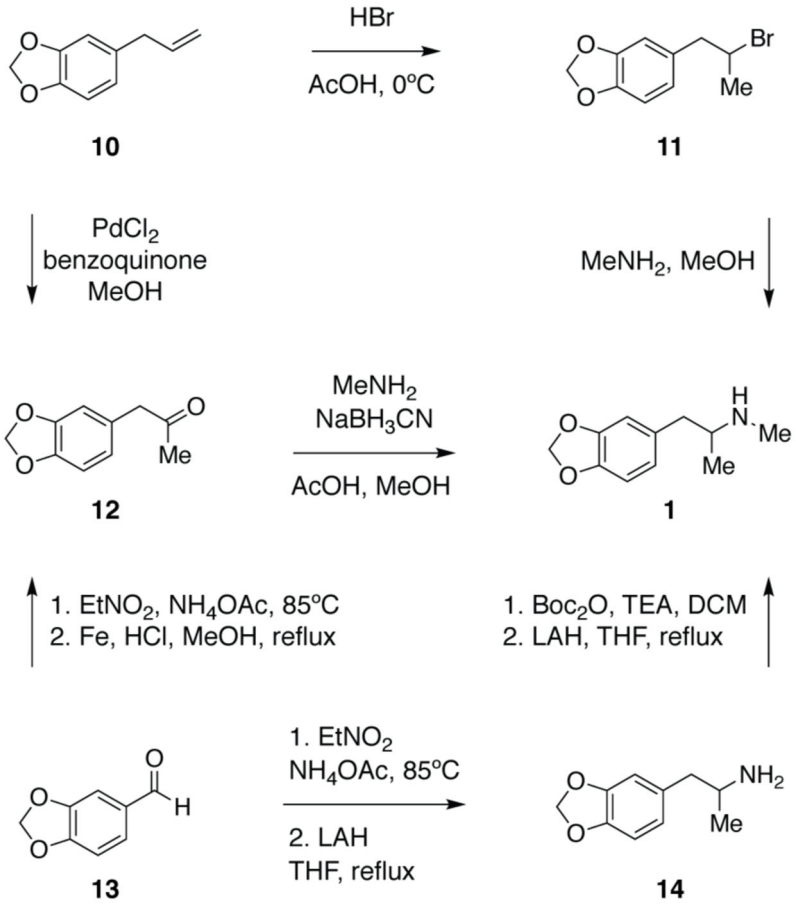

Figure 2.
Common synthetic strategies used to produce racemic MDMA.

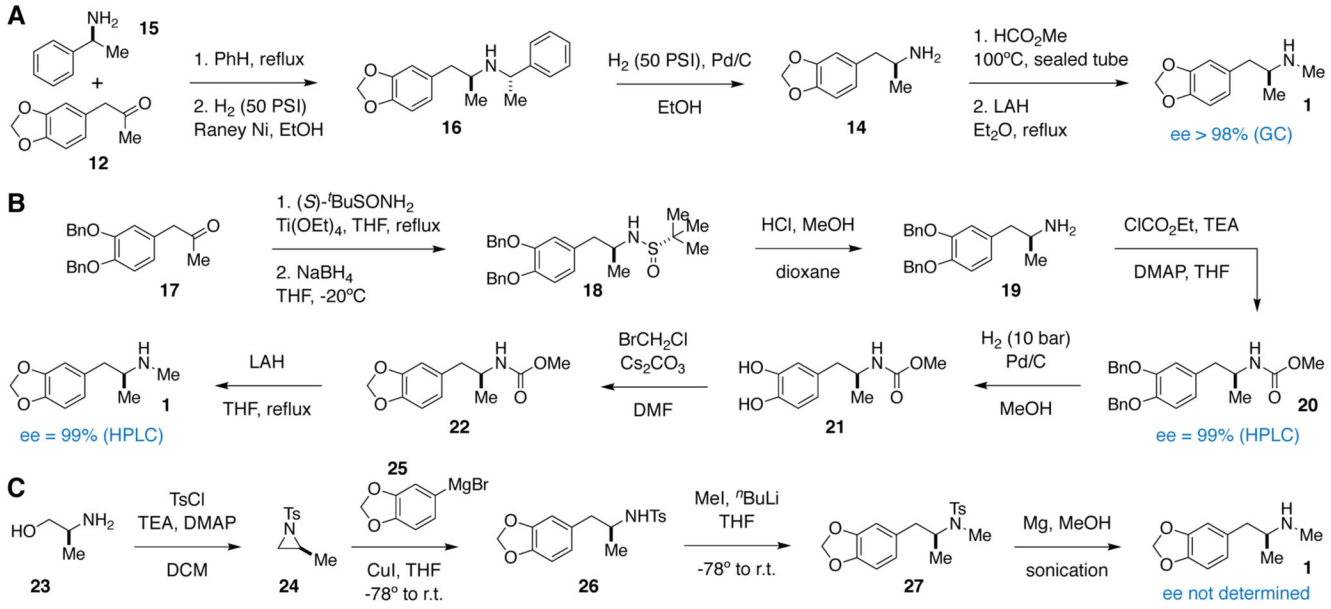

Figure 3.

Synthetic strategies used to synthesize enantiopure MDMA. (A) Reductive amination using (*S*)-α-methylbenzylamine (B) Reductive amination using Ellman's sulfinamide (C) Ring opening of an (*S*)-alanine-derived-aziridine.

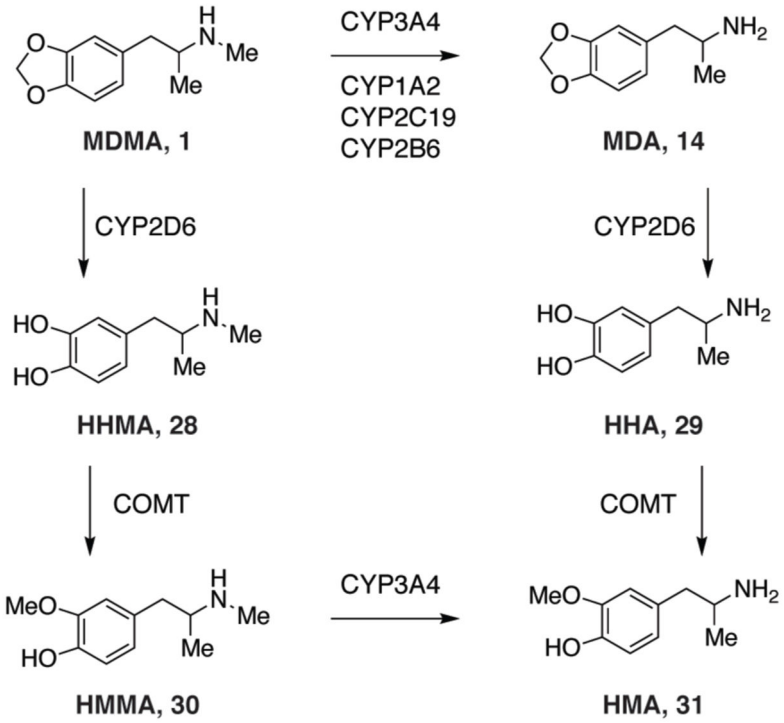

Figure 4.
Common metabolites of MDMA. CYP = cytochrome P450; COMT = catechol-O-methyltransferase.

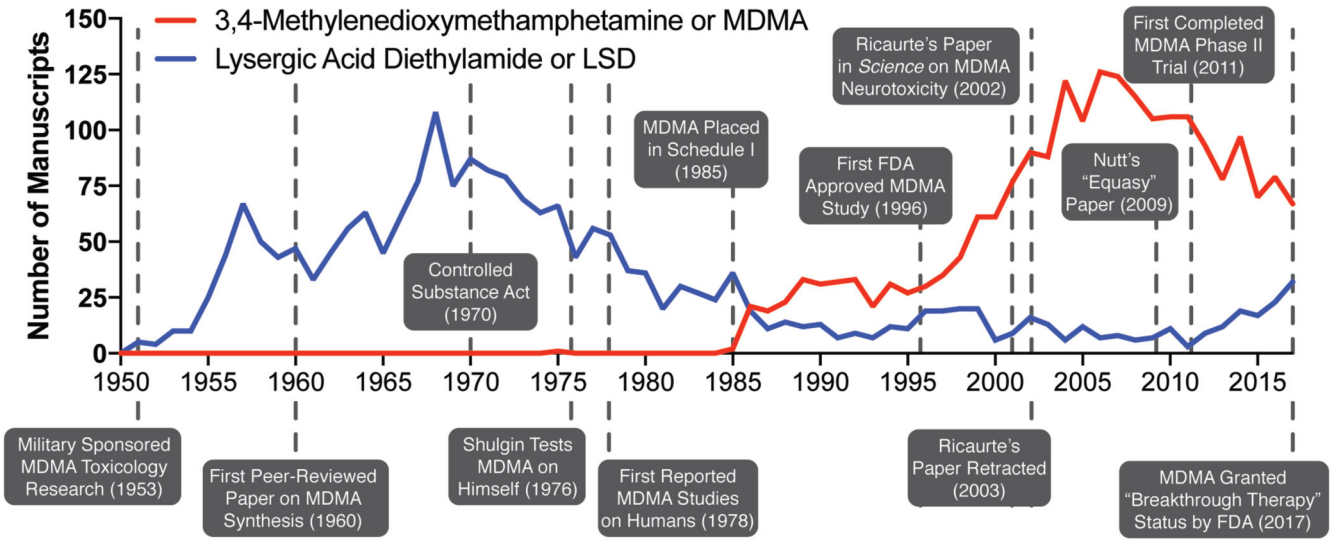

Figure 5.

Timeline of important events related to research on MDMA and classical psychedelics. Note the different peaks for research on MDMA and LSD. The data were obtained from a PubMed search for papers having titles that contained the search terms "3,4-methylenedioxymethamphetamine or MDMA" and "lysergic acid diethylamide or LSD" conducted on March 20, 2018.

Table 1.

Effects of MDMA on monoamine reuptake using synaptosomes prepared from rat brains. Values for K_i (nM) are reported ± standard deviations.[65] NE = norepinephrine; DA = dopamine; 5-HT = serotonin.

Compound	NE Uptake	DA Uptake	5-HT Uptake
S-(+)-Amph	38.9 ± 1.8	34 ± 6	3,830 ± 170
(±)-MDMA	462 ± 18	1,572 ± 59	238 ± 13

Table 2.

Effects of MDMA on monoamine transport inhibtion using HEK293 cells stably expressing human monoamine transporters. Values for IC_{50} (μM) are reported with 95% confidence intervals in parentheses.[62] NE = norepinephrine; DA = dopamine; 5-HT = serotonin.

Compound	NE Uptake	DA Uptake	5-HT Uptake
S-(+)-Amph	0.094 (0.06–0.14)	1.30 (0.83–2.0)	>10
(±)-MDMA	0.447 (0.33–0.60)	17 (12–24)	1.36 (1.0–2.0)

Table 3.

Effects of MDMA on monoamine release using synaptosomes prepared from rat brains. Values for EC_{50} (nM) are reported ± standard deviations.[65] NE = norepinephrine; DA = dopamine; 5-HT = serotonin.

Compound	NE Release	DA Release	5-HT Release
S-(+)-Amph	7.07 ± 0.95	24.8 ± 3.5	1,765 ± 94
(±)-MDMA	77.4 ± 3.4	376 ± 16	56.6 ± 2.1

Table 4.

Effects of MDMA on monoamine release using monoamine-preloaded HEK293 cells stably expressing human monoamine transporters. Values for EC_{50} (μM) are reported with 95% confidence intervals in parentheses.[62] NE = norepinephrine; DA = dopamine; 5-HT = serotonin.

Compound	DA Release	5-HT Release
S-(+)-Amph	1.76 (1.1–2.9)	>33
(±)-MDMA	22 (8.9–53)	5.63 (3.5–9.2)

Table 5.

Binding affinity profile for (±)-MDMA with values for K_i reported in nM. Radioligand binding assays were performed using stably or transiently expressing cell lines (HEK, HEKT, or CHO) unless noted otherwise.

Receptor	Radiolabeled Ligand	Ligand Classification	Species	K_i (nM)	Reference
5-HT1A	^{3}H-8-OH-DPAT	Agonist	Human	>10,000	77
5-HT1A	^{3}H-8-OH-DPAT	Agonist	Human	12,200	62
5-HT 1B	^{3}H-GR-125743	Antagonist	Human	>10,000	77
5-HT 1D	^{3}H-GR-125743	Antagonist	Human	>10,000	77
5-HT 1E	^{3}H-5-HT	Agonist	Human	>10,000	77
5-HT2A	^{3}H-Ketanserin	Antagonist	Rat	>10,000	77
5-HT2A	^{3}H-Ketanserin	Antagonist	Human	7,800	62
5-HT2B	^{3}H-LSD	Agonist	Human	500	77
5-HT2C	^{3}H-Mesulergine	Antagonist	Rat	>10,000	77
5-HT2C	^{3}H-Mesulergine	Antagonist	Human	>13,000	62
5-HT3	^{3}H-Zacopride	Antagonist	Human	>10,000	77
5-HT5	^{3}H-LSD	Agonist	Human	>10,000	77
5-HT6	^{3}H-LSD	Agonist	Human	>10,000	77
5-HT7	^{3}H-LSD	Agonist	Human	>10,000	77
Alpha1A	^{125}I-HEAT	Antagonist	Human	>10,000	77
Alpha1A	^{3}H-Prazosin	Inverse Agonist	Human	>6,000	62
Alpha1B	^{125}I-HEAT	Antagonist	Human	>10,000	77
Alpha2A	^{3}H-Clonidine	Agonist	Human	2,532	77
Alpha2A	^{3}H- Rauwolscine	Antagonist	Human	15,000	62
Alpha2B	^{3}H-Clonidine	Agonist	Human	1,785	77
Alpha2C	^{3}H-Clonidine	Agonist	Human	1,123	77
Beta1	^{125}I-Pindolol	Partial Agonist	Rat	>10,000	77
Beta2	^{125}I-Pindolol	Partial Agonist	Rat	>10,000	77
CB1	^{3}H-CP-55940	Agonist	Rat (brain)	>10,000	77
M1	^{3}H-QNB	Antagonist	Human	>10,000	77
M2	^{3}H-QNB	Antagonist	Human	>10,000	77
M3	^{3}H-QNB	Antagonist	Human	1,851	77
M4	^{3}H-QNB	Antagonist	Human	8,245	77
M5	^{3}H-QNB	Antagonist	Human	6,339	77
Nicotinic Alpha1Beta2	^{3}H-Epibatidine	Agonist	Human	>10,000	77
Nicotinic Alpha2Beta2	^{3}H-Epibatidine	Agonist	Human	>10,000	77
Nicotinic Alpha2Beta4	^{3}H-Epibatidine	Agonist	Human	>10,000	77

Receptor	Radiolabeled Ligand	Ligand Classification	Species	K_i (nM)	Reference
Nicotinic Alpha3Beta2	^{3}H-Epibatidine	Agonist	Human	>10,000	77
Nicotinic Alpha3Beta4	^{3}H-Epibatidine	Agonist	Human	>10,000	77
Nicotinic Alpha7	^{3}H-Epibatidine	Agonist	Human	>10,000	77
D1	^{3}H-SCH23390	Antagonist	Human	>10,000	77
D1	^{3}H-SCH23390	Antagonist	Human	>13,600	62
D2	^{3}H-NMSP	Antagonist	Human	>10,000	77
D2	^{3}H-Spiperone	Antagonist	Human	25,200	62
D3	^{3}H-NMSP	Antagonist	Human	>10,000	77
D3	^{3}H-Spiperone	Antagonist	Human	>17,700	62
D4	^{3}H-NMSP	Antagonist	Rat	>10,000	77
D5	^{3}H-SCH23390	Antagonist	Human	>10,000	77
GABA A	^{3}H-Muscimol	Agonist	Rat (forebrain)	>10,000	77
GABA B	^{3}H-Baclofen	Agonist	Rat (forebrain)	>10,000	77
NMDA	^{3}H-MK-801	Antagonist	Rat (forebrain)	>10,000	77
H1	^{3}H-Pyrilamine	Antagonist	Human	2,138	77
H1	^{3}H-Pyrilamine	Antagonist	Human	>14,400	62
H2	^{3}H-Pyrilamine	Antagonist	Human	>10,000	77
Prostaglandin EP3	^{3}H-PGE2	Agonist	Human	>10,000	77
Prostaglandin EP4	^{3}H-PGE2	Agonist	Human	>10,000	77
NET	^{3}H-Nisoxetine	Inhibitor	Human	>10,000	77
NET	^{3}H-Nisoxetine	Inhibitor	Human	30,500	62
DAT	^{3}H-GBR 12935	Inhibitor	Human	>10,000	77
DAT	^{3}H-WIN35,428	Inhibitor	Human	6,500	62
SERT	^{3}H-Citalopram	Inhibitor	Human	>10,000	77
SERT	^{3}H-Citalopram	Inhibitor	Human	13,300	62
TAAR1	^{3}H-RO5166017	Agonist	Rat	370	62
TAAR1	^{3}H-RO5166017	Agonist	Mouse	2,400	62

Table 6.

Binding affinity profile for (±)-MDMA, *R*-(−)-MDMA, and *S*-(+)-MDMA with values for K_i reported in nM ± SEM.[247]

Receptor	Hot Ligand	Hot Ligand Activity	(±)-MDMA	*R*-(−)-MDMA	*S*-(+)-MDMA
5-HT 1	^{3}H-5-HT	Agonist	6,850 ± 1,300	4,200 ± 500	>10,000
5-HT2	^{3}H-Ketanserin	Antagonist	8,300 ± 1,100	3,310 ± 140	>10,000
D2	^{3}H-NMSP	Antagonist	>10,000	>10,000	>10,000