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# Ecstasy: pharmacology and neurotoxicity

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In part because it is amphetamine derived, ecstasy has inherited some of its parent compound's reputation for being neurotoxic. However, whereas amphetamine and methamphetamine undoubtedly cause irreversible brain damage with long-term use, the jury is still out on the party drug ecstasy. The deadly reputation of ecstasy has been fuelled by the tragic fates of healthy young clubbers who have died after taking the drug. However, compared with other recreational drugs, there have been very few ecstasy-related deaths. Further, there is little evidence for short-term neurotoxicity of ecstasy at recreational doses. That is not to say that ecstasy leaves the user neutral. Chronic ecstasy use causes depletion of serotonin, which has subtle but important long-term effects on cognition and mood. Although it seems unlikely that we will be faced with a generation of party goers who suffer from premature Parkinson's disease, so little is known about the long-term effects of ecstasy on mood, emotional states and cognitive function that at present we cannot predict what impact their use of ecstasy will have on the middle-age of the average ecstasy user.

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## Abbreviations

<b>5-HT</b>	5-hydroxytryptamine
<b>DA</b>	dopamine
<b>MDMA</b>	3,4-methylene-dioxymethamphetamine
<b>NE</b>	norepinephrine
<b>PD</b>	Parkinson's disease

## Introduction

Ecstasy is the colloquial name given by its users to 3,4-methylene-dioxymethamphetamine (MDMA). It is a ring-substituted amphetamine derivative that is also related to the hallucinogenic compound mescaline. Although it is classified as a hallucinogen, ecstasy does not produce the profound sensory disruptions or hallucinations

associated with classical hallucinogens such as lysergic acid diethylamine (LSD), phencyclidine or mescaline. Rather, it increases emotional sensitivity and empathy, with users reporting a loss of inhibitions, reduced anxiety and an increased sense of closeness with other people.

MDMA was patented by Merck in 1914, but never marketed. Its toxicological effects were tested by the US military [1]. They were presumably seeking new chemical weapons or drugs for interrogation purposes; the lack of further development in this field is perhaps not surprising given that its main effect is to engender a feeling of closeness and empathy with strangers without impairing intellectual efficiency. Ecstasy went unnoticed for many years until it became the drug of choice at all-night dancing parties (raves) that were popular in the mid-1980s. The sub-culture associated with raves, the affordability of the drug and its highly desirable behavioural effects (with apparently few side effects) led to an explosion of recreational ecstasy use. In recent years, although the popularity of raves has declined, the use of ecstasy has shifted to nightclubs and discos, where despite its illegality (Box 1) it remains a highly popular recreational drug. Ecstasy is thought to be the second most commonly used controlled drug (after cannabis) in Europe [2], and it is estimated that more than 8.3 million people worldwide have taken ecstasy (UN World Drug Report, 2004). The aim of this review is to review recent advances in the pharmacology of ecstasy, and in particular to review the evidence relating to the potential for long-term damage to the brain caused by ecstasy.

## Pharmacological action of MDMA in the brain

The pharmacology and the cell biology of MDMA have recently been comprehensively reviewed [3,4,5], so only an overview of the pharmacology of MDMA is given here. The action of MDMA in the central nervous system is complex, with several molecular sites of action. MDMA has major effects on serotonin (5-hydroxytryptamine [5-HT]) pathways, but also affects two other major transmitter systems in the brain: dopamine (DA) and norepinephrine (norepinephrine [NE]). MDMA binds to all three of the monoamine presynaptic transporters with highest affinity for the 5-HT transporter (see review by Elliott and Beveridge, this issue). It also binds to several classical receptors, having the highest affinity for 5-HT<sub>2</sub>,  $\alpha_2$ -adrenergic, M<sub>1</sub> muscarinic and H<sub>1</sub> receptors, with lower affinity for M<sub>2</sub> muscarinic  $\alpha_1$ - and  $\beta$ -adrenergic and 5-HT<sub>1</sub> receptors. MDMA administration causes an acute and rapid increase in extracellular 5-HT through

**Box 1** History of ecstasy: illegality.

In the UK, ecstasy/MDMA was classified as a class A, schedule 1 drug in 1977. As such, it is illegal to possess, sell or give it away. (Unlawful possession can attract a maximum penalty of seven years imprisonment or an unlimited fine or both; supply can attract life imprisonment or an unlimited fine or both.) In 2001, a modification order was made, adding 36 'ecstasy-like' substances to Schedule 2 of the Misuse of Drugs Act 1971. In the US, because of its high abuse potential, lack of clinical application, lack of accepted safety for use under medical supervision and because of evidence that a related compound and major metabolite 3,4-methylenedioxymphetamine induced serotonergic nerve terminal damage in rat brain, MDMA was added to Schedule 1 of the controlled substances act by the US Food and Drug Administration in 1985. This means it is illegal to buy, sell or possess it without a license.

release from synaptic vesicles, blockade of 5-HT re-uptake into the presynaptic terminals and inhibition of monoamine oxidase. This results in a marked depletion of 5-HT and 5-hydroxyindoleacetic acid from brain tissue in the first few hours following drug administration. Although the 5-HT levels recover within 24 h after a single dose of MDMA, a higher dose of MDMA can cause sustained depletion of 5-HT and 5-hydroxyindoleacetic acid content that can last for up to 12 months in the rat. MDMA also blocks the activity of tryptophan hydroxylase (the rate-limiting enzyme in the biosynthesis of 5-HT) within 15 min after administration, an effect that can last for up to two weeks. Following administration of MDMA, there is a dose-dependent persistent decrease in the number of 5-HT transporter sites and 5-HT receptors in the rat brain, as well as a loss of fine axons projecting from the dorsal raphe nucleus. These changes are region specific, with the greatest changes being seen in the striatum, hippocampus and prefrontal cortex. (For individual references, drug doses and greater detail of the pharmacology, see [3\*\*].)

As well as affecting the 5-HT system, MDMA causes a rapid release of DA from brain tissue (reviewed in [4\*\*]). There are important species differences in the sensitivity to MDMA. In rats and primates, the neurotoxic potential of MDMA appears to be restricted primarily to 5-HT neurones. Following a neurotoxic regime of MDMA administration (for doses, see [4\*\*]), there is a pronounced decrease in 5-HT, but no long-term depletion of NE and no change in catecholamine uptake sites. Even with a more intensive MDMA treatment regime, there is a significant depletion of 5-HT and NE, but not DA, in rats [6]. By contrast, the deleterious effect of high doses of MDMA in mice is DA-specific, with no effect on the 5-HT system (for references, see [4\*\*]).

**Acute toxic effects of MDMA**

Hyperthermia is the most dangerous clinical symptom of MDMA intoxication and most deaths (Box 2) result from a syndrome of persistent hyperthermia which leads to the

**Box 2** Deaths from ecstasy use.

Following publicity about the dangers of hyperthermia associated with ecstasy use, a number of users who had taken ecstasy mistakenly attempted to compensate for the effect of the drug by drinking large amounts of water — in some cases, enough to fatally intoxicate themselves. Water intoxication occurs when a person drinks so much water that the blood becomes diluted and sodium balance is disturbed (hyponatremia). Thus 'water intoxication', rather than a direct toxic effect of ecstasy, has been the cause of death in a number of these cases.

breakdown of skeletal muscle with subsequent kidney and other organ failure [7,8]. The mechanism for this is unknown, but recent evidence points to a possible role for uncoupling protein-3, a mitochondrial protein known to play a role in thermogenesis [9]. It is impossible to predict whether or not an individual will become hyperthermic after taking MDMA, because the effects of MDMA are unusually sensitive to small variations in dose and individual differences. However, it has been known for some time that increased ambient temperature can potentiate both the behavioural effects and the neurotoxicity of MDMA [7], and thus using MDMA under 'party' conditions (i.e. hot, crowded and noisy) is likely to be more dangerous than using it under laboratory conditions. This idea is supported by a study by Brown and Kiyatkin [10\*\*], who showed that brain hyperthermia induced in rats by MDMA at 23 °C was potentiated not only by increased ambient temperature or by restriction of heat dissipation but also by social interaction with a female rat. Interestingly, heat also increases self-administration of MDMA in rats [11]. Together these data suggest that, although MDMA tested in the laboratory might have a low toxic potential, the high individual variability in response to the drug, its long duration of action and strong modulation of its effects by environmental factors suggest that extrapolating 'safety' data from the laboratory will underestimate the risks to some individuals.

**Non-neuronal effects of MDMA**

MDMA has important consequences on non-neuronal systems in the body. For example, MDMA can induce pathological cerebrovascular responses [12] that increase the vulnerability of neurones to MDMA [10\*\*]. There is also a growing literature showing that MDMA affects the immune system [13]. A detailed discussion of non-neuronal effects is beyond the scope of this review, but these effects should be taken into account when long-term effects on the brain are considered.

**Neuropsychological consequences of depletion of 5-HT in brain**

The subjective effects reported by recreational users of ecstasy and subjects given MDMA in the laboratory are similar, with users reporting euphoria, changes in perception (sound and light), a reduction in defensiveness (negative affect), emotional openness, empathy and a

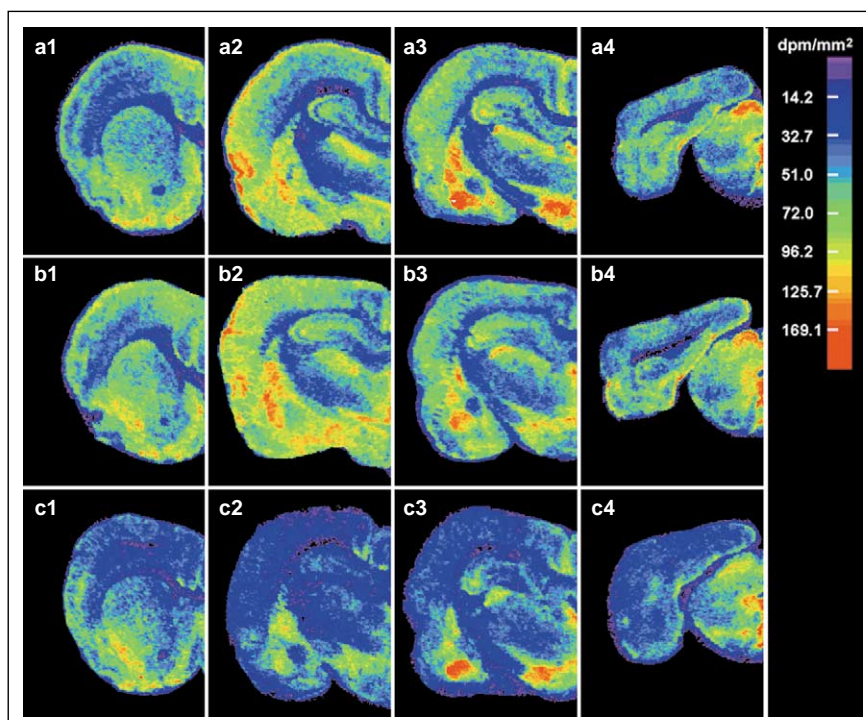
reduction of inhibitions. Most of these effects are likely to be mediated via the 5-HT-system, hence the concern about the potential of long-lasting deleterious effects of MDMA, as 5-HT modulates numerous processes in the central nervous system, including mood, anxiety, sleep, appetite and reward systems.

Although users take ecstasy to enhance mood, the drug does not leave the user neutral. While there is typically no 'hangover', as there is with alcohol, there is an 'offset' period after taking ecstasy in which mood worsens. This low mood persists for several days [14,15] and is known as the 'midweek blues'. Additionally, there are several studies suggesting that an increase in aggression and anger occurs after taking ecstasy [16,17]. As with the depressive effects, this tends to peak four days after taking the drug [15]. The effects of ecstasy on mood appear to be reversible. This is supported by a study showing that there was no difference in aggression between MDMA users and non-users after three weeks of abstinence [18]. Note,

however, that all of the non-user subjects in this study used cannabis. Because withdrawal from daily cannabis use is associated with increased aggression [19], it is possible that the lack of any difference between non-users and ecstasy users may be a due to an abstinence effect of cannabis in controls rather than a lack of effect of MDMA.

Evidence that MDMA users are prone to anxiety and depression has been mirrored in rats, where long-lasting increases in anxiety-like behaviours have been shown for up to three months after MDMA administration [20,21]. The effects are dose-dependent, and are related to changes in both 5-HT transporter and receptor (5-HT<sub>1A,2A/C</sub>) density (Figure 1) [22\*,23]. Interestingly, a low dose of MDMA increased anxiety-like behaviours, even though it did not produce long-lasting depletion of 5-HT [23]. This suggests that changes in receptors and transporter levels might be sufficient to produce long-lasting behavioural effects in the absence of long-lasting

Figure 1



Representative autoradiograms demonstrating [<sup>125</sup>I]RTI-55 binding to 5-HT transporter (SERT) of rats treated with 0.9% saline (a1–4, top row), low-dose MDMA (b1–4, middle row) or high-dose MDMA (c1–4, bottom row). Autoradiographic images were captured and analyzed using the Scion Image Analysis Program (v. 1.62, Scion Corporation, USA, PC version of NIH Image). The density of binding was calculated by converting the optical density of the image to dpm.mm<sup>2</sup> with the aid of a standard curve generated with calibrated microscalers. The highest density of binding is shown as red, the lowest as purple. The low dose was a single intraperitoneal injection of MDMA (5 mg/kg) intended to simulate a typical human use of 1–2 tablets of MDMA. The high dose was given intraperitoneally as 5 mg/kg every 4 h on two consecutive days to give a cumulative total of 40 mg/kg. This dose regime was intended to simulate a weekend of heavy MDMA use by a human user, given that the typical self-administered human dose is equivalent to 1–4 mg/kg MDMA. Quantification of these data showed that in the low-dose group there was a decreased level of expression of SERT in the medial hypothalamus, but increased expression in the prefrontal and perirhinal/entorhinal cortex. By contrast, brains from the high-dose MDMA group had higher levels of expression of SERT than did controls in nearly every brain region examined, including the cingulate cortex, hippocampus and the medial hypothalamus (for full details, see [22\*]. This figure was reproduced with permission from [22\*] [<http://www.nature.com/>].

depletion of 5-HT. Changes in receptor function, rather than depletion of 5-HT, might also explain changes in prepulse inhibition in chronic MDMA users [24]. (Prepulse inhibition is the process whereby a relatively mild stimulus — the prepulse — suppresses the response to a strong, startle-eliciting stimulus. A reduction in prepulse inhibition occurs in several cognitive disorders, including schizophrenia, Huntington's disease and obsessive-compulsive disorder.)

### Long-term deleterious effects of MDMA on mood and cognition

Several studies have shown long-term (weeks to months) impairments in memory and learning; in particular, working memory, planning ability, executive control and cognitive impulsivity [25–30]. This has led to the suggestion that ecstasy is a risk factor for earlier onset and/or more severe decline of age-related memory deficits in later years. Indeed, primary memory dysfunction is associated with heavy ecstasy use ([25]; in this study, 'heavy' use was defined as 'use on 30–1000 occasions'). Further support for deleterious effects of MDMA on cognition comes from a study using new and old world monkeys [31] in which repeated (daily for four days) MDMA exposure revealed cognitive dysfunction, particularly in spatial working memory.

Although there is clear evidence for some cognitive dysfunction in humans following long-term MDMA use, the evidence is not always straightforward. Indeed, it is possible that cannabis, rather than MDMA, may be responsible for some of the cognitive changes reported [28,32]. Most studies on the effect of recreational use of ecstasy have (necessarily) been done retrospectively. These studies are confounded by the possibility not only that the drug taken as 'ecstasy' might not have been MDMA but also that many users also take additional drugs. In at least one study where polydrug use has been controlled, many of the deleterious effects attributed to ecstasy have been found at similar levels in the polydrug users [33]. However, in a study that addressed the use of other illicit drugs directly [34], residual cognitive deficits attributable to MDMA were found in young ecstasy users. The authors used subjects who reported minimal exposure to other drugs (including alcohol) and compared them to subjects who had never used ecstasy, although they were similarly involved in the rave subculture. These data support the idea that MDMA alone has deleterious effects on cognitive function.

There have been limited studies on the long-term consequences of MDMA administration on cognitive function in rats, although those that exist have shown deficits caused by MDMA [35,36]. MDMA impaired passive avoidance retention (measured 24 h after the drug was given) and prevented training-associated increases in the N-methyl-D-aspartate receptor subunit NR1 and

Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CAMKII) [36]. Because NR1 and CaMKII are key molecules in memory consolidation, this suggests a mechanism by which MDMA may cause impairments in passive avoidance learning in rats.

### MDMA as a potential cause of Parkinson's disease

For more than 15 years, it has been known that MDMA produces depletion of 5-HT from the brains of laboratory animals. This reflects a loss of 5-HT from presynaptic terminals, rather than loss of the 5-HT cell bodies [37,38], although a recent study using flouorojade (an indicator dye) showed widespread neurodegeneration in rat cortex [39]. However, there is much debate over whether similar effects are seen in humans following the use of MDMA, and brain imaging studies showing such loss have been subject to criticism [40].

In 2002, there appeared to be a major new development, with the publication of a paper claiming that a recreational dose of MDMA caused death and extensive damage, not to 5-HT neurones, but to DA neurones in monkeys [41]. At the time of its publication, this paper generated a heated debate [42–44], because the toxicity data were at odds both with previously published laboratory studies and with epidemiological data. Nevertheless, the prospect that a single dose of ecstasy could cause damage to DA neurones was alarming, because Parkinson's disease (PD) is caused by a loss of DA-containing neurones in the substantia nigra. The cause of idiopathic PD is unknown; however, there is considerable evidence that environmental factors such as drugs, exposure to herbicides or other toxins can cause or contribute to the loss of DA-containing neurones. Because more than 80% of DA neurones need to be lost before the symptoms of PD appear [45,46], this study raised the spectre that MDMA could cause a sub-threshold loss of DA neurons. This could have gone unnoticed for years (in the same way the average PD sufferer does not know he/she has the disease until the symptoms appear) — until there was a demographic shift in the population of people presenting with PD. Given the number of people who have taken a recreational dose of ecstasy, this could reach epidemic proportions. This 'worst case' scenario now seems unlikely because the paper was withdrawn in 2003 [47]. A mix-up over the drugs used had occurred and, instead of receiving MDMA, the monkeys had been given methamphetamine at a dose known to cause lasting damage to the DA system. However, this has left unresolved the question of the long-term effect of MDMA on DA neurons (Box 3). Indeed, the growing evidence for a role for DA in the long-term effects of MDMA [48] suggests that there is no room for complacency. For example, a recent study found that, in mice, *in vivo* administration of MDMA causes the formation of ubiquitinated inclusions in the substantia nigra and the striatum [48]. Inclusions are

**Box 3** Current ecstasy use.

In the past two years, the number of admissions to the emergency room for ecstasy-related problems has fallen, suggesting a reduced use of ecstasy ([www.whitehousedrugpolicy.gov](http://www.whitehousedrugpolicy.gov)). The reason for this trend is not clear; it might be part of a general trend of decreased alcohol and drug intake following September 11. Alternatively, it could be a response by MDMA users to avoid using ecstasy following the wide publicity given to the possibility that a single dose of ecstasy could cause PD. It would be ironic if the latter possibility was the case, given that the use of methamphetamines (with their known dopaminergic toxic potential) continues to rise.

abnormal intracellular aggregates of ubiquitinated protein that are a hallmark of the pathology in PD and *in vitro* models of PD. Although this might be expected, given that the DA system in mice is vulnerable to MDMA toxicity, interestingly (given that the DA system in rats is not vulnerable to MDMA) the authors also found similar inclusions in a rat pheocromocytoma cell line. There is also evidence to suggest that MDMA toxicity of 5-HT neurones may be, in part, mediated by DA [49].

The increased attention paid to the association between the role of DA and MDMA use has highlighted some important gaps in the literature. Because MDMA primarily affects the 5-HT system, most attention, understandably, has been focused on 5-HT-related aspects of behaviours (i.e. emotion, attention, cognition and perception): little attention has been paid to DA-mediated behaviours such as motor control, motivation and reward. For example, psychomotor effects of MDMA have not been investigated fully. This is likely to change in the next few years, particularly given the potential effect of MDMA on motor control systems (see below).

Although the evidence for a neurotoxic effect of MDMA on the DA system in primates remains controversial, evidence for long-term deleterious effects on the 5-HT system in human has been consolidated. Several criticisms were levelled at some of the earlier positron emission tomography studies into MDMA-induced damage of the 5-HT system, including small sample size, lack of tracer selectivity, unreliability in ascertaining MDMA doses and poorly-matched comparison groups [40]. However, in recent studies [50,51], some of these issues have been addressed; comparisons were made between MDMA users, MDMA (polydrug) users and naïve subjects, and the reported drug history was checked with hair sample analysis. The findings support the idea that MDMA use causes long-lasting but reversible changes in the 5-HT system that contribute to the deficits described above.

### MDMA as treatment for dyskinesia in Parkinson's disease

At the same time as ecstasy was being implicated in the pathology of PD, a British television program caused

quite a different flurry of interest in the PD community. The program was a BBC documentary, in which the subject was a young man with early-onset PD. He was taking L-DOPA to control the symptoms of PD, but his disease had progressed to the stage at which his treatment caused dyskinesia (uncontrollable arm and leg movements that plague PD sufferers). He discovered that taking ecstasy markedly reduced his dyskinesia to a level where normal function was restored. In a controlled experiment, MDMA was shown to reduce both his dyskinesia and the dose of L-DOPA required to control his symptoms. Interestingly, an earlier study had shown that MDMA reverses haloperidol-induced parkinsonism in rats [52]. Further, in a study aimed at assessing the effects of a single dose of ecstasy on psychomotor and driving-related task performance, MDMA improved psychomotor performance, but impaired the subject's ability to predict object movement [53]. In a follow-up to the case study, MDMA was shown to improve L-DOPA-induced dyskinesia in a monkey model of PD [54\*\*], with this action being mediated via the 5-HT system. Because the deleterious side effects of MDMA add too great a risk for patients suffering from PD, it cannot be considered as a potential treatment for dyskinesia in PD sufferers. PD patients already have an increased risk of psychological side effects (e.g. hallucinations, confusion and depression) from many medicines and, although MDMA reduced this single patient's tremor and dyskinesia and improved his mobility, it also interfered with his thought processes and stopped him working (a diary account by the subject can be found on [www.ecstasy.org](http://www.ecstasy.org)). Nevertheless, these studies pave the way for investigation of the use of MDMA analogues in the treatment of dyskinesia. Searching for analogues of MDMA or other agents that interact with the 5-HT system to mimic the beneficial effects of ecstasy (while minimising cognitive side effects) will be key to advances in this area.

### Prospects for the use of ecstasy in post-traumatic stress disorder

Finally, a therapeutic opportunity for MDMA of quite a different sort has emerged recently. In 2003, the Multi-disciplinary Association for Psychedelic Studies (MAPS) was granted approval for human testing of MDMA for the treatment of post-traumatic stress disorder [55,56]. People with post-traumatic stress disorder are often withdrawn and anxious, and the scientists involved believed that the effects of MDMA reported by recreational users — lowering of inhibitions, reducing anxiety and promoting a sense of closeness and empathy with other people — could help patients 'open up' and develop a rapport with a therapist that might continue without the drug. The search for serotonergic drugs that might be useful in cognitive therapy is already underway [57]. It remains to be seen how useful MDMA will prove for the treatment of psychiatric disorders.

## Conclusions

The debate about the use/abuse of MDMA seems set to continue. On the one hand, there are those who think that studies showing ecstasy causing neurodegeneration are flawed, and that there is little proof that occasional use of the drug does any harm. On the other, there are those who think that MDMA is neurotoxic and that the widespread use of ecstasy is creating a neurological time-bomb. If this is the case, then given that this bomb has been ticking for nearly 20 years it will not be long before it goes off. It seems most likely that, as with many controversies in science, the answer will lie in the middle ground. What is abundantly clear, however, is that the recreational use of ecstasy is not yet proven to be 'safe'. There are no well-controlled longitudinal studies looking at the long-term effects of MDMA on neurologically normal users. Further, although MDMA will soon be tested as a possible aid to psychotherapy for post-traumatic stress disorder, there have been no studies evaluating the effect of MDMA on individuals with mental disturbances. More worryingly, there is a growing literature showing that 'hidden' symptoms, in particular subtle cognitive deficits and long-term changes in mood, are linked to the recreational use of MDMA. These might be reversible with long-term abstinence but, until a rational approach to investigating the effects of MDMA on the individual is taken, some of the most interesting aspects of the pharmacology of MDMA will remain under-investigated.

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