

Is MDMA ('Ecstasy') Neurotoxic in Humans? An Overview of Evidence and of Methodological Problems in Research

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Key Words

MDMA · Ecstasy · Neurobiology · Neurotoxicity ·
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Evidence

Abstract

Evidence from research with a range of animal species, from rodents to non-human primates, has shown that MDMA ($\pm$ 3,4-methylenedioxymethamphetamine) is neurotoxic. This article explores the evidence that MDMA may be neurotoxic in humans by briefly over-viewing three types of research: (1) neurobiological, (2) psychological/somatic and (3) psychiatric. The first type of evidence derives from neuropharmacological and neuroendocrine studies, the second type focuses on psychological function and somatic symptoms in MDMA users, and the third involves studies of psychiatric cases in people who have taken MDMA. Evidence from these types of studies is indirect and differs in the degree to which any causative links are implied between observed effects, MDMA use and human neurotoxicity. These issues are critically discussed within the context of the wide-ranging methodological problems in human research with MDMA.

Introduction

MDMA ('ecstasy') is a popular drug of abuse, often taken in dance clubs for its acute 'euphoric' psychoactive effects. Despite current widespread use, and despite the fact that large numbers of people have now been taking MDMA regularly for several years, we know relatively little of either the short- or the long-term consequences of using this drug.

MDMA is a potent, indirect monoaminergic agonist which both inhibits the reuptake and promotes the release of serotonin (5-HT) and, to a lesser extent, of dopamine [1–3]. Animal studies have shown that following administration of acute doses of MDMA, there can be a reduction in the number of 5-HT containing neurones, depletion in brain 5-HT and 5-hydroxyindolacetic acid (5-HIAA), inhibition of the activity of tryptophan hydroxylase (TPH: the rate-limiting enzyme in 5-HT synthesis) and in the density of 5-HT reuptake sites. In primates, there is persisting damage to axonal terminals whereas in other species there is recovery [4, 5]. Even though the evidence that MDMA has serotonergic neurotoxic effects in non-human primates is substantial, the precise mechanism of 5-HT toxicity induced by MDMA in animals remains debated [6].

Although there may be some degree of overlap between the doses of MDMA given in animal studies and those

ingested recreationally by people, there are many problems in generalising even from primate studies to humans. As researchers cannot 'administer' known doses of MDMA over specified periods to people, the evidence in humans of possible neurotoxic effects is inevitably indirect, and studies are fraught with methodological difficulties.

If MDMA does produce serotonergic neurotoxicity in humans, there would be important ramifications for the mental health and psychological function of people who use this drug. 5-HT is thought to play a role in regulating mood, sleep, appetite and cognitive function. Low levels of 5-HT are associated with depression in vulnerable people [7], and antidepressants may work by increasing levels of 5-HT in the brain. It is therefore possible that current ecstasy users may be more vulnerable to clinical depression in the future. Further, because of potential damage to serotonergic neurones, they may not respond optimally to some current drug treatments for depression. 5-HT may also mediate aspects of cognitive function, as rapid depletion of 5-HT by a tryptophan challenge has been found to impair learning and memory [8]. Further, animal studies have shown that the greatest reduction in 5-HT content induced by MDMA occurs in those brain regions containing an abundance of 5-HT terminals and axons – the frontal cortex and hippocampus – areas known to play crucial roles in cognitive function and memory. Thus, current users may have increased risk of neurodegenerative changes in later life.

Studies of humans which may provide insights into possible neurotoxic effects can be classified into three main types. Firstly, neurobiological research which assesses markers of serotonergic function in MDMA users, and this includes neuropharmacological and neuroendocrine studies. A second type of research focuses upon psychological function and somatic symptoms in recreational users of MDMA. Thirdly, there are studies which have focused on psychiatric morbidity, retrospectively associating MDMA use with patients' presenting symptomatology. These three types of studies are briefly over-viewed in the first part of this article; the second part presents a discussion of the wide-ranging methodological issues in human research on MDMA.

Neurobiological Studies

These studies use differing ways of assessing serotonergic function in human MDMA users. The most informative study to date is a PET study by McCann et al. [9]

which used a radioligand which selectively labels the 5-HT transporter. Fourteen people who self-reported a history of MDMA use and of abstinence from use for 3 weeks were compared with 15 non-user controls. MDMA users were found to display decreased global and regional brain 5-HT binding, and the degree of decrease in 5-HT binding was positively correlated with the subjects' reports of extent of MDMA use. This is the most direct evidence to date in humans that long-term use of MDMA is associated with altered serotonergic function. Other studies have used more indirect means of looking at the potentially neurotoxic effects of MDMA.

There is some evidence that MDMA is cytotoxic to certain human serotonergic cells [10]. Simantov and Tauber [10] were able to determine that MDMA neurotoxicity increased with dopamine and its precursor, *L*-DOPA. They suggest this implies that MDMA increases dopamine synthesis which in turn is mediated by the activation of 5-HT₂ receptors. Hence, an indirect interaction is implicated with regard to MDMA and serotonergic neurotoxicity in humans.

There is also evidence that the concentration of 5-HIAA (the metabolite of 5-HT) in the cerebrospinal fluid of regular MDMA users is reduced compared with non-users [11, 12]. This reflects the rapid depletion of brain hydroxyindols within hours of MDMA use. It also reflects a longer-term lowering of indolamine levels. However, the relationship between short- and long-term effects is unclear at present.

A study by Gerra et al. [13] is notable for the careful selection of a rare subgroup of MDMA users who did not also abuse a range of other drugs. Further this study appropriately took urine samples for three consecutive weeks to ensure inclusion of participants only if they had been drug free for this minimum time. Control, non-users were also assessed to validate that they did not use illicit drugs. The response of both groups was assessed to a challenge with *D*-fenfluramine – a 5-HT agonist. The control group showed the normal response to this serotonergic stimulant of increased levels of prolactin and cortisol. However, in comparison, MDMA users had significantly blunted prolactin and cortisol responses suggesting impaired central serotonergic function.

5-HT uptake blockers such as fluoxetine or citalopram can prevent MDMA from eliciting a neurochemical response in animals which again supports the serotonergic mediation of these effects. If fluoxetine is co-administered with MDMA to rats, brain 5-HT levels remain the same as in control animals [1]. In humans there is little relevant evidence. One study of 4 subjects who took fluoxetine

before MDMA implied users report the same euphoric rush and positive effects as they remembered experiencing on MDMA alone [14]. However, some reported reduced adverse effects of MDMA (e.g. bruxism) when fluoxetine was also taken. The authors suggest that the psychoactive effects of MDMA are therefore not linked to 5-HT release.

Studies of Psychological Function and Somatic Effects

These types of studies assess psychological function and somatic symptoms in MDMA users. The rationale for this research is that acute and long-term alterations in neurochemistry may manifest themselves in alterations to mood, cognitive function, sleep and appetite. Some of these studies focus on acute effects of MDMA, some on residual effects a few days after acute dosing, and others have compared drug-free MDMA users with controls. The distinction between acute, residual and long-term effects is not always made clear, and often studies do not report how long users have actually been 'drug free' prior to testing.

Two early prospective studies were conducted prior to governmental legislation on MDMA. Greer and Tolbert [15] gave one dose of 75–150 mg MDMA (with a further 50–75 mg being administered 2 h later) to 29 volunteers as an adjunct to group psychotherapy. Generally, the acute effects reported were positive with most participants reporting an increased feeling of intimacy with others present at the session. The day after taking MDMA, 16 volunteers reported negative emotional side-effects which included anxiety (5), mild depression (2) and paranoia (1), whilst others described a more general emotional vulnerability. Downing [16] assessed acute effects of MDMA (mean dose 165 mg) in 21 volunteers who had previous MDMA experience. Again, reported acute effects were generally positive and included euphoria, heightened sensual awareness, and increased physical and emotional energy. Some volunteers experienced gait instability, trismus and increased deep tendon reflection. Only 3 had any apparent adverse cognitive effects as indexed by problems in performing mathematical calculations. Appetite was suppressed in all subjects throughout the 24 h of the experiment. As with Greer and Tolbert's study, subjects were self-selected and therefore had expectations of MDMA euphoria.

More recently, a controlled study was conducted [17] in which a single dose of MDMA (1.7 mg·kg⁻¹) and placebo

was administered under double-blind conditions on separate occasions to 13 healthy volunteers who reported no previous use of MDMA or other illicit drugs. MDMA produced a positive acute enhancement of mood and a moderate derealization effect. MDMA-induced somatic effects included bruxism, insomnia, loss of appetite and restlessness, and these symptoms persisted for 24 h beyond the initial dosing.

The same study also included a cognitive assessment. The Stroop task was used as an objective assessment of attentional function. This task requires subjects to name the colours in which words are printed, with some words being congruent (e.g. BLUE presented in a blue font) and others being incongruent (e.g. BLUE presented in a red font). It is probably the one cognitive task where one would predict an improved performance following MDMA, given that this drug increases the intensity with which colours are experienced [18], and therefore subjects would be less distracted by the written word in the incongruent condition. Indeed, this effect ('colours were more intense' [19, p. 248]) was reported by the authors. MDMA did not impair performance on the Stroop, which could reflect this perceptual heightening and/or a lack of effect of the drug on divided attention and response inhibition.

Parrott and Lasky [19] assessed novice MDMA users (defined as use of the drug on <10 occasions), regular users (use on 10 or more occasions) and non-users. Baseline assessments were administered before and then 2–16 h after the users had taken a dose of MDMA. Regular users performed worse at baseline than novice or non-users, respectively, and this decrement was exacerbated after users had taken MDMA. A visual search task did not show any marked baseline differences between groups, but performance was impaired following MDMA in both groups of users. The acute euphoria generally reported following MDMA was not found in this study, probably because of the wide variation in times after drug consumption at which assessments were given. Two days following MDMA use, a pattern of negative mood effects was found in MDMA users which was similar to that reported elsewhere [20].

Several retrospective studies have been carried out which rely on MDMA users' ability to accurately recall effects of the drug. For example, in a questionnaire study of 100 students aged 18–25 years who had used the drug between 1 and 38 times, the main acute effect reported by 90% of subjects was an increased sense of closeness, and 50% reported increased alertness [21]. The day following consumption of MDMA, 38% reported being drowsy, 33% insomnia, 21% depression and 21% difficulty con-

centrating. Similar effects were reported in a questionnaire survey of 500 young people [22]. The retrospective experiences of 20 psychiatrists who had used MDMA between 1 and 25 times [18] also included enhanced social interaction, increased emotional awareness and changes in visual perception. After 1 week, the most prevalent effects reported were loss of sleep and decreased appetite. It has been suggested that evidence of neurotoxicity of MDMA in humans may be shown in disturbed sleep patterns and suppression of REM sleep. One study found that total sleep time in MDMA users was significantly less than in drug-naïve controls [23].

Cognitive function was assessed in 9 people reporting a history of MDMA use, most of whom also used other psychotropic drugs [24]. Their performance was compared with normative data on the standard neuropsychological tests used. No test showed impairments across the group of users, although a prose recall task (from the Weschler Memory Scale) revealed mild impairments in 5 subjects. Another study which looked at the potential relationship between memory impairment and MDMA use [25] divided subjects into 3 groups of 10, depending on their level of experience with MDMA: drug-naïve controls, novice users (used the drug on <10 occasions) and regular users (>10 occasions). Reaction times and vigilance performance did not differ between groups. Word list recall (immediate and delayed) showed group differences, with MDMA users being significantly impaired compared to controls (surprisingly, novice users were slightly more impaired than regular users).

Cognitive function and mood of MDMA users was compared with a control group of alcohol users in a study which followed subjects through from initial testing in a dance club for 5 subsequent days [19]. The subjects in the alcohol group did not take any other psychoactive drug during the session, but both groups reported a similar history of using illicit drugs. Scores on the Beck Depression Inventory were similar the following day, but by mid-week, MDMA users were significantly more depressed than alcohol users, with some scoring in the range for mild clinical depression. Residual effects of MDMA several days after acute dosing may conceivably relate to the time course of TPH activity, which is reduced in experimental animals for up to 2 weeks. The synthesis of new 5-HT depends on the availability of the enzyme, and thus, persisting mood and cognitive effects beyond an acute dose of MDMA may reflect the time course of regeneration of 5-HT.

MDMA users in that study had lower scores on immediate and delayed prose recall tasks and were significantly

impaired on a task tapping working memory, possibly reflecting a deficit in executive function. Impaired performance on the same prose task has also been reported in a comparison of polydrug users who use MDMA with polydrug users who do not use MDMA [26]. This study also found that performance was *less* impaired in MDMA users the longer the time interval since last MDMA use. This may mean that working or episodic memory impairments are not a reflection of neurotoxicity, but are transient effects which recover following increased abstinence from MDMA use.

Recreational MDMA users appear cognisant of residual effects of the drug on mood and cognition. A recent survey of 469 ecstasy users in the UK found that 83% said they experienced mid-week 'low mood', and 80% experienced concentration and/or memory problems [Verheyden and Curran, unpubl. data]. Effects of MDMA on cognition and mood may be related to each other, as clinical depression in non-drug users can be associated with poor concentration and working memory.

Studies of Psychiatric Symptomatology

In recent years, concern has been increasingly expressed about possible psychiatric consequences of MDMA use. The vast majority of relevant reports are of single cases where one or two people have experienced panic attacks, depression or psychotic symptoms. The majority of these people had self-referred to psychiatric or drug abuse services after taking MDMA and nearly all were polydrug users. These patients are therefore atypical of the larger population of MDMA users who seldom seek professional help.

The largest study to date of psychiatric symptoms and MDMA was by Schifano et al. [27], who assessed 150 patients attending a drug treatment service who had taken ecstasy on 'at least one occasion'. Based on a semi-structured interview, 31% of the patients were classified as depressed, 28% as experiencing psychotic episodes and 27% as having cognitive impairments. Psychiatric disorder was more pronounced in those who had consumed a greater number of MDMA tablets over a longer time. However, typical of the population who attend substance abuse services, all patients were polydrug users, and many were heroin addicts. As the authors acknowledge, this makes it impossible to draw any causal links between use of MDMA and psychopathology. Those patients using MDMA who also used opiates were less likely to display psychopathology, whereas those who also used alcohol

were more likely to do so. However, the non-opiate users were younger than the opiate users, had an earlier age of first MDMA consumption, were likely to consume a greater number of tablets and to mix alcohol with their MDMA use. Such factors may in themselves be more directly relevant to the manifestation of psychopathology than the use of opiates as a variable in its own right.

One attempt to infer some causality between MDMA use and psychiatric symptomatology has been to establish a time link between onset of symptoms and ingestion of MDMA. Such studies mainly rely on single-case methodology and the majority of patients self-referred to psychiatric services months after taking MDMA. Panic disorder, agoraphobia, obsessions, psychotic symptoms and depression have all been reported in a range of such studies. Some reports have claimed that MDMA users with no previous psychiatric history can experience negative symptoms after a single dose [28, 29]. In many cases where a synchronicity of MDMA use and symptom onset is inferred, patients have other vulnerability factors which may contribute to their psychopathology [30].

Methodological and Ethical Issues in MDMA Research

Studies of MDMA in humans are clearly subject to ethical and methodological constraints given that the drug is illicit, has potential neurotoxicity and has resulted in some fatalities. These constraints concern: verification of acute drug usage and of drug use histories, establishment of baseline (pre-morbid) levels of function, time course of MDMA effects, use of placebo controls and blind conditions, and representativeness of user populations.

What Drug at what Dose Was Actually Taken?

Except in rare studies where ethical permission has been given to acutely administer MDMA at a known dose to healthy participants [17], it is impossible to determine what drug at what dose was taken. This is true for club studies of recreational drug users, where people might be assessed shortly after taking a drug, and for psychiatric cases presenting after acute MDMA use. Analyses of tablets sold as 'ecstasy' has shown that these may contain MDMA at doses ranging from 40 to 150 mg. However, they may also contain 'ecstasy-related' drugs (particularly 3,4-methylenedioxymethamphetamine and 3,4-methylenedioxymphetamine), amphetamines, ketamine, LSD or a range of other chemicals and combinations of chemicals. Dosages differ widely in both pure and combination tab-

lets. Biochemical markers can be used to verify which drugs have been taken, but these are seldom practical in club studies, where collection of blood or urine can be difficult for health and safety reasons. Another strategy would be to take samples for analysis of the tablet before it was ingested.

How Reliable is Information on History of Drug Use?

Given that street tablets may contain a variety of chemicals under the name of ecstasy, it follows that users' knowledge of their own drug history can be based on inaccurate information about what they had actually taken. Another consideration may be that users do not wish to divulge the extent of their drug use given fears about confidentiality of information about an illegal activity.

Moreover, retrospective accounts of drug history rely on memory, and when participants have used drugs like MDMA which can impair memory of events (episodic memory), their recall of drug history may be particularly unreliable. Conjoint use of other psychotropics which also impair episodic memory (e.g. alcohol, benzodiazepines, cannabinoids, ketamine) compounds these problems. Even the study by McCann et al. [9] relied on self-reported history of MDMA use. Hair analysis can now detect drugs like ecstasy and offers potential for objectively verifying drug history.

The vast majority of people who take ecstasy also use other drugs, most commonly alcohol, cannabis, amphetamines or cocaine. A recent survey of 476 MDMA users in the UK found only 1.5% did not combine use of ecstasy with use of alcohol, amphetamines, cocaine, benzodiazepines or other psychotropics on the same evening [Verheyden, Curran and Henry, unpubl. data]. This polydrug use is particularly important to consider in studies which compare groups of MDMA users with a control group. One strategy is to match groups as closely as possible for drug use, comparing polydrug users who use MDMA with polydrug users who do not use MDMA [27].

Are There Baseline Differences between MDMA Users and other Groups?

If MDMA is a human neurotoxin, then baseline performance would be expected to be lower in users than controls. However, independent group designs have the problem that MDMA users may differ from controls (non-users or other drug users) regardless of having used ecstasy. For example, impulsiveness and sensation seeking would be predictably higher in young people who go on to use MDMA than in those who stick to the more 'traditional' drugs like alcohol. It is also conceivable that people

with higher levels of depression or aggression [13] may be more prone to use MDMA as a form of self-medication. Memory function may be poorer initially in people who go on to use MDMA than in those who do not. A major prospective study, following a large number of young people over a period of years and testing them before they begin drug use would be needed to tease apart lower performance levels of those people who go on to use MDMA from lower performance levels induced by MDMA consumption. Given that drug 'fashions' change over time, this approach might say more about newer illicit compounds than it would about MDMA.

Some studies have assessed baselines by comparing MDMA users at other time points than when they had recently consumed the drug. One possible approach would be to assess people both before and after they took a single dose of MDMA. Although this has been done successfully [25], many ethical committees would feel that assessing people before they were about to take MDMA would, in effect, mean the researcher is condoning the use of this illicit substance, and they would not wish their own institution to be associated with this. Further, even pre-drug testing with regular users may pick up the residual effects of the last MDMA ingestion, and this would need to be controlled for. Post-drug baselines can be used as an ethical alternative to pre-drug baselines, though again persisting residual effects of MDMA need to be avoided.

Time Course of Effects of MDMA

Problems often arise from the lack of information about how long subjects abstained from MDMA before testing takes place. Blood and urine samples can detect drugs like cannabis 2–3 weeks after use, but MDMA and other amphetamine derivatives can be detected only 24–48 h after the last dose, even though they have psychological and somatic effects which last longer. So, in studies where participants are asked to abstain from taking psychoactive drugs for several weeks prior to assessment, this cannot be objectively confirmed from bodily fluids taken only once before the study.

Many studies of psychological function or psychiatric symptomatology do not provide even self-report information on time since last dose of MDMA. Given the acute effects on 5-HT and the longer-lasting effects on TPH, studies comparing groups of MDMA users and controls should try to ensure that participants are assessed several weeks after the last MDMA dose if they are to make inferences about long-term effects of this drug. Many studies tap acute or residual effects and say nothing about potential neurotoxicity. The acute, euphoric effects of this drug

are very different from the low mood often experienced a few days later, and neither may reflect possible neurotoxic effects.

Blind Conditions and Placebo Controls

An issue in many group studies is that experimenters are not blind to whether a subject is an MDMA user, and if so, how often they have used it. This is straightforward to overcome by having one person obtain drug histories and another administer the tests. Traditional psychopharmacological designs would explore acute effects of the drug using standard double blind conditions with active or inactive placebo controls. Again, this leads to an ethical quagmire where an illicit drug which has caused some fatalities and which could be neurotoxic is given to MDMA users or drug-naïve controls, and to date only one such study has been published [17].

Without blind conditions, participants' expectations regarding acute effects of MDMA will inevitably play a major part in determining drug effects, especially those obtained by self-ratings. It is also possible that expectations regarding residual effects will influence such measures, akin to the 'nocebo' effect in drug withdrawal. A related issue concerns the interpretation of fluctuations in mood over time. After the MDMA 'high' at the week-end, people may be more likely to feel comparatively 'low' on a normal week-day.

Representativeness of MDMA Using Population

In studies of psychiatric symptomatology, the recruitment procedure relies on patients self-presenting at psychiatric or drug services. A pre-disposition to psychiatric illness may be a mediating factor in determining whether someone experiences psychopathology following MDMA use. Moreover, this population is heavily biased towards opiate use and cannot therefore be considered representative of the more usual MDMA-using population who revolve around the dance scene. Psychiatric evidence is therefore the weakest evidence in terms of any causative link between MDMA and neurotoxicity. Vulnerability factors to the more negative effects of MDMA are not yet known. Further, in both psychological and psychiatric studies, participants are self-selected, often following advertisements for volunteers, and this also constitutes an unknown bias.

Regular MDMA users often report that the positive effects of the drug decrease over time, whilst the more negative aspects increase in frequency. It has been argued [31] that this suggests neurotoxicity rather than neuroadaptation, as the acute effects of MDMA are finished within

a few hours. However, differences in reported experiences over time may equally reflect 'psychological tolerance' deriving from repeated exposure to the psychoactive effects of the drug and consequent changes in the expectations of users.

Conclusions

MDMA has been shown to cause serotonergic neuronal toxicity in every animal species tested, although recovery in some. In humans, such direct causation is more difficult to infer. The most direct evidence in humans is the demonstration by McCann et al. [9] of decreased 5-HT binding in brains of MDMA users compared with controls, a decrease which positively correlated with the self-reported level of MDMA use. Neither this nor any other study to date tells us whether serotonergic neurotoxicity is reversible after long periods of abstinence. This remains an unanswered key question.

There are other questions which need addressing by research. It is not yet clear how frequency of use and amount used affect outcomes in terms of psychological function or somatic symptoms. Nor do we understand the

vulnerability factors which may predispose some people to experience more negative effects following MDMA use. Presumably, there are important psychological risk factors as well as factors relating to individual differences in serotonergic function.

Given the extent of use of this drug, MDMA research with humans is vital, despite being fraught with methodological problems. If ecstasy is neurotoxic in humans, as it is known to be in other species, then it is conceivable that its current widespread use will present a major public health problem in years to come. This problem will emerge in primary care medicine and in psychiatry rather than in substance abuse services. There may be considerable delay before problems emerge and we discover whether people who have used MDMA are more likely to experience early neurodegeneration or increased risk of clinical depression in years to come.

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