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REVIEW

3,4-methylenedioxymethamphetamine (MDMA): current perspectives

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Jerrold S Meyer

Department of Psychology, Neuroscience and Behavior Program, University of Massachusetts, Amherst, MA, USA

Abstract: Ecstasy is a widely used recreational drug that usually consists primarily of 3,4-methylenedioxymethamphetamine (MDMA). Most ecstasy users consume other substances as well, which complicates the interpretation of research in this field. The positively rated effects of MDMA consumption include euphoria, arousal, enhanced mood, increased sociability, and heightened perceptions; some common adverse reactions are nausea, headache, tachycardia, bruxism, and trismus. Lowering of mood is an aftereffect that is sometimes reported from 2 to 5 days after a session of ecstasy use. The acute effects of MDMA in ecstasy users have been attributed primarily to increased release and inhibited reuptake of serotonin (5-HT) and norepinephrine, along with possible release of the neuropeptide oxytocin. Repeated or high-dose MDMA/ecstasy use has been associated with tolerance, depressive symptomatology, and persisting cognitive deficits, particularly in memory tests. Animal studies have demonstrated that high doses of MDMA can lead to long-term decreases in forebrain 5-HT concentrations, tryptophan hydroxylase activity, serotonin transporter (SERT) expression, and visualization of axons immunoreactive for 5-HT or SERT. These neurotoxic effects may reflect either a drug-induced degeneration of serotonergic fibers or a long-lasting downregulation in 5-HT and SERT biosynthesis. Possible neurotoxicity in heavy ecstasy users has been revealed by neuroimaging studies showing reduced SERT binding and increased 5-HT_{2A} receptor binding in several cortical and/or subcortical areas. MDMA overdose or use with certain other drugs can also cause severe morbidity and even death. Repeated use of MDMA may lead to dose escalation and the development of dependence, although such dependence is usually not as profound as is seen with many other drugs of abuse. MDMA/ecstasy-dependent patients are treated with standard addiction programs, since there are no specific programs for this substance and no proven medications. Finally, even though MDMA is listed as a Schedule I compound by the Drug Enforcement Agency, MDMA-assisted psychotherapy for patients with chronic, treatment-resistant posttraumatic stress disorder is currently under investigation. Initial results show efficacy for this treatment approach, although considerably more research must be performed to confirm such efficacy and to ensure that the benefits of MDMA-assisted therapy outweigh the risks to the patients.

Keywords: MDMA, ecstasy, mood, cognition, neurotoxicity, dependence, PTSD

Introduction

3,4-methylenedioxymethamphetamine (MDMA [commonly known on the street as "ecstasy," "E," "X," or "Molly"]), is an amphetamine-like compound with chemical similarities to 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDE), and methamphetamine. The first synthesis of MDMA and its subsequent history have been well documented in several reviews[1–3] and, therefore,

Correspondence: Jerrold S Meyer
Department of Psychology, Tobin Hall, 135 Hicks Way, University of Massachusetts, Amherst, MA 01003, USA
Tel +1 413 545 2168
Fax +1 413 545 0996
Email jmeyer@psych.umass.edu

only the key points will be mentioned here. MDMA was synthesized in 1912 by the German pharmaceutical company Merck KGaA (Darmstadt, Germany) as part of a program to identify new hemostatic (blood-clotting) agents. Merck secured a patent for MDMA and its chemists later investigated some of the compound's pharmacological properties; however, none of this research revealed anything of particular interest to the company and, consequently, it never developed MDMA for clinical use. The first major toxicological study of MDMA in animals was conducted in the 1950s at the University of Michigan under the sponsorship of a classified contract with the US Army. The results were later declassified and published in 1973 by Hardman et al.[4] MDMA was subsequently "rediscovered" by Alexander Shulgin, a chemist who had previously worked for the Dow chemical company, until his burgeoning interest in the subjective effects of psychoactive drugs led to his departure from the company. In 1978, Shulgin, along with David Nichols of Purdue University, published the first report on the subjective effects of MDMA in human subjects.[5] The authors stated that:

> the drug appears to evoke an easily controlled altered state of consciousness with emotional and sensual overtones. It can be compared in its effects to marijuana, to psilocybin devoid of the hallucinatory component, or to low levels of MDA.[5]

MDA, which is also psychoactive, had earlier been promoted as a potentially beneficial adjunct to psychotherapy due to its reported ability to facilitate the accessing of deep-seated emotions.[6] Upon determining that MDMA might be superior to MDA in this regard, Shulgin recommended MDMA to a psychotherapist named Leo Zeff, who began using the compound in his clinical practice (Zeff called the drug "Adam" when administering it to his patients) and who, additionally, began spreading the word of MDMA's benefits to other therapists. By the early 1980s, MDMA (ecstasy) was becoming widely available recreationally and was drawing the attention of the US Drug Enforcement Agency (DEA).[1–3] In 1985, the DEA issued an emergency Schedule I classification for MDMA, and this classification has been maintained up to the present time, except for a brief period from 1987 to 1988.[3]

Despite over 30 years of intensive research on MDMA both in humans and in animal models, there remain several major controversies that have yet to be resolved. Does repeated MDMA exposure cause long-lasting mood changes and/or cognitive deficits? When used recreationally, does MDMA have toxic effects on the human brain? If so, what is the nature of such neurotoxicity? Can MDMA cause dependence, and, if so, what treatment approaches are currently available? Finally, does MDMA have potential benefit as an adjunct to psychotherapy, as first claimed many years ago? The present review offers a critical perspective on the current status of MDMA with particular emphasis on the abovementioned controversies.

Tablets sold on the street as ecstasy have variable purity and sometimes contain little or no MDMA.[7–9] For this reason, the term "MDMA" will be used in reference to administration of the pure compound in controlled human and animal studies, whereas the term "ecstasy" will be used in reference to studies of recreational use in which dose and purity are usually unknown.

Recreational use of MDMA/ecstasy

Prevalence and characteristics of use

Recreational ecstasy use is a worldwide problem. Discovery of illicit synthesis laboratories and seizures of ecstasy tablets are common occurrences not only in Western countries (eg, the US, Europe, and Australia) but also throughout the regions of Asia.[10] In the US, data from the 2011 National Survey on Drug Use and Health estimate that about 14.5 million individuals aged 12 or older had used ecstasy at least once in their lifetime; about 2.4 million had used the substance at least once in the previous year; and about 540,000 were current users (defined as use during the previous month).[11] In addition, approximately 900,000 individuals tried ecstasy for the first time in 2011.[11] Ecstasy is sometimes called a "club drug" due to its frequent use at dance parties, especially "raves." However, some users take ecstasy at regular house parties, small social gatherings with friends, or with a sexual partner.[12]

Ecstasy is usually taken orally in the form of tablets or capsules; however, the drug can also be snorted intranasally or injected. Current MDMA dose levels can be estimated from laboratory analyses of ecstasy (or Molly) tablets and capsules submitted to the website http://www.ecstasydata.org for testing. Of 65 tablets/capsules analyzed between December 2012 and April 2013, 32 contained 67%–100% MDMA as the active ingredient, whereas 33 contained <67% (and in many cases 0%) MDMA.[13] Of the 32 that were composed mainly of MDMA, the average amount per tablet/capsule was 205 mg (range 66–465 mg), although this value is likely an overestimate because most of the data entries do not account for the weight of inactive binder used in each tablet.[13] Nevertheless, if we use the 205 mg value along with a user body weight of 60–70 kg, we can calculate a typical

recreational MDMA dose as being approximately 3 mg/kg. Novice ecstasy users usually take one to two tablets per occasion; however, experienced users sometimes take four or more tablets per occasion.[14] Consumption of multiple doses can reflect "stacking" (taking more than one tablet at a time) and/or "boosting" (taking additional tablets later in a session to maintain drug-induced effects).[15] Evidence for increased MDMA consumption over time is thought to reflect drug-related tolerance, which has been confirmed in experimental animal studies (see Tolerance section below).

Ecstasy users report a variety of reasons for using the drug. From an Internet survey conducted several years ago in the UK, six major themes emerged as positive reasons for using ecstasy. In descending order of frequency mentioned, these themes were "changed outlook on life;" "understanding of self;" "improved relationships;" "increased sociability;" "improved psychological functioning;" and "healthiness."[16] A different survey study conducted in both the UK and US found many of the same reasons for ecstasy use as noted above, but several additional reasons were cited, such as increased enjoyment of music and/or dancing, enhancement of sex, becoming closer to nature, and simply a desire to experience an altered state of consciousness.[12]

Regular ecstasy users also report various problems that they relate to their drug use. Examples of such problems include poor concentration and memory; fluctuating mood; increased feelings of anxiety, depression, and/or irritability; difficulty sleeping; weight loss; and tremors or twitches.[16,17] Although these findings suggest that regular ecstasy use may be associated with a variety of different negative consequences, there are important limitations to keep in mind. First, many ecstasy tablets contain psychoactive substances other than MDMA. Second, as discussed in the next section, most ecstasy users are polydrug users and, therefore, it is often unclear to what extent the psychological problems reported by these individuals are specifically attributable to their MDMA consumption.

Polydrug use

Ecstasy users are almost always users of other substances, including both licit (eg, alcohol and tobacco) and illicit (eg, marijuana, cocaine, methamphetamine, hallucinogens, and opiates).[18] Polydrug use constitutes a major complication for interpreting studies of recreational ecstasy use, as it can be difficult to ascribe the results specifically to repeated MDMA exposure. Some investigators have attempted to deal with this confounding factor by statistically controlling for exposure to other substances of abuse.[19] Another important approach, which is discussed below, is to perform experimental animal studies in which pure MDMA is administered to animal subjects with controlled dosing regimens. Laboratory studies have also permitted an analysis of the acute effects of MDMA in humans; however, simulation of heavy recreational ecstasy exposure cannot be performed for ethical reasons.

Several different patterns of ecstasy polydrug use have been identified. For example, analysis of data from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) revealed three subtypes of ecstasy users: 1) extensive use of many different drugs of abuse (37% of ecstasy-using respondents); 2) heavy marijuana and cocaine use with moderate use of amphetamines, including ecstasy (29% of respondents); and 3) heavy marijuana use along with a low use of prescription drugs, primarily opiates (23% of respondents).[20] The majority of category 1 respondents were found to suffer from multiple substance-use disorders involving tobacco, alcohol, cocaine, hallucinogens, and/or marijuana. The frequent co-occurrence of ecstasy and marijuana use has been confirmed in more recent studies and, therefore, is of particular concern, as chronic cannabis exposure has been associated with some of the same cognitive deficits and mood changes observed in heavy ecstasy users (see below).[18,19]

Acute effects and aftereffects of MDMA/ecstasy use

Acute subjective and physiological effects

Survey studies have identified some of the subjective effects of ecstasy taken in recreational settings. Euphoria, arousal, relaxation, and increased sociability and closeness with others are among the commonly reported desirable effects of recreational ecstasy use.[21,22] As mentioned earlier, the history of MDMA includes a period in which psychiatrists administered the compound to assist patients in accessing painful, deep-seated emotions. This ability of MDMA and a few closely related compounds to enhance not only empathy for others but also self-awareness led David Nichols to coin the novel term "entactogens," meaning agents "producing a touching within."[23] The unique aspects of the MDMA experience were captured by Vollenweider et al,[24] using the previously developed Altered States of Consciousness rating scale, and by Sumnall et al,[12] using principal components analysis of a newly designed questionnaire targeting the likely effects of moderate MDMA consumption. Vollenweider et al found that orally administered MDMA at a dose of 1.5 to 1.7 mg/kg produced some of the same effects as the classic hallucinogen psilocybin (eg, depersonalization, perceptual

disturbances, and thought disorder), but, in contrast to psilocybin, there was little in the way of overt hallucinations.[24] The six principal components of the ecstasy experience identified by Sumnall et al, along with the question that loaded most strongly on that component are as follows: 1) perceptual alterations ("Everything I look at seems to vibrate or pulse when I am on ecstasy"); 2) entactogenesis ("On ecstasy I can deliberately generate insights concerning myself, my personality, and my relationships with other people"); 3) prosocial effects ("When I am on ecstasy I have strong feelings of caring or compassion for people I am with"); 4) aesthetic and mood effects ("On ecstasy it is pleasurable to move and dance"); 5) negative intoxication effects ("When I am on ecstasy I find that I have problems remembering things"); and 6) sexual effects ("Sexual orgasm has new qualities when on ecstasy").[12]

Along with the various positive effects associated with ecstasy, users report a number of adverse reactions, such as nausea, headache, agitation, tachycardia, dry mouth, bruxism, and trismus. Increased anxiety may also be experienced, particularly in inexperienced users.[21,22] Like the positive effects of ecstasy, these adverse effects are dose-dependent. When the subjective effects of ecstasy consumption were related to the MDMA content of the tablet, positive effects dominated the subjective responses up to approximately 100 mg of MDMA, after which the positive effects began to diminish and the adverse effects to increase.[21] In fact, MDMA doses greater than 180 mg were found to produce only adverse responses in users.[21] To reconcile this finding with the ecstasy tablet weights reported on the ecstasydata.org website, we may speculate either that the 205 mg average weight is a significant overestimate of the MDMA content or that the consumers of large ecstasy tablets have developed sufficient tolerance to the drug that they seek out large doses and experience more positive than negative effects of such doses.

Administration of known doses of pure MDMA to regular ecstasy users has enabled researchers to determine the subjective, behavioral, and physiological effects of the drug under controlled laboratory conditions. In accordance with the reported effects of recreational ecstasy use, MDMA administration in the laboratory leads to dose-related increases in euphoria, extroversion, mood changes (enhanced mood or anxiety, depending on the dose and other factors), and mental confusion.[25] Hallucinogenic-like effects are reported using certain rating instruments, but, based on the evidence from Vollenweider et al,[24] it is unclear whether these are true hallucinations. Acute MDMA administration at doses ranging from 1 to about 2 mg/kg additionally leads to a constellation of physiological effects, including increased heart rate and blood pressure, increased body temperature, and elevated circulating levels of the hormones cortisol and prolactin.[25] MDMA-induced hyperthermia has been demonstrated not only in the laboratory but also in ecstasy users studied in dance club settings. This effect results from a combination of increased heat production and deficient heat dissipation.[26] Although many users are aware of the dangers of overheating, dehydration, and dysregulated electrolyte balance when dancing under the influence of MDMA, some fatalities have been reported (see later Morbidity and mortality section). Table 1 summarizes the acute subjective, physiological, and adverse effects of MDMA/ecstasy based on a combination of survey and laboratory studies.

Aftereffects

The aftereffects of ecstasy use (typically at a weekend dance) have been investigated by assessing mood and cognitive function a few days after drug consumption. Early studies found a lowering of mood in both novice and experienced ecstasy users measured 2 or 5 days after use, a phenomenon that has sometimes been termed the "midweek blues."[27–29] Verheyden et al subsequently reported greater depressive symptomatology in female compared to male ecstasy users.[30] In a survey of over 400 regular ecstasy users in the UK, 80% also reported impaired concentration between drug-taking sessions.[31] Moreover, a controlled laboratory study of ecstasy users given MDMA during the evening and then kept awake

Table 1 Summary of the acute subjective, physiological, and adverse effects of 3,4-methylenedioxymethamphetamine (MDMA)/ecstasy use

Subjective effects
Euphoria
Arousal
Increased sociability/extroversion
Enhanced self-awareness
Sexual effects
Mental confusion
Perceptual alterations
Physiological effects
Increased heart rate and blood pressure
Hyperthermia
Cortisol and prolactin release
Adverse effects
Nausea
Headache
Agitation
Dry mouth
Bruxism
Trismus

Note: Data from[12,21,22,24,25].

all night found significant memory impairment the following morning that exceeded the memory impairment produced by sleep deprivation alone.[32] In a later section, we will discuss evidence for persistent cognitive deficits that have been associated with repeated ecstasy use over time.

Neurochemical mechanisms

The acute neurochemical effects of MDMA are well established, based on numerous studies conducted either in vitro or in laboratory animals. MDMA binds to the plasma membrane transporter proteins used by the monoamine neurotransmitters serotonin (5-HT), dopamine (DA), and norepinephrine (NE). These transporters are responsible for reuptake of the respective transmitter following release from the nerve terminal, and members of the amphetamine family (including MDMA) can enter the terminal via the transporter and cause a reversal of its function (ie, transporter-mediated release of the transmitter). Consequently, MDMA acts on the serotonin transporter (SERT) to block 5-HT reuptake and stimulate 5-HT release, the DA transporter (DAT) to block DA reuptake and stimulate DA release, and the NE transporter (NET) to block NE reuptake and stimulate NE release.[33,34] Although most of the research on MDMA interactions with monoamine transporters has involved rodent cells or tissues, this compound exerts qualitatively similar effects on human monoamine transporter proteins.[35,36]

There is substantial evidence both from clinical and preclinical studies demonstrating a key role for DA in the stimulant, euphoric, and rewarding actions of amphetamine and methamphetamine,[37] raising the possibility that DA might serve a similar function in the case of MDMA. Yet there is surprisingly little direct evidence for this supposition apart from the finding that pretreatment with haloperidol, a DA receptor antagonist with partial selectivity for the D_2 subtype, led to a decrease in MDMA-induced euphoria;[38] however, the antagonist alone led to a somewhat dysphoric mood, which raises questions about the interpretation of the results.

In contrast to the lack of research on DA involvement in the acute effects of MDMA, a number of pharmacological studies using various transporter inhibitors and receptor antagonists have provided information regarding the role of the serotonergic and noradrenergic systems in the subjective and physiological effects of MDMA in humans. Thus, pretreatment with either SERT inhibitors (ie, selective serotonin reuptake inhibitors [SSRIs]) or NET inhibitors have demonstrated significant, though incomplete, attenuation of many of the subjective, mood, and, in some cases, physiological effects of MDMA.[38–41] Moreover, a recent study with the dual SERT/NET inhibitor duloxetine found an even greater diminution of MDMA's subjective and physiological effects than seen following blockade of either SERT or NET alone.[42] Importantly, administration of clonidine, a drug that inhibits noradrenergic neuronal firing by activating α_2-adrenergic autoreceptors on the cells, failed to alter either the psychoactive or physiological effects of MDMA.[43] Animal studies have additionally demonstrated that MDMA actually suppresses the firing of both serotonergic and noradrenergic neurons in the brainstem.[44] Thus, it appears that many of MDMA's acute effects result from a combined release of both 5-HT and NE, apparently by transporter reversal rather than a stimulation of neuronal firing.

Serotonin acts on more than a dozen different receptor subtypes, which complicates the task of elucidating which of these subtypes might underlie the various effects of MDMA. The general approach to this problem has been to coadminister either a 5-HT receptor antagonist or placebo along with MDMA to determine whether any subjective or physiological responses are blunted or blocked by the antagonist. Studies with the 5-HT_2 antagonist ketanserin (which is partially selective for the 5-HT_{2A} subtype), but not pindolol, a combined 5-HT_{1A} and β-adrenergic receptor antagonist, demonstrated a blunting of both the positive mood and perceptual effects of MDMA.[38,45,46] Interestingly, 5-HT_{2A} receptors have been implicated in the perceptual distortions and hallucinations produced by LSD (lysergic acid diethylamide) and other classic hallucinogens.[47] On this basis, it seems reasonable to conclude that this same serotonergic receptor subtype contributes to the perceptual changes experienced by ecstasy users. Nevertheless, it remains unclear which subtypes, if any, might play a role in the other subjective and physiological effects of MDMA. With respect to NE, α_1-, α_{2A}-, and β_3-adrenergic receptors are involved in various ways in MDMA-induced hyperthermia,[48] but there is currently no information on which adrenergic receptor subtypes might contribute to MDMA-related mood changes.

The pro-social, empathic effects of MDMA in humans have often been associated with the drug's 5-HT releasing actions.[23,39] Research over the past few years suggests that 5-HT-mediated release of the neuropeptide oxytocin may contribute to this effect. First, MDMA administration was shown to elevate plasma oxytocin levels and increase social interactions in laboratory rats.[49] The increases in both oxytocin and pro-social behavior were blocked by pretreatment with the 5-HT_{1A} receptor antagonist WAY 100,635. Furthermore, the oxytocin receptor antagonist tocinoic acid administered directly into the cerebral ventricles attenuated

the effect of MDMA on social behavior in the animals. A subsequent study of regular ecstasy users given 100 mg MDMA in a controlled laboratory setting likewise found increased plasma oxytocin concentrations that were correlated with increases in subjective amicability and gregariousness.[50] One caveat regarding the interpretation of plasma oxytocin results is that central (ie, within the brain) and peripheral (ie, in the bloodstream) oxytocin are derived from different populations of neurons; circulating oxytocin is thought to have poor penetrance across the blood–brain barrier, and it is the central oxytocin that is considered to be most important for the peptide's pro-social effects.[51] Nevertheless, we must consider the possibility that the increased sociality observed following MDMA consumption is mediated, at least in part, by a serotonergic enhancement of central and/or peripheral oxytocin release.

Lastly, it is important to consider the possible mechanisms underlying the aftereffects of a session of MDMA use. Numerous animal studies have shown that, following the acute 5-HT release produced by MDMA, there is a temporary period of 5-HT depletion.[33] This effect is due to a combination of factors, including MDMA-induced inhibition of tryptophan hydroxylase, the rate-limiting enzyme in 5-HT biosynthesis, and an inability of the serotonergic neurons to take up and recycle the released 5-HT because of the blockade of SERT activity. Some investigators have hypothesized that the aftereffects of recreational ecstasy use (eg, midweek blues) are due to a temporary 5-HT depletion,[29] after which the symptoms wane as brain 5-HT levels are restored. However, because of the limitations associated with performing neurochemical measurements in living human subjects, this hypothesis remains unproven at the present time. On the other hand, there is substantial evidence that long-term ecstasy use is associated with serotonergic dysfunction, a topic that is taken up later in this review.

Effects of repeated or high-dose MDMA/ecstasy use

Heavy ecstasy users can accumulate hundreds of lifetime exposures to the drug. Moreover, a subset of users transition to a bingeing pattern of use that can produce very high peak drug levels in the bloodstream.[14,15,17] This section will review our current knowledge regarding the adverse effects of heavy exposure to MDMA produced either by many episodes of use or by binge use. The consequences of these different kinds of exposure patterns may not be identical, but they are covered together because most studies of ecstasy users characterize the subjects by their lifetime exposure, whereas laboratory animal studies typically use a binge-like dosing regimen to enhance MDMA's neurotoxic effects (see Neurotoxicity section below). In contrast to the acute effects of MDMA, which are not in dispute, there are several controversies about the long-term effects of repeated exposure to this compound in heavy ecstasy users. Although it is impossible to resolve these controversies at the present time, relevant research findings will be summarized with the aim of determining the current status of each dispute.

Tolerance

Many psychoactive drugs produce tolerance (ie, diminished responsiveness) upon repeated exposure. Several kinds of tolerance can occur, most notably pharmacokinetic or drug disposition tolerance due to an increased rate of drug inactivation, and pharmacodynamic tolerance due to reduced cellular sensitivity to the drug. Animal studies involving repeated MDMA administration have provided some evidence for tolerance development, although the opposite effect, which is called sensitization or reverse tolerance, occurred in some cases.[15] Differences in dosing regimen and/or specific outcome measures likely account for these discrepant findings. Regular ecstasy users often report diminished responsiveness to the drug and a consequent need for dose escalation, both of which imply the development of tolerance. In a different approach, Farré et al[52] and Peiró et al[53] studied the pharmacodynamic and pharmacokinetic effects of administering two doses of MDMA to human subjects at an interval of either 2 or 24 hours. Both studies found a higher than expected plasma concentration of MDMA after the second dose, which is a consequence of the drug inhibiting its own metabolism. In contrast, the subjective and physiological effects produced by the second dose were lower than expected based on the plasma concentration. These results suggest that tolerance to MDMA can develop quite rapidly, even potentially within a single session of drug use.

Mood changes

The ecstasy literature is replete with reported associations between use of this substance and abnormal mood changes. Two Internet studies of ecstasy users in the UK found a high incidence of self-reported mood fluctuations, feelings of depression, increased anxiety, and heightened impulsivity.[16,54] These effects were more pronounced in heavy compared to novice users. Numerous other studies have provided more systematic data by comparing ecstasy polydrug users with polydrug users who were not taking ecstasy and/or with controls who were not taking any illicit drugs.[20] Two reviews

of this literature that were published in 2005 and 2007 focused on depressive symptomatology assessed by means of the Hamilton Rating Scale for Depression, the Beck Depression Inventory, the Symptom Checklist 90, or the Center for Epidemiological Studies Depression Scale.[55,56] Both reviews noted a mix of results, in which some studies found a statistically significant increase in depressive symptomatology in the ecstasy users compared to the reference group, whereas other studies did not. A meta-analysis performed in conjunction with one of the reviews found a statistically significant overall association of ecstasy use with increased depression, although the effect size was relatively small.[56]

Despite the apparent association between ecstasy use and depressed mood, there are several reasons why it is premature to conclude that exposure to MDMA causes such a mood change. First, many of the cited studies failed to control adequately for the influence of polydrug use. Indeed, there are several reports suggesting that use of other substances (including cannabis) as well as environmental factors are at least as important as ecstasy itself in the heightened depression and anxiety seen in ecstasy users.[57–60] Second, in many studies, the selection of subjects may not have yielded a representative sample of ecstasy users. Third, the possibility must be considered that depressed mood precedes rather than follows the onset of ecstasy use in many individuals. The plausibility of this notion is supported by the mood-elevating effects of MDMA discussed earlier. Moreover, three different longitudinal studies found evidence that mood disturbances are often present before the onset of ecstasy use.[61–63] One study, conducted in The Netherlands, found that children (mean age of approximately 10 years) with elevated ratings of anxiety or depression were twice as likely to have used ecstasy when surveyed 14 years later than children without such a rating.[61] Two other studies, one conducted in Ohio, USA and the other in Munich, Germany, found that the first occurrence of a clinical psychiatric disorder, including major depression, commonly preceded rather than followed the onset of ecstasy use.[62,63] These findings raise the intriguing possibility that at least some ecstasy users may be taking the drug for the purpose of "self-medication."

Neuropsychological deficits

A large number of studies, described in this section, have compared neuropsychological functioning in current ecstasy users (polydrug users in almost all cases) with non-ecstasy polydrug users or controls that do not consume any illicit substances. In these studies, the subjects are requested to abstain from drug use for at least some minimum number of days so as to avoid confounding by acute drug effects. We will begin this section by focusing on assessments of memory, after which we will consider other aspects of neuropsychological function.

Ecstasy users have been tested on several different kinds of memory, including short-term memory (unprocessed information stored for a brief period of time, eg, immediate word recall in the Rey Auditory Verbal Learning Test); verbal working memory (briefly stored verbal information subjected to processing, eg, *n*-back task); visuospatial memory (working memory of visuospatial information, eg, Rey-Osterrieth Complex Figure Test); and long-term memory (information held in a longer-term store, eg, delayed recall tasks). Because the individual studies in this area have typically suffered from relatively small sample sizes, have used differing criteria for subject inclusion in the ecstasy-using and control groups, have tested the subjects on a variety of different tasks, and have yielded conflicting findings, a number of investigators have performed meta-analyses to determine the overall direction and strength of these findings. A 2007 meta-analysis of short-term, long-term, verbal, and visual memory by Laws and Kokkalis[64] found statistically significant deficits in all of these types of memory except for visual memory. Effect sizes were generally moderate or large, which supports the contention that regular ecstasy use is associated with a broad range of memory deficits. A more refined 2010 meta-analysis by Nulsen et al[65] differentiated between tests of short-term and working memory (verbal and visuospatial in both cases) and found that the ecstasy users performed more poorly in all memory domains. Results were significant regardless of whether the control group was composed of non-ecstasy polydrug users or individuals who had not been exposed to any illicit drugs. Moreover, estimated lifetime ecstasy consumption was related to the effect size in working (but not short-term) memory. An even more recent (2012) meta-analysis by Murphy et al[66] focused on visuospatial memory tasks. Significant deficits in ecstasy users were found for tasks requiring memory of the spatial distribution of stimulus items, tasks requiring figure recognition, and tasks requiring production or reproduction of figures. In contrast to the results of Nulsen et al,[65] estimated lifetime ecstasy consumption did not predict effect sizes in the analysis of visuospatial memory performance. It should be noted that, at least with respect to long-term memory, memory deficits in ecstasy users are more clearly seen in high-complexity than in low-complexity tasks.[67] If this is also true for other memory domains, it may help explain some of the conflicting findings in the literature.

Fisk and Sharp[68] proposed that working memory consists of a central executive function along with four subcomponents which they termed "updating," "attention shifting," "inhibition," and "access to long-term memory." A recent meta-analysis comparing ecstasy users to polydrug-using controls on these four subcomponents found significant ecstasy-associated deficits in updating, attention shifting, and access to long-term memory.[69] Effect sizes were generally moderate for the three significant subcomponents, whereas the inhibition subcomponent was not significantly affected. Meta-analyses that examined aspects of cognitive function other than memory found significant impairment in attention and concentration, verbal comprehension, processing speed, and motor/psychomotor speed.[70,71] Together with the reviews of memory performance, these findings suggest that regular ecstasy users suffer from widespread problems across a wide range of cognitive domains.

Despite the positive findings from a number of different analyses, the literature on cognitive deficits in ecstasy users suffers from some of the same interpretive problems as the literature on mood changes. For example, Gouzoulis-Mayfrank and Daumann[19] discuss the issue that, even if ecstasy users are compared to drug users who do not consume ecstasy, the latter often have a more moderate pattern of drug consumption than the ecstasy-using group. Cannabis is particularly problematic in studies of cognitive function, given the evidence for significant cognitive deficits in heavy cannabis users.[72] Comorbidity of psychopathology with ecstasy use may additionally contribute to the cognitive impairment observed in some studies.[73] Finally, the typical use of cross-sectional studies again makes it impossible, in such cases, to ascertain whether cognitive differences between the ecstasy-using and control group(s) preceded or followed the onset of ecstasy use. Two prospective studies have addressed this issue by recruiting new ecstasy users, assessing their cognitive function at baseline, and then retesting the subjects from 1 to 3 years later.[74,75] Interestingly, in both cases, the users did not differ from controls at baseline but did exhibit significant deficits in immediate and delayed verbal recall memory. These findings point up the limitations inherent in cross-sectional studies in which baseline mood or cognitive function prior to the onset of ecstasy use is not known. Importantly, the results suggest that, at least for some ecstasy users, repeated exposure to the drug leads to later impairment in certain cognitive domains.

Longitudinal studies of up to 2 years in length have also asked whether cognitive function keeps declining with continued ecstasy use, and whether cessation of use leads to a recovery of cognitive function. In general, such studies have found neither further deterioration in users nor recovery of function in subjects who discontinued ecstasy use[76–78] (see Zakzanis and Campbell[79] for an exception to these findings). Because in these studies the ecstasy users already differed from controls at the time of initial testing, the results are difficult to interpret. There may have been preexisting cognitive differences that were unchanged by ecstasy use, or the typical use patterns of the subjects in the first three studies may have caused an asymptotic decline in cognitive performance that neither got worse over time nor recovered upon 2 years of abstinence.

Neurotoxicity

The abovementioned evidence for mood changes and neuropsychological deficits in ecstasy users raises the question of how MDMA might be acting within the brain to cause these effects. The answer given most often centers around numerous findings obtained from experimental animals, mainly rats and nonhuman primates (eg, squirrel monkeys), for a toxic effect of MDMA on the serotonergic system. The first evidence for MDMA neurotoxicity was published in the mid-1980s, and these and numerous follow-up studies showed that high doses of MDMA (or MDA) lead to a long-lasting depletion of 5-HT, reduced 5-HT uptake and SERT binding sites, and decreased activity of tryptophan hydroxylase in forebrain areas such as the neocortex, hippocampus, and striatum (see Green et al[33]). Time-course studies demonstrated a biphasic action of MDMA consisting of the initial 5-HT depletion discussed earlier, a short-term recovery of 5-HT levels seen at 1–2 days following dosing, and then a secondary, more long-lasting depletion measured at 1–2 weeks and beyond.[33] Histological examination of brain tissues from treated rats and monkeys consistently showed a persistent reduction in the density of axons immunoreactive for 5-HT or for SERT (Figure 1). Moreover, staining of brain tissues obtained at

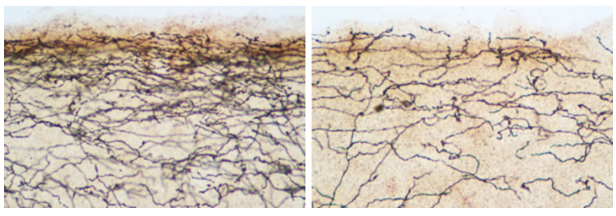

Figure 1 Photomicrograph of serotonin transporter-immunoreactive axons in the upper layers of occipital cortex of a control rat (**A**) compared to a 3,4-methylenedioxymethamphetamine (MDMA)-treated rat (**B**).
Notes: The animals received twice-daily injections of either saline or MDMA (10 mg/kg per injection) from the first to the fourth day of life and then were killed at 9 months of age (see Meyer et al[80] for experimental details). These results illustrate the long-lasting nature of MDMA-induced serotonergic deficits when the drug is administered early in development.

earlier time points revealed swollen axons and a positive reaction for silver staining, both of which are consistent with the notion of drug-induced axonal degeneration.[33,81]

The latter observations coupled with the apparent loss of serotonergic axons stained with immunohistochemical methods quickly gave rise to the hypothesis that high doses of MDMA cause a degeneration of rostral forebrain serotonergic fibers.[33,81] Nevertheless, other experimental approaches suggest that MDMA may not be causing long-lasting physical damage to the serotonergic fibers; rather, there is evidence that serotonergic neurons are responding to the drug by dramatically reducing expression of the genes for SERT and for tryptophan hydroxylase.[82,83] According to this downregulation hypothesis, long-lasting reductions in gene expression can explain both the persistent depletion of 5-HT (because tryptophan hydroxylase activity is too low to sustain normal levels of this neurotransmitter) and the seeming disappearance of fibers that are immunoreactive for 5-HT or SERT (ie, the "lost" fibers are still present but are difficult to visualize due to the substantial decrease in both 5-HT and SERT protein; see Biezonski and Meyer[83] for a discussion of the neurodegeneration versus downregulation hypothesis of MDMA neurotoxicity). Regardless of which hypothesis is proven correct, two important points should be noted. First, proponents of the neurodegeneration hypothesis focus on the apparent loss of serotonergic fibers in the forebrain; the cell bodies of the serotonergic neurons in the midbrain raphe nuclei appear to be spared (ie, MDMA is generally not thought to cause serotonergic nerve cell death). Second, even if forebrain serotonergic fibers are not physically damaged, as postulated by the downregulation hypothesis, long-lasting deficits in 5-HT levels and in SERT expression would still cause severe dysfunction of the serotonergic system. In this broader sense, MDMA is a serotonergic neurotoxin according to both hypotheses.

Long-term studies of MDMA-treated animals indicate that a reappearance of serotonergic fibers and 5-HT reuptake sites occurs over time; however, recovery may take many months following extremely high doses of the drug.[33] Moreover, some rats and monkeys exhibited abnormal fiber patterns after recovery had occurred,[33] and, in one highly cited paper from Hatzidimitriou et al, forebrain 5-HT-immunoreactive fibers were still abnormal in monkeys at 7 years after dosing.[84] Such findings are remarkable in showing the potential persistence of MDMA-related disturbances in serotonergic function.

Several factors influence the extent and the characteristics of MDMA-induced neurotoxicity. The first factor is dose of the drug. Not surprisingly, the greatest degree of 5-HT depletion is produced by high (and typically multiple) doses of MDMA (eg, four injections of 10 mg/kg given to rats at 2-hour intervals in a single day). However, serotonergic deficits have been reported following single doses at lower levels. A recent example comes from Mueller et al,[85] who reported that single oral doses as low as 5.7 mg/kg given to squirrel monkeys produced statistically significant reductions in 5-HT concentrations and SERT binding in many forebrain areas when measured 1 week after drug administration. Do and Schenk[86] also found that intravenous self-administration of a relatively low dose of MDMA (0.5–1.0 mg/kg per infusion) by rats eventually led to 30%–35% reductions in forebrain 5-HT, though the cumulative amount of drug taken by the animals over time was 315 mg/kg. Second, there are important species differences in MDMA neurotoxicity. For example, in laboratory mice, MDMA exerts much greater deleterious effects on the dopamine system than on the serotonergic system.[87] Whereas rats do exhibit some dopaminergic effects at high MDMA doses, there is relatively little actual depletion of dopamine compared to that found in mice.[87,88] The reason for this species difference has not yet been determined. Third, ambient temperature can modulate the extent of MDMA-induced neurotoxicity. As mentioned earlier, at the typical temperatures found in a laboratory animal colony room, a human residence, or a dance club, MDMA elevates core body (and brain) temperature. The significance of this hyperthermic effect can be seen by the fact that, in rats maintained in a slightly cooler environment, MDMA administration led to a hypothermic instead of a hyperthermic response, and the hypothermic animals failed to exhibit reductions in brain 5-HT.[89] Finally, prior exposure to low-to-moderate doses of MDMA can blunt or even prevent the neurotoxic effects of a subsequent high-dose treatment regimen.[90,91] It is not yet known whether this effect, which has been termed "MDMA preconditioning," applies to human recreational ecstasy users.

Substantial effort has been devoted to elucidating the cellular and molecular mechanisms of MDMA neurotoxicity. One of the important findings to emerge from this work is that MDMA must be administered systemically for neurotoxicity to occur. That is, microinjection of the drug directly into the brain fails to produce 5-HT depletion despite causing acute release of 5-HT.[92] This finding has been interpreted by some researchers to mean that MDMA must be subjected to peripheral metabolism (eg, in the liver) to produce neurotoxicity.[93,94] Consistent with that view, neurotoxic metabolites of MDMA have been detected in rat brain and in human urine after

MDMA ingestion.[93,94] Other studies, however, do not support the neurotoxic metabolite hypothesis.[95,96] Regardless of the exact nature of the toxic agent, it is believed that this substance is carried into the serotonergic neurons by way of the 5-HT uptake system, because blockade of SERT with an SSRI attenuates or even blocks MDMA-induced neurotoxicity.[97] Once inside the serotonergic neurons, the toxic agent is thought to exert its effects by increasing the formation of oxygen-containing free radicals (ie, reactive oxygen species [ROS]), thereby producing oxidative stress on the cells. The central concept that MDMA-induced neurotoxicity is mediated by ROS is supported by studies demonstrating the formation of such species within the brains of MDMA-treated animals and the ability of antioxidants and free radical scavengers to block the drug's neurotoxic effects.[98,99] An alternate neurotoxicity model hypothesizes that DA levels are increased within the serotonergic neurons due to a combination of direct DA uptake via SERT and uptake of tyrosine with subsequent conversion to the DA precursor dihydroxyphenylalanine (DOPA) and then to DA.[98,99] According to this model, metabolism of the abnormally accumulated DA by monoamine oxidase B (MAO-B) within the serotonergic cells generates hydrogen peroxide, which can then undergo further chemical reactions to produce ROS and oxidative stress. On the other hand, studies by Yuan et al[100] have yielded evidence against the DA hypothesis. To summarize, oxidative stress is likely to play a key role in MDMA-induced neurotoxicity; however, the cellular and molecular events that lead to ROS formation are not yet fully understood.

Of critical importance is whether repeated use of ecstasy (or even a single dose) exerts neurotoxic effects in the human brain. Some investigators have questioned the relevance of animal (particularly rat) studies of MDMA neurotoxicity because the doses typically administered to the animals are much higher than those taken by most recreational ecstasy users and because of important differences in MDMA metabolism between rodents and humans.[101–103] The latter issue limits the potential accuracy of using interspecies dose scaling to translate rodent MDMA doses to the amounts estimated to be consumed by recreational ecstasy users. On the other hand, a combination of biochemical and neuroimaging findings from the human ecstasy literature support the contention that "heavy" users may suffer from serotonergic deficits as well as other neurobiological abnormalities. Early studies found reduced levels of 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid of ecstasy users as well as blunted hormonal responses to various serotonergic drugs.[33] More recently, Kish et al[104,105] reported on a single case study of a 26-year-old man who used extremely large amounts of ecstasy (along with some cocaine and heroin) for several years before dying of an apparent drug overdose. Biochemical analyses of postmortem brain tissues revealed massive reductions in 5-HT and 5-HIAA levels in both the cortex and striatum compared to control tissues. These changes were accompanied by substantial decreases in SERT and tryptophan hydroxylase protein levels, which are further indications of serotonergic neurotoxicity in this subject.

In addition to the important information gleaned from cerebrospinal fluid and postmortem tissue analyses, researchers have made extensive use of modern neuroimaging methods (including positron emission tomography [PET], single photon emission computed tomography [SPECT], magnetic resonance imaging [MRI], diffusion tensor imaging [DTI], and magnetic resonance spectroscopy [MRS]) to probe markers of the serotonergic system along with other markers of brain structure, function, and chemistry. Such studies have consistently shown that SERT binding in various cortical as well as subcortical areas is significantly reduced in ecstasy/polydrug users compared to matched controls.[78,106–111] This effect could reflect either loss of forebrain serotonergic axons (as proposed by the neurodegeneration hypothesis of MDMA neurotoxicity in experimental animals[81]) or an MDMA-induced downregulation of SERT expression by the serotonergic neurons (as proposed by Biezonski and Meyer[82,83]). Some (though not all) of these studies found an inverse relationship between SERT binding and amount of ecstasy consumed, and some also found evidence for recovery of binding following abstinence from the drug. A second common finding concerns changes in cortical 5-HT_2 receptor binding by PET or SPECT imaging. Binding was typically found to be significantly upregulated in ecstasy users,[106,107,109,111,112] although a few studies found a downregulation instead.[106–109] Considering the typical regulation of G protein-coupled receptors (like the 5-HT_{2A} receptor) found in animal studies, it is possible that initial ecstasy use causes a receptor downregulation due to excessive 5-HT release, whereas the 5-HT depletion thought to occur with chronic heavy ecstasy use leads to a compensatory receptor upregulation. Further studies are needed to substantiate this hypothesis. Importantly, there may be a causal relationship between the mood and cognitive changes observed in heavy ecstasy users and the dysregulated serotonergic transmission implied by the above mentioned 5-HT depletion and altered SERT and 5-HT_{2A} receptor expression, as well as potentially other serotonergic effects yet to be identified.

Such a relationship has been proposed by Parrott[113] and other investigators[106,107,109] and is summarized in Table 2.

The use of structural and functional MRI, DTI, and MRS has revealed additional differences between ecstasy users and control subjects under some conditions. Although the results of this work cannot be detailed here due to space limitations, interested readers are referred to the appropriate references.[106,107,109,110,114–117]

Because animal studies of MDMA neurotoxicity have typically used large and/or repeated drug doses, we may ask whether one or a few modest doses of ecstasy are capable of exerting neurotoxic effects in users. This question has been addressed by several prospective studies of new ecstasy users participating in the Netherlands XTC Toxicity (NeXT) study. The results thus far have failed to show any serotonergic deficits in these low-dose users; however, other abnormalities were found related to brain vasculature and white matter structure.[114,115] Thus, the jury is still out on whether damaging effects can be produced by consuming even a few ecstasy tablets.

Morbidity and mortality

MDMA toxicity is not limited to the brain. This compound can also produce serious adverse effects on the heart and cardiovascular system, immune system, liver, and kidneys.[118–122] Most notably, case reports have identified instances of severe morbidity and even death following a single session of ecstasy use. For example, Kahn et al[123] described three cases of intracranial hemorrhage that were likely related to the consumption of "Molly," a form of ecstasy marketed as highly purified MDMA without common adulterants. Even more striking are recent reports of severe morbidity and several fatalities stemming from ecstasy consumption at raves in San Francisco and Los Angeles, CA, USA.[124,125] In the San Francisco event, 12 patients were admitted to area hospitals with a variety of symptoms, including hyperthermia (up to 43°C, which is equivalent to 109°F), tachycardia, acute kidney injury, hypotension, acidosis, disseminated intravascular coagulation (formation of blood clots throughout the body), rhabdomyolysis (muscle breakdown), seizures, and altered mental state. Two of the patients died, and four others had persisting neurologic, musculoskeletal, or kidney problems.[124] In the Los Angeles event, 18 individuals with confirmed use of ecstasy at the rave sought help at area hospitals. The presenting symptoms in this case were generally not as severe as those in San Francisco, although three patients were hospitalized (one requiring intensive care) and one patient later died at home after consuming multiple substances both during and after the event.[125] Other studies have documented ecstasy-related fatalities in the US, UK, and elsewhere.[126,127]

Table 2 Selected cognitive, psychomotor, and psychobiological changes in ecstasy users that may be related to serotonergic dysfunction

Cognitive deficits
Retrospective memory impairment
Prospective memory impairment
Working memory impairment
Deficits in complex cognition
Psychomotor deficits
Increased occurrence of twitches and tremors
Reduced motor speed
Impaired dexterity
Psychobiological changes
Sleep disturbances
Increased pain perception and reduced pain tolerance
Disturbed appetite and eating behavior
Depressed mood
Heightened anxiety
Increased aggressiveness

Note: Adapted from *Neurosci Biobehav Rev*, 37, Parrott AC, MDMA, serotonergic neurotoxicity, and the diverse functional deficits of recreational 'Ecstasy' users, 1466–1484, copyright (2013), with permission from Elsevier.[113]

As in the case of animals, high (often multiple) doses of MDMA are almost always responsible for acute toxic reactions in humans. Drug-induced hyperthermia that is exacerbated by vigorous exercise in a hot rave environment plays a central role in these toxic effects. However, an overdose-like reaction can occur following a single ingestion in susceptible individuals who are genetically deficient in their ability to metabolize MDMA.[128] A constellation of symptoms known as the "serotonin syndrome" (which constitutes many of the symptoms observed in the San Francisco rave patients) may also occur when MDMA is consumed along with other drugs (including certain prescription medications) that enhance serotonergic transmission by stimulating 5-HT release, blocking 5-HT reuptake, and/or inhibiting 5-HT metabolism.[129] Finally, polydrug users may suffer severe morbidity or mortality due to toxic combinations of MDMA with other abused substances, particularly stimulants such as cocaine, amphetamine, or methamphetamine. Taken together, these observations highlight the risks of ecstasy consumption, which are greatest in the case of vulnerable individuals and when the substance is taken at high drug doses, in a hot environment, and/or in combination with various other prescription or illicit drugs.

Dependence on MDMA/ecstasy

Characteristics and prevalence of dependence

Users often consider ecstasy to lack the potential for dependence or addiction, but this is not the case. As reviewed

by Degenhardt et al,[130] evidence for dependence in ecstasy users comes from a combination of published case studies and assessments of user symptoms based on the Composite International Diagnostic Interview, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV, and/or the Severity of Dependence Scale. Users frequently endorsed a variety of dependence-related symptoms including the development of tolerance, increasing amounts of ecstasy use, significant time spent using and/or recovering from ecstasy use, difficulty reducing or stopping ecstasy use despite the recognition of drug-related problems, reduced time spent in other activities, higher levels of risky behavior, and withdrawal symptoms accompanied by drug craving. Importantly, DSM-IV criteria for MDMA abuse and dependence showed substantial test/retest reliability in a study of 593 ecstasy users recruited from St Louis, MO, USA; Miami, FL, USA; and Sydney, NSW, Australia.[131] These results strengthen the argument favoring the existence of an MDMA/ecstasy dependence syndrome.

Two structural analyses have proposed that ecstasy dependence is bifactorial, consisting of a compulsive use factor and an escalating use factor.[132,133] The compulsive use factor pertains to symptoms like continuing ecstasy use despite problems, difficulty stopping use, excessive time associated with use along with declining time spent in other activities, and withdrawal symptoms. The escalating use factor pertains to the development of tolerance and an increase in the amount of ecstasy used. It should be noted that escalation of ecstasy use may include not only the stacking and boosting patterns mentioned earlier, but also progression to a bingeing pattern of consumption. Interestingly, the bifactorial nature of ecstasy dependence is similar to that postulated for hallucinogens, whereas DSM-IV criteria for dependence on alcohol, cocaine, opioids, and cannabis are unifactorial.[130] This difference may be related to the strong serotonergic aspects of both MDMA and hallucinogen action, although such a hypothesis must be qualified in light of animal studies showing that 5-HT release may actually blunt, rather than enhance, the reinforcing effects of MDMA.[134]

Despite having a compulsive use factor, ecstasy dependence is not typically as profound as the dependence that can occur in heavy users of alcohol, cocaine, methamphetamine, opioids, and tobacco. Withdrawal symptoms do not include significant physical symptoms as is the case with some of the abovementioned substances.[130,132] Moreover, a prospective longitudinal study of 2,446 ecstasy/stimulant/hallucinogen users (participants reporting primarily use of ecstasy but sometimes other stimulants or hallucinogens as well) in Germany found both a low prevalence of initial abuse or dependence as well as a substantial decline in both categories at 12-month follow-up.[135] Although these findings may not apply to all groups of ecstasy users, they suggest that ecstasy abuse and dependence may be transient phenomena in many, if not most, instances. Taken together, the features of dependence in human ecstasy users fit well with the results from animal self-administration studies showing that, although rodents and nonhuman primates will self-administer MDMA intravenously, they do so much less avidly than in the case of cocaine, amphetamine, methamphetamine, or opioids such as heroin or morphine.[136,137]

Treatment

Based on the available literature, it appears that relatively few ecstasy users seek professional treatment for problems with abuse or dependence.[130] For those that do seek help, typical treatment approaches include individual and group counseling, cognitive behavioral therapy, and relapse prevention techniques.[138] To the author's knowledge, there are no published data at this time regarding treatment outcomes for ecstasy-dependent patients, including rates of relapse after the completion of therapy. There are also no currently approved drugs for the treatment of ecstasy dependence. However, users who present with signs of MDMA overdose must first be treated for the symptoms of acute drug intoxication, which may entail the administration of appropriate medications.[139]

Potential therapeutic applications of MDMA

As recounted earlier, the rediscovery of MDMA in the early 1970s led to the use of this substance as an adjunct to therapy by many psychiatrists and psychotherapists. According to Rosenbaum and Doblin,[140] approximately 500,000 doses of MDMA were taken within this context during the 1970s and early 1980s. Once MDMA was given a Schedule I designation, it was no longer legally possible to administer the substance for therapeutic purposes, although Greer and Tolbert[141] later published a description of the methods they developed for using MDMA in a therapeutic setting.

Interestingly, research on the potential therapeutic benefits of MDMA has reemerged, largely due to the efforts of the Multidisciplinary Association for Psychedelic Studies (MAPS), a non-profit, Boston-based organization whose mission is to help people "benefit from the careful uses of psychedelics and marijuana" (http://www.maps.org/). MAPS is financially supporting research on MDMA therapeutics in a number of different countries, and several publications have

already appeared reporting the results of MDMA-assisted psychotherapy in patients with treatment-resistant posttraumatic stress disorder (PTSD). The first major study of this kind was conducted on 20 adult patients in South Carolina, USA who met DSM-IV criteria for crime- or war-related PTSD and who had exhibited treatment-resistant symptoms with a minimum score of 50 on the Clinician Administered PTSD Scale (CAPS).[142] The study consisted of two phases: an initial double-blind, placebo-controlled phase in which all patients received psychotherapy accompanied by either MDMA or placebo, followed by an open-label, cross-over phase in which patients assigned to the placebo arm were given the opportunity to receive additional therapy that included MDMA administration. At 3–5 days following the second of two treatment sessions, the MDMA group showed an average reduction of 49.9 points on their CAPS score compared to baseline, whereas the placebo group showed an average reduction of only 12.8 points on their CAPS score. A similar degree of symptom reduction occurred in the placebo-treated patients who were given MDMA in the cross-over phase of the study. Moreover, a prospective follow-up study of the same patients examined from 17–74 months after the final MDMA session found strong evidence for persisting recovery.[143] A recently published Swiss study also showed an improvement in the CAPS scores of treatment-resistant PTSD patients given MDMA-assisted psychotherapy, although the results did not quite reach statistical significance, possibly because the study was severely underpowered.[144]

These initial findings provide hope that the addition of a few low doses of MDMA (ie, around 2 mg/kg or less) to established psychotherapeutic approaches may be beneficial to patients with chronic treatment-resistant PTSD. Indeed, Johansen and Krebs[145] have offered a summary of potential neurobiological mechanisms that could underlie such an effect of MDMA. Other potential applications of MDMA-assisted therapy include depression and substance abuse.[146,147] Nonetheless, the notion of using MDMA therapeutically must still be approached with caution.[148] Even though no major adverse events have thus far been reported in PTSD patients who received MDMA, we cannot rule out the possibility of subtle long-term neurological consequences that might require extensive neuropsychological testing and/or brain imaging to detect. Virtually all medications involve some degree of risk, as a result of which, standard medical practice requires that the benefit obtained from a drug significantly outweighs the risk to the patient. It seems reasonable that the future of MDMA-assisted psychotherapy be held to the same standard, no more and no less.

Summary and conclusion

Ecstasy (MDMA) is a widely used recreational drug for the positive effects it engenders. Although it is not yet clear whether a few MDMA doses are harmful to the user, heavier use has been associated with significant mood changes and cognitive deficits. Another major concern is possible serotonergic dysfunction produced by repeated and/or high doses of the drug. MDMA overdose can be dangerous, even fatal. Moreover, long-term use, particularly with dose escalation, can lead to dependence on the drug. Yet, recent studies have revealed that MDMA-assisted psychotherapy may be beneficial to patients with chronic, treatment-resistant PTSD. Based on current evidence, therefore, the status of this intriguing compound seems best characterized as somewhere between the extremes put forth by its most vociferous detractors versus its most ardent supporters.

Disclosure

The author reports no conflicts of interest in this work.

References

1. Benzenhöfer U, Passie T. Rediscovering MDMA (ecstasy): the role of the American chemist Alexander T. Shulgin. *Addiction.* 2010;105(8):1355–1361.
2. Freudenmann RW, Oxler F, Bernschneider-Reif S. The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents. *Addiction*. 2006;101(9):1241–1245.
3. Pentney AR. An exploration of the history and controversies surrounding MDMA and MDA. *J Psychoactive Drugs.* 2001;33(3):213–221.
4. Hardman HF, Haavik CO, Seevers MH. Relationship of the structure of mescaline and seven analogs to toxicity and behavior of five species of laboratory animals. *Toxicol Appl Pharmacol.* 1973;25(2):299–309.
5. Shulgin AT, Nichols DE. Characterization of three new psychotomimetics. In: Stillman RC, Willette RE, editors. *The Psychopharmacology of Hallucinogens*. New York: Pergamon Press; 1978:74–83.
6. Naranjo C, Shulgin AT, Sargent T. Evaluation of 3,4-methylenedioxyamphetamine (MDA) as an adjunct to psychotherapy. *Med Pharmacol Exp.* 1967;17(4):359–364.
7. Tanner-Smith EE. Pharmacological content of tablets sold as "ecstasy": results from an on-line testing service. *Drug Alcohol Depend.* 2006;83(3):247–254.
8. Vogels N, Brunt TM, Rigter S, van Dijk P, Vervaeke H, Niesink RJ. Content of ecstasy in The Netherlands: 1993–2008. *Addiction.* 2009;104(12):2057–2066.
9. Wood DM, Stribley V, Dargan PI, Davies S, Holt DW, Ramsey J. Variability in the 3,4-methylenedioxymethamphetamine content of 'ecstasy' tablets in the UK. *Emerg Med J.* 2011;28(9):764–765.
10. United Nations Office on Drugs and Crime, Global SMART Programme. *Amphetamines and Ecstasy: 2011 Global ATS Assessment*. Vienna: United Nations Publication; 2011. Available from: http://www.unodc.org/documents/ATS/ATS_Global_Assessment_2011.pdf. Accessed April 27, 2013.
11. Substance Abuse and Mental Health Services Administration. *Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings*. NSDUH Series H-44, HHS Publication No (SMA) 12-4713. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2012.

12. Sumnall HR, Cole JC, Jerome L. The varieties of ecstatic experience: an exploration of the subjective experiences of ecstasy. *J Psychopharmacol.* 2006;20(5):670–682.
13. EcstasyData.org [homepage on the Internet]. Available from: http://www.ecstasydata.org. Accessed April 28, 2013.
14. Scholey AB, Parrott AC, Buchanan T, Heffernan TM, Ling J, Rodgers J. Increased intensity of Ecstasy and polydrug usage in the more experienced recreational Ecstasy/MDMA users: a WWW study. *Addict Behav.* 2004;29(4):743–752.
15. Parrott AC. Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy. *J Psychopharmacol.* 2005;19(1):71–83.
16. Rodgers J, Buchanan T, Pearson C, et al. Differential experiences of the psychobiological sequelae of ecstasy use: quantitative and qualitative data from an internet study. *J Psychopharmacol.* 2006;20(3):437–446.
17. Soar K, Turner JJ, Parrott AC. Problematic versus non-problematic ecstasy/MDMA use: the influence of drug usage patterns and pre-existing psychiatric factors. *J Psychopharmacol.* 2006;20(3):417–424.
18. Wish ED, Fitzelle DB, O'Grady KE, Hsu MH, Arria AM. Evidence for significant polydrug use among ecstasy-using college students. *J Am Coll Health.* 2006;55(2):99–104.
19. Gouzoulis-Mayfrank E, Daumann J. The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview. *J Psychopharmacol.* 2006;20(2):188–193.
20. Wu LT, Parrott AC, Ringwalt CL, Yang C, Blazer DG. The variety of ecstasy/MDMA users: results from the National Epidemiologic Survey on alcohol and related conditions. *Am J Addict.* 2009;18(6):452–461.
21. Brunt TM, Koeter MW, Niesink RJM, van den Brink W. Linking the pharmacological content of ecstasy tablets to the subjective experiences of drug users. *Psychopharmacology (Berl).* 2012;220(4):751–762.
22. Peroutka SJ, Newman H, Harris H. Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology.* 1988;1(4):273–277.
23. Nichols DE. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. *J Psychoactive Drugs.* 1986;18(4):305–313.
24. Vollenweider FX, Liechti ME, Gamma A, Greer G, Geyer M. Acute psychological and neurophysiological effects of MDMA in humans. *J Psychoactive Drugs*. 2002;34(2):171–184.
25. Dumont GJ, Verkes RJ. A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers. *J Psychopharmacol.* 2006;20(2):176–187.
26. Parrott AC. MDMA and temperature: a review of the thermal effects of 'Ecstasy' in humans. *Drug Alcohol Depend.* 2012;121(1–2):1–9.
27. Curran HV, Travill RA. Mood and cognitive effects of ±3,4--methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. *Addiction.* 1997;92(7):821–831.
28. Parrott AC, Lasky J. Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology (Berl)*. 1998;139(3):261–268.
29. Parrott AC. Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. *Pharmacol Biochem Behav.* 2002;71(4):837–844.
30. Verheyden SL, Hadfield J, Calin T, Curran HV. Sub-acute effects of MDMA (±3,4-methylenedioxymethamphetamine, "ecstasy") on mood: evidence of gender differences. *Psychopharmacology (Berl)*. 2002;161(1):23–31.
31. Verheyden SL, Henry JA, Curran HV. Acute, sub-acute and long-term subjective consequences of 'ecstasy' (MDMA) consumption in 430 regular users. *Hum Psychopharmacol*. 2003;18(7):507–517.
32. Kuypers KP, Wingen M, Ramaekers JG. Memory and mood during the night and in the morning after repeated evening doses of MDMA. *J Psychopharmacol.* 2008;22(8):895–903.
33. Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). *Pharmacol Rev.* 2003;55(3):463–508.
34. Gudelsky GA, Yamamoto BK. Actions of 3,4-methylenedioxymethamphetamine (MDMA) on cerebral dopaminergic, serotonergic and cholinergic neurons. *Pharmacol Biochem Behav.* 2008;90(2):198–207.
35. Han DD, Gu HH. Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. *BMC Pharmacol.* 2006;6:6.
36. Verrico CD, Miller GM, Madras BK. MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced neurotoxicity and treatment. *Psychopharmacology (Berl).* 2007;189(4):489–503.
37. Di Chiara G, Bassareo V, Fenu S, et al. Dopamine and drug addiction: the nucleus accumbens shell connection. *Neuropharmacology.* 2004;47 Suppl 1:227–241.
38. Liechti ME, Vollenweider FX. Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. *Hum Psychopharmacol.* 2001;16(8):589–598.
39. Tancer M, Johanson CE. The effects of fluoxetine on the subjective and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology (Berl)*. 2007;189(4):565–573.
40. Farré M, Abanades S, Roset PN, et al. Pharmacological interaction between 3,4-methylenedioxymethamphetamine (Ecstasy) and paroxetine: pharmacological effects and pharmacokinetics. *J Pharmacol Exp Ther.* 2007;323(3):954–962.
41. Hysek CM, Simmler LD, Ineichen M, et al. The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA ("Ecstasy") in humans. *Clin Pharmacol Ther*. 2011;90(2):246–255.
42. Hysek CM, Simmler LD, Nicola VG, et al. Duloxetine inhibits effects of MDMA ("ecstasy") in vitro and in humans in a randomized placebo-controlled laboratory study. *PLoS One*. 2012;7(5):e36476.
43. Hysek CM, Brugger R, Simmler LD, et al. Effects of the α_2-adrenergic agonist clonidine on the pharmacodynamics and pharmacokinetics of 3,4-methylenedioxymethamphetamine in healthy volunteers. *J Pharmacol Exp Ther*. 2012;340(2):286–294.
44. Piercey MF, Lum JT, Palmer JR. Effects of MDMA ('ecstasy') on firing rates of serotonergic, dopaminergic, and noradrenergic neurons in the rat. *Brain Res.* 1990;526(2):203–206.
45. Hasler F, Studerus E, Lindner K, Ludewig S, Vollenweider FX. Investigation of serotonin-1A receptor function in the human psychopharmacology of MDMA. *J Psychopharmacol.* 2009;23(8):923–935.
46. van Wel JH, Kuypers KP, Theunissen EL, Bosker WM, Bakker K, Ramaekers JG. Effects of acute MDMA intoxication on mood and impulsivity: Role of the 5-HT2 and 5-HT1 receptors. *PLoS One.* 2012;7(7):e40187.
47. Halberstadt AL, Nichols DE. Serotonin and serotonin receptors in hallucinogen action. In: Müller CP, Jacobs BL, editors. *Handbook of the Behavioral Neurobiology of Serotonin*. London: Academic Press; 2010:621–636.
48. Docherty JR, Green AR. The role of monoamines in the changes in body temperature induced by 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and its derivatives. *Br J Pharmacol.* 2010;160(5):1029–1044.
49. Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS. A role for oxytocin and 5-HT(1A) receptors in the prosocial effects of 3,4-methylenedioxymethamphetamine ("ecstasy"). *Neuroscience.* 2007;146(2):509–514.
50. Dumont GJ, Sweep FC, van der Steen R, et al. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci.* 2009;4(4):359–366.
51. Churchland PS, Winkielman P. Modulating social behavior with oxytocin: how does it work? What does it mean? *Horm Behav.* 2012;61(3):392–399.
52. Farré M, de la Torre R, Mathúna BO, et al. Repeated doses administration of MDMA in humans: pharmacological effects and pharmacokinetics. *Psychopharmacology (Berl)*. 2004;173(3–4):364–375.

53. Peiró AM, Farré M, Roset PN, et al. Human pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) after repeated doses taken 2 h apart. *Psychopharmacology (Berl)*. 2013;225(4): 883–893.
54. Parrott AC, Buchanan T, Scholey AB, Heffernan T, Ling J, Rodgers J. Ecstasy/MDMA attributed problems reported by novice, moderate and heavy recreational users. *Hum Psychopharmacol.* 2002;17(6): 309–312.
55. Guillot C. Is recreational Ecstasy (MDMA) use associated with higher levels of depressive symptoms? *J Psychoactive Drugs.* 2007;39(1): 31–39.
56. Sumnall HR, Cole JC. Self-reported depressive symptomatology in community samples of polysubstance misusers who report Ecstasy use: a meta-analysis. *J Psychopharmacol.* 2005;19(1):84–92.
57. Bedi G, Van Dam NT, Redman J. Ecstasy (MDMA) and high prevalence psychiatric symptomatology: somatic anxiety symptoms are associated with polydrug, not ecstasy, use. *J Psychopharmacol.* 2010;24(2): 233–240.
58. Daumann J, Hensen G, Thimm B, Rezk M, Till B, Gouzoulis-Mayfrank E. Self-reported psychopathological symptoms in recreational ecstasy (MDMA) users are mainly associated with regular cannabis use: further evidence from a combined cross-sectional/longitudinal investigation. *Psychopharmacology (Berl)*. 2004;173(3–4):398–404.
59. Matthews AJ, Bruno R. An investigation of factors associated with depressive symptoms among a sample of regular ecstasy users. *Neuropsychobiology*. 2010;61(4):215–222.
60. Scott RM, Hides L, Allen JS, Burke R, Lubman DI. Depressive and anxiety symptomatology in ecstasy users: the relative contribution of genes, trauma, life stress and drug use. *Psychopharmacology (Berl)*. 2010;209(1):25–36.
61. Huizink AC, Ferdinand RF, van der Ende J, Verhulst FC. Symptoms of anxiety and depression in childhood and use of MDMA: prospective, population based study. *BMJ.* 2006;332(7545):825–828
62. Falck RS, Carlson RG, Wang J, Siegal HA. Psychiatric disorders and their correlates among young adult MDMA users in Ohio. *J Psychoactive Drugs.* 2006;38(1):19–29.
63. Lieb R, Schuetz CG, Pfister H, von Sydow K, Wittchen H-U. Mental disorders in ecstasy users: a prospective-longitudinal investigation. *Drug Alcohol Depend.* 2002;68(2):195–207.
64. Laws KR, Kokkalis J. Ecstasy (MDMA) and memory function: a meta-analytic update. *Hum Psychopharmacol.* 2007;22(6):381–388.
65. Nulsen CE, Fox AM, Hammond GR. Differential effects of ecstasy on short-term and working memory: a meta-analysis. *Neuropsychol Rev.* 2010;20(1):21–32.
66. Murphy PN, Bruno R, Ryland I, et al. The effects of 'ecstasy' (MDMA) on visuospatial memory performance: findings from a systematic review with meta-analyses. *Hum Psychopharmacol Clin Exp.* 2012;27(2):113–138.
67. Brown J, McKone E, Ward J. Deficits in long-term memory in ecstasy users are related to cognitive complexity of the task. *Psychopharmacology (Berl).* 2010;209(1):51–67.
68. Fisk JE, Sharp CA. Age-related impairment in executive functioning: updating, inhibition, shifting, and access. *J Clin Exp Neuropsychol.* 2004;26(7):874–890.
69. Verbaten MN. Deterioration of executive functioning in chronic ecstasy users; evidence for multiple drugs effects. *Curr Drug Abuse Rev.* 2010;3(3):129–138.
70. Kalechstein AD, De La Garza R 2nd, Mahoney JJ 3rd, Fantegrossi WE, Newton TF. MDMA use and neurocognition: a meta-analytic review. *Psychopharmacology (Berl)*. 2007;189(4):531–537.
71. Zakzanis KK, Campbell Z, Jovanovski D. The neuropsychology of ecstasy (MDMA) use: a quantitative review. *Hum Psychopharmacol.* 2007;22(7):427–435.
72. Solowij N, Battisti R. The chronic effects of cannabis on memory in humans: a review. *Curr Drug Abuse Rev.* 2008;1(1):81–98.
73. Krebs TS, Johansen PØ, Jerome L, Halpern JH. Importance of psychiatric confounding in non-randomized studies of heavy ecstasy users. *Psychol Med.* 2009;39(5):876–878.
74. Shilt T, de Win MM, Koeter M, et al. Cognition in novice ecstasy users with minimal exposure to other drugs: a prospective cohort study. *Arch Gen Psychiatry.* 2007;64(6):728–736.
75. Wagner D, Becker B, Koester P, Gouzoulis-Mayfrank E, Daumann J. A prospective study of learning, memory, and executive function in new MDMA users. *Addiction*. 2012;108(1):136–145.
76. de Sola Llopis S, Miguelez-Pan M, Peña-Casanova J, et al. Cognitive performance in recreational ecstasy polydrug users: a two-year follow-up study. *J Psychopharmacol.* 2008;22(5):498–510.
77. Gouzoulis-Mayfrank E, Fischermann T, Rezk M, Thimm B, Hensen G, Daumann J. Memory performance in polyvalent MDMA (ecstasy) users who continue or discontinue MDMA use. *Drug Alcohol Depend.* 2005;78(3):317–323.
78. Thomasius R, Zapletalova P, Petersen K, et al. Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective. *J Psychopharmacol.* 2006;20(2): 211–225.
79. Zakzanis KK, Campbell Z. Memory impairment in now abstinent MDMA users and continued users: a longitudinal follow-up. *Neurology*. 2006;66(5):740–741.
80. Meyer JS, Grande M, Johnson K, Ali SF. Neurotoxic effects of MDMA ("ecstasy") administration to neonatal rats. *Int J Dev Neurosci.* 2004;22(5–6):261–271.
81. Ricaurte GA, Yuan J, McCann UD. (±)3,4-Methylenedioxymethamphetamine ('Ecstasy')-induced serotonin neurotoxicity: studies in animals. *Neuropsychobiology*. 2000;42(1):5–10.
82. Biezonski DK, Meyer JS. Effects of 3,4-methylenedioxymethamphe tamine (MDMA) on serotonin transporter and vesicular monoamine transporter 2 protein and gene expression in rats: implications for MDMA neurotoxicity. *J Neurochem.* 2010;112(4):951–962.
83. Biezonski DK, Meyer JS. The nature of 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonergic dysfunction: evidence for and against the neurodegeneration hypothesis. *Curr Neuropharmacol.* 2011;9(1):84–90.
84. Hatzidimitriou G, McCann UD, Ricaurte GA. Altered serotonin innervation patterns in the forebrain of monkeys treated with (±)3,4-methylenedioxymethamphetamine seven years previously: Factors influencing abnormal recovery. *J Neurosci.* 1999;19(12): 5096–5107.
85. Mueller M, Yuan J, McCann UD, Hatzidimitriou G, Ricaurte GA. Single oral doses of (±) 3,4-methylenedioxymethamphetamine ('Ecstasy') produce lasting serotonergic deficits in non-human primates: relationship to plasma drug and metabolite concentrations. *Int J Neuropsychopharmacol.* 2013;16(4):791–801.
86. Do J, Schenk S. Self-administered MDMA produces dose- and time-dependent serotonin deficits in the rat brain. *Addict Biol.* 2013;18(3): 441–447.
87. Colado MI, O'Shea E, Green AR. Acute and long-term effects of MDMA on cerebral dopamine biochemistry and function. *Psychopharmacology (Berl)*. 2004;173(3–4):249–263.
88. Biezonski DK, Piper BJ, Shinday NM, Kim PJ, Ali SF, Meyer JS. Effects of a short-course MDMA binge on dopamine transporter binding and on levels of dopamine and its metabolites in adult male rats. *Eur J Pharmacol.* 2013;701(1–3):176–180.
89. Malberg JE, Seiden LS. Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat. *J Neurosci.* 1998;18(13):5086–5094.
90. Bhide NS, Lipton JW, Cunningham JI, Yamamoto BK, Gudelsky GA. Repeated exposure to MDMA provides neuroprotection against subsequent MDMA-induced serotonin depletion in brain. *Brain Res.* 2009;1286:32–41.
91. Piper BJ, Ali SF, Daniels LG, Meyer JS. Repeated intermittent methylenedioxymethamphetamine exposure protects against the behavioral and neurotoxic, but not hyperthermic, effects of an MDMA binge in adult rats. *Synapse*. 2010;64(6):421–431.
92. Esteban B, O'Shea E, Camarero J, Sanchez V, Green AR, Colado MI. 3,4-Methylenedioxymethamphetamine induces monoamine release, but not toxicity, when administered centrally at a concentration occurring following a peripherally injected neurotoxic dose. *Psychopharmacology (Berl).* 2001;154(3):251–260.

93. Erives GV, Lau SS, Monks TJ. Accumulation of neurotoxic thioether metabolites of 3,4-(±)-methylenedioxymethamphetamine in rat brain. *J Pharmacol Exp Ther.* 2008;324(1):284–292.
94. Perfetti X, O'Mathúna B, Pizarro N, et al. Neurotoxic thioether adducts of 3,4-methylenedioxymethamphetamine identified in human urine after ecstasy ingestion. *Drug Metab Dispos.* 2009;37(7):1448–1455.
95. Mueller M, Yuan J, Felim A, et al. Further studies on the role of metabolites in (±)-3,4-methylenedioxymethamphetamine-induced serotonergic neurotoxicity. *Drug Metab Dispos*. 2009;37(10): 2079–2086.
96. Neudörffer A, Mueller M, Martinez CM, et al. Synthesis and neurotoxicity profile of 2,4,5-trihydroxymethamphetamine and its 6-(N-acetylcystein-S-yl) conjugate. *Chem Res Toxicol.* 2011;24(6): 968–978.
97. Li IH, Huang WS, Shiue CY, et al. Study on the neuroprotective effect of fluoxetine against MDMA-induced neurotoxicity on the serotonin transporter in rat brain using micro-PET. *Neuroimage.* 2010;49(2): 1259–1270.
98. Capela, JP, Carmo H, Remião F, Bastos ML, Meisel A, Carvalho F. Molecular and cellular mechanisms of ecstasy-induced neurotoxicity: an overview. *Mol Neurobiol.* 2009;39(3):210–271.
99. Puerta E, Hervias I, Aguirre N. On the mechanisms underlying 3,4-methylenedioxymethamphetamine toxicity: the dilemma of the chicken and the egg. *Neuropsychobiology*. 2009;60(3–4):119–129.
100. Yuan J, Cord BJ, McCann UD, Callahan BT, Ricaurte GA. Effect of depleting vesicular and cytoplasmic dopamine on methylenedioxymethamphetamine neurotoxicity. *J Neurochem*. 2002;80(6): 960–969.
101. Baumann MH, Wang X, Rothman RB. 3,4-Methylenedioxymethamphetamine (MDMA) neurotoxicity in rats: a reappraisal of past and present findings. *Psychopharmacology (Berl)*. 2007;189(4):407–424.
102. de la Torre R, Farré M. Neurotoxicity of MDMA (ecstasy): the limitations of scaling from animals to humans. *Trends Pharmacol Sci.* 2004;25(10):505–508.
103. Green AR, King MV, Shortall SE, Fone KCF. Lost in translation: preclinical studies on 3,4-methylenedioxymethamphetamine provide information on mechanisms of action, but do not allow accurate prediction of adverse events in humans. *Br J Pharmacol.* 2012;166(5): 1523–1536.
104. Kish SJ, Fitzmaurice PS, Chang LJ, Furukawa Y, Tong J. Low striatal serotonin transporter protein in a human polydrug MDMA (ecstasy) user: a case study. *J Psychopharmacol.* 2010;24(2):281–284.
105. Kish SJ, Furukawa Y, Ang L, Vorce SP, Kalasinsky KS. Striatal serotonin is depleted in brain of a human MDMA (Ecstasy) user. *Neurology*. 2000;55(2):294–296.
106. Cowan RL. Neuroimaging research in human MDMA users: a review. *Psychopharmacology (Berl)*. 2007;189(4):539–556.
107. Cowan RL, Roberts DM, Joers JM. Neuroimaging in human MDMA (Ecstasy) users. A cortical model. *Ann N Y Acad Sci.* 2008;1139: 291–298.
108. Erritzoe D, Frokjaer VG, Holst KK, et al. In vivo imaging of cerebral serotonin transporter and serotonin(2A) receptor binding in 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") and hallucinogen users. *Arch Gen Psychiatry*. 2011;68(6): 562–576.
109. Gouzoulis-Mayfrank E, Daumann J. Neurotoxicity of drugs of abuse – the case of methylenedioxymethamphetamines (MDMA, ecstasy), and amphetamines. *Dialogues Clin Neurosci.* 2009;11(3):305–317.
110. Kish SJ, Lerch J, Furukawa Y, et al. Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[(11)C]DASB and structural brain imaging study. *Brain*. 2010;133(6):1779–1797.
111. Urban NB, Girgis RR, Talbot PS, et al. Sustained recreational use of ecstasy is associated with altered pre and postsynaptic markers of serotonin transmission in neocortical areas: a PET study with [^{11}C]DASB and [^{11}C]MDL 100907. *Neuropsychopharmacology*. 2012;37(6):1465–1473.
112. Di Iorio CR, Watkins TJ, Dietrich MS, et al. Evidence for chronically altered serotonin function in the cerebral cortex of female 3,4-meth ylenedioxymethamphetamine polydrug users. *Arch Gen Psychiatry*. 2012;69(4):399–409.
113. Parrott AC. MDMA, serotonergic neurotoxicity, and the diverse functional deficits of recreational 'Ecstasy' users. *Neurosci Biobehav Rev.* 2013;37(8):1466–1484.
114. de Win MM, Jager G, Booij J, et al. Sustained effects of ecstasy on the human brain: a prospective neuroimaging study in novel users. *Brain*. 2008;131(Pt 11):2936–2945.
115. de Win MM, Reneman L, Jager G, et al. A prospective cohort study on sustained effects of low-dose ecstasy use on the brain in new ecstasy users. *Neuropsychopharmacology*. 2007;32(2):458–470.
116. Jager G, de Win MM, Vervaeke HK, et al. Incidental use of ecstasy: no evidence for harmful effects on cognitive brain function in a prospective fMRI study. *Psychopharmacology (Berl)*. 2007;193(3):403–414.
117. Salomon RM, Karageorgiou J, Dietrich MS, et al. MDMA (Ecstasy) association with impaired fMRI BOLD thalamic coherence and functional connectivity. *Drug Alcohol Depend*. 2012;120(1–3): 41–47.
118. Baumann MH, Rothman RB. Neural and cardiac toxicities associated with 3,4-methylenedioxymethamphetamine (MDMA). *Int Rev Neurobiol.* 2009;88:257–296.
119. Shenouda SK, Carvalho F, Varner KJ. The cardiovascular and cardiac actions of ecstasy and its metabolites. *Curr Pharm Biotechnol.* 2010;11(5):470–475.
120. Boyle NT, Connor TJ. Methylenedioxymethamphetamine ('Ecstasy')-induced immunosuppression: a cause for concern? *Br J Pharmacol.* 2010;161(1):17–32.
121. Antolino-Lobo I, Meulenbelt J, van den Berg M, van Duursen MB. A mechanistic insight into 3,4-methylenedioxymethamphetamine ("ecstasy")-mediated hepatotoxicity. *Vet Q.* 2011;31(4):193–205.
122. Campbell GA, Rosner MH. The agony of ecstasy: MDMA (3,4-methylenedioxymethamphetamine) and the kidney. *Clin J Am Soc Nephrol.* 2008;3(6):1852–1860.
123. Kahn DE, Ferraro N, Benveniste RJ. 3 cases of primary intracranial hemorrhage associated with "Molly", a purified form of 3,4-methylenedioxymethamphetamine (MDMA). *J Neurol Sci*. 2012;323(1–2):257–260.
124. Armenian P, Mamantov TM, Tsutaoka BT, et al. Multiple MDMA (ecstasy) overdoses at a rave event: a case series. *J Intensive Care Med.* 2013;28(4):252–258.
125. Centers for Disease Control and Prevention (CDC). Ecstasy overdoses at a New Year's Eve rave – Los Angeles, California, 2010. *MMWR Morb Mortal Wkly Rep.* 2010;59(22):677–681.
126. Milroy CM. "Ecstasy" associated deaths: what is a fatal concentration? Analysis of a case series. *Forensic Sci Med Pathol.* 2011;7(3): 248–252.
127. Schifano F. A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities. *Psychopharmacology (Berl).* 2004;173(3–4):242–248.
128. Nadkarni GN, Hoskote SS, Piotrkowski J, Annapureddy N. Serotonin syndrome, disseminated intravascular coagulation, and hepatitis after a single ingestion of MDMA in an Asian woman. *Am J Ther.* Epub June 16, 2012.
129. Pilgrim JL, Gerostamoulos D, Drummer OH. Deaths involving MDMA and the concomitant use of pharmaceutical drugs. *J Anal Toxicol.* 2011;35(4):219–226.
130. Degenhardt L, Bruno R, Topp L. Is ecstasy a drug of dependence? *Drug Alcohol Depend.* 2010;107(1):1–10.
131. Cottler LB, Leung KS, Abdallah AB. Test-re-test reliability of DSM-IV adopted criteria for 3,4-methylenedioxymethamphetamine (MDMA) abuse and dependence: a cross-national study. *Addiction*. 2009;104(10):1679–1690.
132. Topp L, Hall W, Hando J. *Is there a dependence syndrome for ecstasy?* NDARC Technical Report No 51. Sydney: National Drug and Alcohol Research Centre (NDARC); 1997. Available from: http://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/TR.051.pdf. Accessed July 19, 2013.

133. Bruno R, Matthews AJ, Topp L, Degenhardt L, Gomez R, Dunn M. Can the severity of dependence scale be usefully applied to 'ecstasy'? *Neuropsychobiology*. 2009;60(3–4):137–147.
134. Bradbury S, Bird J, Colussi-Mas J, Mueller M, Ricaurte G, Schenk S. Acquisition of MDMA self-administration: pharmacokinetic factors and MDMA-induced serotonin release. *Addict Biol.* Epub June 14, 2013.
135. von Sydow K, Lieb R, Pfister H, Höfler M, Wittchen HU. Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults-a transient phenomenon? Results from a longitudinal community study. *Drug Alcohol Depend.* 2002;66(2):147–159.
136. De La Garza R 2nd, Fabrizio KR, Gupta A. Relevance of rodent models of intravenous MDMA self-administration to human MDMA consumption patterns. *Psychopharmacology (Berl)*. 2007;189(4):425–434.
137. Schenk S. MDMA self-administration in laboratory animals: a summary of the literature and proposal for future research. *Neuropsychobiology*. 2009;60(3–4):130–136.
138. MDMA (Ecstasy) abuse [webpage on the Internet]. National Institute on Drug Abuse; 2006. Available from: http://www.drugabuse.gov/publications/research-reports/mdma-ecstasy-abuse. Accessed July 21, 2013.
139. Ferigolo M, Machado AG, Oliveira NB, Barros HM. Ecstasy intoxication: the toxicological basis for treatment. *Rev Hosp Clin Fac Med Sao Paolo*. 2003;58(6):332–341.
140. Rosenbaum M, Doblin R. Why MDMA should not have been made illegal. In: Inciardi JA, editor. *The Drug Legalization Debate*. Thousand Oaks, CA: Sage Publications; 1991:135–146.
141. Greer GR, Tolbert R. A method of conducting therapeutic sessions with MDMA. *J Psychoactive Drugs*. 1998;30(4):371–379.
142. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of {±}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol.* 2011;25(4):439–452.
143. Mithoefer MC, Wagner MT, Mithoefer AT, et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-met hylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *J Psychopharmacol.* 2013; 27(1):28–39.
144. Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (±3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorders (PTSD). *J Psychopharmacol.* 2013;27(1):40–52.
145. Johansen PØ, Krebs TS. How could MDMA (ecstasy) help anxiety disorders? A neurobiological rationale. *J Psychopharmacol.* 2009;23(4): 389–391.
146. Riedlinger TJ, Riedlinger JE. Psychedelic and entactogenic drugs in the treatment of depression. *J Psychoactive Drugs.* 1994;26(1):41–55.
147. Jerome L, Schuster S, Yazar-Klosinski BB. Can MDMA play a role in the treatment of substance abuse? *Curr Drug Abuse Rev.* 2013;6(1):54–62.
148. Parrott AC. The psychotherapeutic potential of MDMA (3,4-methylenedioxymethamphetamine): an evidence-based review. *Psychopharmacology (Berl)*. 2007;191(2):181–193.