

**(+/-)-3,4-methylenedioxymethamphetamine
(MDMA, "Ecstasy")
Investigator's Brochure**

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Preface

In 2001, Baggott, Jerome and Stuart collaborated on a comprehensive review of the literature concerning 3,4-methylenedioxymethamphetamine, or MDMA (Baggott et al. 2001). After writing this monumental work, three additional reviews were created to assist and support the Multidisciplinary Association for Psychedelic Studies (MAPS), first by Jerome and Baggott in 2003, and then Jerome in 2004 and 2005 (Jerome 2004; 2005; Jerome and Baggott 2003). As the amount and pace of research accelerated, and after gaining more knowledge about investigator's brochures, the present author (Jerome) concluded that information on MDMA should be presented in a more accessible and compact format. Fortunately, a number of excellent reviews of nearly all aspects of MDMA have appeared in the past four years, making the task of summarizing and presenting this research easier. As in all previous documents, this brochure is based on literature located through the electronic database PubMed, examining relevant journals and communication with researchers. With the exception of some information on ongoing studies and conference presentations, most of the information has been drawn from reports appearing in print or electronic editions of relevant journals.

This document is intended to encapsulate the current state of our knowledge concerning MDMA, especially as it pertains to humans. Rather than follow the format of its predecessors, this document will follow the outline used for recently created investigator's brochures for LSD and psilocybin. There will be a greater focus on proposed mechanisms of action, cataloguing acute physiological, behavioral and therapeutic effects in humans, and information on planned or ongoing use in medical settings. Readers interested learning more about MDMA or specific areas are strongly encouraged to read reviews by Cole and Sumnall, Dumont and Verkes, Laws and Kokkalis, Zakzanis and others on the pharmacology, acute and potential long-term effects and risks of MDMA and ecstasy, with ecstasy defined here as material represented as containing MDMA (Baylen and Rosenberg 2006; Cole and Sumnall 2003a; b; Dumont and Verkes 2006; Green et al. 2003; Guillot 2007; Laws and Kokkalis 2007; Sumnall and Cole 2005; Zakzanis et al. 2007).

New Developments

Three major developments have transformed our understanding of previous and current findings in the area of MDMA research since the last update of the literature review. The first development affects interpretation of nonhuman animal studies, and the second development relates to our understanding of the presence and degree of long-term effects of ecstasy use. The third development relates to primate studies examining the impact of ambient temperature on the effects of MDMA on body temperature.

MDMA research and Interspecies Scaling

Up until as recently as 2006, investigations of the pharmacology, functional effects or toxicity of MDMA in nonhuman animals injected large and often repeated doses of MDMA (see Baggott et al. 2001). Some of the earliest research used high doses in order to study mechanisms of neurotoxicity. Most researchers continued to employ these doses, and some later explained these dosing regimens in terms of using interspecies scaling to

arrive at human-equivalent doses. Interspecies scaling is a pharmacological model intended to account for species-specific differences in metabolism (Mahmood and Balian 1996; Mordenti and Chappell 1989). However, interspecies scaling assumes that the target compound has linear pharmacokinetics, and requires data from at least two species to arrive at human-equivalent doses. Findings first reported in humans and later in monkeys (de la Torre et al. 2000; Mehan et al. 2006) demonstrate that MDMA has nonlinear pharmacokinetics, with larger doses producing greater increases in blood MDMA levels than would be expected from linear pharmacokinetics. Furthermore, contrary to earlier reports that found that route of administration had no impact on plasma MDMA levels (Finnegan et al. 1988; Ricaurte et al. 1988), a recent study of MDMA in monkeys found that sub-cutaneous doses produced higher peak plasma MDMA levels than intra-gastric administrations (Mehan et al. 2006). Some recent reports describe findings suggesting that even the doses of MDMA employed in rodent studies are inappropriately high (Baumann et al. 2006; Wang et al. 2005), though see work by Xie and colleagues (Xie et al. 2006). After examining these recent findings, it appears that much of the previous research in nonhuman animals has used inappropriately high doses of MDMA, and this occurred not only in studies of MDMA neurotoxicity, but also in studies of behavioral or pharmacological effects. Studies conducted subsequent to the discovery began employing mg/kg doses similar or identical to those used by humans (e.g. Taffe et al. 2006; Von Huben et al. 2006). Most drug-discrimination and self-administration studies in rodents (De La Garza et al. 2007) have employed and continue to employ doses identical or similar to those used by humans. However, the discoveries concerning the inadequacy of interspecies scaling mean that findings from the majority of previous studies must be considered with caution.

The Netherlands XTC Toxicity (NeXT) Studies

A team of researchers in the Netherlands embarked upon an ambitious program of research that included prospective studies of people who planned on using ecstasy in the future (De Win et al. 2005). Participants expressing interest in using ecstasy were assessed prior to use. After some reported their first use of ecstasy or soon afterwards, the team assessed these participants as well as another group that had not yet used ecstasy. The researchers studied brain activity, estimated brain serotonin transporter (SERT) sites, neurochemical markers of brain injury, working memory, and cognitive function including verbal memory. These studies are unique in their examination of people before and after drug self-administration rather than making cross-group comparisons between ecstasy users and non-user controls. Hence findings from these prospective studies far more relevant to examining risks and benefits in human MDMA studies than the majority of previous work. In general, studies from this research program failed to find any long-term effects of low to moderate ecstasy use. They did not find any changes in serotonin uptake sites nor chemical markers of brain injury, and they found only minor region-specific changes in cerebral blood volume (de Win et al. 2007; de Win et al. 2006; Jager et al. 2007b). While an examination of change scores before and after use indicated greater improvement in non-users than in ecstasy users, they failed to find impaired working memory after low ecstasy use (Jager et al. 2007b; Schilt et al. 2007). There are a number of problems with this research, including use of change scores and the inclusion of an individual whose ecstasy use was considerably greater than others in the cognitive

function assessment. However, despite these findings, the general picture from the NeXT studies is that low to moderate ecstasy use produces very few long-term effects and is not comparable to effects found after heavy use of ecstasy and other drugs.

No Interaction between MDMA and Ambient Temperature on Human Body Temperature

To date, the only novel and relevant finding from human MDMA studies is a study that sought to detect an interaction between MDMA and ambient temperature on human body temperature after 2 mg/kg MDMA (Freedman et al. 2005). Freedman and colleagues found that human body temperature was unaffected by the combination of MDMA and ambient temperature, and that the desirable effects of MDMA are not increased by warm ambient temperature (Freedman et al. 2005). One of two research teams reached similar conclusions in rhesus monkeys (Crean et al. 2006; Von Huben et al. 2006).

1. Drug Substance and Formulation

(+/-) 3,4-methylenedioxyamphetamine (MDMA, 3,4-methylenedioxy-n-methylamphetamine, N-methyl-3,4-methylenedioxyamphetamine,) has the chemical formula of $C_{11}H_{15}NO_2$. It is a phenylisopropylamine derived from safrole, an aromatic oil found in sassafras, nutmeg, and other plants (Shulgin 1986). Merck patented MDMA in 1912 as an intermediate chemical involved in the production of the stypic hydrastinine (Freudenmann et al. 2006). No significant investigations examined the pharmacological, physiological or psychological effects of MDMA until the 1950s, when the US Army administered MDMA to guinea pigs, monkeys, mice, rats and dogs, but not humans, as part of a military research program, possibly intended to develop chemical incapacitants or means of enhancing interrogation (Hardman et al. 1973). While evidence exists for intentional use of MDMA as early as the late 1960s (see Shulgin and Shulgin 1991), and there are records of a police seizure of MDMA in the early 1970s that suggests either intentional or unintentional use (Gaston 1972), Shulgin and Nichols were the first to report on the effects MDMA in humans (Shulgin and Nichols 1978). Shulgin introduced MDMA to a psychotherapist he knew, and the psychotherapist went on to introduce MDMA as a psychotherapeutic adjunct to others, with MDMA-assisted psychotherapy first occurring during the mid to late 1970s. Some have estimated that up to 4000 people underwent MDMA-assisted psychotherapy in North America prior to its placement in Schedule 1. Psychotherapists used it to treat anxiety and depression, and posttraumatic stress disorder (Greer and Tolbert 1998; Metzner and Adamson 2001). However, none of the therapists conducted controlled studies or published any formal descriptions or analyses of MDMA-assisted therapy at this time. Therapeutic use continued up until its placement in US Schedule 1 in 1986 (Adamson 1985; Greer and Tolbert 1998; Stolaroff 1997). During the early 1980s, increasing numbers of people began using MDMA outside the therapeutic context (Beck and Rosenbaum 1994). The first wave of non-medical use occurred not only in dance clubs but in small groups of people, in a self-exploratory or spiritual context or while attending concerts. Non-medical use continues today in the same contexts (Carlson et al. 2004; Sumnall et al. 2006).

A few uncontrolled human studies of MDMA occurred in the 1980s (Downing 1986; Greer and Tolbert 1986), including Greer and Tolbert's study of MDMA in a

psychotherapeutic context. However, controlled human studies of MDMA did not commence until early to mid-1990s, with the publication of research conducted by Grob and colleagues (Grob et al. 1996). Currently, ongoing investigations in the US and Switzerland are examining the use of MDMA in psychotherapy (Halpern 2006; Mithoefer 2006; Oehen 2006).

Many researchers categorize MDMA as belonging to a unique class of drugs, the entactogens (Nichols 1986; Vollenweider et al. 1998a), of which it is considered the first identified member, and perhaps a prototype of the class. Entactogens are reported to produce changes in mood, social interactions or feelings of interpersonal closeness and changes in perception. MDMA shares some of the pharmacological effects of stimulants and serotonergic hallucinogens (Cami et al. 2000; Gouzoulis-Mayfrank et al. 1999; Liechti et al. 2001b; Tancer and Johanson 2003), but it also appears to possess qualities it shares in common with a small number of related compounds, as methylenedioxyethylamphetamine (MDE) (Gouzoulis-Mayfrank et al. 1999). Retrospective reports and surveys have assessed the social cognitive effects of MDMA or ecstasy (Liester et al. 1992; Peroutka et al. 1988; Solowij et al. 1992). To date only two controlled studies have sought to measure these effects (Farre et al. 2007; Harris et al. 2002). Although researchers have offered several models and explanations for the source of entactogenic effects, it appears that release of serotonin plays a significant role in producing at least some of these effects. Indirect action on 5HT_{1A} or 5HT_{2A} receptors, and neuroendocrine responses, as increases in the hormones oxytocin, vasopressin and cortisol may also play a role in producing the unique effects of MDMA.

2. Pharmacological and toxicological effects

Overview

MDMA possesses a complex pharmacological profile, but it is dominated by its effects on monoamine release and reuptake. MDMA prevents uptake of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) and is involved in the release of these three transmitters, with the greatest effects on serotonin release. While MDMA also has some affinity for specific serotonin, norepinephrine, acetylcholine and histamine receptors, strength of activity on these receptors is low (Battaglia et al. 1988; Setola et al. 2003, see also values listed on NIMH Psychoactive Drug Screening Program). There are a few studies of changes in gene expression seen after MDMA, but given that these studies use high doses of MDMA and examination of gene expression occurred at times falling between acute and sub-acute effects, the significance of these findings are unclear.

MDMA is chiral, possessing two enantiomers, S-(+)-MDMA and R-(-)-MDMA, with S-(+)-MDMA is more potent than R-(-)-MDMA (Lyon et al. 1986; Shulgin 1986). Rodent drug-discrimination and behavioral studies (Fantegrossi et al. 2003; Yarosh et al. 2007) and self-administration studies in monkeys (Fantegrossi 2007), suggest that not only do the enantiomers produce different effects, but that there may be some synergy between the two. One microdialysis study suggests that S-(+)-MDMA is associated with greater dopamine release in specific brain areas (Acquas et al. 2007). However, most if not all street doses are racemic, meaning they contain roughly equal amounts of both enantiomers, and all controlled studies to date also employed a racemic mixture. The

nature of differential effects of the two enantiomers of MDMA remain unknown in humans. An early uncontrolled study suggests differential effects (Anderson et al. 1978), and an a controlled study comparing the enantiomers of the related compound MDE reported R-(-)-MDE to more strongly affect visual perception than the S-(+)-enantiomer (Spitzer et al. 2001).

Intravenous MDMA has an LD50 of 97 mg/kg in mice and 49 mg/kg in rats, 14 to 18 mg/kg in dogs and 22 mg/kg in monkeys (Frith et al. 1987; Hardman et al. 1973). Estimating from this data, LD50 in humans is liable to fall between 10 and 20 mg/kg (Shulgin 1986). One team of researchers reported that in mice, aggregate LD50 was 20 mg/kg, considerably lower than values in isolated animals, and recent studies in mice confirm lower LD50 when mice are housed together (Davis et al. 1987; Fantegrossi et al. 2003). Typically, human trials have used doses between 1 and 2 mg/kg.

MDMA and Monoamines

While the pharmacology of MDMA is complex, its chief effect is the release of monoamines, particularly serotonin. MDMA also releases norepinephrine and dopamine (Cole and Sumnall 2003b) and prevents uptake of all three monoamines. Recent in vitro studies suggest that MDMA inhibits norepinephrine uptake more strongly than dopamine uptake (Mlinar and Corradetti 2003; Verrico et al. 2007) and that MDMA does not have as strong an affinity for the dopamine transporter as methamphetamine (Han and Gu 2006). MDMA appears to alter the configuration of the serotonin transporter so that it works in reverse of its usual mode, transporting serotonin outside of neurons rather than shuttling extracellular serotonin into these neurons (Cole and Sumnall 2003b; Johnson et al. 1986; see also Rudnick and Wall 1992). While MDMA has some affinity for some serotonin, norepinephrine, acetylcholine and histamine receptors, its direct activity at these receptors is weaker than its activity on monoamine transporters.

Early studies of the pharmacological affinity of MDMA reported after detecting strong affinity for serotonin, norepinephrine and dopamine transporters, binding at α_1 , 5HT₂, α_2 adrenergic receptors, H₁ histamine receptors and acetylcholine muscarinic M₁ receptors, β adrenergic receptors, dopamine D₂ and D₁ dopamine receptors, roughly in that order (Battaglia et al. 1988). This study failed to detect any direct pharmacological effects on GABA, glutamate or opioid receptors. Later reports and investigations have clarified and for the most part supported this data (e.g. Jones et al. 2004, see also NIMH PDSP database; Setola et al. 2003), providing more specific affinity assays and with only one significant disagreement, concerning the muscarinic M₁ receptor. However, it appears that the effects of MDMA at all receptors investigated to date is considerably lower than its activity at any of the monoamine transporters, suggesting that any receptor-mediated effects reported in humans or nonhuman animals arise indirectly from monoamine release or inhibition of reuptake. For instance, MDMA may cause acetylcholine release and changes in the GABAergic systems through serotonin release activating 5HT₄ receptors (Nair and Gudelsky 2005; 2006). Indirect effects of monoamine are likely involved in producing therapeutic effects, as facilitated recall and changed meaning of perceptions and events, increased positive mood and increased interpersonal closeness, empathy or compassion for the self and others.

Table 1: Affinity assays from Battaglia et al. 1988: Affinities of MDMA at receptors wherein K_i is below 500 mcM. Male rat brain samples used in assays.

Transporter/Receptor	K _i (mcM)	Hot Ligand	Species	Source	Reference
Serotonin Transporter	0.61 +/- 0.05	3H-paroxetine	Rat	Fr. Cortex	(Battaglia et al. 1988)
Norepinephrine Transporter	15.8 +/- 1.7	3H-Mazindol	Rat	Fr. Cortex	(Battaglia et al. 1988)
Dopamine Transporter	24.4 +/- 1.9	3H-GBR-12935	Rat	Striatum	(Battaglia et al. 1988)
α ₂	3.6 +/- 0.8	3H-aminoclonidine	Rat	Fr. cortex	(Battaglia et al. 1988)
5HT ₂	5.1 +/- 0.3	3H-ketanserin	Rat	Fr. Cortex	(Battaglia et al. 1988)
H ₁	5.7 +/- 2.4	3H-mepyramine	Rat	Fr. Cortex	(Battaglia et al. 1988)
M ₁	5.8 +/- 0.3	3H-QNB	Rat	Fr. Cortex	(Battaglia et al. 1988)
M ₂	15.1 +/- 0.1	3H-QNB	Rat	Brainstem	(Battaglia et al. 1988)
α ₁	18.4 +/- 1.2	3H-prazosin	Rat	Fr. Cortex	(Battaglia et al. 1988)
B	19.2 +/- 2.1	3H-dihydroalprenolol	Rat	Fr. Cortex	(Battaglia et al. 1988)
5HT ₁	23 +/- 1.5	3H-serotonin	Rat	Fr. Cortex	(Battaglia et al. 1988)
D ₂	95 +/- 15	3H-Spiperone	Rat	Striatum	(Battaglia et al. 1988)
D ₁	148 +/- 14	3H-SCH-23390	Rat	Striatum	(Battaglia et al. 1988)

Fr. Cortex = Frontal cortex

Table 2: Receptor binding profiles for MDMA recorded from the NIMH Psychoactive Drug Screening Program Database (PDSP)

Receptor	K _i (mcM)	Hot Ligand	Species	Source	Reference
Serotonin transporter	0.072 or 0.102	Functional (1), 3H-citalopram (2)	Rat, Human	Brain, Cloned	(Jones et al. 2004; Setola et al. 2003)
Norepinephrine Transporter	0.110	Functional	Rat	Brain	(Setola et al. 2003)
Dopamine transporter	0.278	Functional	Rat	Caudate	(Setola et al. 2003)
5HT _{2B}	0.5 or 0.7	3H-LSD	Human	Cloned	(Setola et al. 2003), (PDSP 2007)
α _{2C}	1.12	3H-Clonidine	Human	Cloned	(PDSP 2007)
Calcium Channel	1.2	3H-Nitrendipine	Rat	Heart	(PDSP 2007)
α _{2B}	1.8	3H-Clonidine	Human	Cloned	(PDSP 2007)
M ₃	1.8	3H-QNB	Human	Cloned	(PDSP 2007)
H ₁	2.1	3H-Pyramine	Human	Cloned	(PDSP 2007)
α _{2A}	2.5	3H-Clonidine	Human	Cloned	(PDSP 2007)
M ₅	6.3	3H-QNB	Human	Cloned	(PDSP 2007)
M ₄	8.2	3H-QNB	Human	Cloned	(PDSP 2007)
5HT _{2A}	8.3	3H-ketanserin	Rat	Cortex	(Lyon et al. 1986)

Human MDMA studies suggest that serotonin release plays a prominent role in producing the effects of MDMA. Preventing serotonin release through administration of selective serotonin reuptake inhibitors (SSRIs) appears to attenuate or eliminate most subjective, physiological and immunological effects of MDMA (Farre et al. 2007; Liechti et al. 2000a; Liechti and Vollenweider 2000b; Pacifici et al. 2004; Tancer and Johanson 2007). Pre-treatment or coadministration with SSRIs attenuated the effects of MDMA on mood and perception, though leaving intact specific effects, as nervousness or excitability (Liechti et al. 2000a). Some researchers reported that SSRIs attenuated MDMA-induced increases in heart rate and blood pressure (Farre et al. 2007; Liechti and Vollenweider 2000b) while others only reported that SSRIs attenuated elevated heart rate only (Tancer and Johanson 2007). All three studies of SSRI pre-treatment suggest that co-administration of SSRIs with MDMA is safe, but that this combination prevents or

significantly reduces the appearance of the subjective effects of MDMA. The perceptual effects of MDMA appear to be the result of direct or indirect action on 5HT_{2A} receptors, as coadministration of the 5HT_{2A} antagonist ketanserin reduced reported perceptual alterations after 1.5 mg/kg MDMA and eliminated slight elevation in body temperature (Liechti et al. 2000b). At least some MDMA effects on mood and anxiety may result from dopamine release indirectly activating D₂ receptors, as administering the D₂ antagonist haloperidol diminished positive mood and increased anxiety in humans (Liechti and Vollenweider 2000a). There are no reports examining the contribution of norepinephrine release to MDMA effects in humans. Investigations in rodents suggest that norepinephrine plays a role in cardiovascular effects (Quinn et al. 2006).

In rats, relatively large doses of MDMA (10 or 20 mg/kg) elevated serum corticosterone (a rodent cortisol analog) and prolactin (Connor et al. 2000; Nash et al. 1988), with elevation lasting up to four hours after dosing, and attenuated by a 5HT₂ receptor antagonist. Given the large dosage used, it is unclear if this response is analogous to elevated cortisol in humans or whether it reflects a different process. A study of isolated rat hypothalamus reported arginine vasopressin and oxytocin release after MDMA and the MDMA metabolite HMMA (Fallon et al. 2002).

Receptor Affinity and Direct and Indirect Actions on Receptors

Most effects of MDMA on brain receptors likely arise indirectly from monoamine release. MDMA probably stimulates 5HT_{1A} receptors indirectly through serotonin release, though it is possible that MDMA may also act as a partial 5HT_{1A} antagonist in some brain areas (Giannaccini et al. 2007). Early studies in rodents suggest that 5HT_{1A} receptors reduce anxiety and aggression (Brunner and Hen 1997; Graeff et al. 1996), and some drug discrimination studies suggest that the 5HT_{1A} agonist 8-OH-DPAT partially or fully substitutes for MDMA (Glennon and Young 2000; Glennon et al. 2007; Schechter 1986). Administering a 5HT_{1A} antagonist attenuates the prosocial behavior of adjacent lying in rats given MDMA, possibly because it prevents elevation in oxytocin (Morley et al. 2005; Thompson et al. 2007). To date there are no human studies investigating the contribution of 5HT_{1A} receptors to MDMA effects.

MDMA exhibits affinity for two of three 5HT₂ family receptors, 5HT_{2B} and 5HT_{2A}, and for α_{2B} , α_{2C} , histamine H₁ and muscarinic M₃ receptors, with strongest affinity recorded for 5HT_{2B}, α_{2B} , α_{2C} and muscarinic M₃ receptors (Battaglia et al. 1988; Lavelle et al. 1999; Lyon et al. 1986; Setola et al. 2003), additional data from PDSP database. A pair of reports suggests MDMA may have some affinity for the trace amine receptor (TAR). In contrast with Battaglia's work, later investigations did not find high affinity for M₁ receptors. It is possible but not yet demonstrated that MDMA agonism at 5HT_{2B} and α_2 receptors might play a role in producing some of the subjective or psychological effects of MDMA. Most 5HT_{2B} receptors are found on tissues outside the brain (Setola et al. 2003). However, 5HT_{2B} receptors are also present within the amygdala (Duxon et al. 1997), and so it is possible that these receptors may be involved in regulating emotional reactivity or other amygdalar responses. For example, MDMA and fenfluramine can produce increased or decreased anxiety, or both at once, and feelings of dreaminess, suggesting a few commonalities between the two serotonin releasers and 5HT_{2B} agonists

(Bond et al. 1995; Mortimore and Anderson 2000). Clonidine and other α_2 agonists are associated with increased feelings of calmness and relaxation, and it is possible that, like these compounds, MDMA also induces a calm or relaxed state via α_2 agonism. To date there are no behavioral studies examining the role of 5HT_{2B} or α_2 adrenergic receptors in the subjective or therapeutic effects of MDMA. Even less is known about the significance of MDMA activity at histamine and muscarinic receptors.

At least some direct or indirect effects of MDMA on serotonin receptors may in turn produce additional effects, as changes in GABA uptake in the ventral tegmental area of rats (Bankson and Yamamoto 2004). However, very few publications investigate direct effects of MDMA upon receptors, and it is likely that most effects on serotonin or dopamine receptors result from monoamine release and not direct receptor activation or antagonism.

MDMA and Gene Expression

A number of research teams have studied the effects of MDMA on gene expression in rodents over the past seven years. However, many of these reports used 10 to 20 mg/kg MDMA, leaving it uncertain whether these changes can be generalized to humans given lower doses. These studies reported an increase in transcripts for genes that regulate the GABA transporter (Peng et al. 2002; Thiriet et al. 2002). Some of the increased gene transcriptions are associated with monoamine release (Peng et al. 2002). Investigations with serotonin transporter knockout mice suggest that at least some of these changes in gene transcription are related to serotonin release. A recent publication found that repeated administration with 1 or 5 mg/kg weekly for four weeks increased transcripts for 5HT_{1B} receptors in various brain regions and 5HT_{2C} receptors in the cortex and hypothalamus after MDMA (Kindlundh-Hogberg et al. 2006). However, because transcription was assessed ten hours after the last MDMA administration, it is not clear whether these changes reflect residual acute effects of MDMA or changes related to repeated administration. However, generally speaking it appears that serotonin plays more of a significant role than dopamine in changing gene transcription. Future studies will need to separate direct and indirect effects of MDMA on gene expression or transcription.

Physiological Effects

Moderate to high doses of MDMA elevate body temperature in rodents, often producing hyperthermia (Cole and Sumnall 2003b), and doses of MDMA closer to those used by humans still produce at least a slight increase in body temperature (Reveron et al. 2006), suggesting that this effect may occur only at higher doses. Ambient temperature and MDMA interact on body temperature in rodents, with high ambient temperature significantly increasing body temperature in mice and rats, and low ambient temperature and MDMA producing hypothermia rather than hyperthermia (Dafters 1994; Fantegrossi et al. 2003; Malberg and Seiden 1998).

High doses of MDMA produce significant elevations in body temperature in primates (Bowyer et al. 2003; Mehan et al. 2006), but when they receive doses closer to those humans ingest, monkeys exhibit only slight to moderate elevation in body temperature

(Crean et al. 2007; Crean et al. 2006). In contrast to findings in rodents, human and nonhuman primates are not subject to interactions between ambient temperature and MDMA, exhibiting slight to moderate increases in body temperature in cool, room temperature and warm environments (Crean et al. 2007; Crean et al. 2006; Freedman et al. 2005), though one paper examining monkeys in restraining chairs detected an interaction between MDMA and ambient temperature on monkey body temperature (Banks et al. 2007). The difference between rodent and primate response to MDMA in different ambient temperatures may result from interspecies differences in means of body heat reduction, including differences relating to body mass (Gordon 2007).

While there are few in vivo assessments of cardiovascular effects of MDMA in nonhuman animals, Cole and Sumnall noted in their review that previous findings detected increased sympathetic activity, as seen in humans (Cole and Sumnall 2003b). A team of researchers based in Dublin, Ireland conducted a number of in vitro studies with rat vascular tissue demonstrating that MDMA has both pressor and depressor effects, acting through adrenergic receptors. They reported elevations in blood pressure (Bexis and Docherty 2005; 2006).

A large body of research has examined the neurotoxic potential of MDMA, with the general consensus being that MDMA may be neurotoxic to the axons of serotonergic cells at high or repeated doses (Baumann et al. 2007; Cole and Sumnall 2003b). Studies in rodents and nonhuman primates have found that high and repeated doses of MDMA reduce brain serotonin levels and may damage the axons of serotonergic neurons (Cole and Sumnall 2003b). However, lower doses do not appear to do this (Mechan et al. 2006; Wang et al. 2005), and it is not likely that the dosages and regimens found in controlled studies produce these effects. The issue of MDMA neurotoxicity is addressed further under "Possible Risks" below.

Studies in mice found increased limbic excitability after repeated moderate or high doses of MDMA and increased activity after each dose without reducing brain serotonin or dopamine levels (Frenzilli et al. 2007; Giorgi et al. 2005). The significance of this finding for humans remains unclear, as animals received daily doses of MDMA. However, such changes might be related to increased tolerance to MDMA effects after frequent, repeated doses.

Humans

Onset of MDMA effects occurs 30 to 60 minutes after administration (Cami et al. 2000; Mas et al. 1999), peak effects appear 75 to 120 minutes post-drug (Liechti et al. 2001b; Tancer and Johanson 2003), and duration of effects lasts from three to six hours (Harris et al. 2002; Liechti et al. 2001a; Vollenweider et al. 1998a), with most effects returning to baseline or near-baseline levels six hours after drug administration. MDMA produces sympathomimetic effects that include elevation in blood pressure and heart rate, first recorded by Downing (Downing 1986) and replicated by other research teams in the US and Europe (Lester et al. 2000; Liechti et al. 2001a; Mas et al. 1999; Tancer and Johanson 2001). Elevation in blood pressure met diagnosis for hypertension in approximately 5% of research participants receiving at least 100 mg MDMA in research

studies (Mas et al. 1999; Vollenweider et al. 1998a), but none of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned. Most people do not experience elevations that are greater than seen after moderate exercise. Cardiovascular effects of MDMA first appear 30 to 45 minutes after administration (Downing 1986) and peak between 1 and 2 hours post-drug, with effects waning 3 to 5 hours after drug administration. Men given the same mg/kg dose of MDMA as women exhibited a significantly greater elevation in blood pressure, and they also exhibited a greater elevation in heart rate than women, as reported in a study summarizing and pooling data from a series of human MDMA studies (Liechti et al. 2001a). These studies did not report any discomfort or increased stress accompanying cardiovascular effects.

As previously noted, MDMA produces only a slight elevation in body temperature (Liechti et al. 2001a) and this elevation is unaffected by ambient temperature (Freedman et al. 2005). Doses between 1.5 and 2 mg/kg MDMA (approximately 100-150 mg) fail to produce any clinically significant elevation in body temperature (Freedman et al. 2005; Liechti et al. 2001b). Men seem to exhibit a greater elevation in body temperature than women when given the dose of MDMA in milligrams per kilogram (Liechti et al. 2001a). However, it is notable that participants in controlled studies have not engaged in vigorous exercise and either remained sitting or lying down throughout most drug effects. It may be the case that ambient temperature and vigorous exercise contribute to the occurrence of hyperthermia in people ingesting ecstasy in uncontrolled settings. One of two naturalistic studies reported that ecstasy users had a slight but not statistically significant increase in body temperature, while the other failed to find any significant differences in ecstasy-user body temperature at a club (Cole et al. 2005; Irvine et al. 2006). In the study of Irvine and colleagues, average blood MDMA was 0.31 +/- 0.21 ng/L, though five participants had significantly higher blood MDMA levels.

MDMA and Brain Activity

Gamma and colleagues performed positron emission tomography (PET) brain scans 75 minutes after administering 1.7 mg/kg MDMA, finding increased regional blood flow (rCBF) in prefrontal, inferior temporal and cerebellar areas and decreased rCBF in the left amygdala (Gamma et al. 2000). Decreased amygdalar activity may be indicative of reduced reactivity to potential threats (Phelps et al. 2001). Ecstasy user participants receiving two doses of MDMA exhibited decreases in bilateral visual cortex, caudate, superior parietal, and dorsolateral frontal regions (Chang et al. 2000) ten to 21 days later, with increased rCBF measured in two participants at a later time point. However, a comparison between heavy ecstasy users and non-user controls failed to find differences in rCBF (Gamma et al. 2001), and a report assessing changes before and after initial use found only increase in one area of prefrontal cortex (de Win et al. 2007), suggesting that the changes seen by Chang and colleagues are a transient effect. Electroencephalography recorded after MDMA showed the following changes EEG activity; overall increase in beta activity, reduction in alpha activity, and specific decreases in alpha and delta in frontal areas and increased frontotemporal beta signal (Frei et al. 2001), EEG patterns the authors reported as being similar to those seen with serotonergic and noradrenergic drugs, and to a lesser extent, dopaminergic drugs.

Neuroendocrine Effects of MDMA

MDMA dose-dependently and acutely increases cortisol, prolactin, and adrenocorticotrophic hormone concentrations (Farre et al. 2004; Grob 2001; Grob et al. 1996; Harris et al. 2002; Mas et al. 1999), while growth hormone was unchanged by up to 125 mg MDMA (Mas et al. 1999). Increases in cortisol and prolactin peaked at about 2 hours after MDMA administration. A second dose of 100 mg MDMA given four hours after an initial 100 mg produced a second increase in cortisol during an interval when cortisol levels were declining (Pacifici et al. 2001), and a dose of 100 mg MDMA given 24 hours after an initial dose stimulated a greater release of cortisol, but not prolactin (Farre et al. 2004). In a study of the effects of 0.5 and 1.5 mg/kg MDMA in eight people, there was a trend for increased levels of the hormone dehydroepiandrosterone (DHEA) after 0.5 mg/kg MDMA, and a significant increase after 1.5 mg/kg MDMA, with peak levels appearing 2 to 3 hours post-drug (Harris et al. 2002). Along with these findings from controlled studies, a naturalistic study reported elevated levels of the hormone oxytocin in clubgoers with detectable blood MDMA levels when compared with clubgoers without any detectable levels of MDMA. It is likely that all neuroendocrine changes result from monoamine release, and it is currently unknown what role, if any, they play in producing the effects of MDMA. Exogenous oxytocin increases trust and improves accuracy of emotion perception, and increased cortisol in some circumstances may serve as a signal to seek affiliation or to increase positive mood (Bartz and Hollander 2006; Domes et al. 2007; Kirsch et al. 2005; Wirth and Schultheiss 2006).

Immunological Effects of MDMA

Humans exhibit transient immunological changes after a dose of 100 mg (Pacifici et al. 2004; Pacifici et al. 2000; Pacifici et al. 1999; Pacifici et al. 2002), including reduced numbers of CD4 cells, increased numbers of NK cells, and an increase in levels of immunosuppressive and anti-inflammatory cytokines compared with levels of pro-inflammatory and immunostimulating cytokines. Pacifici and colleagues report that in several respects, these effects are similar to those that occur with other psychoactive substances and are not unique to MDMA. Immunological effects last for approximately 24 hours after administration, and most arise indirectly from serotonin release (Pacifici et al. 2004). The significance of these immunological effects remains unclear. However, we expect the impact of these effects to be modest in most cases.

Behavioral and psychological effects

Researchers investigating how MDMA produces its behavioral and psychological effects on humans and nonhuman animals are only just beginning to approach this topic, and the first controlled studies into the therapeutic potential of this compound are only just reaching completion now. In rodents, doses of MDMA equivalent or only slightly greater in size than human doses produce little to no behavioral effects. However, doses of 5 mg/kg or greater possess several specific behavioral effects, including increased locomotor activity, increased anxiety at moderately high doses and decreased anxiety at higher doses (Cole and Sumnall 2003b; Green et al. 2003). Rats given lower doses of MDMA exhibited increased anxiety in the elevated plus maze (Ho et al. 2004), while higher doses exhibited reduced anxiety on the plus maze. Rats given higher doses also reduced aggressive behavior, but they also reduced social investigation. Rodents

responded to high doses of MDMA by exhibiting flat body posture, forepaw treading and an erect tail ("Straub tail") (Green et al. 2003), all signs of rodent "serotonin syndrome." MDMA produces some repetitive behavior, but not to the same degree as do psychostimulants. MDMA increased locomotor activity in rats, leading them to walk around a cage perimeter, interpreted as an indicator of thigmotaxis, a sign of anxiety (Cole and Sumnall 2003b). However, it is notable that a recent in-press publication failed to find thigmotaxis in rats given 5 mg/kg MDMA (Selken and Nichols 2007). By contrast, rhesus monkeys do not exhibit increased locomotor activity after up to 2.4 mg/kg MDMA (Crean et al. 2006). To date, no one has performed empirical investigations of the effects of MDMA on social interaction in human or nonhuman primates.

Morley and colleagues observed rat behavior after 5 mg/kg MDMA, noting that this dose increased likelihood of prosocial behavior, such as lying next to each other (Morley et al. 2005). Recent studies conducted by the same team of researchers suggest that MDMA increases prosocial behavior in rats by elevating oxytocin in the paraventricular nucleus through 5HT_{1A} receptor agonism (Thompson et al. 2007), with the oxytocin increase arising from indirect effects of MDMA on 5HT_{1A} receptors. To date, there have been no human pharmacological challenge studies combining MDMA with 5HT_{1A} agonists or antagonists, and it is unclear whether the rat behavior is analogous to human reports of increased feelings of empathy or interpersonal closeness while under the influence of MDMA (Liestner et al. 1992; Peroutka et al. 1988; Solowij et al. 1992; Vollenweider et al. 1998).

Humans

MDMA alters mood, perception and cognition. These effects peak 90 to 120 minutes after oral administration and they are near to or at pre-drug levels three to six hours later (Lamers et al. 2003; Tancer and Johanson 2001; Vollenweider et al. 1998a). Sub-acute effects may occur one to three days after drug administration, but are no longer apparent seven to 14 days later (Harris et al. 2002; see also Huxster et al. 2006). Most of the therapeutic effects of MDMA result from changes in affect, cognition and social interaction. When combined with psychotherapy that supports one or more of these effects, MDMA permits people to confront and consider emotionally intense memories, thoughts or feelings, and perhaps through changes in mood and perception, increases empathy and compassion for others and the self. MDMA may also increase accuracy of assessing at least some emotional expressions.

Active doses of MDMA alter mood and cognition and produce slight alterations in perception (Dumont and Verkes 2006; Liechti et al. 2001a). Changes in mood include increased positive mood and anxiety (Cami et al. 2000; Harris et al. 2002; Liechti and Vollenweider 2001; Tancer and Johanson 2003). People reported feeling more talkative and friendly after receiving MDMA, and at least one research team informally reported increased feelings of closeness to others (Vollenweider et al. 1998). Researchers using two items within an instrument designed to assess drug effects and a visual analog scale rating closeness to others failed to detect increased feelings of empathy after 1.5 mg/kg MDMA (Harris et al. 2002), possibly due to the low sensitivity of this measure. However,

a recent investigation into the effects of pretreatment with the SSRI paroxetine on MDMA effects in humans reported MDMA increased feelings of sociality and closeness to others, and that the SSRI paroxetine reduced these effects (Farre et al. 2007). People reported feeling anxious and undergoing negatively experienced derealization, including increased anxiety in relation to loss of control, and experiences of racing or blocked thoughts after MDMA (Cami et al. 2000; Liechti et al. 2001; Vollenweider et al. 1998). Study participants experienced slight changes in visual or auditory perception, including changes in the brightness of the room or colors, sounds seeming closer or farther away, and simple visual distortions. Participants also experienced altered time perception and changed meaning or significance of perceptions after MDMA (Vollenweider et al. 1998). People maintained insight as to their experience, and there was little indication that MDMA produced any strong alterations to the sense of self or control over the experience (Harris et al. 2002; Tancer and Johanson 2003). Women reported experiencing all subjective effects of MDMA more intensely, but especially those related to perceptual changes (Liechti et al. 2001a). Though some researchers had hypothesized that MDMA would produce more positive or rewarding effects when taken in a warm environment (Parrott 2004), researchers comparing the effects of MDMA in a warm and a cool room failed to support this hypothesis (Freedman et al. 2005).

People receiving active doses of MDMA experienced euphoria, positive mood, vigor and positively experienced derealization, consonant with early retrospective reports, and they also experienced anxiety, tension and dysphoria, as concern over losing control over the self (Cami et al. 2000; Harris et al. 2002; Liechti and Vollenweider 2001; Tancer and Johanson 2003). It is uncertain whether the increases in positive and negative mood occur simultaneously or occur at different times throughout the duration of MDMA effects, though there is some suggestion in reports from two different teams that peaks in negative mood may precede peaks for positive mood (Liechti and Vollenweider 2000a; Tancer and Johanson 2003).

MDMA produces modest acute changes in attention and cognition, with previous reports indicating impaired performance on some tasks, as digit-symbol substitution, and not others, as the Stroop task (Cami et al. 2000; Gamma et al. 2000; Vollenweider et al. 1998b). Larger doses of MDMA attenuated prepulse inhibition in rats, defined as a reduced startle response to an intense stimulus when it is preceded by a less intense cue. However, in humans, MDMA enhances PPI (Vollenweider et al. 1999). A recent series of studies conducted in the Netherlands that examined the effects of MDMA on skills needed for driving cars reported transient and selective changes in verbal and visual attention and memory after 75 or 100 mg MDMA (Kuypers and Ramaekers 2005; 2007; Ramaekers and Kuypers 2006). Changes included difficulty learning or remembering lists of words and difficulty recalling object position within an array of objects, but without any impairment in spotting scene changes, reduced weaving in a driving simulation, but excessively cautious response to the actions of another car in an assessment of actual driving. MDMA acutely improved performance on one measure of impulsivity while failing to improve or impair performance on other impulsivity measures (Ramaekers and Kuypers 2006). The cause or causes behind these changes are unclear but may relate to changes in attention, salience of visual objects and altered time

perception. Changes in visuospatial recall and driving skills are likely associated with serotonin release or indirect action on serotonin receptors, as the noradrenergic and dopaminergic drug methylphenidate (Ritalin) did not produce similar changes. These changes in cognitive function and psychomotor skills occurred during peak drug effects but were not detectable 24 hours later.

Retrospective surveys of people who had used MDMA or ecstasy offered similar accounts of MDMA effects to those observed and reported in controlled studies. These studies surveyed or interviewed members of several populations, including college students, psychotherapists, and individuals recruited via word of mouth or in public spaces. Study respondents reported experiencing stimulant-like effects, as greater energy or talkativeness, and hallucinogen-like effects, as perceptual changes or poor concentration. They also reported that MDMA/ecstasy increased feelings of closeness, compassion or empathy toward the self or others (Cohen 1995; Liester et al. 1992; Peroutka et al. 1988; Solowij et al. 1992). The disparity in detection of entactogenic findings in retrospective versus controlled studies is largely due to failure to measure these effects, but might also relate to aspects of setting in controlled studies that do not permit enough unstructured interpersonal contact to produce or facilitate feelings of interpersonal closeness.

3. Pharmacokinetics and biological disposition

MDMA is metabolized in the liver and has a half-life of seven to nine hours (de la Torre et al. 2004), though a half-life of 11 hours has been reported (Pizarro et al. 2004) and is distributed throughout the body (De Letter et al. 2004), though a study in rats reported greater disposition in brain than in plasma (Chu et al. 1996). After 100 mg MDMA, T_{max} is reached at 2 hours, at a time close to peak physiological and subjective effects, and urinary recovery over a 24 hour period is 15% (de la Torre et al. 2004). The pharmacokinetics of MDMA have been primarily characterized by a group of Spanish researchers, with the exception of one publication from researchers in the Netherlands. The Spanish team first reported nonlinear pharmacokinetics for MDMA, findings that are confirmed in recent studies in nonhuman primates (Mechan et al. 2006). MDMA is metabolized by several CYPD enzymes, including but not limited to CYP2D6, CYP1A2 and CYP3A4. Monoamine oxidase and catechol-O-methyltransferase (COMT) also metabolize MDMA.

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Metabolites of MDMA which have been identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called α -methyldopamine), 3,4-dihydroxymethamphetamine (DHMA, also called HHMA), 3,4-methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999).

Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996). Subsequent studies examining metabolism after 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates (Farre et al. 2004; Pizarro et al. 2004; Pizarro et al. 2003; Pizarro et al. 2002; Segura et al. 2001). Urinary excretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8 ± 23.8 mol and 17.7% recovery (Segura et al. 2001). By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% (de la Torre et al. 2004). As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA (Farre et al. 2004).

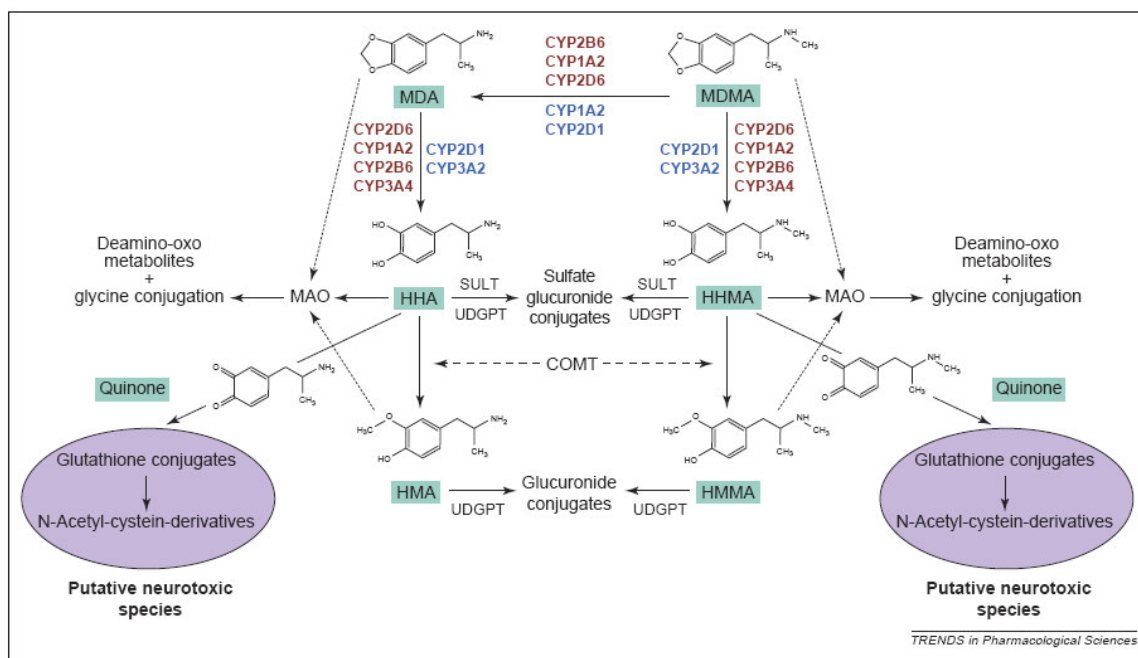


Figure 1: Metabolism of MDMA in rats and humans; enzymes involved in human metabolism in red ink. Reproduced with permission of R de la Torre.

4. Safety and effectiveness in humans obtained from prior clinical studies

When Merck first patented MDMA, it was solely as an intermediate step toward the production of another compound (Freudenmann et al. 2006), and there were no early clinical investigations of MDMA. Published accounts of MDMA-assisted psychotherapy first appeared during the time of hearings for the scheduling of MDMA (Adamson 1985). Shortly afterwards, the only published study of MDMA-assisted therapy appeared, an uncontrolled study conducted in 29 individuals with mild to moderate psychiatric problems (Greer and Tolbert 1986). These accounts suggested that, when combined with psychotherapy in a supportive setting, MDMA offered benefits to people experiencing various forms of anxiety disorder, including PTSD and anxiety in association with a life-threatening illness. The Swiss government permitted psychotherapists to conduct MDMA-assisted psychotherapy between 1988 and 1993 (Gasser 1994; Widmer 1998). These therapists reported that MDMA-assisted psychotherapy was tolerated and did not report any serious adverse events occurring after MDMA administration. The Swiss

psychotherapists did not publish any formal analyses of the treatment. Permission to conduct MDMA-assisted psychotherapy in Switzerland was revoked due to events unrelated to the safety or efficacy of MDMA and due to the lack of any published research results.

Narrative accounts report that individuals experienced less anxiety and sometimes reported feelings of reconciliation with the self or others or greater positive attitudes after MDMA-assisted psychotherapy (Greer and Tolbert 1998; Metzner and Adamson 2001). A majority of the participants in the uncontrolled study of MDMA-assisted psychotherapy followed two months to two years later reported experiencing increased positive mood and more positive attitude changes since undergoing MDMA-assisted therapy (Greer and Tolbert 1986).

To date, there are four investigations underway to study the safety and efficacy of MDMA-related psychotherapy in people with PTSD and in people with anxiety arising from diagnosis with advanced-stage cancer (Halpern 2006). Three planned or ongoing investigations to date are sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), a member-based nonprofit organization dedicated to supporting and developing research into the therapeutic potential of MDMA and psychedelic drugs. The fourth is sponsored by John Halpern MD.

MDMA-assisted psychotherapy for PTSD

Two studies of MDMA-assisted psychotherapy in people with PTSD are underway, one in South Carolina and the other in Switzerland. A third study is nearly underway in Israel. None of these studies are complete as of yet. The first study has enrolled all or nearly all study participants, and the second has enrolled approximately half of the planned participants.

Michael Mithoefer MD has enrolled nineteen participants in a randomized, placebo-controlled study of MDMA-assisted psychotherapy in 20 people with PTSD symptoms that have not responded to psychotherapy or pharmacotherapy, and a 21st subject who will be a veteran with PTSD who has not been willing or able to receive these treatments. He has enrolled all participants, but to date only 16 participants have completed the study. The study includes an open-label continuation for participants who received placebo during the course of the study. MDMA-assisted psychotherapy is conducted during two extended sessions as part of a course of psychotherapy (Mithoefer 2006). Participants who received MDMA during the course of the study are eligible for a third open-label session as well. An independent rater assesses psychotherapy symptoms at the start of the study and two months after participants have had their second MDMA-assisted therapy session. The original study design involved the administration of 125 mg MDMA, and the current design allows for a supplemental administration of 62.5 mg approximately 2.5 hours after the initial dose. MDMA has been tolerated in participants, and there have been no drug-related serious adverse events to date. An informal analysis of preliminary data suggests that participants assigned to receive MDMA experience fewer PTSD symptoms two months after the second MDMA or placebo-assisted session.

There is no indication that receiving MDMA is associated with any changes in cognitive function.

Peter Oehen MD, the principal investigator for the study underway in Switzerland, is assessing the effects of MDMA-assisted psychotherapy in twelve people with PTSD. So far, he has enrolled up to seven participants in this study, and five have undergone at least one MDMA-assisted psychotherapy session. This study is nearly identical to the investigation underway in the US except that it is active placebo controlled, with 25 mg MDMA as the active placebo and a booster dose of 62.5 or 12.5mg respectively after 2.5 hours, and participants undergo three instead of two MDMA-assisted psychotherapy sessions. One individual dropped out of the study owing to distress during the first of three MDMA-assisted sessions, the previous pharmacological treatment was then reinstalled immediately.

A study of MDMA-assisted psychotherapy in twelve people with war or terrorism-related PTSD is recruiting participants and will take place in Israel sometime in early 2008. The study will follow procedures similar to those described in the US and Swiss studies. To date, no one has undergone an MDMA-assisted session in this study.

MDMA for anxiety arising from diagnosis with a potentially life-threatening illness

A randomized, active placebo controlled dose-response study of MDMA-assisted psychotherapy in twelve people with anxiety arising from diagnosis with advanced stage cancer is underway at McLean Hospital, affiliated with Harvard Medical School. John Halpern, MD is currently recruiting participants for this study involving two MDMA-assisted sessions, and will include introductory sessions beforehand and integrative sessions after each MDMA-assisted session. This study also employs 25 mg MDMA followed by 12.5 mg, administered during both occasions, as an active placebo. Participants in the active dose condition will receive 83.3 mg and 41.7 mg during their first MDMA-assisted session, producing a cumulative dose of 125 mg, and 125 mg followed by 62.5 mg during the second session. No participants are enrolled in this study to date.

MDMA and Parkinson's disease

Studies in rodents and nonhuman primates have examined the effects of MDMA and related compounds in alleviating the symptoms of Parkinson's disease (PD), which include slow, halting movements, or in treating dyskinesia, involuntary movements and twitches that can arise from using medications to treat the condition (Iravani et al. 2003; Lebsanft et al. 2005a; Lebsanft et al. 2005b; Sotnikova et al. 2005). Researchers found that MDMA and other entactogens, such as MDE, could attenuate abnormally slow movements in rodents without functioning dopamine systems (Sotnikova et al. 2005), and that monkeys with dopamine systems damaged by MPTP also improved after treatment with MDMA (Iravani et al. 2003). While this program of research is likely inspired by the account of a former stuntman with young-onset PD, there are no human trials of MDMA or any other entactogenic compound as a possible treatment for PD or PD-related dyskinesias underway. Because of the sympathomimetic effects of MDMA and the potential of MDMA neurotoxicity with daily dosing, it seems unlikely that MDMA

will be developed as a medication for PD. It appears that the anti-Parkinsonian effects of MDMA may be due at least in part to indirect activation of 5HT_{1A} receptors, and perhaps to activation of trace amine receptors (Bishop et al. 2006; Sotnikova et al. 2005).

5. Possible Risks and Side Effects

Overview

MDMA was administered to perhaps thousands of people prior to scheduling, and as of late 2007, it has been administered to approximately 300 people in uncontrolled and controlled studies. People continue to use ecstasy around the world in various non-medical settings (Beck and Rosenbaum 1994; Carlson et al. 2005; Cole and Sumnall 2003a; Solowij et al. 1992; Sumnall et al. 2006), including dance events, large gatherings, concerts and small parties. While a number of serious adverse events, including fatalities, have been reported after ecstasy use in unsupervised and uncontrolled settings, these events are relatively rare given the prevalence of ecstasy use (Baggott 2002; Gore 1999). Drug-related serious adverse events have not occurred in any of the human MDMA research studies so far. In 2005, the number of MDMA/ecstasy related emergency room visits logged into the Drug Abuse Warning Network (DAWN) was 10,752 of approximately 1,449,154 ED visits related to any form of drug, approximately 0.007% or calculated to be 3.6 per population of 100,000 (Substance Abuse and Mental Health Services Administration 2007). Operating on national survey data on drug use and emergency department admissions in the US and a study of Australian polydrug users, Baggott and colleagues estimated that between 2.9 and 11 emergency department visits might arise from 10,000 uses of ecstasy (Baggott et al. 2001, pp. 148-150).

Fatalities

Fatalities have occurred after the use of MDMA or related drugs in non-medical settings (Baggott et al. 2001; Henry and Rella 2001). Ecstasy-related fatalities are rare (Baggott 2002; Gore 1999). Most are related to hyperthermia and complications arising from hyperthermia. Other causes of death include hyponatremia and cardiac events (as arrhythmias or heart attack). Some ecstasy-related fatalities may be due to reckless behavior, such as driving under the influence of ecstasy. Baggott and colleagues found that men outnumbered women in most ecstasy-related fatalities except in the case of hyponatremia, where women outnumbered men (Baggott et al. 2001). The association between MDMA/ecstasy and fatalities is generally dose-dependent, except in the case of hyponatremia-related fatalities (see for example Greene et al. 2003). At least half the ecstasy-related fatalities listed seem to involve use of other drugs (Gilhooly and Daly 2002; Raikos et al. 2002; Schifano et al. 2003).

Common Adverse Effects and Side Effects

Common adverse and side effects of MDMA include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils (Cami et al. 2000; Harris et al. 2002; Liechti et al. 2001b; Mas et al. 1999). Some reports indicated decreased rather than increased alertness (Cami et al. 2000). Other common side effects reported in controlled studies of MDMA are listed in Table 2 and include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, impaired gait or balance,

dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or facilitated recall (Vollenweider et al. 1998), and unusual thoughts or ideas (Harris et al. 2002). Other less common side effects include parasthesias (unusual body sensations) such as tingling sensations, or feeling hot or cold. These effects are transient and recede with the waning of drug effects. One study found that women were more likely than men to experience most commonly reported side effects of MDMA, though men were more likely than women to experience the specific side effects of nausea and sweating (Liechti et al. 2001b).

Sub-acute effects appearing 24 to 48 days after MDMA include insomnia, fatigue, weakness, heavy legs, dry mouth, low mood or irritability (Baggott et al. 2001; see also Liechti et al. 2001a), with sub-acute effects waning by or within 72 hours of MDMA administration. While ecstasy users in naturalistic studies reported increased feelings of depression or aggressiveness four days after taking ecstasy (Hoshi et al. 2007a; Verheyden et al. 2003), far fewer participants in controlled studies report mood-related sub-acute effects. Naturalistic studies examining the time course of sub-acute effects of ecstasy use have reported that a similar trajectory for side effects, with sub-acute effects most apparent three to four days later and no longer apparent seven days later (Hoshi et al. 2004; Huxster et al. 2006). The possibility of long-term effects is discussed in more detail below.

Table 3: Acute Side Effects of MDMA

	Overall Incidence After Placebo	Overall Incidence After MDMA	Downing 1986	Gamma et al. 2000	Greer & Tolbert 1986	Liechti, Saur, et al. 2000	Liechti & Vollenweider 2000a	Liechti & Vollenweider 2000b	Vollenweider et al. 1998
N:	13-57	13-112	10	16	29	14	14	16	13
MDMA Dose(s):	0	0.5-4.18 mg/kg	1.76-4.18 mg/kg	1.7 mg/kg	75-150, 200 mg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	1.7 mg/kg
Measurement Time:	-	-	2-5 h	?	?	?	?	?	0-360 min
Lack Of Appetite	2%	70%	100%	63%	97%	50%	50%	50%	62%
Jaw Clenching	0%	63%	60%	64%	76%	57%	71%	44%	62%
Dry Mouth	Na	57%	na	na	Na	57%	57%	na	na
Thirst	4%	48%	na	50%	Na	57%	57%	38%	38%
Restless Legs	0%	45%	na	na	Na	na	na	44%	46%
Impaired Balance/Gait	0%	44%	70%	na	10%	71%	43%	50%	62%
Difficulty Concentrating	16%	42%	30%	50%	3%	71%	50%	63%	62%
Dizziness	2%	40%	na	na	Na	57%	21%	50%	31%
Restlessness	0%	39%	na	na	Na	50%	29%	44%	31%
Sensitivity To Cold	7%	38%	na	na	Na	na	na	na	38%
Private Worries	23%	38%	na	na	Na	na	na	na	38%
Heavy Legs	0%	38%	na	na	Na	na	na	na	38%
Palpitations	0%	33%	na	38%	Na	43%	21%	na	31%
Feeling Cold	4%	33%	na	na	Na	43%	na	na	23%
Perspiration	0%	30%	na	50%	Na	36%	na	na	0%
Drowsiness	50%	23%	na	na	14%	43%	na	na	na
Nystagmus	Na	23%	80%	na	3%	na	na	na	na
Hot Flashes	0%	23%	na	na	Na	na	na	na	23%
Nausea	4%	21%	10%	na	24%	36%	na	na	8%
Trismus	Na	21%	na	na	3%	57%	na	na	na
Inner Tension	0%	17%	na	na	3%	43%	14%	19%	23%
Insomnia	0%	17%	0%	na	Na	na	na	na	31%
Anxiety	0%	16%	na	na	17%	14%	na	na	na
Weakness	0%	16%	na	na	3%	36%	na	na	23%
Urge To Urinate	8%	15%	na	na	Na	na	na	na	15%
Tremor	0%	14%	na	na	3%	21%	14%	na	31%
Muscle Aches / Tension	Na	14%	na	na	21%	na	na	na	0%
Forgetfulness	0%	14%	na	na	3%	na	na	na	38%
Fatigue	26%	13%	na	na	7%	na	29%	na	8%
Parasthesias	0%	12%	na	na	3%	na	na	na	31%
Lack Of Energy	14%	12%	na	na	3%	29%	na	na	na
Brooding	0%	12%	na	na	3%	29%	na	na	na
Fainting	Na	3%	na	na	3%	na	na	na	na
Blurred Vision	Na	3%	na	na	3%	na	na	na	na
Lip Swelling	Na	2%	na	na	3%	na	na	na	0%
Headaches	Na	2%	0%	na	3%	na	0%	na	na

na: not available

Reproduced from Baggott et al. 2001

Medical Emergencies and Adverse Events in Ecstasy Users

An examination of the literature published up through early 2001 located over 205 published case reports or case series concerning adverse events after ecstasy use. The most frequently reported events were hyperthermia (25.1% of 199 case reports), psychological symptoms or psychosis (22.1% of 199), hepatotoxicity, or liver conditions and problems (16.1% of 199 cases), and hyponatremia (9.5%) accounted for the majority of the serious adverse events after ecstasy use (Baggott et al. 2001). A second examination of the literature in 2004 found that these continued to be the most frequently reported problems reported in literature assessed after the initial examination (Jerome 2004), with only two new conditions reported in the literature, gingivitis from maintaining an ecstasy tablet between the lips and gum (Brazier et al. 2003), and chorioretinopathy, an eye condition sometimes associated with use of sympathomimetic drugs that cleared up after cessation of use (Michael et al. 2003). Set and setting may play a role in the development of some ecstasy-related adverse events, such as rigorous exercise, lack of attention to somatic cues and too little or too much hydration in the case of hyperthermia and hyponatremia (Henry and Rella 2001). Hall and Henry address medical emergencies related to ecstasy use, describing all events mentioned in Baggott and colleagues (Hall and Henry 2006). While case reports do not provide an appropriate basis for estimating the relative frequency of these events, they can provide information on the possibility of an event occurring. Most ecstasy-related emergency department admissions are the result of people experiencing anxiety or panic reactions after use and involve supportive care only (Cregg and Tracey 1993; Liechti et al. 2005; Williams et al. 1998). It is notable that none of these events has occurred during a human MDMA study, so that even psychological distress has not required pharmacological intervention or hospitalization.

Other serious adverse events occurring after ecstasy use include cardiac problems (as arrhythmias), cerebrovascular events, hematological, respiratory events (as pneumostadium), dermatological, ophthalmological and dental events (Baggott et al. 2001). As with the four most common serious adverse events, none of these events have occurred in the context of human MDMA research.

In vitro and in vivo investigations of the effects of MDMA on cardiac, hepatic (liver) and kidney tissues or cells have occurred over the past ten years (Baggott et al. 2001; Jerome 2005) (see for example Beitia et al. 2000; Caballero et al. 2002) (Varela-Rey et al. 1999). Researchers conducting in vitro studies often use large doses (in micromoles) that are unlikely to occur after a typical human dose. At these high or extremely high doses, MDMA damages liver cells, particularly under warm ambient temperature, possibly mimicking hyperthermia-related hepatotoxicity in humans. In one case series of postmortem heart tissue, Patel and colleagues determined that 58.3% of the hearts from ecstasy-associated deaths were larger than normal versus 18.7% of the hearts from non-ecstasy related deaths (Patel et al. 2005). Since myocardial hypertrophy (an enlarged heart) is associated with stimulant use, and given the large extent of polydrug use in ecstasy users, this study cannot rule out the possibility that the increase they saw was not a result of psychostimulant use. A recent retrospective comparative study using echocardiograms in 29 heavy ecstasy users (reporting use of 3.6 tablets per week) and 29

age and gender matched undergraduate controls detected abnormalities indicative of potential valvular heart disease (VHD) in eight ecstasy users and none in controls, though less pronounced than abnormalities seen in people taking the anti-Parkinson's disease medication pergolide (Droogmans et al. 2007). The average cumulative dose in people with detectable abnormalities was 943 +/- 1162 tablets versus 242 +/-212 tablets in those without abnormalities). The authors hypothesize that the observed cardiac changes in ecstasy users were less prominent than in people taking pergolide because of weekly rather than daily use, and because drug-induced VHD is reversible. Given the extensive and frequent use in this sample, the risk of similar cardiac abnormalities developing in people taking part in human MDMA studies is very low. However, these findings also suggest that regular use of ecstasy may have some of the same risks as regular use of other 5HT_{2B} agonists, as some migraine medications and the appetite suppressant fenfluramine.

Long-Term Effects

Central Serotonin Function, Cognition and Affect: Retrospective Studies

There is a wealth of research examining the effects of repeated doses of MDMA in nonhuman animals (Cole and Sumnall 2003b; Green et al. 2003). Findings included reduction in brain serotonin, signs of impaired transport of serotonin and some behavioral changes, as increased anxiety (Callahan et al. 2001; Gurtman et al. 2002; Hatzidimitriou et al. 1999). These findings suggested that MDMA could damage serotonin axons, producing a form of neurotoxicity. However, as noted earlier, the majority of these studies employed large doses of MDMA that overestimated human-equivalent doses. It now appears that lower doses of MDMA fail to reduce brain serotonin. Monkeys allowed to self-administer MDMA for an 18-month period had no reductions in brain dopamine, slight reductions in brain serotonin and no chemical markers of neuronal injury (Fantegrossi et al. 2004), and rats receiving lower doses of MDMA do not exhibit signs of neurotoxicity, such as changes in serotonin transporter sites or markers of neuronal injury (Wang et al. 2005). While a recent report detected increases in one marker of neuronal injury without detecting any decreases in brain serotonin after administering two human-equivalent doses of MDMA to rhesus monkeys for two days (Meyer et al. 2006). However, studies in very moderate ecstasy users failed to see an increase in this marker (de Win et al. 2007), and only one of three studies of this marker in humans detected it in heavy users (Chang et al. 1999; Cowan et al. 2007; Reneman et al. 2002).

Changes in Serotonin Function and Indicators of Neuronal Injury or Repair

Spurred on by nonhuman animal studies that found that repeated or high doses of MDMA damaged the axons of serotonin neurons, researchers began studying the effects of repeated non-medical or recreational use of ecstasy in humans (see for example Krystal et al. 1992; McCann et al. 1999; McCann et al. 1994; Semple et al. 1999). These studies detected differences in mood and cognition in ecstasy users, and possible changes in brain serotonin uptake sites. Researchers assumed that if MDMA reduced serotonin function, it should produce observable effects, as reduced brain serotonin uptake sites or changes in mood or psychological well-being. These early investigations possessed a number of methodological flaws, including retrospective design and poor matching of

ecstasy users with appropriate controls (Baggott et al. 2001; Gouzoulis-Mayfrank and Daumann 2006a; b). Later studies sought to remedy some of these problems by using carefully matched polydrug user or cannabis user controls, or by relying on a sample with relatively low exposure to psychoactives, including alcohol (Buchert et al. 2004; Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004; Thomasius et al. 2003). Some of these investigators also conducted longitudinal studies, comparing ecstasy users, sometimes alongside controls, at two separate time points (Daumann et al. 2004b; Gouzoulis-Mayfrank et al. 2005); (Buchert et al. 2006; Zakzanis and Campbell 2006; Zakzanis and Young 2001). For the most part, these studies suggested that heavy but not moderate ecstasy users had impaired verbal memory and lower numbers of estimated SERT sites, with heavy use often defined as being at or greater than 50 times or tablets. Estimated SERT sites returned to control levels after sustained abstinence from ecstasy, while cognitive function did not return to control levels (though see Zakzanis and Campbell 2006). These studies failed to find improved cognitive function after abstinence from ecstasy use, and they failed to find further deterioration after continued use. The different pattern of findings for SERT sites and cognitive function suggested that changes in one domain should not be treated as an indicator of changes in another domain.

Impaired Cognitive Function

Two recent findings concerning cognitive function in ecstasy users have appeared in the literature, with one finding measuring a facet of visual perception and the other pertaining to effects of anxiety over confirming others' negative views might have on ecstasy user participants. In a study of "heading," or perceived self-motion, in ecstasy users and cannabis user controls, Rizzo and associated found that both ecstasy and cannabis users had difficulties with "heading" in a simulated visual perception task, with ecstasy users performing less well than cannabis users under angles (Rizzo et al. 2005). Study participants had to a minimum lifetime ecstasy use of at least ten occasions, and average cumulative use was 36.9 +/- 32.1 occasions, with an average period of abstinence of roughly half a year (226.9 +/- 134 days). Hence while cumulative use was lower than in other studies of cognitive function in ecstasy users, it is greater than expected during human MDMA studies. Ecstasy users performing tests of cognitive function may be affected by stereotype threat, the fear of confirming negative beliefs people hold about a specific group membership, as race or gender. When ecstasy users heard from investigators that ecstasy use had no effects on memory, they scored higher on measures of memory than ecstasy users given information stating that ecstasy use impairs memory, while both groups of ecstasy users scored similarly to non-user controls on measures of executive function (Cole et al. 2006). Hence it may be the case that findings of impaired cognitive function in ecstasy users are due in part to the disruptive effects of stereotype threat.¹

Two independent meta-analyses (cross-study statistical analyses) of memory in ecstasy users arrived at somewhat contradictory conclusions (Laws and Kokkalis 2007; Zakzanis et al. 2007). While both analyses detected an association between ecstasy use and impaired performance on at least some measures of memory, one analysis, that of Laws and Kokkalis, reported that this association had a medium to large effect size and found

¹ The author of this document is a coauthor of the paper on the effects of stereotype threat on memory.

no effect of ecstasy dose, while the other, that of Zakzanis and colleagues, reported that the association had a small to medium effect size and found a dose effect. Zakzanis and colleagues also concluded that use of other drugs independently impaired cognitive function, while Laws and Kokkalis failed to find an association between cannabis use and verbal memory performance, relating it instead to visual memory performance. It is unclear why the two analyses reached somewhat different conclusions. Both examined a similar though not identical set of retrospective studies. It is important to note that minimum cumulative use in both analysis was above ten uses, and that average cumulative use was considerably higher (287 tablets in Zakzanis' analysis and 327 in Laws and Kokkalis' paper).

Previous research has established a link between repeated ecstasy use and impaired executive function, defined here as planning, decision-making, and inhibiting a well-learned response (Baggott et al. 2001; Cole and Sumnall 2003; Jerome 2005). The nature and strength of the association between regular ecstasy use and impaired executive function remains inconclusive, with some reports finding impaired executive function in ecstasy users, particularly heavy users (Halpern et al. 2004; Wareing et al. 2004) while others failed to find differences between ecstasy user and non-user executive function (Thomasius et al. 2003), or found executive function impairments only in male ecstasy users (von Geusau et al. 2004). Current studies continue to support both presence and absence of a relationship between ecstasy use and executive function. It is possible that polydrug use may also contribute to ecstasy users' impaired executive function (Hoshi et al. 2007b; Medina and Shear 2006).

Psychological Well-being, Affect, Impulsivity, and Sleep

Previous reports had found an association between ecstasy use and reporting greater increases in symptoms of depression or anxiety (see for example MacInnes et al. 2001; Parrott et al. 2000). A meta-analysis of self-reported depressive symptoms detected an association between ecstasy use and scores on the Beck Depression Inventory, a popular self-report measure of depression symptoms (Sumnall and Cole 2005). Sumnall and Cole noted that the association was strongest in studies with small samples, and noted that drug use variables are often incompletely reported and not verified through any methods save self-report in these studies. Findings concerning the long-term effects of ecstasy use on mood, including findings from longitudinal studies, suggested that an association between increased feelings or symptoms of anxiety and depression and ecstasy use exists, but that these findings were more strongly related to polydrug use rather than to use of any one substance (Milani et al. 2004; Sumnall et al. 2004) (Medina and Shear 2006). Some studies found that continued use of cannabis rather than ecstasy was associated with self-reported psychological problems (Dafters et al. 2004; Daumann et al. 2004a; Daumann et al. 2001). At least one study found an association between possessing a genetic variation on the serotonin transporter gene and increased self-reported depression in heavy ecstasy users (Roiser et al. 2006), and another study reported finding greater self-reported psychological problems in ecstasy users than cannabis users, though the two samples did not differ on memory task performance (Lamers et al. 2006). On the other hand, a study of heavy ecstasy users failed to find any increase in diagnosis of depression (de Win et al. 2004), and two studies examining large samples of ecstasy users either

failed to find increased depressive symptoms or found increased symptoms only in a subset of heavy users (Falck et al. 2006; Guillot and Greenway 2006).

The relationship between ecstasy use and impulsivity has also been extensively examined, with some researchers reporting greater impulsivity in ecstasy users while others failing to find any differences (see for example McCann et al. 1994; Morgan 1998). Recent studies using both behavioral and self-report measures of impulsivity reached contradictory conclusions (Morgan et al. 2006; Quednow et al. 2007; Roiser et al. 2007). Two recent studies even used the same measure of behavioral impulsivity in samples of heavy ecstasy users, yet obtained different findings concerning the relationship between ecstasy use and impulsivity (Quednow et al. 2007; Roiser et al. 2007). It is possible and likely that people who self-administer ecstasy may already possess above-average levels of sensation-seeking and impulsiveness. To date, all such studies have used retrospective study designs and cannot rule out this possibility. Taken together, self-reported changes or deterioration in psychological well-being and impulsivity in ecstasy users are likely multiply determined and only partially, if at all, uniquely related to ecstasy use.

Drawing conclusions from retrospective studies continued to raise questions concerning the strength and causal link between findings, especially when studies in representative samples suggested that people who chose to use ecstasy and other drugs were liable to have psychological problems prior to use (Huizink et al. 2006; Lieb et al. 2002), and given the fact that polysubstance use is so prevalent among ecstasy users (Gouzoulis-Mayfrank and Daumann 2006a). It is notable that some of the most recent studies have either found that polydrug use was equally associated with impaired cognitive function as was ecstasy use (Hoshi et al. 2007b), or that use of cannabis or other drugs make additional and even greater contributions to differences between ecstasy users and controls (Jager et al. 2007a; Montgomery and Fisk 2007).

Researchers at Johns Hopkins University have investigated the effects of regular ecstasy use on sleep (Allen et al. 1993; McCann et al. 2007). Their earlier study reported detecting less stage II sleep, while a recent study found some differences between ecstasy users and controls, in this case, including less stage II sleep and less reduction in sleep latency after administering a compound that reduced catecholamine neurotransmitters (McCann et al. 2007). To date, no other researchers have examined sleep in ecstasy users, but both studies consisted largely of samples of heavy ecstasy users, and the recent study detected an association between degree of ecstasy use and effects on sleep.

Prospective Studies

The Netherlands XTC Toxicity team mentioned at the beginning of this document is the first to perform prospective research studies comparing ecstasy users before and after their first few uses, sometimes comparing them with controls who have not yet taken ecstasy (De Win et al. 2005). Average cumulative use in these studies ranged from 1.8 to 6 tablets, and maximum use in two of three studies was 10 tablets. In one study, the researchers imaged the brains of 30 people before and approximately seven weeks after having used ecstasy. They failed to find any chemical markers of neuronal injury in

ecstasy users, and they found very few changes in cerebral blood flow, with the exception of decreased cerebral blood volume in the dorsolateral frontal cortex (De Win 2006). Another study examined working memory in 25 people reporting an average use of 2 tablets with 24 controls, failing to find any significant differences either in brain activity as assessed via functional magnetic imagery (fMRI) or on tests of working memory and selective attention (Jager et al. 2007b). A study examining self-reported depression symptoms, failed to find an association between low ecstasy use and symptoms of depression, though they also failed to find a relationship between symptoms of depression and likelihood of taking ecstasy (de Win et al. 2006). Finally, a study comparing 58 people reporting use of 3.2 tablets with 60 controls before and after use, up to 18 months later, and found an association between ecstasy use and performance on measures of verbal memory, and not attention or working memory (Schilt et al. 2007). While all participants exhibited scores within the normal range both times they were tested, people who did not use ecstasy showed greater improvement in performance than did people who used it. Analyses in the study assessing cognitive function apparently included one individual reporting higher cumulative ecstasy use, 30 tablets. In contrast, data from a prospective controlled study that was presented at a conference failed to find impaired cognitive function in drug-naïve individuals after two doses of 1.5 to 1.7 mg/kg MDMA (Ludewig S et al. 2003). Taken together, a majority of the prospective studies failed to find indications of structural or functional change after low ecstasy use, while one study found impairment in memory after low to moderate use. While these prospective studies do not and cannot demonstrate either a definite lack or presence of long-term effects from a few exposures to MDMA, they did not find the types of changes seen in heavy ecstasy users, and they suggest that risks of long-term effects associated with taking part in human MDMA studies are low.

Conclusions

Many studies in nonhuman animals suggest that frequent or high doses of MDMA can damage serotonin neurons, and some studies in ecstasy using humans suggest that repeated use, especially when heavy, can affect serotonergic function and specific domains of cognitive function. Ecstasy users exhibit impairment in specific areas of cognitive function, particularly verbal memory. However, when apparent, most long-term effects seem to be more strongly associated with heavy and not moderate use. The risk of impaired serotonin function or verbal memory after exposure to one to three doses of MDMA in the course of a controlled study remains possible, but evidence from retrospective and prospective studies of ecstasy users suggest that this risk is minimal after a low number of exposures. While there may also be risks related to psychological well-being such as increased symptoms of anxiety or depression, support for these long-term effects are even less strong than for the previously listed changes.

Abuse Potential

The US Drug Enforcement Administration (DEA) placed MDMA in Schedule 1, the most restrictive schedule reserved for compounds with high abuse potential and no medical value, and most other nations followed the lead of the US in making MDMA a tightly controlled substance. Studies in humans and nonhuman animals suggest MDMA possesses some abuse potential. However, it also appears that MDMA has fewer or less

intensely rewarding effects than psychostimulants, and even heavy ecstasy users fail to report the intensive patterns of use seen with other stimulants. Hence MDMA possesses moderate abuse liability that is greater than abuse liability for serotonergic hallucinogens but lesser than for psychostimulants.

Mice, rats and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006), indicating that MDMA has rewarding properties in nonhuman animals. Monkeys chose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans (Fantegrossi et al. 2004), but they reduced their MDMA intake over time. While monkeys will work hard to obtain MDMA, they will work harder to obtain other psychostimulants, such as cocaine or methamphetamine (Lile et al. 2005; Wang and Woolverton 2007). Of the small number of individuals assessed in a representative sample of Munich residents aged 14 to 24, only 1% were diagnosed with ecstasy abuse and 0.6% with dependence (von Sydow et al. 2002), though other reports of non-representative samples have reported higher percentages of MDMA abuse or dependence (Cottler et al. 2001), and approximately 25% of polydrug users who had used ecstasy reported abuse or dependency (Topp et al. 1999).

Reproductive and Developmental Toxicity

Previous research supported a possible link between ecstasy use and birth defects (McElhatton et al. 1999), while an epidemiological study conducted in 2004 in a large cohort of pregnant women in England failed to support this link, at least in respect to a specific cardiac defect (Bateman et al. 2004). However, the authors also stated that exposure to MDMA in their sample was too low to establish risk. An earlier survey of a drug-using population suggests that most women cease using ecstasy when they learn they are pregnant (Ho et al. 2001).

Several teams of researchers have performed studies of developmental toxicity in rodents (see for example (Koprach et al. 2003a; Koprach et al. 2003b; Piper and Meyer 2004; Williams et al. 2005)). In some studies, the researchers administered large, repeated doses to pregnant rats, and in others, the MDMA was administered to neonatal rats. The researchers did not report gross structural abnormalities in rats exposed to high doses of MDMA in utero. However, studies of MDMA in neonatal rats found changes in numbers of serotonin or dopamine cells and impaired learning or memory, particularly when MDMA was administered from the 11th to the 20th day after birth. If this period is similar to the third trimester of human gestation, then it is possible that MDMA in humans could have similar developmental effects. Some researchers found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA (Green et al. 2005), while others found that it attenuated this response (Piper et al. 2005). Given differences in rodent development and thermoregulation, it is not clear whether either or both findings can be generalized to humans. Because there may be a critical period during which exposure to MDMA could alter development, and as a result of the relative lack of information concerning its developmental toxicity, women who are pregnant or who are not using an effective means of birth control should not receive MDMA.

Some investigators have claimed that MDMA affects sub-adult rats differently than adults. Giving somewhat large doses of MDMA to sub-adult rats produced long-term reductions in anxiety and impaired object recognition (Piper et al. 2004). An initial dose of MDMA in young rats also produced less of an increase in BT and fewer signs of "serotonin syndrome" when given another dose of MDMA in adulthood (Piper et al. 2005). These nonhuman animal studies suggest that adolescents could be more vulnerable to some effects of MDMA.

6. Research trial data

Information is being gathered and prepared. Side effects reported in the first clinical trials are similar to those reported in controlled studies, though anxiety may be more prevalent, due in part to the condition under study and in part to the nature of the setting, as participants are encouraged to confront emotionally upsetting thoughts, memories and feelings. In this setting anxiety is not chiefly viewed as a side effect, but as an element of the underlying disorder and the therapeutic process.

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