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 $\alpha 1$, $5HT_2$, $\alpha 2$ adrenergic receptors, H_1 histamine receptors and acetylcholine muscarinic M_1 receptors, β adrenergic receptors, dopamine D_2 and D_1 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 M_1 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 $5HT_4$ 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 K1 is below 500 mcM. Male rat brain samples used in assays.

Transporter/Receptor	Ki (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	Ki (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-Pyrilamine	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 D_2 receptors, as administering the D_2 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 $5HT_2$ 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 $5HT_2$ family receptors, $5HT_{2B}$ and $5HT_{2A}$, and for α_{2B}, α_{2C}, histamine H_1 and muscarinic M_3 receptors, with strongest affinity recorded for $5HT_{2B}$, α_{2B}, α_{2C} and muscarinic M_3 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 M_1 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; Mechan 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 adrenocorticotropic 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 (Liester 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).

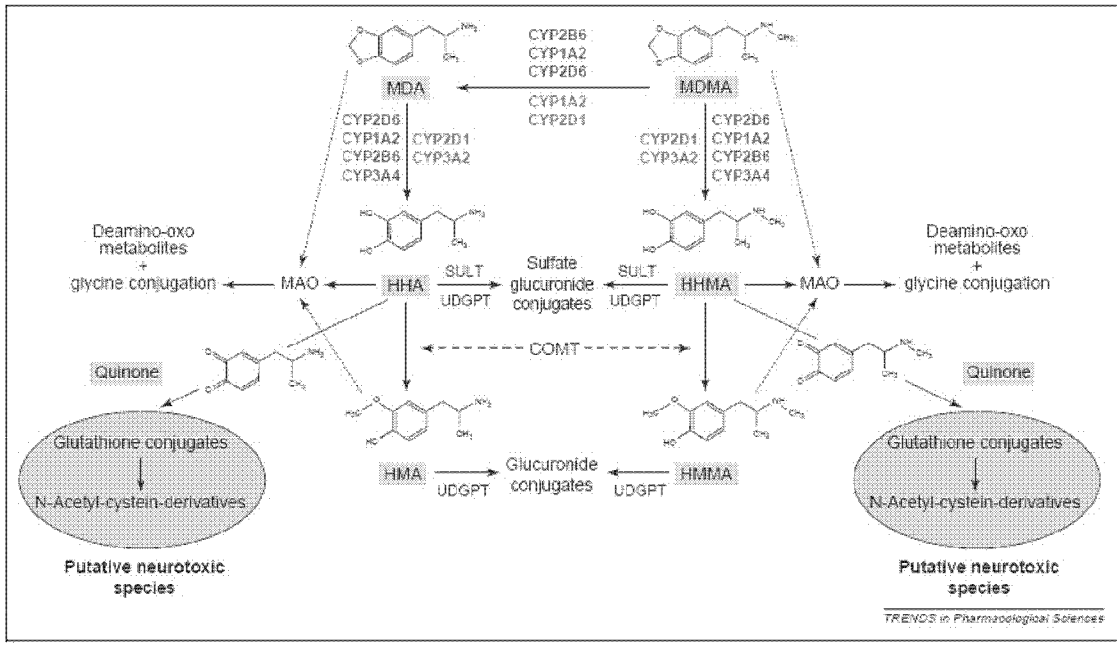

Figure 1: Metabolism of MDMA in rats and humans; enzymes involved in human metabolism in red ink. Reproduced with permission of R de la Torre.

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 planed 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 being 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 390 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 are 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 hours (1 to 2 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	Vollen-weider 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 there 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 (Koprich et al. 2003a; Koprich 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 11^{th} to the 20^{th} 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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References

Acquas E, Pisanu A, Spiga S, Plumitallo A, Zernig G, Di Chiara G (2007) Differential effects of intravenous R,S-(+/-)-3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) and its S(+)- and R(-)-enantiomers on dopamine transmission and extracellular signal regulated kinase phosphorylation (pERK) in the rat nucleus accumbens shell and core. J Neurochem 102: 121-32

Adamson S (1985) Through the gateway of the heart: Accounts of experiences With MDMA and other empathogenic substances. Four Trees Publications, Four Trees Publications

Allen RP, McCann UD, Ricaurte GA (1993) Persistent effects of (+/-)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on human sleep. Sleep 16: 560-4

Anderson GMd, Braun G, Braun U, Nichols DE, Shulgin AT (1978) Absolute configuration and psychotomimetic activity. NIDA Res Monogr 22: 8-15

Baggott M, Jerome L, Stuart R (2001) 3,4-Methylenedioxymethamphetamine (MDMA); A review of the English-language scientific and medical literature Original Investigator's Brochure for MDMA. Multidiscplinary Association for Psychedelic Studies

Baggott MJ (2002) Preventing problems in Ecstasy users: reduce use to reduce harm. J Psychoactive Drugs 34: 145-62

Banks ML, Sprague JE, Kisor DF, Czoty PW, Nichols DE, Nader MA (2007) Ambient Temperature Effects on 3,4-methylenedioxymethamphetamine (MDMA)-induced Thermodysregulation and Pharmacokinetics in Male Monkeys. Drug Metab Dispos

Bankson MG, Yamamoto BK (2004) Serotonin-GABA interactions modulate MDMA-induced mesolimbic dopamine release. J Neurochem 91: 852-9

Bartz JA, Hollander E (2006) The neuroscience of affiliation: forging links between basic and clinical research on neuropeptides and social behavior. Horm Behav 50: 518-28

Bateman DN, McElhatton PR, Dickinson D, Wren C, Matthews JN, O'Keeffe M, Thomas SH (2004) A case control study to examine the pharmacological factors underlying ventricular septal defects in the North of England. Eur J Clin Pharmacol 60: 635-41

Battaglia G, Brooks BP, Kulsakdinun C, De Souza EB (1988) Pharmacologic profile of MDMA (3,4-methylenedioxymethamphetamine) at various brain recognition sites. Eur J Pharmacol 149: 159-63

Baumann MH, Wang X, Rothman RB (2007) 3,4-Methylenedioxymethamphetamine (MDMA) neurotoxicity in rats: a reappraisal of past and present findings. Psychopharmacology (Berl) 189: 407-24

Baylen CA, Rosenberg H (2006) A review of the acute subjective effects of MDMA/ecstasy. Addiction 101: 933-47

Beck J, Rosenbaum M (1994) In Pursuit of Ecstasy: The MDMA Experience. SUNY Press, SUNY Press

Beitia G, Cobreros A, Sainz L, Cenarruzabeitia E (2000) Ecstasy-induced toxicity in rat liver. Liver 20: 8-15

Bexis S, Docherty JR (2005) Role of alpha2A-adrenoceptors in the effects of MDMA on body temperature in the mouse. Br J Pharmacol 146: 1-6

Bexis S, Docherty JR (2006) Effects of MDMA, MDA and MDEA on blood pressure, heart rate, locomotor activity and body temperature in the rat involve alpha-adrenoceptors. Br J Pharmacol 147: 926-34

Bishop C, Taylor JL, Kuhn DM, Eskow KL, Park JY, Walker PD (2006) MDMA and fenfluramine reduce L-DOPA-induced dyskinesia via indirect 5-HT1A receptor stimulation. Eur J Neurosci 23: 2669-76

Bond AJ, Feizollah S, Lader M (1995) The effects of d-fenfluramine on mood and performance, and on neuroendocrine indicators of 5-HT function. J Psychopharmacol 9: 1-8

Bowyer JF, Young JF, Slikker W, Itzak Y, Mayorga AJ, Newport GD, Ali SF, Frederick DL, Paule MG (2003) Plasma levels of parent compound and metabolites after doses of either d-fenfluramine or d-3,4-methylenedioxymethamphetamine

(MDMA) that produce long-term serotonergic alterations. Neurotoxicology 24: 379-90

Brazier WJ, Dhariwal DK, Patton DW, Bishop K (2003) Ecstasy related periodontitis and mucosal ulceration -- a case report. Br Dent J 194: 197-9

Brunner D, Hen R (1997) Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice. Ann N Y Acad Sci 836: 81-105

Buchert R, Thomasius R, Petersen K, Wilke F, Obrocki J, Nebeling B, Wartberg L, Zapletalova P, Clausen M (2006) Reversibility of ecstasy-induced reduction in serotonin transporter availability in polydrug ecstasy users. Eur J Nucl Med Mol Imaging 33: 188-99

Buchert R, Thomasius R, Wilke F, Petersen K, Nebeling B, Obrocki J, Schulze O, Schmidt U, Clausen M (2004) A voxel-based PET investigation of the long-term effects of "Ecstasy" consumption on brain serotonin transporters. Am J Psychiatry 161: 1181-9

Caballero F, Lopez-Navidad A, Cotorruelo J, Txoperena G (2002) Ecstasy-induced brain death and acute hepatocellular failure: multiorgan donor and liver transplantation. Transplantation 74: 532-7.

Callahan BT, Cord BJ, Ricaurte GA (2001) Long-term impairment of anterograde axonal transport along fiber projections originating in the rostral raphe nuclei after treatment with fenfluramine or methylenedioxymethamphetamine. Synapse 40: 113-21.

Cami J, Farre M, Mas M, Roset PN, Poudevida S, Mas A, San L, de la Torre R (2000) Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. J Clin Psychopharmacol 20: 455-66

Carlson RG, Falck RS, McCaughan JA, Siegal HA (2004) MDMA/Ecstasy use among young people in Ohio: perceived risk and barriers to intervention. J Psychoactive Drugs 36: 181-9

Carlson RG, Wang J, Falck RS, Siegal HA (2005) Drug use practices among MDMA/ecstasy users in Ohio: a latent class analysis. Drug Alcohol Depend 79: 167-79

Chang L, Ernst T, Grob CS, Poland RE (1999) Cerebral (1)H MRS alterations in recreational 3, 4-methylenedioxymethamphetamine (MDMA, "ecstasy") users. J Magn Reson Imaging 10: 521-6

Chang L, Grob CS, Ernst T, Itti L, Mishkin FS, Jose-Melchor R, Poland RE (2000) Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow: a co-registered SPECT and MRI study. Psychiatry Res 98: 15-28

Chu T, Kumagai Y, DiStefano EW, Cho AK (1996) Disposition of methylenedioxymethamphetamine and three metabolites in the brains of different rat strains and their possible roles in acute serotonin depletion. Biochem Pharmacol 51: 789-96

Cohen RS (1995) Subjective reports on the effects of the MDMA ('ecstasy') experience in humans. Prog Neuropsychopharmacol Biol Psychiatry 19: 1137-45

Cole JC, Michailidou K, Jerome L, Sumnall HR (2006) The effects of stereotype threat on cognitive function in ecstasy users. J Psychopharmacol 20: 518-25

Cole JC, Sumnall HR (2003a) Altered states: the clinical effects of Ecstasy. Pharmacol Ther 98: 35-58

Cole JC, Sumnall HR (2003b) The pre-clinical behavioural pharmacology of 3,4-methylenedioxymethamphetamine (MDMA). Neurosci Biobehav Rev 27: 199-217

Cole JC, Sumnall HR, Smith GW, Rostami-Hodjegan A (2005) Preliminary evidence of the cardiovascular effects of polysubstance misuse in nightclubs. J Psychopharmacol 19: 67-70

Connor TJ, Kelly JP, Leonard BE (2000) An assessment of the acute effects of the serotonin releasers methylenedioxymethamphetamine, methylenedioxyamphetamine and fenfluramine on immunity in rats. Immunopharmacology 46: 223-35

Cottler LB, Womack SB, Compton WM, Ben-Abdallah A (2001) Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria. Hum Psychopharmacol 16: 599-606

Cowan RL, Bolo NR, Dietrich M, Haga E, Lukas SE, Renshaw PF (2007) Occipital cortical proton MRS at 4 Tesla in human moderate MDMA polydrug users. Psychiatry Res

Crean RD, Davis SA, Taffe MA (2007) Oral administration of (+/-)3,4-methylenedioxymethamphetamine and (+)methamphetamine alters temperature and activity in rhesus macaques. Pharmacol Biochem Behav 87: 11-9

Crean RD, Davis SA, Von Huben SN, Lay CC, Katner SN, Taffe MA (2006) Effects of (+/-)3,4-methylenedioxymethamphetamine, (+/-)3,4-methylenedioxyamphetamine and methamphetamine on temperature and activity in rhesus macaques. Neuroscience 142: 515-25

Cregg MT, Tracey JA (1993) Ecstasy abuse in Ireland. Ir Med J 86: 118-20

Dafters RI (1994) Effect of ambient temperature on hyperthermia and hyperkinesis induced by 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") in rats. Psychopharmacology (Berl) 114: 505-8

Dafters RI, Hoshi R, Talbot AC (2004) Contribution of cannabis and MDMA ("ecstasy") to cognitive changes in long-term polydrug users. Psychopharmacology (Berl) 173: 405-10

Daumann J, Hensen G, Thimm B, Rezk M, Till B, Gouzoulis-Mayfrank E (2004a) 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) 173: 398-404

Daumann J, Jr., Fischermann T, Heekeren K, Thron A, Gouzoulis-Mayfrank E (2004b) Neural mechanisms of working memory in ecstasy (MDMA) users who continue or discontinue ecstasy and amphetamine use: evidence from an 18-month longitudinal functional magnetic resonance imaging study. Biol Psychiatry 56: 349-55

Daumann J, Pelz S, Becker S, Tuchtenhagen F, Gouzoulis-Mayfrank E (2001) Psychological profile of abstinent recreational Ecstasy (MDMA) users and significance of concomitant cannabis use. Hum Psychopharmacol 16: 627-633

Davis WM, Hatoum HT, Waters IW (1987) Toxicity of MDA (3,4-methylenedioxyamphetamine) considered for relevance to hazards of MDMA (Ecstasy) abuse. Alcohol Drug Res 7: 123-34

de Boer D, Tan LP, Gorter P, van de Wal RM, Kettenes-van den Bosch JJ, de Bruijn EA, Maes RA (1997) Gas chromatographic/mass spectrometric assay for profiling the enantiomers of 3,4-methylenedioxymethamphetamine and its chiral metabolites using positive chemical ionization ion trap mass spectrometry. J Mass Spectrom 32: 1236-46

De La Garza R, 2nd, Fabrizio KR, Gupta A (2007) Relevance of rodent models of intravenous MDMA self-administration to human MDMA consumption patterns. Psychopharmacology (Berl) 189: 425-434

de la Torre R, Farre M, Ortuno J, Mas M, Brenneisen R, Roset PN, Segura J, Cami J (2000) Non-linear pharmacokinetics of MDMA ('ecstasy') in humans. Br J Clin Pharmacol 49: 104-9

de la Torre R, Farre M, Roset PN, Pizarro N, Abanades S, Segura M, Segura J, Cami J (2004) Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition. Ther Drug Monit 26: 137-44

De Letter EA, Bouche MP, Van Bocxlaer JF, Lambert WE, Piette MH (2004) Interpretation of a 3,4-methylenedioxymethamphetamine (MDMA) blood level: discussion by means of a distribution study in two fatalities. Forensic Sci Int 141: 85-90

De Win M, Jager, G., Reneman, L., Booij, J., van den Brink, W., Den Heeten, G., et al. (2006) Ecstasy: Is It Safe for the Brain? First Prospective Study on Effects of Low Doses of Ecstasy on the Brain in New Ecstasy Users, Using a Combination of Advanced MR Imaging Techniques and [123I]ß-CIT SPECT Radiological Society of North America (RSNA), Chicago, IL

De Win MM, Jager G, Vervaeke HK, Schilt T, Reneman L, Booij J, Verhulst FC, Den Heeten GJ, Ramsey NF, Korf DJ, Van den Brink W (2005) The Netherlands XTC Toxicity (NeXT) study: objectives and methods of a study investigating causality, course, and clinical relevance. Int J Methods Psychiatr Res 14: 167-85

de Win MM, Reneman L, Jager G, Vlieger EJ, Olabarriaga SD, Lavini C, Bisschops I, Majoie CB, Booij J, den Heeten GJ, van den Brink W (2007) A Prospective Cohort Study on Sustained Effects of Low-Dose Ecstasy Use on the Brain in New Ecstasy Users. Neuropsychopharmacology 32: 458-470

de Win MM, Reneman L, Reitsma JB, den Heeten GJ, Booij J, van den Brink W (2004) Mood disorders and serotonin transporter density in ecstasy users--the influence of long-term abstention, dose, and gender. Psychopharmacology (Berl) 173: 376-82

de Win MM, Schilt T, Reneman L, Vervaeke H, Jager G, Dijkink S, Booij J, van den Brink W (2006) Ecstasy use and self-reported depression, impulsivity, and sensation seeking: a prospective cohort study. J Psychopharmacol 20: 226-35

Domes G, Heinrichs M, Glascher J, Buchel C, Braus DF, Herpertz SC (2007) Oxytocin Attenuates Amygdala Responses to Emotional Faces Regardless of Valence. Biol Psychiatry

Downing J (1986) The psychological and physiological effects of MDMA on normal volunteers. J Psychoactive Drugs 18: 335-40

Droogmans S, Cosyns B, D'Haenen H, Creeten E, Weytjens C, Franken PR, Scott B, Schoors D, Kemdem A, Close L, Vandenbossche JL, Bechet S, Van Camp G (2007) Possible association between 3,4-methylenedioxymethamphetamine abuse and valvular heart disease. Am J Cardiol 100: 1442-5

Dumont GJ, Verkes RJ (2006) A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers. J Psychopharmacol 20: 176-87

Duxon MS, Kennett GA, Lightowler S, Blackburn TP, Fone KC (1997) Activation of 5-HT2B receptors in the medial amygdala causes anxiolysis in the social interaction test in the rat. Neuropharmacology 36: 601-608

Falck RS, Wang J, Carlson RG, Siegal HA (2006) Prevalence and correlates of current depressive symptomatology among a community sample of MDMA users in Ohio. Addict Behav 31: 90-101

Fallon JK, Shah D, Kicman AT, Hutt AJ, Henry JA, Cowan DA, Forsling M (2002) Action of MDMA (ecstasy) and its metabolites on arginine vasopressin release. Ann N Y Acad Sci 965: 399-409

Fantegrossi WE (2007) Reinforcing effects of methylenedioxy amphetamine congeners in rhesus monkeys: are intravenous self-administration experiments relevant to MDMA neurotoxicity? Psychopharmacology (Berl) 189: 471-82

Fantegrossi WE, Godlewski T, Karabenick RL, Stephens JM, Ullrich T, Rice KC, Woods JH (2003) Pharmacological characterization of the effects of 3,4-methylenedioxymethamphetamine ("ecstasy") and its enantiomers on lethality, core temperature, and locomotor activity in singly housed and crowded mice. Psychopharmacology (Berl) 166: 202-11

Fantegrossi WE, Woolverton WL, Kilbourn M, Sherman P, Yuan J, Hatzidimitriou G, Ricaurte GA, Woods JH, Winger G (2004) Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys. Neuropsychopharmacology 29: 1270-81

Farre M, Abanades S, Roset PN, Peiro AM, Torrens M, B OM, Segura M, de la Torre R (2007) Pharmacological Interaction Between 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) and Paroxetine: Pharmacological effects and pharmacokinetics. J Pharmacol Exp Ther

Farre M, de la Torre R, Mathuna BO, Roset PN, Peiro AM, Torrens M, Ortuno J, Pujadas M, Cami J (2004) Repeated doses administration of MDMA in humans: pharmacological effects and pharmacokinetics. Psychopharmacology (Berl) 173: 364-75

Finnegan KT, Ricaurte GA, Ritchie LD, Irwin I, Peroutka SJ, Langston JW (1988) Orally administered MDMA causes a long-term depletion of serotonin in rat brain. Brain Res 447: 141-4

Freedman RR, Johanson CE, Tancer ME (2005) Thermoregulatory effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology (Berl) 183: 248-56

Frei E, Gamma A, Pascual-Marqui R, Lehmann D, Hell D, Vollenweider FX (2001) Localization of MDMA-induced brain activity in healthy volunteers using low resolution brain electromagnetic tomography (LORETA). Hum Brain Mapp 14: 152-65

Frenzilli G, Ferrucci M, Giorgi FS, Blandini F, Nigro M, Ruggieri S, Murri L, Paparelli A, Fornai F (2007) DNA fragmentation and oxidative stress in the hippocampal formation: a bridge between 3,4-methylenedioxymethamphetamine (ecstasy) intake and long-lasting behavioral alterations. Behav Pharmacol 18: 471-481

Freudenmann RW, Oxler F, Bernschneider-Reif S (2006) The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents. Addiction 101: 1241-5

Frith CH, Chang LW, Lattin DL, Walls RC, Hamm J, Doblin R (1987) Toxicity of methylenedioxymethamphetamine (MDMA) in the dog and the rat. Fundam Appl Toxicol 9: 110-9

Gamma A, Buck A, Berthold T, Liechti ME, Vollenweider FX (2000) 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H(2)(15)O]-PET in healthy humans. Neuropsychopharmacology 23: 388-95

Gamma A, Buck A, Berthold T, Vollenweider FX (2001) No difference in brain activation during cognitive performance between ecstasy (3,4-methylenedioxymethamphetamine) users and control subjects: a [H2(15)O]-positron emission tomography study. J Clin Psychopharmacol 21: 66-71

Gasser P (1994) Psycholytic therapy with MDMA and LSD in Switzerland. MAPS Bulletin 5: 3-7

Gaston TR, Rasmussen, G. T. (1972) Identification of 3,4-methylenedioxy-n-methylamphetamine;. Microgram 5: 60-63

Giannaccini G, Betti L, Pirone A, Palego L, Fabiani O, Fabbrini L, Mascia G, Giusti L, Macchia M, Giusiani M, Martini C, Lucacchini A (2007) Short-term effects of 3,4-methylen-dioxy-metamphetamine (MDMA) on 5-HT(1A) receptors in the rat hippocampus. Neurochem Int 51: 496-506

Gilhooly TC, Daly AK (2002) CYP2D6 deficiency, a factor in ecstasy related deaths? Br J Clin Pharmacol 54: 69-70.

Giorgi FS, Pizzanelli C, Ferrucci M, Lazzeri G, Faetti M, Giusiani M, Pontarelli F, Busceti CL, Murri L, Fornai F (2005) Previous exposure to (+/-) 3,4-methylenedioxymethamphetamine produces long-lasting alteration in limbic brain excitability measured by electroencephalogram spectrum analysis, brain metabolism and seizure susceptibility. Neuroscience 136: 43-53

Glennon RA, Young R (2000) MDMA stimulus generalization to the 5-HT(1A) serotonin agonist 8-hydroxy-2- (di-n-propylamino)tetralin. 66: 483-488

Glennon RA, Young R, Dukat M, Chang-Fong J, El-Zahabi M (2007) N-Methyl-1-(4-methoxyphenyl)-2-aminopropane (PMMA) and N-Methyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane (MDMA) produce non-identical discriminative stimuli in rats. Pharmacol Biochem Behav 86: 477-84

Gordon CJ (2007) Thermophysiological responses to hyperthermic drugs: extrapolating from rodent to human. Prog Brain Res 162: 63-79

Gore SM (1999) Fatal uncertainty: death-rate from use of ecstasy or heroin. Lancet 354: 1265-6

Gouzoulis-Mayfrank E, Daumann J (2006a) The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview. J Psychopharmacol 20: 188-93

Gouzoulis-Mayfrank E, Daumann J (2006b) Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: how strong is the evidence for persistent brain damage? Addiction 101: 348-61

Gouzoulis-Mayfrank E, Fischermann T, Rezk M, Thimm B, Hensen G, Daumann J (2005) Memory performance in polyvalent MDMA (ecstasy) users who continue or discontinue MDMA use. Drug Alcohol Depend 78: 317-23

Gouzoulis-Mayfrank E, Thelen B, Habermeyer E, Kunert HJ, Kovar KA, Lindenblatt H, Hermle L, Spitzer M, Sass H (1999) Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers. Results of an experimental double-blind placebo-controlled study. Psychopharmacology (Berl) 142: 41-50

Gouzoulis-Mayfrank E, Thimm B, Rezk M, Hensen G, Daumann J (2003) Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users. Prog Neuropsychopharmacol Biol Psychiatry 27: 819-27

Graeff FG, Guimaraes FS, De Andrade TG, Deakin JF (1996) Role of 5-HT in stress, anxiety, and depression. Pharmacol Biochem Behav 54: 129-41

Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI (2003) The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacol Rev 55: 463-508

Green AR, O'Shea E, Saadat KS, Elliott JM, Colado MI (2005) Studies on the effect of MDMA ('ecstasy') on the body temperature of rats housed at different ambient room temperatures. Br J Pharmacol 146: 306-12

Greene SL, Dargan PI, O'Connor N, Jones AL, Kerins M (2003) Multiple toxicity from 3,4-methylenedioxymethamphetamine ("ecstasy"). Am J Emerg Med 21: 121-4

Greer G, Tolbert R (1986) Subjective reports of the effects of MDMA in a clinical setting. J Psychoactive Drugs 18: 319-27

Greer GR, Tolbert R (1998) A method of conducting therapeutic sessions with MDMA. J Psychoactive Drugs 30: 371-379

Grob C (2001) Unpublished data on human study of psychological and physiological effects of MDMA

Grob CS, Poland RE, Chang L, Ernst T (1996) Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations. Behav Brain Res 73: 103-7

Guillot C (2007) Is recreational ecstasy (MDMA) use associated with higher levels of depressive symptoms? J Psychoactive Drugs 39: 31-9

Guillot C, Greenway D (2006) Recreational ecstasy use and depression. J Psychopharmacol 20: 411-6

Gurtman CG, Morley KC, Li KM, Hunt GE, McGregor IS (2002) Increased anxiety in rats after 3,4-methylenedioxymethamphetamine: association with serotonin depletion. Eur J Pharmacol 446: 89-96.

Hall AP, Henry JA (2006) Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management. Br J Anaesth 96: 678-85

Halpern JH (2006) Update on the MDMA-Assisted Psychotherapy Study for Treatment-Resistant Anxiety Disorders Secondary to Advanced Stage Cancer. MAPS Bulletin 16: 16

Halpern JH, Pope HG, Jr., Sherwood AR, Barry S, Hudson JI, Yurgelun-Todd D (2004) Residual neuropsychological effects of illicit 3,4-methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs. Drug Alcohol Depend 75: 135-47

Han DD, Gu HH (2006) Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. BMC Pharmacol 6: 6

Hardman HF, Haavik CO, Seevers MH (1973) Relationship of the structure of mescaline and seven analogs to toxicity and behavior in five species of laboratory animals. Toxicol Appl Pharmacol 25: 299-309

Harris DS, Baggott M, Mendelson JH, Mendelson JE, Jones RT (2002) Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology (Berl) 162: 396-405

Hatzidimitriou G, McCann UD, Ricaurte GA (1999) Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/-)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. J Neurosci 19: 5096-107

Helmlin HJ, Bracher K, Bourquin D, Vonlanthen D, Brenneisen R (1996) Analysis of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolites in plasma and urine by HPLC-DAD and GC-MS. J Anal Toxicol 20: 432-40

Helmlin HJ, Brenneisen R (1992) Determination of psychotropic phenylalkylamine derivatives in biological matrices by high-performance liquid chromatography with photodiode-array detection. J Chromatogr 593: 87-94

Henry JA, Rella JG (2001) Medical risks associated with MDMA use. In: Holland J (ed) Ecstasy: A Complete Guide. Inner Traditions, Rochester, VT, pp 71-86.

Ho E, Karimi-Tabesh L, Koren G (2001) Characteristics of pregnant women who use Ecstasy (3, 4- methylenedioxymethamphetamine). Neurotoxicol Teratol 23: 561-7.

Ho YJ, Pawlak CR, Guo L, Schwarting RK (2004) Acute and long-term consequences of single MDMA administration in relation to individual anxiety levels in the rat. Behav Brain Res 149: 135-44

Hoshi R, Bisla J, Curran HV (2004) The acute and sub-acute effects of 'ecstasy' (MDMA) on processing of facial expressions: preliminary findings. Drug Alcohol Depend 76: 297-304

Hoshi R, Cohen L, Lemanski L, Piccini P, Bond A, Curran HV (2007a) Ecstasy (MDMA) does not have long-term effects on aggressive interpretative bias: a study comparing current and ex-ecstasy users with polydrug and drug-naive controls. Exp Clin Psychopharmacol 15: 351-8

Hoshi R, Mullins K, Boundy C, Brignell C, Piccini P, Curran HV (2007b) Neurocognitive function in current and ex-users of ecstasy in comparison to both matched polydrug-using controls and drug-naive controls. Psychopharmacology (Berl) 194: 371-9

Huizink AC, Ferdinand RF, van der Ende J, Verhulst FC (2006) Symptoms of anxiety and depression in childhood and use of MDMA: prospective, population based study. Bmj 332: 825-8

Huxster JK, Pirona A, Morgan MJ (2006) The sub-acute effects of recreational ecstasy (MDMA) use: a controlled study in humans. J Psychopharmacol 20: 281-90

Iravani MM, Jackson MJ, Kuoppamaki M, Smith LA, Jenner P (2003) 3,4-methylenedioxymethamphetamine (ecstasy) inhibits dyskinesia expression and normalizes motor activity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primates. J Neurosci 23: 9107-15

Irvine RJ, Keane M, Felgate P, McCann UD, Callaghan PD, White JM (2006) Plasma drug concentrations and physiological measures in 'dance party' participants. Neuropsychopharmacology 31: 424-30

Jager G, de Win MM, van der Tweel I, Schilt T, Kahn RS, van den Brink W, van Ree JM, Ramsey NF (2007a) Assessment of Cognitive Brain Function in Ecstasy Users and Contributions of Other Drugs of Abuse: Results from an fMRI Study. Neuropsychopharmacology

Jager G, de Win MM, Vervaeke HK, Schilt T, Kahn RS, van den Brink W, van Ree JM, Ramsey NF (2007b) Incidental use of ecstasy: no evidence for harmful effects on cognitive brain function in a prospective fMRI study. Psychopharmacology (Berl)

Jerome L (2004) MAPS' Investigator's Brochure Update #2: A Review of Research in Human and Non-human animals. Multidisciplinary Association for Psychedelic Studies

Jerome L (2005) MDMA Literature update; March 2004-January 2005. Multidisciplinary Association for Psychedelic Studies

Jerome L, Baggott M (2003) MAPS' MDMA investigator's brochure update #1: A review of research in humans and non-human animals. Multidisciplinary Association for Psychedelic Studies

Johnson MP, Hoffman AJ, Nichols DE (1986) Effects of the enantiomers of MDA, MDMA and related analogues on [3H]serotonin and [3H]dopamine release from superfused rat brain slices. Eur J Pharmacol 132: 269-76

Jones DC, Lau SS, Monks TJ (2004) Thioether metabolites of 3,4-methylenedioxyamphetamine and 3,4-methylenedioxymethamphetamine inhibit human serotonin transporter (hSERT) function and simultaneously stimulate dopamine uptake into hSERT-expressing SK-N-MC cells. J Pharmacol Exp Ther 311: 298-306

Kindlundh-Hogberg AM, Svenningsson P, Schioth HB (2006) Quantitative mapping shows that serotonin rather than dopamine receptor mRNA expressions are affected after repeated intermittent administration of MDMA in rat brain. Neuropharmacology 51: 838-47

Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, Gruppe H, Mattay VS, Gallhofer B, Meyer-Lindenberg A (2005) Oxytocin modulates neural circuitry for social cognition and fear in humans. J Neurosci 25: 11489-93

Koprich JB, Campbell NG, Lipton JW (2003a) Neonatal 3,4-methylenedioxymethamphetamine (ecstasy) alters dopamine and serotonin neurochemistry and increases brain-derived neurotrophic factor in the forebrain and brainstem of the rat. Brain Res Dev Brain Res 147: 177-82

Koprich JB, Chen EY, Kanaan NM, Campbell NG, Kordower JH, Lipton JW (2003b) Prenatal 3,4-methylenedioxymethamphetamine (ecstasy) alters exploratory behavior, reduces monoamine metabolism, and increases forebrain tyrosine hydroxylase fiber density of juvenile rats. Neurotoxicol Teratol 25: 509-17

Krystal JH, Price LH, Opsahl C, Ricaurte GA, Heninger GR (1992) Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: effects on mood and neuropsychological function? Am J Drug Alcohol Abuse 18: 331-41

Kuypers KP, Ramaekers JG (2005) Transient memory impairment after acute dose of 75mg 3.4-Methylene-dioxymethamphetamine. J Psychopharmacol 19: 633-9

Kuypers KP, Ramaekers JG (2007) Acute dose of MDMA (75 mg) impairs spatial memory for location but leaves contextual processing of visuospatial information unaffected. Psychopharmacology (Berl) 189: 557-63

Lamers CT, Bechara A, Rizzo M, Ramaekers JG (2006) Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls. J Psychopharmacol 20: 302-11

Lamers CT, Ramaekers JG, Muntjewerff ND, Sikkema KL, Samyn N, Read NL, Brookhuis KA, Riedel WJ (2003) Dissociable effects of a single dose of ecstasy (MDMA) on psychomotor skills and attentional performance. J Psychopharmacol 17: 379-87

Lanz M, Brenneisen R, Thormann W (1997) Enantioselective determination of 3,4-methylene-dioxymethamphetamine and two of its metabolites in human urine by cyclodextrin-modified capillary zone electrophoresis. Electrophoresis 18: 1035-43

Lavelle A, Honner V, Docherty JR (1999) Investigation of the prejunctional alpha2-adrenoceptor mediated actions of MDMA in rat atrium and vas deferens. Br J Pharmacol 128: 975-80

Laws KR, Kokkalis J (2007) Ecstasy (MDMA) and memory function: a meta-analytic update. Hum Psychopharmacol

Lebsanft HB, Kohles T, Kovar KA, Schmidt WJ (2005a) 3,4-Methylenedioxymethamphetamine counteracts akinesia enantioselectively in rat rotational behavior and catalepsy. Synapse 55: 148-55

Lebsanft HB, Kovar KA, Schmidt WJ (2005b) 3,4-Methylenedioxymethamphetamine and naloxone in rat rotational behaviour and open field. Eur J Pharmacol 516: 34-9

Lester SJ, Baggott M, Welm S, Schiller NB, Jones RT, Foster E, Mendelson J (2000) Cardiovascular effects of 3,4-methylenedioxymethamphetamine. A double-blind, placebo-controlled trial. Ann Intern Med 133: 969-73

Lieb R, Schuetz CG, Pfister H, von Sydow K, Wittchen H (2002) Mental disorders in ecstasy users: a prospective-longitudinal investigation. Drug Alcohol Depend 68: 195-207.

Liechti ME, Baumann C, Gamma A, Vollenweider FX (2000a) Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. Neuropsychopharmacology 22: 513-21

Liechti ME, Gamma A, Vollenweider FX (2001a) Gender differences in the subjective effects of MDMA. Psychopharmacology (Berl) 154: 161-8

Liechti ME, Gamma A, Vollenweider FX (2001b) Gender differences in the subjective effects of MDMA. Psychopharmacology (Berl) 154: 161-8.

Liechti ME, Kunz I, Kupferschmidt H (2005) Acute medical problems due to Ecstasy use. Case-series of emergency department visits. Swiss Med Wkly 135: 652-7

Liechti ME, Saur MR, Gamma A, Hell D, Vollenweider FX (2000b) Psychological and physiological effects of MDMA ("Ecstasy") after pretreatment with the 5-HT(2) antagonist ketanserin in healthy humans. Neuropsychopharmacology 23: 396-404

Liechti ME, Vollenweider FX (2000a) Acute psychological and physiological effects of MDMA ("Ecstasy") after haloperidol pretreatment in healthy humans. Eur Neuropsychopharmacol 10: 289-95

Liechti ME, Vollenweider FX (2000b) The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers. J Psychopharmacol 14: 269-74

Liechti ME, Vollenweider FX (2001) Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. Hum Psychopharmacol 16: 589-598

Liester MB, Grob CS, Bravo GL, Walsh RN (1992) Phenomenology and sequelae of 3,4-methylenedioxymethamphetamine use. J Nerv Ment Dis 180: 345-52; discussion 353-4

Lile JA, Ross JT, Nader MA (2005) A comparison of the reinforcing efficacy of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") with cocaine in rhesus monkeys. Drug Alcohol Depend 78: 135-40

Ludewig S, Ludewig K, Hasler F, FX V (2003) No lasting effects of moderate doses of MDMA (Ecstasy) on memory performance and mood states in health humans. . Biol Psychiatry 52 (Suppl) . 205S

Lyon RA, Glennon RA, Titeler M (1986) 3,4-Methylenedioxymethamphetamine (MDMA): stereoselective interactions at brain 5-HT1 and 5-HT2 receptors. Psychopharmacology (Berl) 88: 525-6

MacInnes N, Handley SL, Harding GF (2001) Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms. J Psychopharmacol 15: 181-6.

Mahmood I, Balian JD (1996) Interspecies scaling: a comparative study for the prediction of clearance and volume using two or more than two species. Life Sci 59: 579-85

Malberg JE, Seiden LS (1998) 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 18: 5086-94

Mas M, Farre M, de la Torre R, Roset PN, Ortuno J, Segura J, Cami J (1999) Cardiovascular and neuroendocrine effects and pharmacokinetics of 3, 4-methylenedioxymethamphetamine in humans. J Pharmacol Exp Ther 290: 136-45

McCann UD, Mertl M, Eligulashvili V, Ricaurte GA (1999) Cognitive performance in (+/-) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. Psychopharmacology (Berl) 143: 417-25

McCann UD, Peterson SC, Ricaurte GA (2007) The Effect of Catecholamine Depletion by Alpha-Methyl-Para-Tyrosine on Measures of Cognitive Performance and Sleep in Abstinent MDMA Users. Neuropsychopharmacology

McCann UD, Ridenour A, Shaham Y, Ricaurte GA (1994) Serotonin neurotoxicity after (+/-)3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy"): a controlled study in humans. Neuropsychopharmacology 10: 129-38

McElhatton PR, Bateman DN, Evans C, Pughe KR, Thomas SH (1999) Congenital anomalies after prenatal ecstasy exposure [letter]. Lancet 354: 1441-2

Mechan A, Yuan J, Hatzidimitriou G, Irvine RJ, McCann UD, Ricaurte GA (2006) Pharmacokinetic profile of single and repeated oral doses of MDMA in squirrel monkeys: relationship to lasting effects on brain serotonin neurons. Neuropsychopharmacology 31: 339-50

Medina KL, Shear PK (2006) Anxiety, depression, and behavioral symptoms of executive dysfunction in ecstasy users: Contributions of polydrug use. Drug Alcohol Depend

Metzner R, Adamson S (2001) sing MDMA in healing, psychotherapy and spiritual practice. In: J H (ed) cstasy, A Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA. Inner Traditions, Rochester VT, pp 182-207

Meyer JS, Brevard ME, Piper BJ, Ali SF, Ferris CF (2006) Neural effects of MDMA as determined by functional magnetic resonance imaging and magnetic resonance spectroscopy in awake marmoset monkeys. Ann N Y Acad Sci 1074: 365-76

Michael JC, Pak J, Pulido J, de Venecia G (2003) Central serous chorioretinopathy associated with administration of sympathomimetic agents. Am J Ophthalmol 136: 182-5

Milani RM, Parrott AC, Turner JJ, Fox HC (2004) Gender differences in self-reported anxiety, depression, and somatization among ecstasy/MDMA polydrug users, alcohol/tobacco users, and nondrug users. Addict Behav 29: 965-71

Mithoefer M (2006) MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD): ninth update on study progress. MAPS Bulletin 16: 14-15

Mlinar B, Corradetti R (2003) Endogenous 5-HT, released by MDMA through serotonin transporter- and secretory vesicle-dependent mechanisms, reduces hippocampal excitatory synaptic transmission by preferential activation of 5-HT1B receptors located on CA1 pyramidal neurons. Eur J Neurosci 18: 1559-71

Montgomery C, Fisk J (2007) Everyday memory deficits in ecstasy-polydrug users. J Psychopharmacol

Mordenti J, Chappell W (1989) The use of interspecies scaling in toxicokinetics. In: Yacobi A, Kelly J, Batra V (eds) Toxicokinetics in new drug development. Pergamon Press, New York, NY, pp 42-96

Morgan MJ (1998) Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 19: 252-64

Morgan MJ, Impallomeni LC, Pirona A, Rogers RD (2006) Elevated impulsivity and impaired decision-making in abstinent Ecstasy (MDMA) users compared to polydrug and drug-naive controls. Neuropsychopharmacology 31: 1562-73

Morley KC, Arnold JC, McGregor IS (2005) Serotonin (1A) receptor involvement in acute 3,4-methylenedioxymethamphetamine (MDMA) facilitation of social interaction in the rat. Prog Neuropsychopharmacol Biol Psychiatry 29: 648-57

Mortimore C, Anderson IM (2000) d-Fenfluramine in panic disorder: a dual role for 5-hydroxytryptamine. Psychopharmacology (Berl) 149: 251-8

Nair SG, Gudelsky GA (2005) 3,4-Methylenedioxymethamphetamine (MDMA) enhances the release of acetylcholine by 5-HT4 and D1 receptor mechanisms in the rat prefrontal cortex. Synapse 58: 229-35

Nair SG, Gudelsky GA (2006) 3,4-Methylenedioxymethamphetamine enhances the release of acetylcholine in the prefrontal cortex and dorsal hippocampus of the rat. Psychopharmacology (Berl) 184: 182-9

Nash JF, Jr., Meltzer HY, Gudelsky GA (1988) Elevation of serum prolactin and corticosterone concentrations in the rat after the administration of 3,4-methylenedioxymethamphetamine. J Pharmacol Exp Ther 245: 873-9

Nichols DE (1986) Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. J Psychoactive Drugs 18: 305-13

Oehen P (2006) MDMA/PTSD psychotherapy study in Switzerland launched. MAPS Bulletin 16: 15

Ortuno J, Pizarro N, Farre M, Mas M, Segura J, Cami J, Brenneisen R, de la Torre R (1999) Quantification of 3,4-methylenedioxymetamphetamine and its metabolites in plasma and urine by gas chromatography with nitrogen-phosphorus detection. J Chromatogr B Biomed Sci Appl 723: 221-32

Pacifici R, Pichini S, Zuccaro P, Farre M, Segura M, Ortuno J, Di Carlo S, Bacosi A, Roset PN, Segura J, de la Torre R (2004) Paroxetine inhibits acute effects of 3,4-methylenedioxymethamphetamine on the immune system in humans. J Pharmacol Exp Ther 309: 285-92

Pacifici R, Zuccaro P, Farre M, Pichini S, Di Carlo S, Roset PN, Lopez CH, Ortuno J, Segura J, Cami J, de la Torre R (2000) Immunomodulating activity of MDMA. Ann N Y Acad Sci 914: 215-24

Pacifici R, Zuccaro P, Farre M, Pichini S, Di Carlo S, Roset PN, Ortuno J, Pujadas M, Bacosi A, Menoyo E, Segura J, de la Torre R (2001) Effects of repeated doses of MDMA ("ecstasy") on cell-mediated immune response in humans. Life Sci 69: 2931-41

Pacifici R, Zuccaro P, Farre M, Pichini S, Di Carlo S, Roset PN, Ortuno J, Segura J, de la Torre R (1999) Immunomodulating properties of MDMA alone and in combination with alcohol: a pilot study. Life Sci 65: PL309-16

Pacifici R, Zuccaro P, Farre M, Pichini S, Di Carlo S, Roset PN, Palmi I, Ortuno J, Menoyo E, Segura J, de la Torre R (2002) Cell-mediated immune response in MDMA users after repeated dose administration: studies in controlled versus noncontrolled settings. Ann N Y Acad Sci 965: 421-33

Parrott AC (2004) MDMA (3,4-Methylenedioxymethamphetamine) or ecstasy: the neuropsychobiological implications of taking it at dances and raves. Neuropsychobiology 50: 329-35

Parrott AC, Sisk E, Turner JJ (2000) Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. Drug Alcohol Depend 60: 105-10

Patel MM, Belson MG, Wright D, Lu H, Heninger M, Miller MA (2005) Methylenedioxymethamphetamine (ecstasy)-related myocardial hypertrophy: an autopsy study. Resuscitation 66: 197-202

PDSP (2007) MDMA receptor binding profiles from Psychoactive Drug Screening Program Database. National Institute of Mental Health

Peng W, Premkumar A, Mossner R, Fukuda M, Lesch KP, Simantov R (2002) Synaptotagmin I and IV are differentially regulated in the brain by the

recreational drug 3,4-methylenedioxymethamphetamine (MDMA). Brain Res Mol Brain Res 108: 94-101.

Peroutka SJ, Newman H, Harris H (1988) Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. Neuropsychopharmacology 1: 273-7

Phelps EA, O'Connor KJ, Gatenby JC, Gore JC, Grillon C, Davis M (2001) Activation of the left amygdala to a cognitive representation of fear. Nat Neurosci 4: 437-41

Piper BJ, Fraiman JB, Meyer JS (2005) Repeated MDMA ("Ecstasy") exposure in adolescent male rats alters temperature regulation, spontaneous motor activity, attention, and serotonin transporter binding. Dev Psychobiol 47: 145-57

Piper BJ, Meyer JS (2004) Memory deficit and reduced anxiety in young adult rats given repeated intermittent MDMA treatment during the periadolescent period. Pharmacol Biochem Behav 79: 723-31

Pizarro N, Farre M, Pujadas M, Peiro AM, Roset PN, Joglar J, de la Torre R (2004) Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites in human samples including the catechol-type metabolite (3,4-dihydroxymethamphetamine). Drug Metab Dispos 32: 1001-7

Pizarro N, Llebaria A, Cano S, Joglar J, Farre M, Segura J, de la Torre R (2003) Stereochemical analysis of 3,4-methylenedioxymethamphetamine and its main metabolites by gas chromatography/mass spectrometry. Rapid Commun Mass Spectrom 17: 330-6

Pizarro N, Ortuno J, Farre M, Hernandez-Lopez C, Pujadas M, Llebaria A, Joglar J, Roset PN, Mas M, Segura J, Cami J, de la Torre R (2002) Determination of MDMA and its metabolites in blood and urine by gas chromatography-mass spectrometry and analysis of enantiomers by capillary electrophoresis. J Anal Toxicol 26: 157-65

Quednow BB, Kuhn KU, Hoppe C, Westheide J, Maier W, Daum I, Wagner M (2007) Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA ("Ecstasy"). Psychopharmacology (Berl) 189: 517-30

Quinn ST, Guiry PJ, Schwab T, Keenan AK, McBean GJ (2006) Blockade of noradrenaline transport abolishes 4-methylthioamphetamine-induced contraction of the rat aorta in vitro. Auton Autacoid Pharmacol 26: 335-44

Raikos N, Tsoukali H, Psaroulis D, Vassiliadis N, Tsoungas M, Njau SN (2002) Amphetamine derivative related deaths in northern Greece. Forensic Sci Int 128: 31-4

Ramaekers JG, Kuypers KP (2006) Acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on behavioral measures of impulsivity: alone and in combination with alcohol. Neuropsychopharmacology 31: 1048-55

Reneman L, Majoie CB, Flick H, den Heeten GJ (2002) Reduced N-acetylaspartate levels in the frontal cortex of 3,4- methylenedioxymethamphetamine (Ecstasy) users: preliminary results. AJNR Am J Neuroradiol 23: 231-7.

Reveron ME, Maier EY, Duvauchelle CL (2006) Experience-dependent changes in temperature and behavioral activity induced by MDMA. Physiol Behav 89: 358-63

Ricaurte GA, DeLanney LE, Wiener SG, Irwin I, Langston JW (1988) 5-Hydroxyindoleacetic acid in cerebrospinal fluid reflects serotonergic damage induced by 3,4-methylenedioxymethamphetamine in CNS of non-human primates. Brain Res 474: 359-63

Rizzo M, Lamers CT, Sauer CG, Ramaekers JG, Bechara A, Andersen GJ (2005) Impaired perception of self-motion (heading) in abstinent ecstasy and marijuana users. Psychopharmacology (Berl) 179: 559-66

Roiser JP, Rogers RD, Cook LJ, Sahakian BJ (2006) The effect of polymorphism at the serotonin transporter gene on decision-making, memory and executive function in ecstasy users and controls. Psychopharmacology (Berl) 188: 213-27

Roiser JP, Rogers RD, Sahakian BJ (2007) Neuropsychological function in ecstasy users: a study controlling for polydrug use. Psychopharmacology (Berl) 189: 505-16

Rudnick G, Wall SC (1992) The molecular mechanism of "ecstasy" [3,4-methylenedioxy-methamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release. Proc Natl Acad Sci U S A 89: 1817-21

Schechter MD (1986) Discriminative profile of MDMA. Pharmacol Biochem Behav 24: 1533-7

Schenk S, Gittings D, Johnstone M, Daniela E (2003) Development, maintenance and temporal pattern of self-administration maintained by ecstasy (MDMA) in rats. Psychopharmacology (Berl) 169: 21-7

Schifano F, Oyefeso A, Corkery J, Cobain K, Jambert-Gray R, Martinotti G, Ghodse AH (2003) Death rates from ecstasy (MDMA, MDA) and polydrug use in England and Wales 1996-2002. Hum Psychopharmacol 18: 519-24

Schilt T, de Win MM, Koeter M, Jager G, Korf DJ, van den Brink W, Schmand B (2007) Cognition in novice ecstasy users with minimal exposure to other drugs: a prospective cohort study. Arch Gen Psychiatry 64: 728-36

Segura M, Ortuno J, Farre M, McLure JA, Pujadas M, Pizarro N, Llebaria A, Joglar J, Roset PN, Segura J, de La Torre R (2001) 3,4-Dihydroxymethamphetamine (HHMA). A Major in Vivo 3,4- methylenedioxymethamphetamine (MDMA) Metabolite in Humans. Chem Res Toxicol 14: 1203-1208.

Selken J, Nichols DE (2007) α1-Adrenergic Receptors Mediate the Locomotor Response to Systemic Administration of (±)-3,4-Methylenedioxymethamphetamine (MDMA) in rats. Pharmacol Biochem Behav In press: xx-xx

Semple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone EC (1999) Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. Br J Psychiatry 175: 63-9

Setola V, Hufeisen SJ, Grande-Allen KJ, Vesely I, Glennon RA, Blough B, Rothman RB, Roth BL (2003) 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. Mol Pharmacol 63: 1223-9

Shulgin A, Shulgin A (1991) Pihkal: A Chemical Love Story, 1st edn. Transform Press, Transform Press

Shulgin AT (1986) The background and chemistry of MDMA. J Psychoactive Drugs 18: 291-304

Shulgin AT, Nichols DE (1978) Characterization of three new psychotomimetics. In: Stillman RC, Willette RE (eds) The Pharmacology of Hallucinogens. Pergamon, New York

Solowij N, Hall W, Lee N (1992) Recreational MDMA use in Sydney: a profile of 'Ecstacy' users and their experiences with the drug. Br J Addict 87: 1161-72

Sotnikova TD, Beaulieu JM, Barak LS, Wetsel WC, Caron MG, Gainetdinov RR (2005) Dopamine-independent locomotor actions of amphetamines in a novel acute mouse model of Parkinson disease. PLoS Biol 3: e271

Spitzer M, Franke B, Walter H, Buechler J, Wunderlich AP, Schwab M, Kovar K, Hermle L, Gron G (2001) Enantio-selective cognitive and brain activation effects of N-ethyl-3,4- methylenedioxyamphetamine in humans. Neuropharmacology 41: 263-71.

Stolaroff M (1997) The Secret Chief: Conversations with a pioneer of the underground therapy movement. Multidisciplinary Association for Psychedelic Studies, Multidisciplinary Association for Psychedelic Studies

Substance Abuse and Mental Health Services Administration OoAS (2007) Drug Abuse Warning Network 2005: National Estimates of Emergency Department Visits DAWN Series D-29,. DHHS, Rockville, MD,

Sumnall HR, Cole JC (2005) Self-reported depressive symptomatology in community samples of polysubstance misusers who report Ecstasy use: a meta-analysis. J Psychopharmacol 19: 84-92

Sumnall HR, Cole JC, Jerome L (2006) The varieties of ecstatic experience: an exploration of the subjective experiences of ecstasy. J Psychopharmacol 20: 670-82

Sumnall HR, Wagstaff GF, Cole JC (2004) Self-reported psychopathology in polydrug users. J Psychopharmacol 18: 75-82

Taffe MA, Lay CC, Von Huben SN, Davis SA, Crean RD, Katner SN (2006) Hyperthermia induced by 3,4-methylenedioxymethamphetamine in unrestrained rhesus monkeys. Drug Alcohol Depend 82: 276-81

Tancer M, Johanson CE (2003) Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP. Drug Alcohol Depend 72: 33-44

Tancer M, Johanson CE (2007) The effects of fluoxetine on the subjective and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology (Berl) 189: 565-73

Tancer ME, Johanson CE (2001) The subjective effects of MDMA and mCPP in moderate MDMA users. Drug Alcohol Depend 65: 97-101.

Thiriet N, Ladenheim B, McCoy MT, Cadet JL (2002) Analysis of ecstasy (MDMA)-induced transcriptional responses in the rat cortex. Faseb J 16: 1887-94.

Thomasius R, Petersen K, Buchert R, Andresen B, Zapletalova P, Wartberg L, Nebeling B, Schmoldt A (2003) Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. Psychopharmacology (Berl) 167: 85-96

Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS (2007) A role for oxytocin and 5-HT(1A) receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine ("ecstasy"). Neuroscience

Topp L, Hando J, Dillon P, Roche A, Solowij N (1999) Ecstasy use in Australia: patterns of use and associated harm. Drug Alcohol Depend 55: 105-15

Trigo JM, Panayi F, Soria G, Maldonado R, Robledo P (2006) A reliable model of intravenous MDMA self-administration in naive mice. Psychopharmacology (Berl) 184: 212-20

Varela-Rey M, Montiel-Duarte C, Beitia G, Cenarruzabeitia E, Iraburu MJ (1999) 3,4-methylenedioxymethamphetamine ("Ecstasy") stimulates the expression of alpha1(I) procollagen mRNA in hepatic stellate cells. Biochem Biophys Res Commun 259: 678-82

Verheyden SL, Henry JA, Curran HV (2003) Acute, sub-acute and long-term subjective consequences of 'ecstasy' (MDMA) consumption in 430 regular users. Hum Psychopharmacol 18: 507-17

Verrico CD, Miller GM, Madras BK (2007) MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced neurotoxicity and treatment. Psychopharmacology (Berl) 189: 489-503

Vollenweider FX, Gamma A, Liechti M, Huber T (1998a) Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. Neuropsychopharmacology 19: 241-51

Vollenweider FX, Gamma A, Liechti M, Huber T (1999) Is a single dose of MDMA harmless? Neuropsychopharmacology 21: 598-600

Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H, Hell D (1998b) Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport 9: 3897-902

von Geusau NA, Stalenhoef P, Huizinga M, Snel J, Ridderinkhof KR (2004) Impaired executive function in male MDMA ("ecstasy") users. Psychopharmacology (Berl) 175: 331-41

Von Huben SN, Lay CC, Crean RD, Davis SA, Katner SN, Taffe MA (2006) Impact of Ambient Temperature on Hyperthermia Induced by (+/-)3,4-Methylenedioxymethamphetamine in Rhesus Macaques. Neuropsychopharmacology

von Sydow K, Lieb R, Pfister H, Hofler M, Wittchen HU (2002) 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 66: 147-59

Wang X, Baumann MH, Xu H, Morales M, Rothman RB (2005) (+/-)-3,4-Methylenedioxymethamphetamine administration to rats does not decrease levels of the serotonin transporter protein or alter its distribution between endosomes and the plasma membrane. J Pharmacol Exp Ther 314: 1002-12

Wang Z, Woolverton WL (2007) Estimating the relative reinforcing strength of (+/-)-3,4-methylenedioxymethamphetamine (MDMA) and its isomers in rhesus monkeys: comparison to (+)-methamphetamine. Psychopharmacology (Berl) 189: 483-8

Wareing M, Fisk JE, Murphy P, Montgomery C (2004) Verbal working memory deficits in current and previous users of MDMA. Hum Psychopharmacol 19: 225-34

Widmer S (1998) Listening into the heart of things: The awakening of love: On MDMA and LSD: The undesired psychotherapy. . Basic Editions, Basic Editions

Williams H, Dratcu L, Taylor R, Roberts M, Oyefeso A (1998) "Saturday night fever": ecstasy related problems in a London accident and emergency department. J Accid Emerg Med 15: 322-6

Williams MT, Schaefer TL, Ehrman LA, Able JA, Gudelsky GA, Sah R, Vorhees CV (2005) 3,4-Methylenedioxymethamphetamine administration on postnatal day 11 in rats increases pituitary-adrenal output and reduces striatal and hippocampal serotonin without altering SERT activity. Brain Res 1039: 97-107

Wirth MM, Schultheiss OC (2006) Effects of affiliation arousal (hope of closeness) and affiliation stress (fear of rejection) on progesterone and cortisol. Horm Behav 50: 786-95

Xie T, Tong L, McLane MW, Hatzidimitriou G, Yuan J, McCann U, Ricaurte G (2006) Loss of serotonin transporter protein after MDMA and other ring-substituted amphetamines. Neuropsychopharmacology 31: 2639-51

Yarosh HL, Katz EB, Coop A, Fantegrossi WE (2007) MDMA-like behavioral effects of N-substituted piperazines in the mouse. Pharmacol Biochem Behav

Zakzanis KK, Campbell Z (2006) Memory impairment in now abstinent MDMA users and continued users: a longitudinal follow-up. Neurology 66: 740-1

Zakzanis KK, Campbell Z, Jovanovski D (2007) The neuropsychology of ecstasy (MDMA) use: a quantitative review. Hum Psychopharmacol 22: 427-35

Zakzanis KK, Young DA (2001) Memory impairment in abstinent MDMA ("Ecstasy") users: a longitudinal investigation. Neurology 56: 966-9.

Study Synopsis
A Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Canada

Sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS)
Study Number: MP-4

Principal Investigator: Ingrid Pacey MB BS FRCP[C]
Co-Investigator and Sub-Investigator: Andrew Feldmar MA; Karen Tallman PhD

Expected Study Dates Jan 2009-April 2010
Approved by: IRB Services, BC Committee, November 5, 2008

Background and Rationale

Background: This proposed Canadian pilot study is a randomized, double-blind, active placebo controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in twelve patients with treatment-resistant posttraumatic stress disorder (PTSD). PTSD is a debilitating psychiatric disorder that arises after a personally threatening life-event. PTSD can severely reduce quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems.

PTSD affects an estimated 8% of the general population at some point during their lifetime [1], as reported in a national survey of mental disorders in the general population of the US. To date the treatment of PTSD has primarily been psychotherapeutic, the effect size for psychotherapy being higher than for psychopharmacologic treatment. Cognitive behavioral therapy is considered one of the most effective psychotherapies. Other methods such as psychodynamic therapy and eye-movement desensitization and reprocessing (EMDR) also proved to be effective in treating some aspects of PTSD symptoms [2]. Some people may have to undergo more than one treatment to reduce or resolve PTSD symptoms [3]. A recent meta-analysis concluded that all "bona fide" psychotherapies, including all those listed above, are similarly effective with PTSD [4].

However, a significant minority of PTSD patients fail to respond to established PTSD psychotherapies [5, 6], and at least one study of the selective serotonin uptake inhibitor paroxetine, approved by the FDA in the treatment of PTSD, indicated that men did not respond to this drug [7]. These findings suggest that there is still substantial need for innovative treatments for PTSD.

One innovative avenue of treatment is MDMA-assisted psychotherapy, which uses psychotherapy in combination with 3,4-methylenedioxymethamphetamine (MDMA), a pharmacological adjunct that enhances and amplifies particular aspects of psychotherapy. MDMA is a ring-substituted phenethylamine that bears structural and pharmacological similarities to amphetamines and the psychedelic compound mescaline. However, it possesses unique pharmacological and psychological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients [8-11]. MDMA was initially patented by Merck as an intermediary product and then rediscovered by chemist Alexander Shulgin in the 1970s [12, 13]. In the United States, MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists before it was placed in Schedule 1 in 1985 as a result of extensive non-medical use [10, 14, 15]. Placement in Schedule 1 prohibited it for use except in a federally-approved research setting.

There has been no evidence of significant or lasting toxicity in more than 400 subjects participating in Phase I or Phase 2 studies of MDMA conducted in the US, Israel, the Netherlands, Spain, and Switzerland. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens [e. g.16, 17, 18] and some studies suggest clinically subtle neurocognitive changes may occur in a subset of heavy users of illicit Ecstasy and other drugs [19-22]. In

contrast, all available Phase I and Phase 2 data indicate that it is unlikely that the MDMA exposures proposed in this protocol will cause persisting measurable reduction in serotonin function or lasting neurocognitive deficits. Recent retrospective and prospective studies suggest that receiving MDMA in a controlled, therapeutic setting bears little to no attendant risks of serotonin system neurotoxicity or of functional consequences of this possible toxicity.

Rationale: Prior to scheduling, MDMA in combination with psychotherapy was used in the treatment of neuroses, relationship problems and PTSD [8, 9, 23, 24]. Case reports and narrative accounts of MDMA-assisted therapy suggest that the treatment was often successful. Based on these experiences, assertions have been made that MDMA, used in the proper therapeutic setting, can act in several beneficial ways. Specifically, MDMA can "reduce or somehow eliminate fear of a perceived threat to one's emotional integrity" [8]. Elimination of these "conditioned fear responses" can lead to more open and comfortable communication about past traumatic events, greater access to information about them, and a more accurate perspective about their significance in the present. Some clinicians and researchers have asserted that MDMA causes increased empathy or compassion for self and others, decreased defensiveness and strengthening of the therapeutic alliance, and that the above factors taken together can provide the opportunity for a corrective emotional experience [8]. Some investigators suggest that MDMA be categorized as part of a new class of psychotropic agents referred to as entactogens [25]. The term refers to MDMA and similar substances that produce increased sensitivity to emotions, increased insights about the self, especially in the context of interpersonal relationships, and increased feelings of closeness to others. Though the psychopharmacology and neuropsychological underpinnings of the therapeutic effects of MDMA are largely unknown at present, Gamma and colleagues found that MDMA reduced activity in the left amygdala [26], suggesting reduced responsiveness to anxiety or fear-provoking stimuli.

Preliminary data from a MAPS-sponsored study conducted in the US by Mithoefer and colleagues are promising, suggesting significant improvements in PTSD symptoms after MDMA-assisted psychotherapy [27]. This study employed the Clinical Administered PTSD Scale (CAPS) as the primary outcome measure, with PTSD symptoms measured by a blinded, independent assessor at baseline, a week after each experimental (MDMA or placebo) session, and two months after the final experimental session. To date, all participants in this study have tolerated MDMA, and preliminary data indicates that MDMA is associated with greater improvement in PTSD than placebo. A recent analysis conducted by the independent rater detected a significant decline in CAPS score in the MDMA condition when compared with placebo [28]. A one-year+ follow-up study is currently underway.

Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to be an innovative treatment for PTSD, particularly in people who fail to respond to currently available therapies, and that the modest risks of administering MDMA within a therapeutic context are greatly outweighed by the possibility that this treatment may offer significant benefits.

Trial Objectives

Primary Efficacy and Safety Objectives: The primary objective of this study is to gather preliminary data on the safety and efficacy of MDMA-assisted psychotherapy in people with treatment-resistant PTSD. Symptoms of PTSD will be assessed via Clinician-Administered PTSD Scale (CAPS). The Posttraumatic Diagnostic Scale (PDS) will be used as a secondary measure of PTSD symptoms. The investigators compare baseline CAPS and PDS scores with scores obtained at follow-up six weeks after the third experimental (blinded) session.

The investigators will also gather information on physiological effects and side effects after MDMA.

Secondary Objectives: The secondary objective of this study is to investigate the effects of MDMA-assisted psychotherapy on symptoms of depression in people with PTSD. Depression will be assessed via the Beck Depression Inventory (BDI). The investigators will compare BDI scores at baseline with BDI scores at follow-up six weeks after the third experimental session.

Study Design and Duration

The proposed pilot study will employ a randomized, double-blind, active placebo-controlled design. Twelve patients with treatment-resistant PTSD will be randomly assigned after baseline assessment to receive either an experimental (fully active) dose of 125 mg MDMA followed by a supplemental dose of 62.5 mg MDMA administered 1.5 to 2.5 h later, or to an active placebo dose of 25 mg MDMA followed by 12.5 mg MDMA 1.5 to 2.5 h later. After undergoing three introductory psychotherapy sessions with a male/female co-therapist team, study participants will undergo three eight-hour long experimental sessions during which they will randomly receive either the experimental or active placebo dose of MDMA. Each subsequent session will be scheduled three to five weeks after the previous session. Participants will undergo one non-drug-psychotherapy session on the morning of the day after each MDMA session and integrative psychotherapy sessions on a weekly basis after each experimental session.
Symptoms of PTSD and depression will be assessed by an independent assessor who will be blind to condition assignment and not present during any of the psychotherapy sessions, once prior to MDMA-assisted psychotherapy and once six weeks after the third double-blind (experimental) session. The assessor will also assess symptoms of depression with the Beck Depression Inventory (BDI). Neurocognitive function will be assessed at study baseline and six weeks after the third experimental (blinded) session via Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and Paced Auditory Serial Addition Task (PASAT). The blind will be broken after completing this assessment.

Participants in the active placebo condition will have the opportunity to enroll in an open-label study segment, Stage 2, wherein they will undergo three open-label sessions of MDMA-assisted psychotherapy. The independent rater will assess PTSD and depression

symptoms six weeks after the third open-label session. Measures of symptoms of depression and PTSD will be used to examine treatment efficacy, and examining neurocognitive function and collecting information on physiological and side effects will be used to assess treatment safety.

The entire study will be completed when the twelfth participant undergoes the final study visit. This is expected to occur from a year and a half to three years after enrolling the first participant (18 to 36 months). The investigators expect to begin enrolling participants upon obtaining clearance from Health Canada. The expected start date of the study is March 2009 and the expected end date would be August 2010, with actual date of study completion dependent upon ease of recruitment and study completion.

The randomized, double-blind, active-placebo controlled study segment will last approximately four months from screening and baseline evaluation up until the evaluation six weeks after the third experimental session.

The open-label study segment for participants assigned to active placebo will last an additional four months from the single introductory and review psychotherapy session to the evaluation six weeks after the final open-label MDMA-assisted therapy session, for a total of about 8 months.

Number of Centres

The study will take place at one location in Vancouver, BC. All psychotherapy, including both non-drug and MDMA-assisted sessions, Assessments of PTSD symptoms and neurocognitive function will be performed in the offices of the independent rater, Dr. Karen Tallman.

List of Investigators

Ingrid Pacey MBBS FRCP[C] is the principal investigator for this study. She is a practicing psychiatrist in Vancouver, BC. She has worked as a psychiatrist for 36 years. She has a private practice in Vancouver, BC. She has performed Holotropic Breathwork, a therapeutic breathing practice capable of producing alterations in consciousness, in people with PTSD. She will be present during every psychotherapy session, including each experimental or open-label MDMA-assisted psychotherapy session.

Other investigators will be Andrew Feldmar M.A. and Karen Tallman PhD. Andrew Feldmár, M.A., has practiced psychotherapy as a psychologist for almost 40 years in Vancouver, Canada. He has given workshops, lectures and seminars on psychotherapy and topics of psychotherapeutic interest. He is a member of the Canadian Psychological Association and the Canadian Registry of Health Service Providers in Psychology. He will be present during every psychotherapy session, including each experimental and open-label MDMA-assisted psychotherapy session. Karen Tallman Ph.D will be the independent rater who will assess participant symptoms and neurocognitive function. She

is a clinical psychologist who has 15 years of experience and has conducted psychiatric diagnostic and competency assessments.

Sample Size

The study will enroll twelve (12) individuals. Study drop-outs or withdrawals will be replaced until twelve participants have completed the study.

Patient Population (Target population)

The investigators will seek to enroll individuals diagnosed with PTSD who score 50 or higher on the Clinician-Administered PTSD Scale (CAPS). The study will enroll both men and women who are 21 years or older. The study will not exclude anyone on the basis of race or ethnicity. Participants must meet all the inclusion criteria listed below without meeting any exclusion criteria. Participants must reside in Canada.

Inclusion Criteria

Participants who meet the following criteria will be considered for inclusion in this study:

1. Participants must meet DSM IV criteria for current PTSD. They must have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
2. They must either:
    a. have had at least one unsuccessful attempt at treatment with a selective serotonin uptake inhibitor (SSRI), mirtazapine or a monoamine oxidase inhibitor (MAOI) and one unsuccessful treatment with any form of psychotherapy for which there exist a controlled trial indicating efficacy in the treatment of PTSD. This includes cognitive-behavioral therapy (including exposure therapy), stress inoculation training, including anxiety management, and insight-oriented psychotherapy, and eye movement desensitization (EMDR) [5, 29-31]. Treatment with an SSRI must have lasted for at least three months, or the participant must have refused to take SSRIs. Psychotherapy must have lasted for six months and included at least twelve sessions. Treatment will be deemed to have been unsuccessful if the participant continues to meet criteria for current PTSD following the treatment.
    b. Be a veteran who meets all criteria listed above in 2a and with PTSD symptoms that have persisted for no longer than ten years.
3. Participants may also meet criteria for a mood disorder (except bipolar affective disorder, see exclusions) and for other anxiety disorders. The inclusion of subjects with other mood and anxiety disorders is essential because there is marked frequency of co-existence of other psychiatric disorders among people with PTSD [32, 33].
4. Participants must be willing to commit to medication dosing, experimental sessions, and follow-up sessions and to complete evaluation instruments.

5. Participants must be willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. If they are being treated with psychoactive drugs at the time they are recruited into the study, the prospective participant will be encouraged to discuss medication withdrawal with his or her outside treating physician, and will be required to give Dr. Pacey permission to do so as well. The drugs will then be tapered in an appropriate fashion to avoid withdrawal effects. They will be discontinued long enough before the first MDMA/placebo session to avoid the possibility of any drug-drug interaction (the interval will be at least 5 times the particular drug's half-life). No new medications may be started until after the evaluation session, which will occur six weeks after the third experimental session. An exception to this may arise in the case of designated rescue medication that may be administered in the event of a crisis during or after the experimental session.
6. Participants who are in ongoing psychotherapy at the time they are recruited into the study may continue to see their outside therapist during the course of the study. They must sign a release if they want to permit the investigators to communicate directly with their therapist. They may not change therapists, increase the frequency of therapy or commence any new type of therapy until after the evaluation session six weeks after the third experimental session.
7. Participants must agree that, for one week preceding each MDMA/placebo session:
    a. They will refrain from taking any herbal supplement (except with prior approval of the research team).
    b. They will not take any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
    c. With the permission of their physician they will not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).
8. Participants must agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each experimental session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each active placebo dose/experimental dose MDMA session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of drug.
9. Participants must be willing to [redacted] after each experimental session until the non-drug session occurring the next morning. An attendant will be present to assist with personal needs if requested and offer dinner and breakfast. The attendant will be an individual with previous training in managing psychological distress, including distress occurring after use of psychedelic drugs and of the same sex as the participant, and he or she will be trained for assisting in this study. The attendant may be anyone with some training or background in health care, particularly in psychiatric health care. The attendant will be instructed to contact Dr. Pacey at the request of the participant or if there are signs that the participant is under physical or psychological distress. At the participant's request and with Dr. Pacey's approval, a significant other can

remain with the participant for support between the end of the experimental session and the non-drug session the next morning.
10. Participants will be asked to locate an individual willing to drive them home the morning after the experimental sessions, after the non-drug therapy session. If a participant is unable to locate someone to transport them home, the investigators will assist the participant in obtaining transport from the clinic to the participant's home or any other location where he or she is staying temporarily.
11. Participants must be willing to be contacted via telephone on a daily basis by one of the investigators for a week after each experimental session.
12. Female participants of childbearing potential must have a negative pregnancy test and must agree to use an effective form of birth control.
13. Participants must be literate. They must be proficient in reading documents written in English.

Exclusion Criteria

Prospective participants will be excluded from the study if they have the following conditions or characteristics:

1. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.
2. People with a history of or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder.
3. People with dissociative identity disorder or an eating disorder with active purging, or borderline personality disorder.
4. People with evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder. (Participants with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).
5. People with hypertension using the standard criteria of the American Heart Association of values of 140/90 or higher assessed on three separate occasions [34], peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.
6. People weighing less than 48 kg
7. People with prior use of "Ecstasy" (illicit drug preparations purported to contain MDMA) more than 5 times or at any time within the previous 6 months.
8. People who would present a serious suicide risk, or who are likely to require hospitalization during the course of the study, with suicide risk ascertained via face to face interview and and through the use of the Adult Suicidal Ideation Questionnaire (ASIQ).
9. People requiring ongoing concomitant therapy with a psychotropic drug.
10. People meeting DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 6 months.
11. Any person who is not able to give adequate informed consent.