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 α1, 5HT2, α2 adrenergic receptors, H1 histamine receptors and acetylcholine muscarinic M1 receptors, β adrenergic receptors, dopamine D2 and D4 dopamine receptors, roughly in that order (Battaglia et al. 1988). This study failed to detect any direct pharmacological effects on GABA, glutamate or opioid receptors. Later reports and investigations have clarified and for the most part supported this data (e.g. Jones et al. 2004, see also NIMH PDSP database; Setola et al. 2003), providing more specific affinity assays and with only one significant disagreement, concerning the muscarinic M1 receptor. However, it appears that the effects of MDMA at all receptors investigated to date is considerably lower than its activity at any of the monoamine transporters, suggesting that any receptor-mediated effects reported in humans or nonhuman animals arise indirectly from monoamine release or inhibition of reuptake. For instance, MDMA may cause acetylcholine release and changes in the GABAergic systems through serotonin release activating 5HT3 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.
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 suggests that co-administration of SSRIs with MDMA is safe, but that this combination prevents or attenuates the effects of MDMA.

Table 1: Affinity assays from Battaglia et al. 1988: Affinities of MDMA at receptors wherein KI is below 500 nM. Rat and human brain samples used in assays.

<table>
<thead>
<tr>
<th>Transporter/Receptor</th>
<th>KI (nM)</th>
<th>Hot Ligand</th>
<th>Species</th>
<th>Source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin Transporter</td>
<td>0.61 +/- 0.05</td>
<td>3H-paroxetine</td>
<td>Rat</td>
<td>Fr. Cortex (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>Noradrenaline Transporter</td>
<td>15.8 +/- 1.7</td>
<td>3H-Mazindol</td>
<td>Rat</td>
<td>Fr. Cortex (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>Dopamine Transporter</td>
<td>24.4 +/- 1.9</td>
<td>3H-GBR-12935</td>
<td>Rat</td>
<td>Striatum  (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>a2</td>
<td>3.6 +/- 0.8</td>
<td>3H-aminoclonidine</td>
<td>Rat</td>
<td>Fr. Cortex (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>5HT1</td>
<td>5.1 +/- 0.3</td>
<td>3H-ketanserin</td>
<td>Rat</td>
<td>Fr. Cortex (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>H1</td>
<td>5.7 +/- 2.4</td>
<td>3H-mepyramine</td>
<td>Rat</td>
<td>Fr. Cortex (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>M3</td>
<td>5.8 +/- 0.3</td>
<td>3H-QNB</td>
<td>Rat</td>
<td>Fr. Cortex (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td>15.1 +/- 0.1</td>
<td>3H-QNB</td>
<td>Rat</td>
<td>Brainstem (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>a1</td>
<td>18.4 +/- 1.2</td>
<td>3H-prazosin</td>
<td>Rat</td>
<td>Fr. Cortex (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>19.2 +/- 2.1</td>
<td>3H-dihydroalprenolol</td>
<td>Rat</td>
<td>Fr. Cortex (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>5HT1</td>
<td>23 +/- 1.5</td>
<td>3H-serotonin</td>
<td>Rat</td>
<td>Fr. Cortex (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>D2</td>
<td>95 +/- 15</td>
<td>3H-Spiperone</td>
<td>Rat</td>
<td>Striatum  (Battaglia et al. 1988)</td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>148 +/- 14</td>
<td>3H-SPC-23390</td>
<td>Rat</td>
<td>Striatum  (Battaglia et al. 1988)</td>
<td></td>
</tr>
</tbody>
</table>

Fr. Cortex = Frontal cortex

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

<table>
<thead>
<tr>
<th>Receptor</th>
<th>KI (nM)</th>
<th>Hot Ligand</th>
<th>Species</th>
<th>Source</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin transporter</td>
<td>0.072 or 0.102</td>
<td>Functional (1), 3H-citalopram (2)</td>
<td>Rat, Human</td>
<td>Brain, Cloned (Jones et al. 2004; Setola et al. 2003)</td>
<td></td>
</tr>
<tr>
<td>Noradrenaline Transporter</td>
<td>0.110</td>
<td>Functional</td>
<td>Rat</td>
<td>Brain</td>
<td>(Setola et al. 2003)</td>
</tr>
<tr>
<td>Dopamine transporter</td>
<td>0.278</td>
<td>Functional</td>
<td>Rat</td>
<td>Caudate</td>
<td>(Setola et al. 2003)</td>
</tr>
<tr>
<td>5HT2B</td>
<td>0.5 or 0.7</td>
<td>3H-LSD</td>
<td>Human</td>
<td>Cloned (Setola et al. 2003), (PDSP 2007)</td>
<td></td>
</tr>
<tr>
<td>a2C</td>
<td>1.12</td>
<td>3H-Clonidine</td>
<td>Human</td>
<td>Cloned (PDSP 2007)</td>
<td></td>
</tr>
<tr>
<td>Calcium Channel</td>
<td>1.2</td>
<td>3H-Nitrendipine</td>
<td>Rat</td>
<td>Heart</td>
<td>(PDSP 2007)</td>
</tr>
<tr>
<td>a2B</td>
<td>1.8</td>
<td>3H-Clonidine</td>
<td>Human</td>
<td>Cloned (PDSP 2007)</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>1.8</td>
<td>3H-QNB</td>
<td>Human</td>
<td>Cloned (PDSP 2007)</td>
<td></td>
</tr>
<tr>
<td>H1</td>
<td>2.1</td>
<td>3H-Pyrilamine</td>
<td>Human</td>
<td>Cloned (PDSP 2007)</td>
<td></td>
</tr>
<tr>
<td>a2A</td>
<td>2.5</td>
<td>3H-Clonidine</td>
<td>Human</td>
<td>Cloned (PDSP 2007)</td>
<td></td>
</tr>
<tr>
<td>M3</td>
<td>6.3</td>
<td>3H-QNB</td>
<td>Human</td>
<td>Cloned (PDSP 2007)</td>
<td></td>
</tr>
<tr>
<td>M4</td>
<td>8.2</td>
<td>3H-QNB</td>
<td>Human</td>
<td>Cloned (PDSP 2007)</td>
<td></td>
</tr>
<tr>
<td>5HT2A</td>
<td>8.3</td>
<td>3H-ketanserin</td>
<td>Rat</td>
<td>Cortex</td>
<td>(Lyon et al. 1986)</td>
</tr>
</tbody>
</table>

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 SSR1 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 5HT2A receptors, as coadministration of the 5HT2A antagonist ketanserin reduced reported perceptual alterations after 1.5 mg/kg MDMA and eliminated slight elevation in body temperature (Liechti et al. 2000b). At least some MDMA effects on mood and anxiety may result from dopamine release indirectly activating D2 receptors, as administering the D2 antagonist haloperidol diminished positive mood and increased anxiety in humans (Liechti and Vollenweider 2000a). There are no reports examining the contribution of norepinephrine release to MDMA effects in humans. Investigations in rodents suggest that norepinephrine plays a role in cardiovascular effects (Quinn et al. 2006).

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

**Receptor Affinity and Direct and Indirect Actions on Receptors**

Most effects of MDMA on brain receptors likely arise indirectly from monoamine release. MDMA probably stimulates 5HT1A receptors indirectly through serotonin release, though it is possible that MDMA may also act as a partial 5HT1A antagonist in some brain areas (Giannaccini et al. 2007). Early studies in rodents suggest that 5HT1A receptors reduce anxiety and aggression (Brunner and Hen 1997; Graeff et al. 1996), and some drug discrimination studies suggest that the 5HT1A agonist 8-OH-DPAT partially or fully substitutes for MDMA (Glennon and Young 2000; Glennon et al. 2007; Schechter 1986). Administering a 5HT1A 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 5HT1A receptors to MDMA effects.

MDMA exhibits affinity for two of three 5HT2 family receptors, 5HT2B and 5HT2A, and for α2B, α2C, histamine H1 and muscarinic M3 receptors, with strongest affinity recorded for 5HT2B, α2B, α2C and muscarinic M3 receptors (Battaglia et al. 1988; Lavelle et al. 1999; Lyon et al. 1986; Setola et al. 2003), additional data from PDSP database. A pair of reports suggests MDMA may have some affinity for the trace amine receptor (TAR). In contrast with Battaglia’s work, later investigations did not find high affinity for M1 receptors. It is possible but not yet demonstrated that MDMA agonism at 5HT2B and α2 receptors might play a role in producing some of the subjective or psychological effects of MDMA. Most 5HT2B receptors are found on tissues outside the brain (Setola et al. 2003). However, 5HT2B 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 5HT2B agonists.
(Bond et al. 1995; Mortimore and Anderson 2000). Clonidine and other α2 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 α2 agonism. To date there are no behavioral studies examining the role of 5HT1B or α2 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 5HT1B receptors in various brain regions and 5HT2C 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.
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.
 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 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

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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
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
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-methylenedioxymethamphetamine, and N-hydroxy-3,4-methylenedioxymethamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999).

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\text{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 (Meehan 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-methylenedioxymethamphetamine (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-methylenedioxymethylacetone, and N-hydroxy-3,4-methylenedioxymethamphetamine (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).

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

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

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

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

**MDMA-assisted psychotherapy for PTSD**

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

Michael Mithoefer MD has enrolled nineteen participants in a randomized, placebo-controlled study of MDMA-assisted psychotherapy in 20 people with PTSD symptoms that have not responded to psychotherapy or pharmacotherapy, and a 21st subject who will be a veteran with PTSD who has not 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 Ochen 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 12.5 mg 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 \( \text{SHT}_{1A} \) 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 (Beggott 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, Beggott and colleagues estimated that between 2.9 and 11 emergency department visits might arise from 10,000 uses of ecstasy (Beggott et al. 2001, pp. 148-150).

Fatalities

Fatalities have occurred after the use of MDMA or related drugs in non-medical settings (Beggott et al. 2001; Henry and Rella 2001). Ecstasy-related fatalities are rare (Beggott 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. Beggott and colleagues found that men outnumbered women in most ecstasy-related fatalities except in the case of hyponatremia, where women outnumbered men (Beggott 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,
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

<table>
<thead>
<tr>
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<td>MDMA Dose(s):</td>
<td>0 mg/kg</td>
<td>0.5-4.18 mg/kg</td>
<td>1.76-4.18 mg/kg</td>
<td>1.7 mg/kg</td>
<td>75-150, 200 mg</td>
<td>1.5 mg/kg</td>
<td>1.5 mg/kg</td>
<td>1.5 mg/kg</td>
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<td>Lack Of Appetite</td>
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<td>70%</td>
<td>100%</td>
<td>63%</td>
<td>97%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>62%</td>
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<td>60%</td>
<td>64%</td>
<td>76%</td>
<td>57%</td>
<td>71%</td>
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<td>62%</td>
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<td>10%</td>
<td>71%</td>
<td>43%</td>
<td>50%</td>
<td>62%</td>
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<td>Difficulty Concentrating</td>
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<td>42%</td>
<td>30%</td>
<td>50%</td>
<td>3%</td>
<td>71%</td>
<td>50%</td>
<td>63%</td>
<td>62%</td>
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<tr>
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**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 5HT2B 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 Kokkkalis 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 Kokkkalis, 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
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

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

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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

Conclusions

Many studies in nonhuman animals suggest that frequent or high doses of MDMA can damage serotonin neurons, and some studies in ecstasy using humans suggest that repeated use, especially when heavy, can affect serotonergic function and specific domains of cognitive function. Ecstasy users exhibit impairment in specific areas of cognitive function, particularly verbal memory. However, when apparent, most long-term effects seem to be more strongly associated with heavy and not moderate use. The risk of impaired serotonin function or verbal memory after exposure to one to three doses of MDMA in the course of a controlled study remains possible, but evidence from retrospective and prospective studies of ecstasy users suggests 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

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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 11th to the 20th day after birth. If this period is similar to the third trimester of human gestation, then it is possible that MDMA in humans could have similar developmental effects. Some researchers found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA (Green et al. 2005), while others found that it attenuated this response (Piper et al. 2005). Given differences in rodent development and thermoregulation, it is not clear whether either or both findings can be generalized to humans. Because there may be a critical period during which exposure to MDMA could alter development, and as a result of the relative lack of information concerning its developmental toxicity, women who are pregnant or who are not using an effective means of birth control should not receive MDMA.
Some investigators have claimed that MDMA affects sub-adult rats differently than adults. Giving somewhat large doses of MDMA to sub-adult rats produced long-term reductions in anxiety and impaired object recognition (Piper et al. 2004). An initial dose of MDMA in young rats also produced less of an increase in BT and fewer signs of “serotonin syndrome” when given another dose of MDMA in adulthood (Piper et al. 2005). These nonhuman animal studies suggest that adolescents could be more vulnerable to some effects of MDMA.

6. Research trial data

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

7. Acknowledgements

I am grateful to Matthew Baggott for collaborating in creation of the first two documents and for continued support, knowledge and wisdom concerning the topics of MDMA and especially pharmacology. I am also thankful for the occasional help and information from a number of respected researchers for their insight, information and debate. I am thankful for the principal investigators Michael Mithoefer MD, John Halpern MD and Peter Oehen MD for embarking or continuing on their work, and I thank the Multidisciplinary Association for Psychedelic Studies (MAPS) and Rick Doblin PhD for supporting this work. Receptor binding profiles for MDMA was generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, a publicly available database of drug pharmacological activity, Contract # NO1MH32004 (NIMH PDSP), with data accessed between November 12 and November 14, 2007.

References


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

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. Multidisciplinary Association for Psychedelic Studies


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


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

32
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
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

Investigator's Brochure: MDMA

MAPS: 12/2007
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


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


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


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


Hoshi R, Mullins K, Bounby 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


Jager G, de Win MM, Vervaek 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, 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


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
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
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
Liechtli 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


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


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
Morgan MJ (1998) Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 19: 252-64
Morley KC, Arnold JC, McGregor IS (2005) Serotonin (1A) receptor involvement in acute 3,4-methylenedioxyamphetamine (MDMA) facilitation of social interaction in the rat. Prog Neuropsychopharmacol Biol Psychiatry 29: 648-57
Nair SG, Gudelsky GA (2005) 3,4-Methylenedioxyamphetamine (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
PDSP (2007) MDMA receptor binding profiles from Psychoactive Drug Screening Program Database. National Institute of Mental Health


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-dihydroxyamphetamine). Drug Metab Dispos 32: 1001-7


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


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


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

46


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


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


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
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 I in 1985 as a result of extensive non-medical use [10, 14, 15]. Placement in Schedule I 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].
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.

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 psychotrophic 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, 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 Ph.D. Andrew Felmár, 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
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.

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.

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.

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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 attend 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 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.