As can be seen in Table 5, MDMA kinetics are dose dependent within the range of commonly administered doses (de la Torre et al. 2000b). These dose-dependent kinetics appear to be due to dose-dependent metabolism rather than changes in absorption or excretion. Mas et al. (1999) reported that 75 mg and 125 mg doses of MDMA had similar absorption constants and absorption half-lives. On the other hand, non-renal clearance for 125 mg MDMA was approximately half that of 75 mg MDMA. The dose-dependent metabolism of MDMA is at least partially due to inhibition of CYP2D6, as discussed below. It has also been established that the fraction of MDMA bound to dog plasma proteins is approximately 0.4 and is concentration-independent over a wide range of concentrations (Garrett et al. 1991). Therefore, changes in plasma partitioning are not likely to be significant.
Farre and colleagues reported the pharmacokinetics of a second dose of 100 mg MDMA given 24 hours after an initial 100 mg dose in nine men (Farre et al. 2004). C\text{max} was 232.± 39 µ/L, AUC\text{24-48} was 2564 ± 762 µg*h/L, T\text{max}(24-48) was 25.5 ± 0.33 h, and AUC/dose was 25.64 ± 7.6 µg*h/1*mg. Maximal MDMA concentration after the second dose was similar to maximal concentration after the slightly higher dose of 125 mg (see Table 4 above), probably as a result of non-linear pharmacokinetics. De la Torre was first to report evidence of non-linear pharmacokinetics, and a recent report supports these findings (de la Torre et al. 2000a; Kolbrich et al. 2008). Based on these findings, metabolism of an initial dose will also be affected by a supplemental dose. However, since the size and timing of this dose are different from the dosing regimen employed by Farre and colleagues, it is not clear whether the supplemental dose will produce slightly

Table 5. MDMA Pharmacokinetics

<table>
<thead>
<tr>
<th>MDMA Dose</th>
<th>N</th>
<th>C\text{max} µg/l</th>
<th>T\text{max} H</th>
<th>AUC \text{0-24} µg*h/L</th>
<th>AUC/dose µg<em>h/(1</em>mg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>2</td>
<td>19.8 and 82.8</td>
<td>2 and 3</td>
<td>100.1 and 813.9</td>
<td>2 and 16.3</td>
<td>de la Torre et al. 2000a</td>
</tr>
<tr>
<td>75</td>
<td>8</td>
<td>130.9 ± 38.6</td>
<td>1.8 ± 0.38</td>
<td>1331.5 ± 646.03</td>
<td>17.8 ± 8.6</td>
<td>Mas et al. 1999</td>
</tr>
<tr>
<td>75</td>
<td>2</td>
<td>178 (no SD)</td>
<td>3</td>
<td>Not reported</td>
<td>NA</td>
<td>Lamers et al. 2003</td>
</tr>
<tr>
<td>100</td>
<td>8</td>
<td>222.5 ± 26.06</td>
<td>2.3 ± 1.1</td>
<td>2431.38 ± 766.52</td>
<td>24.31 ± 7.7</td>
<td>(de la Torre et al. 2000c)</td>
</tr>
<tr>
<td>100</td>
<td>9</td>
<td>180 ± 33</td>
<td>2 ± 0.26</td>
<td>1452 ± 771</td>
<td>14.52 ± 7.7</td>
<td>Farre et al. 2004</td>
</tr>
<tr>
<td>100</td>
<td>7</td>
<td>208.7 ± 17.1</td>
<td>16 ± 0.4</td>
<td>Not reported</td>
<td>NA</td>
<td>(Pizarro et al. 2004)</td>
</tr>
<tr>
<td>100</td>
<td>7</td>
<td>232.9 ± 45.3</td>
<td>1.5</td>
<td>Not reported</td>
<td>NA</td>
<td>Segura et al. 2005</td>
</tr>
<tr>
<td>125</td>
<td>8</td>
<td>236.4 ± 57.97</td>
<td>2.4 ± 0.98</td>
<td>2623.7 ± 572.9</td>
<td>21 ± 4.6</td>
<td>Mas et al. 1999</td>
</tr>
<tr>
<td>150</td>
<td>2</td>
<td>441.9 and 486.9</td>
<td>1.5 and 2</td>
<td>5132.8 and 5232</td>
<td>34.2 and 34.9</td>
<td>(de la Torre et al. 2000a)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MDMA Dose</th>
<th>N</th>
<th>k\text{a} /h</th>
<th>k\text{e} /h</th>
<th>T\text{1/2} H</th>
<th>MDA T\text{1/2a} H</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>2</td>
<td>Na</td>
<td>na</td>
<td>2.7 and 5.1</td>
<td>Na</td>
<td>(de la Torre et al. 2000c)</td>
</tr>
<tr>
<td>75</td>
<td>8</td>
<td>2.3835 ± 2.1362</td>
<td>0.1171 ± 0.0818</td>
<td>7.86 ± 3.58</td>
<td>0.42 ± 0.2</td>
<td>Mas et al. 1999</td>
</tr>
<tr>
<td>100</td>
<td>8</td>
<td>2.7 ± 1.53</td>
<td>0.081 ± 0.018</td>
<td>8.96 ± 2.27</td>
<td>1.31 ± 0.55</td>
<td>(de la Torre et al. 2000c)</td>
</tr>
<tr>
<td>100</td>
<td>7</td>
<td>na</td>
<td>0.07 ± 0.03</td>
<td>11.8 ± 4.4</td>
<td>na</td>
<td>Pizarro et al. 2004</td>
</tr>
<tr>
<td>125</td>
<td>8</td>
<td>2.1253 ± 1.1001</td>
<td>0.0923 ± 0.0428</td>
<td>8.73 ± 3.29</td>
<td>0.41 ± 0.22</td>
<td>Mas et al. 1999</td>
</tr>
<tr>
<td>150</td>
<td>2</td>
<td>Na</td>
<td>na</td>
<td>6.9 and 7.2</td>
<td>Na</td>
<td>(de la Torre et al. 2000a)</td>
</tr>
</tbody>
</table>
higher maximal values than expected after the supplemental dose only or the combined
dose, or whether it will instead lengthen $T_{max}$.

**Summary of Pharmacokinetic Parameters:**
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 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 a-methyladrenaline), 3,4-dihydroxymethamphetamine (DHMA, also called HHMA), 3,4-methylenedioxyphenylacetone, and N-hydroxy-3,4-methylenedioxyamphetamine (de Boer et al. 1997; Helmlin et al. 1996; Helmlin and Brenneisen 1992; Lanz et al. 1997; Ortuno et al. 1999; Pizarro et al. 2002; Segura et al. 2001). Thus far, human plasma levels of MDMA and the metabolites HMMA, HMA, and MDA have been published (de la Torre et al. 2000a; Pizarro et al. 2004; Pizarro et al. 2003; Pizarro et al. 2002)(de la Torre et al. 2000; Pizarro et al. 2002; Pizarro et al. 2003; Pizarro et al. 2004). HMMA appears to be the main metabolite in humans (Pizarro et al. 2004). Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996).

Although a number of researchers hypothesized that genetic variations in CYP2D6 activity might influence risk of MDMA toxicity, an examination of the research does not support this concern. Several in vitro studies have shown that MDMA is not just a substrate for CYP2D6 but also binds to it, forming an inhibitory complex (Brady et al. 1986; Delaforgue et al. 1999; Wu et al. 1997). Compelling in vivo evidence of enzyme inhibition was provided by de la Torre et al. (de la Torre et al. 2000a) who showed that plasma levels and 24-hour urinary recovery of HMMA are dose-independent. The fact that CYP2D6 is apparently easily saturated makes this possible source of individual sensitivity appear less significant.

Relatively recent reports in humans found no evidence that having a CYP2D6 “poor metabolizer” genotype is by itself a major risk factor for acute MDMA toxicity (de la Torre et al. 2004). At least one poor metabolizer has received MDMA as a participant in a study conducted by the Spanish team (de la Torre et al. 2005) (Segura et al. 2005) without any adverse events occurring. The individual had 60% greater MDMA AUC after a first and a second dose, but the only other reported difference for this participant was a statistically significant increase in amount of NK cells. A comparison of MDMA metabolism in poor and extensive metabolizers found that reduced CYP2D6 function was associated with higher MDMA AUC after the first of two doses of MDMA, but similar levels of MDMA and metabolites after the second dose (de la Torre et al. 2005). The same lack of effects was originally reported in a participant given the similar compound methylenedioxyethylamphetamine, or MDE (Kreth et al. 2000).

Two teams of researchers have investigated the enzymes involved in the formation of MDA from MDMA in human liver microsomes (Kreth et al. 2000; Maurer et al. 2000). Maurer et al. reported that formation of MDA was predominantly catalyzed by CYP1A2 (and to a lesser extent by CYP2D6), but did not present detailed results of their
experiments. In a publication focusing on MDE metabolism, Kreth and colleagues reported high correlations between MDMA and MDE N-dealkylation and MDE N-dealkylation and human liver microsome CYP2B6 content. MDE N-dealkylation and CYP1A2 levels were also significantly correlated. This indicates that CYP2B6 and CYP1A2 participate in the formation of MDA. The role of CYP2B6 in human MDMA metabolism is consistent with rodent research (Gollamudi et al. 1989).

MDMA is a chiral compound, meaning it comes in two forms or enantiomers. However, all investigations in humans and most in nonhuman animals have almost exclusively administered the racemate (a mixture of both enantiomers). Studies in human volunteers (Fallon et al. 1999; Hensley and Cody 1999) and rodents (Cho et al. 1990; Fitzgerald et al. 1990; Matsushima et al. 1998) indicate that the disposition of MDMA is stereoselective, with the S-(+)-enantiomer having a shorter elimination half-life and greater excretion than the R-(-)-enantiomer. For example, Fallon et al. (1999) reported that the area under the curve (AUC) of plasma concentrations was two to four times higher for the R-enantiomer than the S-enantiomer after 40 mg, p.o., in human volunteers. Moore et al. (1996) found greater levels of R-(-)-MDMA in blood, liver, vitreous and bile samples from an individual who died shortly after illicit MDMA use. Stereoselective analysis of biosamples in both an MDMA overdose and a traffic fatality had similar findings (Crifasi and Long 1996; Ramcharan et al. 1998). The stereoselective pharmacokinetics of MDMA is reflected in formation of MDA and DHMA enantiomers (Fallon et al. 1999; Pizarro et al. 2004; Pizarro et al. 2003). In the first 24 hours after MDMA administration, greater plasma and urine concentrations of S-(+)-MDA than its R-enantiomer occur (Fallon et al. 1999; Moore et al. 1996). By contrast, R/S ratios of HMMA are more similar to those for MDA (greater amounts of R-(-)-HMMA than S-(+)-HMMA during the first 24 hours), or there is no findings of a difference between concentrations of the two enantiomers of HMMA (Pizarro et al. 2004; Pizarro et al. 2003).

Absorption, Distribution, Metabolism, Excretion

The oxidation of the methylenedioxy group can take place via enzymes such as cytochrome p450 (Hiramatsu et al. 1990; Kumagai et al. 1991; Lim and Foltz 1988; Tucker et al. 1994) or by a non-enzymatic process involving the hydroxyl radical (Lin et al. 1992). The enzymes catalyzing this reaction have been examined in the rabbit (Kumagai et al. 1991, rat (Gollamudi et al. 1989; Hiramatsu and Cho 1990; Hiramatsu et al. 1990; Hiratsuka et al. 1995) and human (Kreth et al. 2000; Lin et al. 1997; Maurer et al. 2000; Tucker et al. 1994; Wu et al. 1997). In human liver microsomes, Michaelis-Menten kinetics for formation of dihydroxylated metabolites are biphasic (Kreth et al. 2000). The low Km component for demethylation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher Km also contribute to MDMA demethylation, including CY1A2 and CYP3A4.
Reproductive Toxicity

Investigations of the reproductive and developmental toxicity of MDMA are described in “Safety Pharmacology” above. These studies include inconclusive findings in humans and findings in rodents suggestive of a critical period during which exposure to MDMA

Table 6. Urinary Recovery for MDMA and Metabolites (de la Torre et al. 2000a)

<table>
<thead>
<tr>
<th>MDMA Dose (mg)</th>
<th>N</th>
<th>MDMA</th>
<th>MDA</th>
<th>HMMA</th>
<th>HMA</th>
<th>Dose Excreted (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 (259)</td>
<td>2</td>
<td>20.7 and 40.9</td>
<td>1.4 and 1.0</td>
<td>152.0 and 89.2</td>
<td>4.7 and 4.2</td>
<td>69.1 and 38.3</td>
</tr>
<tr>
<td>75 (358)</td>
<td>8</td>
<td>71.2 ± 13.7</td>
<td>3.5 ± 0.9</td>
<td>128.3 ± 21.8</td>
<td>5.4 ± 0.4</td>
<td>53.7 ± 11.4</td>
</tr>
<tr>
<td>100 (518)</td>
<td>2</td>
<td>232.6 and 74.7</td>
<td>5.6</td>
<td>124.0</td>
<td>6.8</td>
<td>57.3 and 40.7</td>
</tr>
<tr>
<td>125 (647)</td>
<td>8</td>
<td>169.6 ± 69.5</td>
<td>6.4 ± 2.7</td>
<td>148.3 ± 102.8</td>
<td>6.2 ± 3.7</td>
<td>51.0 ± 16.2</td>
</tr>
<tr>
<td>150 (776)</td>
<td>2</td>
<td>333.3</td>
<td>4.7</td>
<td>82.4</td>
<td>3.7</td>
<td>37.3 and 54.7</td>
</tr>
</tbody>
</table>

The urinary excretion of MDMA and its metabolites was first characterized by de la Torre and colleagues, with data from that study presented in Table 5 above. 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; Segura et al. 2005; Segura et al. 2001). Urinary excretion of the MDMA metabolite HHMA reported after administration of 100 mg MDMA to four men are 91.8 ± 23.8 mol and 17.7% recovery (Segura et al. 2001). 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).

Toxicology

The toxicity of MDMA has been investigated in numerous animal and in vitro studies published in peer-reviewed journals. In addition, hundreds of published case reports describe adverse events in illicit ecstasy users. Finally, 28-day toxicity studies in canines and rodents have been performed (Frith et al. 1987), and are included in the MDMA Drug Master File (DMF #6293). Thus, the toxicity of MDMA is well characterized.

Acute toxicity

Acute toxicity is described above in “Safety Pharmacology”, including both common side effects and effects occurring in ecstasy users. The estimated LD₅₀ for MDMA in humans is between 10 and 20 mg/kg (Frith et al. 1987; Hardman et al. 1973). To date, most controlled studies rarely administered doses above 2 mg/kg. The proposed doses of 150 followed by 75 mg (cumulative dose of 225 mg) or approximately 2.1 mg/kg followed by approximately 1 mg/kg (cumulative dose of 3.21 mg/kg) is below the estimated LD₅₀ in humans.

Reproductive Toxicity

Investigations of the reproductive and developmental toxicity of MDMA are described in “Safety Pharmacology” above. These studies include inconclusive findings in humans and findings in rodents suggestive of a critical period during which exposure to MDMA...
Previous Human Experience
Several accounts describe the use of MDMA as an adjunct to psychotherapy prior to its placement in schedule 1 (Adamson 1985; Stolaroff 2004), and between 1988 and 1993 in Switzerland (Gasser 1994; Widmer 1998). This therapy did not occur in the context of a controlled clinical trial. MDMA may have been given to thousands of individuals during these time periods without any fatalities or serious adverse events (Gasser 1994; Holland 2001; Rosenbaum and Doblin 1991). Psychotherapists used MDMA-assisted psychotherapy in the treatment of moderate psychological difficulties (“neuroses”), relationship difficulties, posttraumatic stress disorder, and anxiety in response to diagnosis with a potentially fatal illness. Therapists described relying on a mixture of therapeutic techniques that included confronting and working with the experience as it occurred and speaking openly with others during the experience.

In the 1980s, two researchers independently published an uncontrolled clinical trial and an uncontrolled investigation into MDMA-assisted psychotherapy (Downing 1986; Greer and Tolbert 1986). The psychotherapy that Greer and Tolbert conducted took place in a setting similar to that used for psychedelic-assisted psychotherapy, including focusing on inner experience. Greer and Tolbert used doses between 75 and 150 mg MDMA, sometimes with supplemental doses administered later (Greer and Tolbert 1986). Participants in the uncontrolled study of MDMA-assisted psychotherapy reported changes in attitudes and benefits afterwards.

The first controlled investigation of MDMA took place almost a decade after the uncontrolled studies (Grob et al. 1996), followed two years later by another controlled trial (Vollenweider et al. 1998). Starting in the mid to late 1990s, at least seven research teams in Europe and the US began conducting and publishing clinical MDMA research using healthy volunteers, and two recent reviews summarized findings from many of these studies (Baylen and Rosenberg 2006; Dumont and Verkes 2006). Since then, a second team of researchers in the Netherlands and a team based in Maryland published their first findings from human MDMA studies (Dumont et al. 2008; Kolbrich et al. 2008). Findings from controlled human studies of MDMA are also discussed in detail in the investigator’s brochure (Baggott et al. 2001; Jerome 2004; 2005; 2007; Jerome and Baggott 2003), and they are addressed earlier in this section. The first studies assessed physiological, subjective, psychological and neuroendocrine effects, and reported that MDMA possessed a unique pharmacological profile. Some of these first studies examined brain activity (Frei et al. 2001; Gamma et al. 2000) cardiac function (Lester et al. 2000), and effects of MDMA on attention and information processing (Cami et al. 2000b; Gamma et al. 2000).

To date, MDMA has been administered to approximately 390 research participants, without any occurrences of drug-related serious adverse events. Human MDMA studies have continued to investigate the subjective and physiological effects of MDMA, and its metabolism and detectability in several body fluids. In published reports, investigators
administered doses ranging from approximately 35 mg (0.5 mg/kg) to 145 to 150 mg (2 mg/kg) (Freedman et al. 2005; Harris et al. 2002; Lester et al. 2000) (Kolbrich et al. 2008), and an in an unpublished report, researchers administered 0.25 and 2.5 mg/kg MDMA as well (Grob 2001). The average dose examined in human MDMA studies is between 1 and 2 mg/kg. Studies of the physiological effects of MDMA include investigations of immunological effects (as Pacifici et al. 2004; Pacifici et al. 1999b; Pacifici et al. 2002; Pacifici et al. 2001b), neuroendocrine effects (Forsling et al. 2001; Grob et al. 1996; Harris et al. 2002; Liechti and Vollenweider 2001), cardiovascular and cardiac effects (Lester et al. 2000; Mas et al. 1999) and body temperature (Freedman et al. 2005), and employed brain imaging and quantitative electroencephalography (Frei et al. 2001; Gamma et al. 2000). Researchers have studied self-reported subjective and reinforcing effects (Cami et al. 2000b; Dumont et al. 2008; Grob et al. 1996; Harris et al. 2002; Liechti et al. 2001; Tancer and Johanson 2003) and observed effects (Harris et al. 2002), and they have studied such specific effects as enhancement of pre-pulse inhibition (Vollenweider et al. 1999), performance on attentional and information processing tasks such as the continuous performance, Stroop and digit symbol tasks (Cami et al. 2000b; Dumont et al. 2008; Gamma et al. 2000), cognitive skills related to driving motor vehicles (Kuypers and Ramaekers 2005; 2007; Kuypers et al. 2006; Ramaekers and Kuypers 2006; Ramaekers et al. 2006), including specific effects of nocturnal dosing (Kuypers et al. 2007), and similarity to a stimulant versus a serotonergic drug (Johanson et al. 2006). As described above, researchers have also examined the role of serotonin release, 5HT2A and D2 receptors in producing MDMA effects and MDMA pharmacokinetics (de la Torre et al. 2004; Farre et al. 2007; Liechti and Vollenweider 2001; Tancer and Johanson 2007).

A team of researchers in the US are about to complete their research study of MDMA-assisted psychotherapy in people with PTSD, while researchers in Switzerland are engaged in an ongoing study of MDMA-assisted psychotherapy (Mithoefer 2007a; b; 2008; Oehen 2006) and researchers in Israel are conducting a study of MDMA-assisted psychotherapy in people with PTSD (Mojeiko 2006). After undergoing introductory and preparatory psychotherapy, study participants in these studies receive two to three day-long sessions of MDMA-assisted psychotherapy scheduled three to five weeks apart. Participants receive integrative psychotherapy on the day after each session and often on a weekly basis in between and after each MDMA-assisted session. These studies employ an initial dose of 125 mg MDMA followed 2 to 2.5 hours later by a supplemental dose of 62.5 mg MDMA. One of the two ongoing studies has enrolled all study participants, and preliminary results appear promising (Mithoefer 2007b). The other study has enrolled half of the 12 subjects planned for this study. Another study will soon be recruiting people with advanced-stage cancer to examine MDMA-assisted psychotherapy as a means of reducing anxiety arising from the cancer diagnosis (Halpern 2006). To date, the Multidisciplinary Association for Psychedelic Studies (MAPS) sponsored three of four studies, with the fourth sponsored by the principal investigator and private benefactors.

Previous experience with MDMA indicates that it can be safely administered to humans within a research or therapeutic setting, and preliminary examination of data from a study of MDMA-assisted psychotherapy in people with PTSD suggests that MDMA improves
PTSD symptoms when used as a psychotherapeutic adjunct. The independent rater conducted a preliminary analysis of CAPS scores at baseline and two months later detected a significant condition effect (p. < 0.05). Average baseline scores for people in both conditions were comparable (79.6 for MDMA condition and 78.4 for placebo), but two months after the second experimental session, the average CAPS score for people in the MDMA condition was 27.6, while the average CAPS for people in placebo was 59.1. Eight of 13 participants no longer met criteria for PTSD two months after the second experimental session while only two of eight placebo participants no longer met criteria for PTSD diagnosis. Furthermore, a comparison of baseline assessment of neurocognitive function and assessment two months after the second experimental session did not find any significant differences in either MDMA or placebo participants (Wagner 2008, personal communication). The data examined in this analysis has not yet been subjected to quality assurance and data from one participant remains to be added, but there were few outliers in the data and it is unlikely that additional data will change results.

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Additional Information

Facilities

Introductory, MDMA-assisted and integrative psychotherapy. The offices consist of a set of three rooms, including a private bathroom and kitchen and include a refrigerator and microwave. The main room is comfortably furnished and private. There is artwork on the walls, and stained glass in some windows. Subjects may sit or lie on a couch. The offices are furnished with beds that allow for two people to remain overnight. The offices are lower than ground level. They can be heated, and fans are used for cooling. The offices have an enclosed courtyard. The office will contain equipment for assessing blood pressure, pulse, and body temperature and an automatic external defibrillator. The offices are not within a hospital, but the location is a five to fifteen minute drive from two hospitals with emergency departments, the University of British Columbia Hospital and St. Paul’s hospital. One therapist can reach the offices within five to ten minutes of contact if necessary.

Abuse Liability

The Drug Enforcement Administration placed MDMA in Schedule 1, a category reserved for drugs with high abuse potential and no known medical use. MDMA was scheduled shortly after people started using it in non-medical settings, as nightclubs or at parties (Beck and Rosenbaum 1994). Despite its classification as a Schedule 1 drug, self-administration studies in nonhuman animals and findings concerning prevalence of ecstasy abuse and dependence do not suggest that its abuse liability is high. Rats, mice and monkeys will self-administer MDMA (Fantegrossi et al. 2004; Schenk et al. 2003; Trigo et al. 2006). However, monkeys will “pay” higher prices in lever presses for psychostimulants than they will for MDMA (Lile et al. 2005; Wee and Woolverton 2006). Studies assessing prevalence of problematic ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop ecstasy use or dependence (Huizink et al. 2006; Lieb et al. 2002), though studies of non-representative samples have reported higher rates of dependence (Cottler et al. 2001). Most regular ecstasy users report taking ecstasy no more often than once a week (von Sydow et al. 2002). Taken together, an examination of findings in humans and nonhuman animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for “classic hallucinogens” like psilocybin, but lower than that reported for psychostimulants such as cocaine or methamphetamine.
Appendix A: Visit by Visit Description

Participants who consent to take part in the study will undergo the following sequence of events:

- **Randomized sessions**
- **Screening/Evaluation (Visit 3):** A two to three hour long medical and psychiatric evaluation. A physician working with the investigators will perform medical history and physical examination and ECG. The independent assessor will diagnose psychiatric disorders with the SCID, and will perform a face to face interview and administer the ASIQ to assess suicide risk. The physician or principal investigator will draw blood for laboratory tests. The independent rater will administer the CAPS and the participant will complete the BDI. The independent rater will administer the RBANS and PASAT. If a participant meets study eligibility criteria after evaluation, he or she will be scheduled for an introductory psychotherapy session. The independent assessor will re-evaluate any participant who undergoes the screening and baseline evaluation prior to discontinuing psychiatric medication. During re-evaluation, the independent assessor will administer the CAPS and the participant will complete the PDS and BDI during a visit occurring after an interval of at least five times drug half-life.

- **Introductory Psychotherapy visits (Visits 4-6):** Three 60 to 90 minute introductory psychotherapy sessions with both psychotherapist investigators. These sessions will help the therapists and participant to learn about each other and discuss the participant’s goals, hopes and fears in relation to upcoming MDMA-assisted psychotherapy, and the events and procedures that will occur during MDMA-assisted psychotherapy. Introductory sessions will be recorded to audio and video, and participants will have an opportunity to review the recordings. On the third introductory session, participants will receive instructions and restrictions relating to food and drug consumption for the night before and morning of the MDMA-assisted session. Participants must be randomized to one of the two conditions (active placebo or experimental dose) prior to the first MDMA-assisted psychotherapy session.

- **MDMA-assisted Psychotherapy Session 1 (Visit 7):** First eight-hour long randomized (active placebo versus experimental dose) MDMA-assisted psychotherapy session. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapists deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of the session recording upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant during the experimental session or at some time after it has ended. The significant other can remain overnight with the participant but does not have to do so. All participants will remain at overnight. A same-sex attendant versed in caring for people
undergoing difficult psychological experiences will remain with the participant during the overnight stay.

- **Integrative Psychotherapy On the Day After Experimental Session (Visit 8):** A ninety-minute long psychotherapy session with both psychotherapist-investigators always occurring on the morning of the day after MDMA-assisted psychotherapy. The participant will discuss his or her thoughts, feelings, memories or experiences that occurred during the experimental session and the participant and investigators will seek to integrate this material into everyday life. The session will be recorded to audio and video and participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy, and the participant will complete the ASIQ after completing psychotherapy.

- **Integrative Psychotherapy Sessions Between Experimental MDMA-assisted Session 1 and 2 (Visit 9-10, 10.x):** Two or more sixty to ninety minute psychotherapy sessions with both psychotherapist-investigators during which they and the participant continue to integrate material from MDMA-assisted psychotherapy sessions. The investigators and participant may schedule additional integrative sessions upon participant request and therapist-investigator mutual agreement. These sessions will be recorded to audio and video and participants may view session recordings upon request.

- **MDMA-Assisted Psychotherapy Session 2 (Visit 11):** The second eight-hour long session of MDMA-assisted psychotherapy with either active placebo or experimental dose MDMA with both therapist-investigators. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with a tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapist-investigators deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of their session recordings upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant, arriving sometime during the experimental session or after the experimental session is over. All participants will remain overnight with significant others may remain overnight with participants but do not have to do so.

- **Integrative Psychotherapy One Day after MDMA-assisted Psychotherapy 2 (Visit 12):** A ninety-minute long psychotherapy session with both psychotherapist-investigators that will take place on the day after the second experimental session. The participant and investigators will discuss participant thoughts, feelings, memories or experiences from one or both experimental sessions, working to integrate this material into everyday life. The session will be recorded to audio and video. Participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy, and the participant will complete the ASIQ after completing psychotherapy.
• **Integrative Psychotherapy After MDMA-Assisted Session 2 (Visits 13-14, 14.x):** At least two sixty to ninety minute psychotherapy sessions with both therapist-investigators occurring after the second MDMA-assisted psychotherapy session. The participant and both therapist-investigators will continue to work toward integrating experimental session material. Additional psychotherapy sessions may be scheduled at the request of the participant. These sessions will be recorded to audio and video, and participants can listen to or view recordings upon request.

• **MDMA-Assisted Psychotherapy Session 3 (Visit 15):** The third eight-hour long session of MDMA-assisted psychotherapy with either active placebo or experimental dose MDMA with both therapist-investigators. Participants arrive at approximately 9:00 AM to undergo urinary drug and pregnancy tests, with positive test results either delaying or rescheduling the session to withdrawal from the study. The investigators will administer a capsule containing either 25 or 125 mg MDMA at 10:00 AM, and participants will be encouraged to sit or lie down comfortably for the duration of the session. The investigators will measure blood pressure and pulse once prior to drug administration and every thirty minutes for the duration of the session, with more frequent measures taken if blood pressure or pulse exceed established cut-offs. The investigators will measure body temperature every 60 to 90 minutes with a tympanic thermometer. The participant will complete the SUD every sixty to ninety minutes. One and a half to 2.5 hours later, if the therapist-investigators deem it appropriate and the participant agrees to it, a supplemental dose of 12.5 or 62.5 mg MDMA will be administered. The entire session will be recorded to audio and video and participants may receive a copy of their session recordings upon request. The male and female therapist will remain with the participant for the duration of the session up until eight hours later (approximately 6:00 PM). A significant other may remain with the participant, arriving sometime during or after the experimental session. All participants will remain overnight with participants but do not have to do so.

• **Integrative Psychotherapy One Day after MOMA-assisted Psychotherapy 3 (Visit 16):** A ninety-minute long psychotherapy session with both psychotherapist-investigators that will take place on the day after the third experimental session. The participant and investigators will discuss participant thoughts, feelings, memories or experiences from one or both experimental sessions, working to integrate this material into everyday life. The session will be recorded to audio and video. Participants may listen to or view recordings upon request. The participant and both therapist-investigators will complete a measure of beliefs concerning participant condition assignment prior to starting psychotherapy, and the participant will complete the ASIQ after completing psychotherapy.

• **Integrative Psychotherapy After MDMA-Assisted Session 3 (Visits 17-18, 18.x):** At least two sixty to ninety minute psychotherapy sessions with both therapist-investigators occurring after the third MDMA-assisted psychotherapy session. The participant and both therapist-investigators will continue to work toward integrating experimental session material. Additional psychotherapy sessions may be scheduled at the request of the participant. These sessions will be recorded to audio and video, and participants can listen to or view recordings upon request.

• **Evaluation Six weeks After Third MOMA-assisted Session (Visit 19):** A ninety to 120 minute long (1.5-2 hour long) evaluation. The independent assessor will administer the CAPS, RBANS and PASAT, and the participant will complete the BDI and PDS.

• **Study Blind Broken for Individual Subject (Visit 19):** A 30 to 60 minute long meeting with the therapist-investigators. The participant and both therapists will learn participant condition assignment. The independent rater will remain blind to participant condition assignment.
assignment. If the individual received active placebo MDMA, then he or she will receive consent materials for the open-label study segment, Stage 2. Any participant who received active placebo and does not consent to take part in Stage 2 will complete the RRPQ.

- **Open-label Sessions for Active Placebo Participants (Stage 2)**
- **Consent for stage 2 (Visit 20):** A 30 to 60 minute meeting with the investigator therapists for participants who learn they received active placebo. They will receive consent materials concerning the open-label study segment. They must give written informed consent to take part in this study segment. Visit 20 may occur on the same day as Visit 19.
- **Stage 2 Baseline Evaluation (Visit 21):** Baseline evaluation for stage 2 (active placebo participants only). CAPS, PDS and BDI scores from the evaluation six weeks after the third experimental session (Visit 19) will serve as baseline scores except in the case where thirty days have passed between those evaluations and the time when the participant entered Stage 2, in which case the independent assessor will perform and additional evaluation, administering the CAPS and BDI prior to entry into Stage 2.
- **Review and Introductory Psychotherapy (Visit 22):** A sixty to ninety minute psychotherapy session with both therapist-investigators and the participant enrolled in Stage 2. The participant and therapist-investigators will re-acquaint themselves with each other, and the participant will review information about MDMA-assisted therapy and all three will discuss, review and possibly revise goals for MDMA-assisted psychotherapy. The session will be recorded to audio and video. Participants may listen to or view recordings upon request.
- **Open-label MDMA session 1 (Visit 23):** The first eight-hour long open-label session with a full dose of MDMA (125 mg), applicable for participants in Stage 2 only. This option is not applicable to participants enrolled in Stage 2. Participants will undergo urinary drug and pregnancy testing, and 125 mg MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants will receive copies of their open-label session recordings. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of 62.5 mg MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the session, with more frequent measures taken only if the established thresholds for normal blood pressure and pulse have not been exceeded. The investigators will measure body temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive during the experimental session or after the session is over. All participants will remain overnight Significant others may remain overnight with participants but do not have to do so.
- **Integrative Psychotherapy One Day after Open-Label MDMA Session 1 (Visit 24):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the first open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to integrative psychotherapy sessions after experimental MDMA-assisted therapy sessions. This session will be recorded to audio and video. Participants can listen to or view recordings upon request.
- **Integrative Psychotherapy Between Open-Label Session 1 and 2 (Visits 25-26, 26.x).** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval between the first and second Stage 2 open-label
MDMA-assisted session. The therapists and investigator will continue working on integrating MDMA session material into everyday life. These sessions will be recorded to audio and video, and participants can review session recordings upon request. Participants will complete the ASIQ after completing psychotherapy.

- **Open-label MDMA session 2 (Visit 28):** The second eight-hour long open-label session with a full dose of MDMA (125 mg), applicable for participants in stage 2 only. Participants not enrolled in Stage 2 may decline to take part in this session. Participants will undergo urinary drug and pregnancy testing, and MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants may receive copies of their open-label sessions upon request. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the session, with more frequent measures taken only if the established thresholds for normal blood pressure and pulse have not been exceeded. The investigators will measure body temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive during or after the experimental session to remain with the participant. All participants will remain overnight. Significant others may remain overnight with participants but do not have to do so.

- **Integrative Psychotherapy One Day after Open-Label MDMA Session 2 (Visit 29):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the second open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to that of integrative psychotherapy sessions after experimental MDMA-assisted psychotherapy. The session will be recorded to audio and video, and participants can listen to or view session recordings upon request. Participants will complete the ASIQ after completing psychotherapy.

- **Integrative Psychotherapy Between Open-Label MDMA 2 and 3 (Visits 30-31, 31.x):** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval between the second and third Stage 2 open-label MDMA-assisted session. These sessions will be recorded to audio and video, and participants can listen to or view session recordings upon request. These will be the final integrative sessions for participants not enrolled in stage 2. The therapists and investigator will continue working on integrating MDMA session material into everyday life.

- **Open-label MDMA session 3 (Visit 32):** The third eight-hour long open-label session with a full dose of MDMA (125 mg) for participants enrolled in Stage 2. Participants will undergo urinary drug and pregnancy testing, and MDMA will be administered at approximately 10:00 AM. Participants will be encouraged to sit or lie down comfortably for the duration of the session and the male and female therapist-investigators will remain with the participant throughout the session. The entire session will be recorded to audio and video, and participants will receive copies of open-label session recordings. One and a half to 2.5 hours later, if the investigators believe it appropriate and the participant agrees to it, a second dose of MDMA will be administered. Blood pressure and pulse will be assessed prior to drug administration and at 30-minute intervals for the duration of the session, with more frequent measures taken only if the established thresholds for normal blood pressure and pulse have not been exceeded. The investigators will measure body
temperature every 60 to 90 minutes with a tympanic thermometer. The SUD will be administered every sixty to ninety minutes. A significant other may arrive sometime during the experimental session or after it has ended or near the end of the session to remain with the participant. All participants will remain overnight. Significant others may remain overnight with participants but do not have to do so.

- **Integrative Psychotherapy One Day after Open-Label MDMA Session 3 (Visit 33):** A 90-minute psychotherapy session with both therapist-investigators on the morning of the day after the third open-label MDMA-assisted psychotherapy session. This session will employ similar procedures and serve a similar goal to that of integrative psychotherapy sessions after experimental MDMA-assisted psychotherapy. This session will be recorded to audio and video. Participants can listen to or view their recordings upon request. Participants will complete the ASIQ after completing psychotherapy.

- **Integrative Psychotherapy After Open-Label Session 3 (Visits 34-35, 35.x):** At least two 60 to 90-minute psychotherapy sessions with the two therapist-investigators scheduled to occur in the time interval after the third open-label session. The therapists and investigator will continue working on integrating MDMA session material into everyday life. These sessions will be recorded to audio and video, and participants can listen to or view session recordings upon request.

- **Evaluation Six weeks after Third Open-Label Session for Participants Enrolled in Stage 2 (Visit 36):** A ninety to 120-minute visit with the independent assessor and the therapist-investigators for participants enrolled in Stage 2 occurring six weeks after the third open-label session. The independent assessor will administer the CAPS and the participant will complete the BDI and PDS.

- **Study Termination for Stage 2 Participants (Visit 37):** After completing CAPS, PDS and BDI, the participant will meet for approximately a half hour (0.5 hours) with the therapist-investigators. The participant will complete the RRPQ.
Appendix B: Case Report Forms

These are sample case report form drafts for the study “A Randomized, Active Placebo-controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Posttraumatic Stress Disorder (PTSD)-Canada.”

The series of case report forms represents the series of events from screening up through the first experimental session of MDMA-assisted psychotherapy. The series does not include CRFs for subsequent experimental sessions or open-label sessions as the information contained is identical or nearly identical in content and format.

CONTAINS

SCREENING AND BASELINE EVALUATION
INTRODUCTORY PSYCHOTHERAPY
FIRST EXPERIMENTAL SESSION
INTEGRATIVE PSYCHOTHERAPY
FINAL EVALUATION
MEDICATION AND ADVERSE EVENTS
Participant Demographics

Date signed consent __ - __ - __  
Date of Enrollment __ - __ - __

Date of Birth: __ - __ - __

Ethnic Origin:  
☐ Asian  
☐ African American  
☐ Caucasian  
☐ Latino/a / Hispanic  
☐ Middle Eastern  
☐ First Nation  
☐ Native Hawaiian/Other Pacific Islander  
☐ Biracial, Specify ________________  
☐ Other, Specify ________________

Sex:  
☐ Male  
☐ Female

Physical Examination

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Blood Pressure (mm Hg) _____ / _____

Heart Rate (BPM) _____

Urine Pregnancy Test
☐ Positive  
☐ Negative  
☐ Not Applicable (Subject is Male, Non-child bearing potential)

Urine Drug Screen
☐ Positive  
☐ Negative

ECG

☐ Normal  
☐ Abnormal*, NOT clinically significant  
☐ Abnormal*, clinically significant

If “Abnormal,” please describe in the space provided below

________________________________________
**Study Entry Criteria**

Subject screened under protocol version: ☐ Original ☐ Amendment # _____

Did subject meet all study entry criteria specified in the protocol ☐ Yes ☐ No

If No, please mark nature of deviation in the chart below and on the following pages

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<th>Criterion number (as listed in protocol)</th>
<th>Protocol deviation entry granted?</th>
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<td>☐ Yes ☐ No</td>
<td>_____ - _____ - _____</td>
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<td>☐ Exclusion met</td>
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<td>_______</td>
<td>☐ Yes ☐ No</td>
<td>_____ - _____ - _____</td>
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<td>☐ Exclusion met</td>
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<td>☐ Inclusion not met</td>
<td>_______</td>
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<td>_____ - _____ - _____</td>
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<tr>
<td>☐ Exclusion met</td>
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<tr>
<td>☐ Inclusion not met</td>
<td>_______</td>
<td>☐ Yes ☐ No</td>
<td>_____ - _____ - _____</td>
</tr>
</tbody>
</table>
Non Psychiatric Medical History

Does the subject have any significant Non Psychiatric past diagnosis (including allergies, abnormalities, injuries, sexually transmitted diseases, major surgeries requiring in-patient hospitalization) or current diagnosis/condition?

- [ ] YES
- [ ] NO

If Yes, specify below.

NOTE: If the Diagnosis date is not known write UNK, try to provide at least a year.

Newly diagnosed or worsening conditions or diseases after this visit are considered adverse events.

<table>
<thead>
<tr>
<th>Diag #</th>
<th>Diagnosis</th>
<th>Start date mm-dd-yyyy</th>
<th>Ongoing?</th>
<th>Stop Date mm-dd-yyyy</th>
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</thead>
<tbody>
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MDMA Psychotherapy for PTSD

Final Copy-Revised: 11/17/08

MAPS Study MP-4

PI: Pacey
### Comprehensive Metabolic Profile

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Unit</th>
<th>Clinically Significant?</th>
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<tbody>
<tr>
<td>AG ratio</td>
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<td></td>
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</tr>
<tr>
<td>Albumin</td>
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<td></td>
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</tr>
<tr>
<td>Alkaline Phosphatase</td>
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<tr>
<td>AST (SGOT)</td>
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<tr>
<td>ALT (SGPT)</td>
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<tr>
<td>Bilirubin Total</td>
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<td>BUN</td>
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<td></td>
<td></td>
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<tr>
<td>Bun/Creatinine</td>
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<tr>
<td>Calcium</td>
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<td>Creatinine</td>
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<tr>
<td>Globulin</td>
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<td>Glucose</td>
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<td>Potassium</td>
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<tr>
<td>Protein Total</td>
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<tr>
<td>Sodium</td>
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### Urinalysis

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<tr>
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<th>Clinically significant?</th>
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<td>Specific gravity</td>
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<td>Ketones</td>
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<td>Occult blood</td>
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<tr>
<td>Leukocyte Esterase</td>
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<td>Nitrite</td>
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<td>Bilirubin</td>
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<tr>
<td>Urobilinogen</td>
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</table>

### Thyroid Panel with TSH

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<tr>
<th>Test</th>
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<th>CS = Clinically significant</th>
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</thead>
<tbody>
<tr>
<td>Thyroxine</td>
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<tr>
<td>Thyroid hormone binding ratio</td>
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<td>Thyroid Stimulating Hormone</td>
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<tr>
<td>Free Thyroxine Index</td>
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</tbody>
</table>

If any clinically significant lab results, please record in Adverse Event CRF. 

MDMA Psychotherapy for PTSD

Baseline Clinical Labs Visit #1

Date of Result

Comprehensive Metabolic Profile

If any clinically significant lab results, please record in Adverse Event CRF.

If any clinically significant lab results, please record in Adverse Event CRF. dd mmm yy
Past Psychiatric Medical History

Record any Psychiatric Diagnosis made prior to visit 1. If Diagnosis date is not known write UNK, try to provide at least a year.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnosis Start date mm-dd-yyyy</th>
<th>Ongoing?</th>
<th>Stop Date mm-dd-yyyy</th>
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<td>□ Yes</td>
<td>□ No</td>
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</table>
**Type and Duration of Previous Therapy**

Record any non-drug therapy prior to visit 1 using the codes provided to the side of this chart. If date is not known write UNK, try to provide at least a year. Record any drug therapy on the Psychotropic Medication page.

<table>
<thead>
<tr>
<th>Type</th>
<th>Other Therapy Type</th>
<th># Sessions</th>
<th>Per</th>
<th>Start Date</th>
<th>Ongoing</th>
<th>Stop Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Yes</td>
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<td>No</td>
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</tbody>
</table>

**Type of Psychotherapy Code**

1 = CBT (Cognitive Behavioral Therapy)  
2 = Behavioral  
3 = Prolonged Exposure  
4 = EMDR  
5 = IPT (Interpersonal Therapy)  
6 = Psychodynamic  
7 = Holotropic Breathwork  
8 = Group Psychotherapy  
9 = Other

**History of Suicide Attempts or Thoughts**

Suicidal Tendencies: Check the box that in your opinion most represents the frequency which the subject has thoughts of death or suicide, as determined via psychiatric interview.

- [ ] None at all  
- [ ] Slight: occasional thoughts of death without suicidal thoughts  
- [ ] Mild: frequent thoughts of being better off dead/occasional thoughts of suicide (without a plan)  
- [ ] Moderate: often thinks of suicide or has thought of specific method  
- [ ] Severe: frequent suicidal thoughts, mentally rehearsed plan, has made a suicide gesture  
- [ ] Very: made recent preparations for serious suicide attempt

**Adult Suicidal Ideation Scale at Screening**

Score at Screening: ________
**Past Use of Ecstasy**

Has the subject ever used “Ecstasy”?  □ YES  □ NO

If Yes, # of Occasions

If Yes, when

□ Within the last six months
□ Seven to 11 months ago
□ 12 to 24 months ago
□ 25 to 36 months ago
□ 37 to 48 months ago
□ 49 to 60 months ago
□ 61 months to 120 months
□ Over 120 months ago.

**Past Substance Use**

Previous Alcohol Abuse/dependence  □ yes  □ no  # of prior treatments____

In the last six months  □ yes  □ no

*Previous Drug Abuse/dependence* □ yes  □ no  # of prior treatments____

*In the last six months*  □ yes  □ no
### CAPS Scoring – Baseline PTSD Diagnosis Visit #3

**Date of Evaluation**: __________ - __________

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Specify</th>
<th>Frequency</th>
<th>Intensity</th>
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</thead>
<tbody>
<tr>
<td>A (traumatic event) met</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>B (re-experiencing) sx (≥ 1)?</td>
<td>Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C (Avoidance) (≥ 3)?</td>
<td>Score</td>
<td></td>
<td></td>
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<tr>
<td>D (Hyperarousal) (≥ 2)?</td>
<td>Score</td>
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<tr>
<td>E (duration ≥ 1 month)?</td>
<td>Duration in Months</td>
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<tr>
<td>F (Distress/impairment)</td>
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<tr>
<td>CURRENT PTSD (Criteria A-F)</td>
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<tr>
<td>PTSD Global</td>
<td>Score</td>
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</table>

- Check this box if assessment occurred after screening and appropriate drug washout

**Associated Features**

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<th>#27</th>
<th>#28</th>
<th>#29</th>
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<tbody>
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</table>
PDS and BDI Scoring – Baseline Visit #3

Date of Evaluation __________ - _________
mmm    dd    yy

Posttraumatic Stress Diagnostic Scale (PDS) Stage 3 Outcome #1

<table>
<thead>
<tr>
<th>PTSD Diagnosis</th>
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<tbody>
<tr>
<td>Symptom Severity Score</td>
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<tr>
<td>Symptom Severity Rating</td>
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<tr>
<td>Level of Impairment of Functioning</td>
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</tbody>
</table>

Beck Depression Inventory (BDI)

___________ BDI score

☐ Check this box if assessment occurred after screening and appropriate drug washout
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<thead>
<tr>
<th>DSM Diagnosis</th>
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<tr>
<td>PTSD</td>
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<tr>
<td>Unipolar Depression</td>
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<td>Panic Disorder</td>
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<tr>
<td>Generalized Anxiety Disorder</td>
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<tr>
<td>Bipolar Affective Disorder-1</td>
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<tr>
<td>Bipolar Affective Disorder-II</td>
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<tr>
<td>Dissociative Identity Disorder</td>
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<td>Psychosis</td>
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<tr>
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<tr>
<td>if Yes Active Purging?</td>
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<tr>
<td>Borderline Personality Disorder</td>
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<td>Substance Abuse or dependence (60 days)</td>
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<tr>
<td>Other DSM IV diagnosis-2</td>
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<td>Visit Date</td>
<td>Subject Demeanor and State of Mind enter code</td>
<td>Subject currently enter code</td>
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<td>Visit #5</td>
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<tr>
<td>Visit #6</td>
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</tbody>
</table>

1= Very stable and calm
2= Stable and calm
3= Slightly stable and calm
4= Slightly distressed
5= Distressed
6= Very distressed

A= Does not face risk of significant deterioration.
B= Probably faces risk of significant deterioration.
C= Faces risk of significant deterioration.

General Well Being -Non-Experimental Sessions- Baseline
Review of Inclusion and Exclusion Criteria

Has the subject refrained from consuming prohibited food or beverages?  □ Yes □ No

Have all meds finished tapering?  □ Yes □ No □ NA

Urine Pregnancy Test
□ Positive
□ Negative
□ Not Applicable (Subject is Male, Non-child bearing potential)

Urine Drug Screen
□ Positive
□ Negative

Does subject continue to meet All Inclusion and No Exclusion Criteria? □ Yes □ No

If No Specify ________________________________

Dosing

Date ______-______-______
dd  mmm  yyyy

Record time initial dose MDMA administered _________

Record Bottle number of active placebo/experimental MDMA _________

Second Dose of active placebo/experimental dose MDMA Administered?  □ Yes □ No

If yes, Record time second dose was administered _________

Record Bottle number of MDMA _________
### Vital Signs - Experimental Session #1 Visit #7

Mark point where supplemental dose given. Make no mark if supplemental dose not given.

#### Monitoring: Blood Pressure and Pulse

<table>
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<th>Time</th>
<th>SBP</th>
<th>DBP</th>
<th>Pulse</th>
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<tbody>
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<tr>
<td>30 min postdrug</td>
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<tr>
<td>1 hour post-drug</td>
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<td>1 h 30 min postdrug</td>
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<tr>
<td>2 h postdrug</td>
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<tr>
<td>2 h 30 min postdrug</td>
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<td>5 h 30 min postdrug</td>
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<td>7 h 30 min postdrug</td>
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<td>8 h postdrug</td>
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Record any additional time points here:

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#### Temperature

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<tr>
<th>Postdrug (h.min)</th>
<th>Time</th>
<th>BT</th>
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Record any additional time points here:

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</table>

SUDS - Experimental Session #1 Visit #7
Integrative Psychotherapy After Experimental Session #1 (Visit 8)

Subject Belief of Condition Assignment Visit #8

Indicate what condition the subject believes they were assigned

☐ Low dose MDMA
☐ Experimental Dose MDMA

Indicate the subject's certainty about this belief of condition assignment

☐ Not at all certain
☐ Somewhat certain
☐ Certain
☐ Very certain

Adult Suicidal Ideation Scale After Experimental Session 1
Please administer the ASIQ after completion of integrative psychotherapy during Visit 8. Record the total score below.

Score: ________