Previous Human Experience: Controlled Clinical Trials and Pharmacology

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Introduction and Overview

This chapter summarizes available information on clinical studies in which MDMA was administered. Three research groups in the United States and three more in Europe have conducted controlled clinical studies with MDMA. Thirty-three publications have documented the effects of MDMA in at least ten independent groups of volunteers. Pharmacokinetics and physiological, neuroendocrine, psychological, neurocognitive, cerebrofunctional, and immunological effects of MDMA have been reported. Studies have also used pharmacological probes to investigate the neurochemical mechanisms that produce the psychological and physiological effects of MDMA. In addition, several reports have been published describing clinical work carried out before MDMA became a controlled substance. Detailed descriptions of individual studies are available in Appendix A. There has been no reported evidence of serious or lasting toxicity to volunteers in these studies or to patients in MDMA-assisted psychotherapy

MDMA has been administered in controlled clinical studies using doses of up to 2.5 mg/kg, with most studies employing doses equivalent to 1.5 to 1.7 mg/kg MDMA. Earlier, uncontrolled studies and reports employed higher doses (e.g., up to 4.18 mg/kg in Downing 1986), but collected few and somewhat inconsistent data on drug effects.

The intoxication produced by MDMA in recent clinical studies is consistent with earlier reports of an easily controlled state characterized by euphoria, increased well being, increased sociability, and decreased anxiety. These effects are also consistent with the hypothesis that MDMA represents a novel class of pharmacological agent, although further research is needed. Participants reportedly experience modest alterations in perception of surroundings and pleasurable loosening of ego boundaries. Subjective effects are accompanied by robust sympathomimetic cardiovascular effects. Acute increases in circulating cortisol, prolactin, ACTH, and antidiuretic hormone occur.

MDMA has been generally well tolerated, with hypertensive episodes being the most important acute adverse effect noted. Other commonly reported side effects include decreased appetite, jaw clenching, and impaired balance/gait. The acute effects of MDMA peak between one and three hours after drug administration and have largely resolved by six hours after drug administration. Documented effects persisting beyond this point include altered immune functioning, probably lasting about two days, and altered cerebral blood flow, lasting at least several weeks. Some volunteers also report feelings of lethargy and other symptoms for several days after MDMA exposure.

Serotonin release seems to be integral to many of the psychological and physiological effects of MDMA, but $5HT_2$ receptors and dopamine release have also been shown to be involved in producing specific MDMA effects.

MDMA has nonlinear pharmacokinetics with decreased non-renal clearance occurring at higher doses, probably due to inhibition of one metabolic pathway, cytochrome P-450 (CYP) isozyme 2D6. Pharmacological studies suggest that CYP 2D6 may be inactivated by MDMA and may therefore have a limited role in MDMA metabolism. Other enzymes playing a role in MDMA metabolism include CYP 2B6, 1A2, and 3A4.

A Note on Use of MDMA in Therapy

It is worth noting that there is considerable previous human experience with the use of MDMA in the context of psychotherapy. Before MDMA was classified as a controlled substance, a number of therapists employed it as an adjunct to psychotherapy. Although no blinded or placebo-controlled trials were conducted, these therapists concluded that MDMA was clinically useful and could be safely administered to a variety of patient populations. Few published reports of this work qualify for inclusion in this review (most of these reports were not published in peer-reviewed journals). Nonetheless, available reports document the clinical experience of these therapists. Reid Stuart's (2000) annotated bibliography on MDMA psychotherapy is a helpful summary of this literature.

The DEA hearings on the scheduling of MDMA provide a useful overview of therapeutic work with MDMA. Rick Ingrasci, MD, MPH, (1985) reported conducting approximately 150 MDMA sessions with about 100 patients, 11 of them cancer patients. Approximately one-third of these 150 sessions were with couples. Joseph Downing, M.D., (1985) reported use of MDMA with 8 patients, 5 of whom were felt to have shown accelerated therapeutic progress. Philip Wolfson, M.D., (1985; 1986) administered MDMA to 3 psychotic patients in the context of family therapy, reporting short-term but no clear long-term benefits of MDMA. George Greer, M.D., (Greer and Strassman 1985; Greer and Tolbert 1986; 1990; 1998) administered MDMA to about 80 individuals. Although not described at the DEA hearings, therapeutic work with MDMA was also carried out in other countries. Manuel Madriz Marin, M.D., chief psychiatrist of a Nicaraguan military hospital, used MDMA in the treatment of 20 patients with “anxiety or depressive disorders” (Saunders and Doblin 1996). After MDMA was made a controlled substance, Samuel Widmer, MD, Peter Gasser, MD, and other members of the Swiss Medical Society for Psycholytic Therapy received permission to administer MDMA to patients from 1988 to 1993 (Gasser 1994; Widmer 1997). During this time, 171 patients received MDMA. In a follow-up survey, 85.1% of 121 responding patients reported good or slight improvement during therapy, which included 6.8 ± 4.3 (1 - 16) MDMA sessions administered in the context of on-going therapy (Gasser 1994).

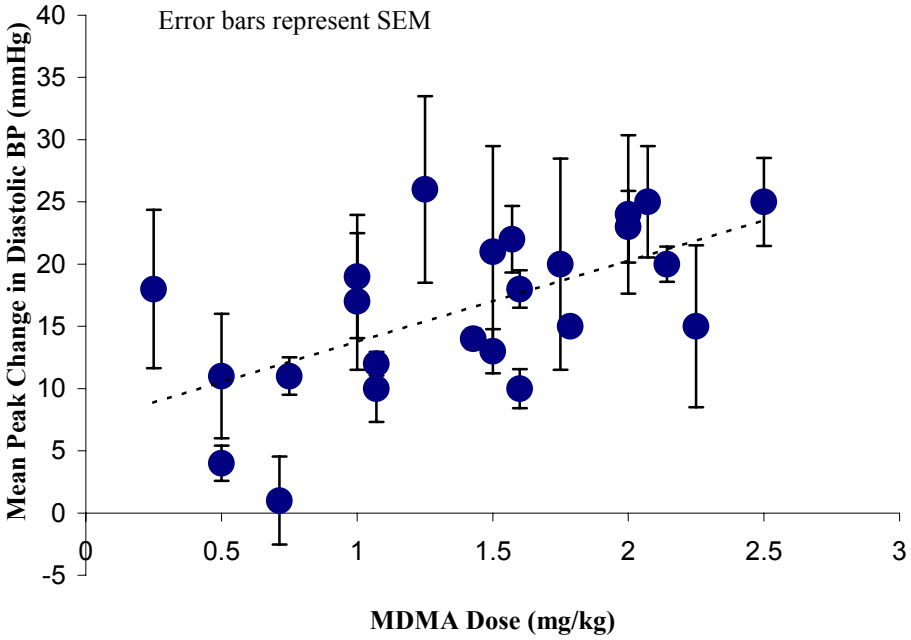
Based on this clinical experience, MDMA was considered to possess a “unique action that enhanced communication” (Greer 1985), especially between people in a significant emotional relationship. Reductions in defenses and fear of emotional injury and a heightened capacity for introspection were reported. MDMA was reported to enhance retrieval of previously suppressed memories, leading to reduction of symptoms (Grinspoon and Bakalar 1986). These effects of MDMA were achieved with relatively modest reported side effects and no indications of chronic toxicity. While these

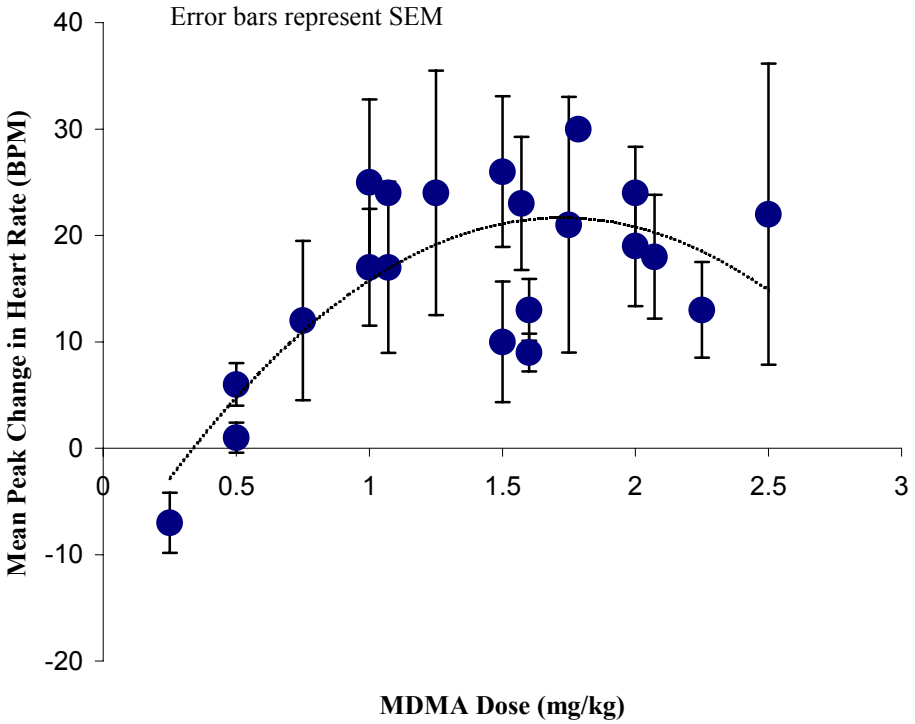
Table 2.1: Peak Acute Physiological Effects of MDMA

Dose	N	Heart Rate (BPM)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Body Temp (°C)	Reference
0.25 mg/kg	2 (1M, 1F)	-7 ± 4	17 ± 21	18 ± 9	-1.36 ± 0.44	Grob et al. 1996
0.5 mg/kg	4 (2M, 2F)	6 ± 4	13 ± 8	11 ± 10	0.4 ± 0.4	Grob et al. 1996
0.5 mg/kg	8 (5 M, 3F)	1 ± 4	4 ± 7	4 ± 4	0.1 ± 0.4	Lester et al. 2000
50 mg	2	?	7 ± 8	1 ± 5	0.95 ± 0.1	de la Torre et al. 2000b
0.75 mg/kg	4 (3M, 1F)	12 ± 15	19 ± 6	11 ± 3	0.5 ± 0.3	Grob et al. 1996
1.0 mg/kg	12 (7M, 5F)	16 ± 17	25 ± 20	18 ± 14	1.0 ± 0.8	Tancer, pers. com.
1.0 mg/kg	4 (3M, 1F)	25 ± 11	25 ± 14	19 ± 7	0.3 ± 0.3	Grob et al. 1996
75mg/70 kg	5F	17 ± 18	21 ± 9	10 ± 6	na	Tancer, pers. com.
75 mg	10	24	25 ± 3	12 ± 3	0.36 ± 0.1	de la Torre et al. 2000b
1.25 mg/kg	4 (2M, 2F)	24 ± 23	31 ± 13	26 ± 15	0.4 ± 0.4	Grob et al. 1996
100 mg	13	na	31 ± 5	14 ± 3	0.4 ± 0.1	de la Torre et al. 2000b
1.5 mg/kg	4 (3M, 1F)	20 ± 8	31 ± 5	21 ± 12	0.9 ± 0.2	Grob et al. in preparation
1.5 mg/kg	8 (5M, 3F)	26 ± 20	20 ± 10	13 ± 5	0.3 ± 0.4	Lester et al. 2000
110mg/70 kg	5 (1M, 4F)	23 ± 14	25 ± 5	22 ± 6	na	Tancer, pers. com.
125 mg	8	na	34 ± 7	15 ± 2	0.41 ± 0.1	de la Torre et al. 2000b
1.35 – 1.8 mg/kg	20F	13 ± 13	22 ± 12	10 ± 7	0.3 ± 0.3	Liechti et al. 2001
1.35 – 1.8 mg/kg	54M	9 ± 13	34 ± 16	18 ± 11	0.3 ± 0.4	Liechti et al. 2001
1.75 mg/kg	4 (3M, 1F)	21 ± 17	29 ± 16	20 ± 12	0.7 ± 0.9	Grob et al. in preparation
2 mg/kg	4 (3M, 1F)	18 ± 8	39 ± 22	24 ± 9	0.8 ± 0.7	Grob et al. in preparation
145 mg/70 kg	5 (4 M, 1 F)	18 ± 13	31 ± 6	25 ± 10	na	Tancer, pers. com.
2 mg/kg	12 (7M, 5F)	25 ± 15	36 ± 19	23 ± 10	1.2 ± 0.8	Tancer, pers. com.
150 mg	2	na	43 ± 2	20 ± 2	0.65 ± 0.6	de la Torre, et al. 2000b
2.25 mg/kg	4 (3M, 1F)	13 ± 9	52 ± 41	15 ± 13	0.5 ± 0.1	Grob et al. in preparation
2.5 mg/kg	2 (1M, 1F)	22 ± 20	36 ± 7	25 ± 5	0.2 ± 0.2	Grob et al. in preparation

Values are Mean ± SD and represent mean peak change from baseline, except for those from de la Torre et al. 2000b, which are maximal value reported (but possibly not peak). Reported statistical significance is not indicated here.
Report by Liechti et al, 2001, averages physiological measures from 0-75 min and 75-150 min.
na = not available (either not measured or not reported).

Figures 2.1 & 2.2: Peak Acute Increase in Diastolic BP and Heart Rate





experiences were not achieved using properly controlled trials and standardized outcome measures, they nonetheless provide an indication of the acute safety and potential therapeutic utility of MDMA when used in a clinical context.

Acute Physiological Effects

MDMA has significant acute cardiovascular effects, as would be expected from its norepinephrine-releasing (Johnson et al. 1991; Rothman et al. 2001) and α-2 adrenergic agonist (Lavelle et al. 1999) properties. MDMA dose-dependently produces robust increases in heart rate and blood pressure (de la Torre et al. 2000a; de la Torre et al. 2000b; Grob et al. In preparation; Lester et al. 2000; Mas et al. 1999; O'Cain et al. 2000; Vollenweider et al. 1998a). Peak cardiovascular effects occur between 1 and 2 hours after MDMA administration and largely subside within 6 hours of drug administration. Lester and colleagues (2000) compared echocardiograms taken one hr after administering 0.5 and 1.5 mg / kg MDMA to eight volunteers with echocardiograms made after administering a series of increasing doses of the beta agonist dobutamine. Echocardiograms conducted after 1.5 mg / kg MDMA indicate that MDMA did not possess positive ionotropic effects, a sign that the heart may be consuming more oxygen than would be predicted from measuring heart rate or blood pressure alone. **Table 2.1** summarizes the peak changes in physiological measures reported after different doses of MDMA. As can be seen, the physiological effects of MDMA are, on the average, robust but clinically insignificant in healthy volunteers.

The relationship between MDMA dose and cardiovascular effects was suggested to be supralinear by de la Torre et al. (2000a) who reported unexpectedly high drug exposures (measured as AUC_{plasma} for MDMA) and diastolic blood pressure increases in two volunteers given 150 mg MDMA. While pharmacokinetic data (discussed below) suggest MDMA has nonlinear kinetics, there is no clear evidence of supralinear relationships between dose and blood pressure or heart rate when available data are graphed (**Figures 2.1 and 2.2**). In fact, there may be less increase in heart rate after higher doses. Although this comparison is across individuals and requires further confirmation, the tendency toward less heart rate increase with higher dose is consistent with a study using both conscious and anesthetized rats (O'Cain et al. 2000). In this rat study, 3 mg/kg IV MDMA decreased heart rate, while lower doses tended to increase it or leave it unchanged.

There is some interindividual variation in cardiovascular effects and a significant minority of volunteers have experienced clinically significant hypertension. Grob et al. (In preparation) reported a transient blood pressure elevation (200/100 mm Hg) in a 26-year-old male who had been administered 1.75 mg/kg MDMA. This response was possibly related to the volunteer's previously undisclosed use of Ventolin [salbutamol/albuterol], an alpha-2-adrenergic agonist and CYP3A substrate (Manchee et al. 1996). A 60-year-old male administered 2.5 mg/kg MDMA by the same research group displayed blood pressures of 220/120 mm Hg for approximately 2 hours. In another study, conducted by Vollenweider et al. (1998a) a 49-year-old male with no previous MDMA experience displayed peak blood pressure values of 240/145 mm Hg

(but no other signs of hypertensive crisis) for about 20 minutes. Cardiovascular indices in all three individuals returned to baseline levels without intervention. Mas et al. (1999) note that four of eight volunteers met diagnostic criteria for hypertension after each of the MDMA doses (75 mg and 125 mg) in their study. Given the small number of volunteers studied, the frequency of these hypertensive episodes highlights the need for careful prescreening and monitoring of volunteers.

In uncontrolled settings, serious acute toxicity after MDMA use is often related to prolonged hyperthermia. In contrast, the administration of MDMA in clinical settings has been associated with small, clinically insignificant increases in core temperature that only achieve statistical significance in some studies (Liechti et al. 2000b). The temperature changes seen in clinical studies are similar in magnitude to those achieved after modest oral doses of other sympathomimetic amphetamines (Mas et al. 1999). Some of this slight increase in core temperature may be secondary to short-lived drug-induced vasoconstriction (Fitzgerald and Reid 1994), which can reduce heat loss and skin temperature. Research conducted by De la Torre and his colleagues may offer some support for this conjecture (de la Torre et al. 2000b). They found a slight decrease in body temperature one hour after MDMA administration followed by an elevation in body temperature two to four hours after MDMA administration in volunteers given MDMA at doses ranging from 75 mg to 150 mg. Peripheral vasoconstriction was offered as a possible explanation for the slight dip in body temperature seen prior to the elevation in body temperature after MDMA administration. Alternatively, central mechanisms may mediate MDMA-induced body temperature changes. Microinjection of 5HT into the anterior hypothalamus can cause an initial decrease followed by an increase in cell temperature in rats and primates (Myers 1975, 1968).

Other measurable acute physiological effects of MDMA include mydriasis (increases in pupillary diameter) and esophoria (altered eye alignment due to increased extraocular muscle tension) (Cami et al. 2000; de la Torre et al. 2000b; Downing 1986). Nystagmus also occurs in some volunteers, as is can be seen in **Table 2.2**.

Acute and Subacute Side Effects of MDMA

Reported side effects of MDMA are modest and generally not associated with great discomfort by volunteers. Reported acute side effects are summarized in **Table 2.2**, subacute effects are listed in **Table 2.3** and **2.4**. Decreased appetite, jaw clenching, and dry mouth are commonly reported during peak MDMA effects, while fatigue may be felt up to several days after MDMA. Less commonly, mild anxiety and depressed mood are reported one and three days after MDMA administration (Liechti et al. 2000b; Liechti and Vollenweider 2000a; b; Vollenweider et al. 1998a). The time course of these symptoms is similar to that reported for amphetamines (Watson et al. 1972). Not all reports have described side effects of MDMA in enough detail to allow inclusion in these tables. Most notably, side effects have not been reported by Grob and colleagues or by the Spanish researchers.

Table 2.2: Acute Side Effects of MDMA

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

Table 2.3: Subacute (Up To Post 24 H) Side Effects Of MDMA

Reported Sequelae	Overall Average Incidence	Downing 1986	Greer & Tolbert 1986	Liechti, Saur, et al. 2000	Liechti & Vollenweider 2000a	Liechti & Vollenweider 2000b	Vollenweider, Gamma, Liechti, & Huber 1998
N	**10-86**	**10**	**29**	**14**	**14**	**16**	**13**
Dose(s)	-	1.76-4.18 mg/kg	75-150, 200 mg	1.5 mg/kg	1.5 mg/kg	1.7 mg/kg	1.5 mg/kg
Measurement Time	-	At 24 h	8-24 h	At 24 h	At 24 h	At 24 h	At 24 h
Fatigue	47%	na	55%	na	50%	38%	38%
Heavy Legs	38%	na	na	na	na	na	38%
Dry Mouth	36%	na	na	36%	36%	na	na
Lack of appetite	29%	na	7%	29%	50%	38%	46%
Insomnia	29%	0%	38%	14%	36%	na	38%
Drowsiness	29%	na	na	29%	na	na	na
Weakness	25%	na	na	21%	29%	19%	31%
Thirst	25%	na	na	21%	36%	0%	46%
Private worries	23%	na	na	na	na	na	23%
Sensitivity to cold	23%	na	na	na	na	na	23%
Trismus	21%	na	na	21%	na	na	na
Jaw tension / tight jaw	21%	na	21%	na	na	na	na
Nystagmus	20%	20%	na	na	na	na	na
Lack of energy	18%	na	na	7%	0%	19%	46%
Difficulty Concentrating	17%	na	3%	14%	29%	25%	31%
Headaches	16%	0%	0%	na	29%	44%	15%
Need more sleep	15%	na	na	14%	na	na	15%
Perspiration	15%	na	na	7%	na	na	23%
Jaw clenching	14%	10%	10%	21%	0%	na	31%
Restlessness	12%	na	na	14%	0%	0%	38%
Decreased libido	12%	na	3%	na	na	na	31%
Urge to urinate	12%	na	3%	na	na	na	31%
Exhaustibility	12%	na	na	0%	na	31%	0%
Brooding	10%	na	3%	21%	na	0%	23%
Muscle aches / tension	10%	na	14%	na	na	na	0%
Anxiety	5%	na	7%	0%	na	na	na
Nausea	5%	na	7%	0%	na	na	na
Forgetfulness	4%	na	na	na	0%	na	8%
Increased appetite	3%	na	3%	na	na	na	na
Body odor	3%	na	3%	na	na	na	na
Constipation	3%	na	3%	na	na	na	na
Hearing impairment	3%	na	3%	na	na	na	na
Hoarseness	3%	na	3%	na	na	na	na
Visual Illusion	3%	na	3%	na	na	na	na
Inner tension	2%	na	na	7%	0%	0%	na
Impaired balance / gait	1%	0%	3%	0%	0%	na	na

na: not available

Table 2.4: Late Subacute (72 H+) Side Effects Of MDMA

	Overall Average Incidence	Greer & Tolbert 1986	Liechti et al. 2000	Liechti & Vollenweider 2000a	Liechti & Vollenweider 2000b
N:	**14-73**	**29**	**14**	**14**	**16**
MDMA Dose:	75 mg – 1.5 mg/kg	75-150, 200 mg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg
Measurement Time:	-	3 days - 1 wk later	At 72 h	At 72 h	At 72 h
Fatigue	29%	na	na	29%	na
Irritability	25%	na	na	na	25%
Drowsiness	14%	na	14%	na	na
Brooding	14%	10%	7%	na	25%
Lack of energy	9%	na	7%	21%	0%
Lack of appetite	7%	3%	0%	29%	0%
Trismus	7%	na	7%	na	na
Need more sleep	7%	na	7%	na	na
Anxiety	7%	na	7%	na	na
Gloomy thoughts	7%	na	0%	0%	19%
Dry mouth	4%	na	7%	0%	na
Jaw clenching	4%	na	7%	0%	na
Increased appetite	3%	3%	na	na	na
Thirst	2%	na	7%	0%	0%
Restlessness	2%	na	7%	0%	0%

na: not available

Acute Hormonal/Neuroendocrine Effects

MDMA dose-dependently increases cortisol, prolactin and adrenocortictropic hormone concentrations (Grob et al. 1996; Mas et al. 1999), while growth hormone is unchanged by up to 125 mg MDMA (Mas et al. 1999). Increases in cortisol and prolactin peak at about 2 hours after MDMA administration. These findings are consistent with rat studies showing MDMA-induced increases in corticosterone and prolactin (Nash et al. 1988).

Henry et al. (1998) reported that 40 mg MDMA increased circulating levels of antidiuretic hormone (arginine vasopressin). MDMA may therefore produce modest alterations in fluid balance. Increased retention of fluid is unlikely to be of any consequences in a clinical setting. However, this finding is consistent with reports of

hyponatremia in illicit users (Box et al. 1997; Hall 1997b; Holmes et al. 1999; Kessel 1994; Magee et al. 1998; Maxwell et al. 1993; O'Connor et al. 1999; Parr et al. 1997; Watson et al. 1997; Wilkins 1996). This finding is probably unrelated to the difficulty urinating experienced by some during acute MDMA intoxication. This occasional side effect of MDMA is more likely to be due to stimulation of α-adrenergic receptors on muscles in the bladder (Bryden et al. 1995).

Acute Self-Reported/Subjective MDMA Effects

MDMA has been hypothesized to represent a new class of psychoactive agents, called entactogens (Nichols 1986), producing feelings of closeness to others and empathy, well being and insightfulness, with little perceived loss of control or hallucinatory effect (Grinspoon and Bakalar 1986; Hegadoren et al. 1999; Nichols 1986; Shulgin and Nichols 1978). As discussed below, clinical studies generally support this hypothesis, although it is also clear that the effects of MDMA overlap with those of psychostimulants and, to a lesser extent, hallucinogens.

Many of the effects of MDMA resemble those of psychostimulants and include self-reported increases in positive mood, activation and self-confidence (Cami et al. 2000; Downing 1986; Gamma et al. 2000b; Greer and Tolbert 1986; Grob et al. 1996; Liechti et al. 2000a; Liechti et al. 2000b; Liechti and Vollenweider 2000a; Vollenweider et al. 1998a). Psychostimulants are characterized in most healthy volunteers by acute, dose-dependent effects such as euphoria and increased positive affect, feelings of vigor and alertness, increased self-confidence, occasional anxiety, and cardiovascular pressor effects (Chait et al. 1986; Johanson and Uhlenhuth 1980; Mendelson et al. 1995; Uhlenhuth et al. 1981). The cardiovascular pressor effects and many of the side effects (dry mouth, jaw or muscle tension, paresthesias) reported by volunteers after MDMA administration are reminiscent of psychostimulants. One effect that clearly distinguishes MDMA from typical psychostimulants is the sedative-like effect reported by Cami et al. (2000). These researchers found that 125 mg MDMA increased self-reported visual analogue ratings of "drunken" and scores on the ARCI questionnaire sedation ("PCAG") subscale.

A few of the self-reported effects of MDMA are consistent with mild hallucinogen-like activity. Hallucinogens characteristically produce sensory and perceptual distortions, alterations in perception of meaning, impaired attention, unpredictable and often rapid mood changes, and feelings of loss of control often leading to anxiety (Haertzen 1966; Hermle et al. 1992; Katz et al. 1968; Langs and Barr 1968; Vollenweider et al. 1998b). MDMA has been found to produce modest sensory and perceptual changes, primarily intensification of colors and tactile awareness and changes in the quality of sounds. Visual illusions such as 3-dimensional vision of flat objects, micropsia, macropsia, and illusory movement have also been noted (Cami et al. 2000; Vollenweider et al. 1998a). True hallucinations have not, however, been reported. Hallucinogen-like alterations in the perception of meanings occur after MDMA administration (Liechti et al. 2000a; Liechti et al. 2000b; Liechti and Vollenweider 2000a). The altered sense of meaning is accompanied by moderate thought disturbances such as accelerated thinking, thought

blocking, and impaired decision making (Vollenweider et al. 1998a). Moderate derealization also occurs, with volunteers reporting that their surroundings feel different or unreal (Cami et al. 2000; Vollenweider et al. 1998a). MDMA also produces alterations in time perception (Vollenweider et al. 1998a), an effect also associated with hallucinogens. Both MDMA and hallucinogens induce self-reported difficulty in concentrating (Cami et al. 2000; Liechti and Vollenweider 2000a), although MDMA-induced changes in neurocognitive performance are less consistently detected (see "Neurocognitive and Psychomotor Performance Effects of MDMA").

Despite these similarities between MDMA and hallucinogens, MDMA differs from typical hallucinogens in several important ways. The subjective effects of MDMA appear to be more consistently pleasurable than those of hallucinogens, which produce labile and unpredictable mood changes. The depersonalization induced by MDMA is modest and has been described as a pleasurable loosening of ego boundaries (Vollenweider et al. 1998a) rather than the profound depersonalization and anxious passivity associated with hallucinogens. In summary, to the extent that MDMA resembles a hallucinogen, it resembles one given at a dose too low to consistently produce the dramatic effects of hallucinogens.

In addition to effects resembling those of psychostimulants and hallucinogens, MDMA has been reported to have effects not typical of either drug class. These reported effects include increased feelings of closeness to others, sociability, and empathy. While these effects were apparently not formally measured (aside from individual items in self-report questionnaires), both the Swiss and Spanish MDMA research groups have noted that volunteers spontaneously reported some entactogenic effects (Cami et al. 2000; Vollenweider et al. 1998a; Vollenweider et al. 1999b). In addition, nearly all subjects participating in an uncontrolled investigation of MDMA psychotherapy reported feeling closer to others (Greer and Tolbert 1986). Vollenweider et al. (1998, p. 247) state "subjects reported experiencing an increased responsiveness to emotions, a heightened openness, and a sense of closeness to other people."

There are a number of issues raised in attempting to measure potentially unique entactogenic effects. One issue concerns appropriate and validated instruments. A number of self-report instruments have been developed to measure empathy (Chlopan et al. 1985; Davis 1983; Layton and Wykle 1990) and sociability and empathy scales exist on some personality instruments (e.g., Eysenck et al. 1985). However, empathy and related constructs are often conceived as 'traits' rather than 'states.' Accordingly, these instruments are not appropriate for use in repeated-measures drug studies. A second issue involves interpreting findings. No consistent relationship has been found between self-ratings of empathy and actual empathic accuracy or initiation of helping behaviors (Davis and Kraus 1997; Eisenberg and Miller 1987). Therefore, feelings of empathy are not necessarily evidence that MDMA is therapeutically useful. Behavioral protocols do exist for measuring empathic accuracy (Ickes et al. 1990) and observer-ratings of empathic rapport have been used in psychotherapy research. These measures may prove useful in establishing the existence and possible usefullness of uniquely "entactogenic" effects.

Overall, data are consistent with the hypothesis that MDMA is a member of a novel pharmacological class with effects only partially overlapping those of psychostimulants and hallucinogens. Most groups conducting MDMA or MDE research have employed the term "entactogen" in their publications. Comparisons of the MDMA analogue, MDE, to hallucinogens and stimulants using the APZ Altered States of Consciousness scale (Dittrich 1998) and other measures suggest that putative entactogens produce a different drug effects syndrome than hallucinogens or psychostimulants (Gouzoulis-Mayfrank et al. 1998; Gouzoulis-Mayfrank et al. 1999a; Gouzoulis-Mayfrank et al. 1999b). However, comparisons have been limited to single doses generally administered to different individuals. For now, the existence of this novel pharmacological class must be considered a "working hypothesis" rather than a fact until putative entactogenic effects are better characterized over a range of doses and these effects are compared, preferably in the same individuals, to those of a range of doses of hallucinogens and psychostimulants.

Table 2.5: Unaltered Neurocognitive Performance after Two MDMA Exposures

	PRE Score	POST Score	t	P (ns)
Attention				
Digit Span	11.0	11.5	-.90	.39
Verbal Memory: Auditory Verbal Learning Test				
Trial 5	12.6	12.5	.13	.90
Interference	10.6	9.9	.91	.38
Delayed recall	9.9	9.7	.21	.84
Recognition	14.0	13.9	.19	.85
Visual Memory: Continuous Visual Memory Test				
Hits	38.8	37.7	.91	.38
False Alarms	15.3	15.1	.11	.92
d"prime	2.2	2.0	1.24	.24
Total	77.4	76.6	.48	.64
Recognition	3.5	4.1	-1.32	.21
Executive/Frontal Lobe				
Consonant Tri.	50.9	49.7	.72	.48
FAS/CFL	43.1	46.1	-1.40	.18

Data are from Boone et al., in preparation, and are reproduced with permission.

Neurocognitive and Psychomotor Performance Effects of MDMA

MDMA appears to have modest acute effects on neurocognitive performance. The acute effects of MDMA have been measured using the digit symbol substitution task (Cami et al. 2000), a simple reaction time task (Cami et al. 2000), a continuous performance attention task (Gamma et al. 2000a), the Stroop task (Vollenweider et al. 1998a), and a prepulse inhibition measure of sensorimotor gating (Liechti et al. 2001b; Vollenweider et al. 1999b). Of these tasks, only the digit symbol substitution task and the prepulse inhibition task have detected MDMA-induced performance alterations. Performance on

the digit symbol substitution task was reduced when individuals were given 100 or 125 mg MDMA, but not 75 mg MDMA (Cami et al. 2000). Prepulse inhibition was increased after 1.5 or 1.7 mg/kg MDMA. A drug interaction study with the SSRI citalopram suggests that serotonin release is important for MDMA-induced prepulse inhibition increase (Liechti et al. 2001b). Dopamine D_2 and $5HT_2$ receptors do not appear to be involved in this effect since it was not altered by pretreatment with either the D2 antagonist haloperidol or the $5HT_2$ antagonist ketanserin (Liechti et al. 2001b). In addition, Downing assessed 10 of his 21 volunteers using poorly described digit repetition, multiplication, memory, and finger-to-nose coordination tasks (Downing 1986). 3 of 10 volunteers had difficulty with the multiplication task. 4 volunteers gave idiosyncratic responses to the decision-making task, suggesting impaired judgment. Finally, 2 of 10 volunteers had difficulty with the finger-to-nose task. Thus, the acute effects of MDMA on neurocognitive performance are modest.

Studies of illicit ecstasy users have suggested that repeated MDMA use may be associated with lowered neurocognitive performance. In contrast, participation in clinical MDMA studies has not been associated with chronic alterations in neurocognitive performance. **Table 2.5** shows neurocognitive data collected before and approximately 2 weeks after 14 volunteers were administered up to 2.5 mg/kg MDMA in the study partially described in Grob et al. (1996). Vollenweider also reports unchanged neurocognitive performance in his volunteers, many of whom were previously MDMA-naive (Dr. Franz Vollenweider, personal communication).

Acute and Subacute Immunomodulating Effects of MDMA

Pacifici and colleagues carried out immunological testing on blood samples collected from volunteers administered 75 or 100 mg MDMA in studies of MDMA-ethanol interactions. Findings from this research are distributed throughout three publications. Four volunteers participated in a pilot study and six individuals took part in a second study (Pacifici et al. 1999; Pacifici et al. 2001), while samples drawn from an additional two individuals are described in a third publication (Pacifici et al. 2000). While total leukocyte count was unchanged, CD4 T-cell count (and therefore also the ratio of CD4 to CD8 T-cells) was decreased. This decrease was similar in magnitude to that produced by 0.8 g/kg ethanol (the equivalent of 4-5 drinks) in the same study. NK cell count was increased. In addition, phytohaemoagglutin A-induced lymphocyte proliferation was decreased. This decrease was approximately twice that produced by ethanol and also appeared to last longer. Lymphocyte proliferation had only partially returned to baseline at 24 hours after drug administration. The concentrations of pro-inflammatory and anti-inflammatory cytokines were reported after MDMA in the later publication (Pacifici et al. 2001). MDMA decreased production of pro-inflammatory cytokines, including IL-2 and interferon-Gamma and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 cytokines and increased the amount of Th2 cytokines measured in blood. The mechanism of this MDMA-induced immunomodulation is unclear but may involve MDMA-induced glucocorticoid release or sympathomimetic activity. Acute alterations in immune functioning after MDMA administration have also been noted in mice (House et al. 1995) and rats (Connor et al. 2000a; Connor et al. 2000b; Connor et al. 1998). This

immunomodulation appears to be an acute pharmacological effect of MDMA and is not likely to persist. Nonetheless, these findings should be considered when evaluating the risks and benefits of administering MDMA to individuals with compromised immunocompetence.

Acute and Chronic Functional Cerebral Imaging Studies

MDMA acutely alters regional cerebral blood flow (rCBF). Gamma et al. (2000a) used [$H_2{}^{15}O$]-Positron Emission Tomography (PET) to measure rCBF at 75 min after 1.7 mg/kg MDMA in 16 volunteers. They detected increases in prefrontal, inferior temporal, and cerebellar cortex rCBF. Decreased rCBF was detected in limbic, paralimbic, central frontal, and temporal areas.

These acute effects of MDMA on rCBF may be followed by long-lasting decreases in rCBF. Chang et al. (2000) assessed rCBF in 10 volunteers before and after participation in clinical MDMA research. MDMA-induced decreases in regional and global cerebral blood flow (CBF) occurred in a subset of eight volunteers assessed 10 to 21 days after last MDMA exposure. CBF was measured using [99mTc]-HMPAO SPECT co-registered with MRI and significant decreases were found bilaterally in the visual cortex, caudate, superior parietal, and dorsolateral frontal regions. Two additional volunteers showed evidence of possibly increased CBF at later time points (43 and 80 days after MDMA, respectively). This suggests that these changes are either a subacute drug effect of limited duration or part of a lasting biphasic effect (with decreases followed by increases). Because each volunteer was only assessed once after study participation, more research is needed to better understand the time course and possible significance of these changes. The authors suggest (but do not provide statistical results supporting) a possible relationship between time elapsed since last MDMA exposure and regional CBF and interpret this relationship as evidence of recovery. In addition, the authors did not find differences in regional or global CBF when 21 MDMA-experienced volunteers (with a reported 211 ± 340 exposures) were compared to 21 nonusers (data are presented in the same paper). Similarly, Gamma et al. (2001) saw no significant differences between 16 MDMA users (most of whom had used MDMA at least 100 times) and 17 nonusers when regional CBF was measured during a vigilance task using [$H_2{}^{15}O$]-PET. Finally, it should also be pointed out that Gamma et al. reportedly did not detect changes in regional CBF using [$H_2{}^{15}O$]-PET in a retrospective analysis of a study in which volunteers received 1.7 mg/kg MDMA (Dr. Alex Gamma, personal communication). It appears that two exposures to as little as 1.25 mg/kg MDMA may alter CBF at least 2 or 3 weeks after last drug exposure. The full time course of these changes is unclear.

Gender Differences in the Psychological and Physiological Effects of MDMA

Men and women may not experience the different psychological and physiological effects of MDMA with the same frequency or magnitude. A survey of Australian illicit ecstasy users found that being female was one of several factors that predicted an increase in experiencing side effects and adverse events after taking ecstasy (Topp et al. 1999). In studies of possible neurotoxicity, it has been suggested that female ecstasy

users may have a greater alterations of serotonergic function (McCann et al. 1994) but may be resistant to neurocognitive changes (Bolla, et al., 1998). An investigation relying on data pooled from three clinical studies found gender differences in the subjective and physiological effects of MDMA (Liechti, et al., 2000). Mood, alteration in consciousness, cardiovascular effects, body temperature and adverse events were measured in 74 individuals, most of them MDMA-naïve, who received 1.35 – 1.8 mg/kg MDMA in the course of three randomized, placebo-controlled clinical studies. Scores on all three scales on a measure of alterations in consciousness were higher in women than in men after MDMA.

When compared to men, women reported greater increases in positive mood, pleasant derealization, thought disorder, fear of loss of body control, alterations in perception, alterations in the meaning of objects, facilitated recall, and facilitated imagination. The gender difference in the intensity of the psychological effects of MDMA was most pronounced for its effects on perception and thought. Women specifically reported a greater increase in the "hallucinogen-like" effects of MDMA, including changes in thought and perception. While the authors failed to find a relationship between higher doses of MDMA and increases in positive mood or fear of ego dissolution in either gender, a relationship was found between higher doses (in mg/kg) and increased alteration of perception in women, but not in men. Men reported being more activated or energetic than women acutely after MDMA, and women reported more anxiety and dysphoric reactions. Anxiety was related to feelings of helplessness, defenselessness, and needing protection. More women than men reported experiencing the acute side effects measured in these studies, including commonly reported side effects, such as jaw-clenching, dry mouth, and loss of appetite. Sweating and nausea were the only side effects more frequently listed by men than women. When sub-acute effects were assessed 24 hours after the participants had received MDMA, women made up a greater percentage of the people reporting sub-acute effects, such as fatigue, dry mouth, and continued lack of appetite.

While women in this sample were more sensitive to some of the psychological effects of MDMA, men seemed to be more sensitive to the physiological effects of the drug. MDMA produced a significant increase in systolic blood pressure in both genders, but the increase was greater in men than in women. While MDMA elevated heart rate in both men and women, this elevation was only significantly different from heart rate at placebo for men. Lastly, it appeared that MDMA only significantly elevated body temperature in men. These findings suggest that men are more sensitive to the sympathomimetic effects of MDMA.

Drug Interaction Studies and the Neurotransmitter Systems Mediating the Effects of MDMA

Researchers in Switzerland have carried out drug interaction studies to investigate the neurotransmitter systems mediating the effects of MDMA in humans. *In vitro* and nonhuman animal studies have established that MDMA induces serotonin, dopamine, norepinephrine, and acetylcholine release (Battaglia et al. 1988a; Fischer et al. 2000;

Gudelsky and Nash 1996; Rudnick and Wall 1992) and can act directly on a number of receptors, including α_2-adrenergic and $5HT_{2A}$ receptors (Battaglia et al. 1988a; Lavelle et al. 1999; Nash et al. 1994). Clinical studies have further elucidated the roles of serotonergic and dopaminergic systems in the psychopharmacology of MDMA. Serotonin release appears to be either directly or indirectly responsible for a large number of the psychological and physiological effects of MDMA. When MDMA-induced serotonin release was attenuated by pretreatment with the SSRI citalopram, volunteers reported a reduction in MDMA-induced changes in mood, perception, and thought (Liechti et al. 2000a). Citalopram pretreatment also reduced the elevated blood pressure and heart rate usually produced by MDMA (Liechti and Vollenweider 2000b). However, serotonin release alone cannot account for all of the effects of MDMA, as volunteers who received MDMA after citalopram pretreatment still had elevated body temperature and increased scores on a measure of "emotional excitability," defined here as emotionality, excitability, and nervousness. Some of these effects seem to arise from stimulation of $5HT_2$ receptors, since pretreatment with the $5HT_{2A}$ / $_{2C}$ antagonist ketanserin reduced subsequent MDMA effects on emotional excitability, changes in perception, diastolic blood pressure and body temperature (Liechti et al. 2000b). The hallucinogen-like effects of MDMA appear to be produced through $5HT_2$ receptors (as would be expected), as ketanserin pretreatment reduced the changes in perception and thought, without greatly altering the increase in mood or anxiety over losing control produced by MDMA. Studies using the dopamine D_2 antagonist haloperidol indicate that the MDMA-induced increase in positive mood is due at least in part to dopaminergic mechanisms. When MDMA was given after haloperidol pretreatment, volunteers reported an increase in state anxiety, particularly as the effects of MDMA first began appearing, as well as difficulty concentrating and fatigue (Liechti and Vollenweider 2000a). Since pretreatment with haloperidol did not reduce MDMA's sympathomimetic effects in humans, it would appear that these are largely due to noradrenergic mechanisms. Although interpretation of these drug interaction studies is complicated by possible pharmacokinetic interactions and possible effects of the pharmacological blocking agents employed, these studies represent dramatic advances in our understanding of MDMA psychopharmacology. Further research is needed to investigate the role of other neurotransmitter systems and receptors, particularly the noradrenergic system and the $5HT_{1A}$ receptor, in the human psychopharmacology of MDMA.

Pharmacokinetics of MDMA

The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA. Basic pharmacokinetic parameters are summarized in **Table 2.6**. 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). 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 alpha-methyldopamine), 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). Additional metabolites have been identified in rodents (Chu et al. 1996; Lim and Foltz 1988; 1989; 1991; Yousif et al. 1990). Thus far, human plasma levels of MDMA and the metabolites HMMA, HMA, and MDA have been published. It appears that the dihydroxylated metabolites are short lived and de la Torre et al. (2000a) were unable to detect them in plasma. At higher doses (above approximately 100 mg), MDMA is excreted mainly as the unmetabolized drug, while at lower doses HMMA is the primary metabolite in urine (de la Torre et al. 2000a; Lanz et al. 1997). Metabolites are primarily excreted as glucuronide and sulfate conjugates (Helmlin et al. 1996).

The enzymes and pathways involved in MDMA metabolism have been examined through *in vitro* studies. The probable pathways of MDMA metabolism are summarized in **Figure 2.3**. 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 nonenzymatic process involving the hydroxyl radical (Lin et al. 1992). The enzymes catalyzing this reaction have been examined in the rabbit

Table 2.6: MDMA Pharmacokinetic Parameters

MDMA Dose	**N**	**Cmax** *μg/l*	**Tmax** *H*	**AUC $_{0-24}$** *μg*h/l*	**AUC/dose** *μg*h/(l*mg)*	**Reference**
50	2	19.8 and 82.8	2 and 3	100.1 and 813.9	2 and 16.3	de la Torre et al. 2000a
75	8	130.9 ± 38.6	1.8 ± 0.38	1331.5 ± 646.03	17.8 ± 8 .6	Mas et al. 1999
100	8	222.5 ± 26.06	2.3 ± 1.1	2431.38 ± 766.52	30.5 ± 11.2	de la Torre et al. 2000b
125	8	236.4 ± 57.97	2.4 ± 0.98	2623.7 ± 572.9	21 ± 4.6	Mas et al. 1999
150	2	441.9 and 486.9	1.5 and 2	5132.8 and 5232	34.2 and 34.9	de la Torre et al. 2000a

MDMA Dose	**N**	**k_a** */h*	**k_e** */h*	**$T_{1/2}$** *H*	**MDA $T_{1/2a}$** *h*	**Reference**
50	2	na	na	2.7 and 5.1	na	de la Torre et al. 2000b
75	8	2.3835 ± 2.1362	0.1171 ± 0.0818	7.86 ± 3.58	0.42 ± 0.2	Mas et al. 1999
100	8	2.70 ± 1.53	0.081 ± 0.018	8.96 ± 2.27	1.31 ± 0.55	De la Torre et al. 2000b
125	8	2.1253 ± 1.1001	0.0923 ± 0.0428	8.73 ± 3.29	0.41 ± 0.22	Mas et al. 1999
150	2	na	na	6.9 and 7.2	na	De la Torre et al. 2000a

(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. 1997b; 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 demethylenation is CYP2D6 as it is selectively inhibited by quinidine. At higher concentrations of MDMA, other enzymes with higher Km also contribute to MDMA demethylenation, including CY1A2 and CYP3A4.

It has been hypothesized that genetic variations in CYP2D6 activity may influence risk of MDMA toxicity. CY2D6 activity is genetically determined and up to 10% of the Caucasian population has deficient CYP2D6 activity. It has therefore been suggested that individuals having this autosomal recessive trait may have increased plasma drug

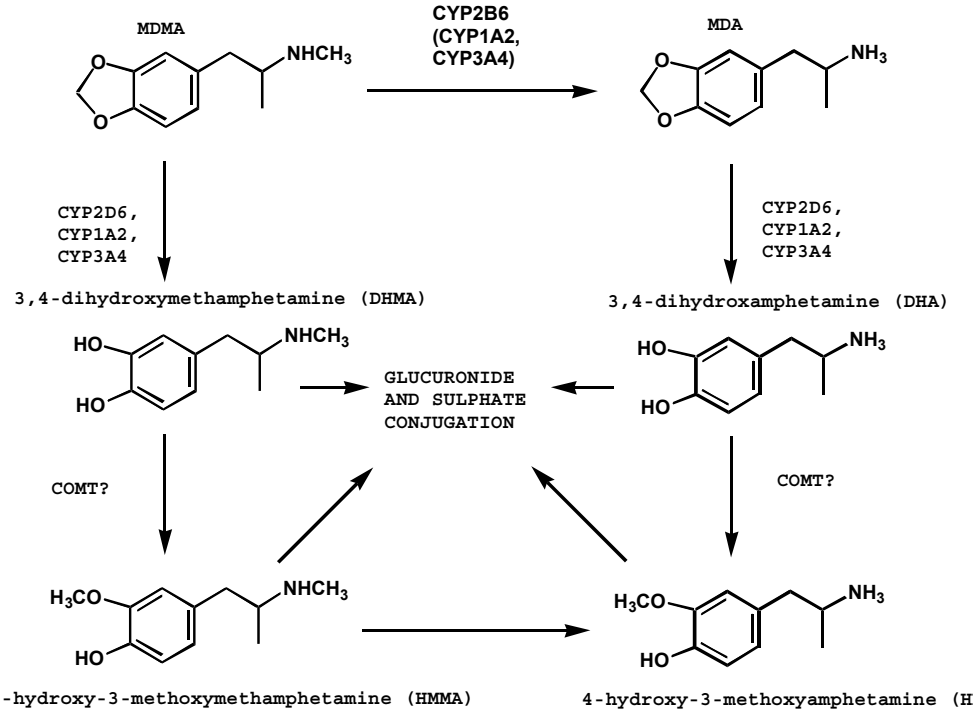
concentrations and increased risk of acute adverse response to MDMA. The fact that CYP2D6 is apparently easily saturated makes this possible source of individual sensitivity appear less significant. In fact, there currently seems to be no evidence that the poor metabolizer genotype is by itself a major risk factor for acute MDMA toxicity. Schwab et al. (1999) found that three illicit MDMA users who developed MDMA-related hepatotoxicity all had extensive CYP2D6 activity. In addition, Kreth et al. (2000) reported that the poor metabolizer trait did not lead to significant alteration in maximal drug plasma concentrations in an individual participating in a clinical study of the MDMA analogue, MDE. Formation of the major demethylenated metabolite (analogue to HMMA) was approximately 44% that of other volunteers, however. This provides further evidence that the role of CYP2D6 in MDMA metabolism is sufficiently limited that it is not a major risk factor in healthy individuals in a clinical setting.

Formation of HMMA and HMA from DHMA and DHA, respectively, has not been directly investigated, but may occur via catechol-o-methyl transferase (de la Torre et al. 2000a). It should be noted that thioether conjugates of DHA (and likely DHMA) have been hypothesized to play a role in MDMA neurotoxicity (Bai et al. 1999; Miller et al. 1996; 1997). The possible role of MDMA metabolites is discussed in Chapter 4.

Enzymes involved in the formation of MDA from MDMA in human liver microsomes have been investigated by two groups (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. Kreth et al., in a publication focusing on MDE metabolism, reported high correlations between MDMA and MDE N-dealkylation ($r=0.97$, $P<0.001$) and MDE N-dealkylation and human liver microsome CYP2B6 content ($r = 0.90$, $P<0.001$). MDE N-dealkylation and CYP1A2 levels were also significantly correlated ($r = 0.58$, $P<0.05$). The role of CYP2B6 in human MDMA metabolism is consistent with rodent research (Gollamudi et al. 1989). Because Maurer et al. did not examine CYP2B6, there is no real discrepancy between the studies of Maurer and Kreth.

MDMA is a chiral compound and has been almost exclusively administered as a racemate. However, an early uncontrolled report suggests that the S-enantiomer is significantly more potent in humans than the R-enantiomer (Anderson et al. 1978). 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 that the R-enantiomer.

Figure 2.3: Metabolic Pathways of MDMA in Humans



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 (Ramcharan, et al., 1998; Crifasi and Long, 1996).

The stereoselective pharmacokinetics of MDMA are reflected in formation of MDA enantiomers. 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). However, R-(-)-MDA becomes the more prevalent enantiomer in urine beginning 24 to 36 hours after MDMA administration (Hensley and Cody 1999). In a suicide attempt involving the ingestion of 90 ecstasy tablets, urine concentrations of S-(+)-MDA remained greater than R-(-)-MDA at 36 hrs, but relative prevalence had reversed at 60 hrs. Other reports have found stereoselective formation of HMMA and HMA although the lack of available standards precluded assignment of absolute enantiomeric identity (de Boer et al. 1997; Lanz et al. 1997).

MDMA kinetics are dose dependent within the range of commonly administered doses (de la Torre et al. 2000b). Thus, when dose is increased, exposure to MDMA (measured as AUC plasma) increases by a greater amount. This phenomenon is illustrated by the changes in the ratio of AUC to dose in **Table 2.5**. This increased exposure is particularly

dramatic when the AUC and Cmax for the two volunteers receiving 150 mg MDMA are compared to the 8 individuals receiving 125 mg MDMA.

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 some metabolic pathways. 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; Delaforge et al. 1999; Wu et al. 1997). Compelling *in vivo* evidence of enzyme inhibition was provided by de la Torre et al. (2000a) who showed that plasma levels and 24-hour urinary recovery of HMMA are dose-independent. This is likely the result of inhibition of CYP2D6-mediated DHMA formation.