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Global Division

Siemens Healthcare
Diagnostics Inc.
1717 Deerfield Road
Deerfield, IL 60015-0778
USA
www.siemens.com/diagnostics

Siemens Global Headquarters

Siemens AG
Wittelsbacherplatz 2
80333 Muenchen
Germany

Global Siemens Healthcare Headquarters

Siemens AG
Healthcare Sector
Henkestrasse 127
91052 Erlangen
Germany
Telephone: +49 9131 84 - 0
www.siemens.com/healthcare

www.usa.siemens.com/diagnostics

**General
Drugs
of Abuse**

Detection of Use of MDMA “Ecstasy”

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Background

Methylenedioxyamphetamine (MDMA), or “Ecstasy” as it is more commonly known, is a drug of abuse receiving notable attention for its use at dance parties called “raves.” Additional names for MDMA include XTC, ADAM, and Lover’s Speed, among many others. Similar derivatives for MDMA are methylenedioxyethylamphetamine (MDEA), called “Eve,” and 3,4-methylenedioxy-alpha-ethyl-N-methylphenethylamine (MBDB), known more commonly as “Eden.” It is very likely that additional amphetamine-like drugs are also in use.

The National Institute on Drug Abuse has a web-site dedicated to information on club drugs¹, while the Office of National Drug Control Policy has a fact sheet on MDMA.² A search of the National Library of Medicine’s MEDLINE database reveals over 1100 articles addressing MDMA.

The structure of MDMA closely resembles methamphetamine, as well as the neurotransmitters dopamine and noradrenaline. Refer to Figure 1.

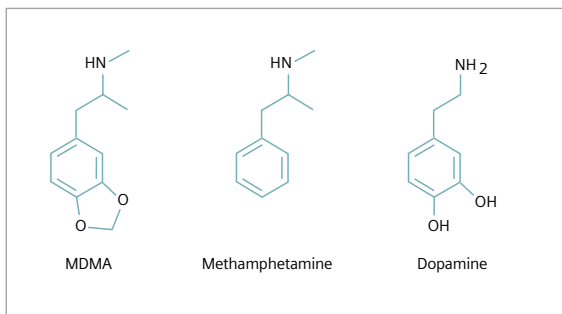


Figure 1: Structures of MDMA, Methamphetamine, and Dopamine

Synthesized in 1912 and patented by Merck in Germany in 1914, as an appetite suppressant, MDMA was never commercialized as a therapeutic agent—recreational use didn't begin until the 1960s and 1970s. In 1985, the Drug Enforcement Agency (DEA) listed MDMA as a Schedule I controlled substance (a drug with no recognized clinical use and with great potential for abuse).³

The recreational use of MDMA continues to escalate. Historically, 1.5% of the general population has admitted to using MDMA, in contrast to 5% of all 18-25 year-olds.⁴ An early 1987 study at one major university found that 39% of its students admitted to using MDMA at least once.⁵ Comparatively, Monitoring the Future, a research organization, conducted a national survey of high school students in the year 2000. The survey results revealed that 1.3 million students in grades 8–12 have used MDMA at one time or another, while 450,000 students use the drug on a regular basis.⁶

A rise in emergency-room mentions, and drug seizures by customs and law enforcement agencies, has been concurrent with the increase in MDMA use. The Drug Abuse Warning Network (DAWN) conducted a survey of hospital emergency rooms, which indicated only 250 mentions for MDMA in 1994; 637 mentions in 1997; and 1142 mentions in 1998.⁷ The U.S. Customs Service seized 300,000 tablets in 1993; 3.5 million tablets in 1999; and 9.3

million tablets in 2000. Similarly, the DEA seized 950,000 tablets in the year 2000. Problems associated with the use of MDMA have also been noted in other countries as well, especially in the UK.

In April 2001, PBS televised “In the Mix” (www.inthemix.org)—a special on “Ecstasy” and its use by young people. In addition, the Office of National Drug Policy addressed the topic of MDMA in two full pages in their National Drug Control Strategy: 2001 Annual Report.⁸

Use and Effects

A typical MDMA dose is 1–2 tablets @ 100–150 mg (\$25–40 each); however, because users rapidly develop tolerance, they typically use the drug only about once a week. Initial clinical effects appear as an amphetamine-like rush 30 minutes after an oral dose; these last 4 to 8 hours.

MDMA has properties of both a stimulant and a mild hallucinogen. Users demonstrate both hyperexcitability and euphoria. MDMA is sometimes placed in its own class and called an “entactogen” because of its ability to enhance understanding, communications, and empathy. Its mode of action is due to its potent release of the neurotransmitters dopamine and serotonin.

When the drug is used at raves, the combination of a hot, crowded environment and the stimulant effect of MDMA cause serious adverse effects of hyperpyrexia and hyponatremia. Drinking excess water (instead of an electrolyte-replenishing beverage) to cool down exacerbates hyponatremia. Numerous fatalities from MDMA use have been reported.

Also, studies have demonstrated that MDMA has caused acute disruption of short-term memory, and long-term damage to serotonergic neurons, as well as verbal, visual, memory, and cognitive deficits. Furthermore, these effects have correlated with extended use of the drug and with reduction in brain serotonin levels.^{9, 10}

Metabolism and Elimination

Few controlled clinical studies exist in which subjects ingest MDMA; indeed, some clinicians consider the safety of even a single dose as controversial.¹¹

The half-life of the drug is about 8 hours. Although primarily eliminated as unchanged MDMA (65% of a dose), 10–15% of a dose is converted by N-demethylation to methylenedioxyamphetamine (MDA)—similar to the small amount of conversion of methamphetamine to amphetamine. (Refer to figure 2)

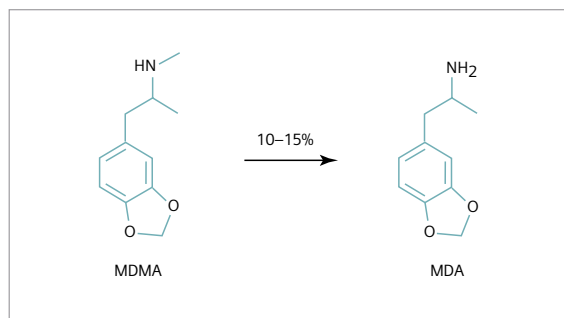


Figure 2: Conversion of MDMA to MDA

Significant amounts of a demethylated ring and conjugated metabolite, 4-hydroxy-3-methoxymethamphetamine (which apparently is the major metabolite) exist. However, a recent report has indicated that the conversion of MDMA to this latter metabolite may be saturable, and accordingly, as the dose increased, the percent of the dose recovered as intact MDMA increased.¹²

Urine Levels from Observational Studies

Urine specimens collected from active-duty U.S. Army personnel were examined in a 1996 study. Thirty-four specimens contained MDMA levels that ranged from 0.38–96.2 $\mu\text{g/mL}$ (average 13.4 $\mu\text{g/mL}$); MDA metabolite levels that ranged from 0.15–8.6 $\mu\text{g/mL}$ (average 1.6 $\mu\text{g/mL}$); and MDA/MDMA ratios that ranged from 0.02–0.65 (average 0.15).¹³

Another 1996 report on a single subject in an MDMA related traffic fatality noted MDMA urine levels of 118.8 $\mu\text{g/mL}$ and MDA levels of 3.9 $\mu\text{g/mL}$.¹⁴ A report in 2000 noted that MDMA and MDA levels reached 157 $\mu\text{g/mL}$ and 15 $\mu\text{g/mL}$, respectively, in routine toxicological screens.¹⁵

Another 2000 report on test results of suspected drug users noted urine MDMA levels ranging from 1.8 $\mu\text{g/mL}$ to >20 $\mu\text{g/mL}$ in seven subjects; five of the subjects had MDMA concentrations over 19 $\mu\text{g/mL}$.¹⁶

A 2001 report examined urine levels for MDMA, MDA, and other amphetamines in subjects who admitted to recent use of MDMA at raves. Specimens were collected between 1–8 hours after claimed use. Forty-four specimens were determined to contain either MDMA or MDA. Twelve specimens had MDMA present but no MDA, and four specimens had MDA present but no MDMA. Note, that most of these sixteen specimens also contained other amphetamine-like compounds. The remaining 28 specimens contained both MDMA and MDA, and MDA levels averaged only 4% of MDMA levels (1–24%). Overall, 40 specimens contained MDMA levels averaging 26.6 $\mu\text{g/mL}$; 22 out of 44 specimens with levels over 10 $\mu\text{g/mL}$; 14 specimens with levels over 20 $\mu\text{g/mL}$; seven specimens with levels over 50 $\mu\text{g/mL}$; and three specimens with levels over 100 $\mu\text{g/mL}$. The highest observed MDMA level was 140 $\mu\text{g/mL}$. Thirty-two specimens contained MDA levels that averaged 1 $\mu\text{g/mL}$ and no greater than 3.5 $\mu\text{g/mL}$.¹⁷ Table 1 summarizes these findings.

Various Reports	Subjects (n)	MDMA ($\mu\text{g/mL}$)	MDA ($\mu\text{g/mL}$)
Kunsmann et al., 1996	34	0.38–96.2 (avg. 13.4)	0.15–8.6 (avg. 1.6)
Crifasi and Long, 1996	1	118.8	3.9
Clauwaert et al., 2000	Not stated	≤ 157	≤ 15
Samyn and van Haeren, 2000	7	1.8—>20	Not Tested
Zhao et al., 2001	40, 32	≤ 140 (avg. 26.6)	≤ 3.5 (avg. 1)

Table 1: MDMA and MDA Levels from Observational Studies

Urine Levels from Controlled Dosing Studies

A 1988 report involving a single 50-mg dose on one subject noted that 62% of the dose was eliminated in the urine over 24 hours as unchanged MDMA, with 6% as MDA. The MDA/MDMA ratio varied from 0.02–0.18 (average 0.12). Unfortunately, urine concentrations were not provided. Assuming that typical 24-hour urine volume is about 1.5 L, then the average urine level of MDMA would have been about 20 µg/mL, with an average MDA level of 2 µg/mL.¹⁸

A controlled dosing study, performed in 1996, examined urinary excretion over 24 hours after MDMA dosing (1.5 mg/kg) on two subjects. The MDMA urine levels ranged from 13–28 µg/mL in one subject and from 0–18 µg/mL in the other. The corresponding MDA levels ranged from 0.1–2.3 µg/mL and 0–1.6 µg/mL. The urine levels after 24 hours were approximately 20 and 17 µg/mL for MDMA and approximately 2 µg/mL for both subjects for MDA. This study also demonstrated that the major metabolite was not MDA but, rather, another conjugated metabolite, 4-hydroxy-3-methoxymethamphetamine, with levels up to 35 µg/mL.¹⁹

A 1997 study reported urinary elimination of MDMA and MDA enantiomers (optical isomers from racemic MDMA) as a percent of dose over 72 hours. Two subjects were dosed with 100 mg MDMA; however, urine concentrations were not provided. Assuming an approximate 72-hour urine output of 4.5 L, the calculated average of MDMA would be 11.7 and 8.4 µg/mL for the two subjects, respectively. The calculated average MDA levels would be 0.9 and 0.3 µg/mL.²⁰

A 1999 study on one subject reported urine MDMA levels of 6.8 µg/mL between 0–4 hours after a 75-mg dose. The study also reported that after a 125-mg dose on another subject, 30% of the

dose was eliminated in urine over 24 hours as unchanged MDMA. Assuming a 24-hour urine output of 1.5 L, the average MDMA urine level could be calculated to be about 25 µg/mL.²¹

A study on 14 subjects in the year 2000 reported 24-hr urine recoveries of MDMA and its metabolites after MDMA doses that varied from 50–150 mg. Although urine concentrations were not provided, such concentrations can be roughly calculated assuming a 24-hr urine output of 1.5 L. The calculated average MDMA levels after 24 hours on two subjects who took a 50-mg dose would be 2.6 and 5.3 µg/mL. Average levels after a 75-mg dose on eight subjects would be 9.1 µg/mL; for two subjects after a 100-mg dose—29.9 and 9.6 µg/mL; for eight subjects after a 125 mg dose—an average of 21.7 µg/mL; and for two subjects after a 150-mg dose—13.7 and 42.9 µg/mL.¹²

A 2001 study examined urine levels from two subjects after a single 100-mg dose. For one subject, urine levels of MDMA peaked between 12–24 hours and averaged 19.5 µg/mL. At 24 hours, the level was 13.4 µg/mL, and at 36 hours the average was 5.8 µg/mL. The second subject demonstrated much lower MDMA levels, which peaked between 6–8 hours and averaged 3.4 µg/mL. Between 12–24 hours, average MDMA levels were only 300 ng/mL, and at 24 hours the average was 600 ng/mL.²² The aforementioned observational and controlled dosing studies indicate that urine levels of MDMA in excess of 10 µg/mL are readily encountered and would likely remain above that level for 1–2 days after dosing. Expectedly, MDA levels would be 10–15% of the MDMA levels. Table 2 summarizes these observational and controlled dosing studies.

Various Reports	Subjects (n)	Dose	MDMA (µg/mL)	MDA (µg/mL)
Vereby et al, 1988	1	50 mg	~20 (0–24 hr)	~2 (0–24 hr)
Helmlin et al, 1996	2	100 mg	13–28 (0–24 hr)	0.1–2.3 (0–24 hr)
		100 mg	0–18 (0–24 hr)	0.1–1.6 (0–24 hr)
		100 mg	20,17 @24 hr	2@24 hr
Lanz et al, 1997	2	100 mg	~12 (0–72 hr)	~1 (0–72 hr)
		100 mg	~8 (0–72 hr)	~0.3 (0–72 hr)
Ortuno et al, 1999	1	75 mg	6.8 (0–4 hr)	Not tested
		125 mg	~25 (0–24 hr)	Not tested
de la Torre et al, 2000	2	50 mg	~2.6 (0–24 hr)	Not tested
		50 mg	~5.3 (0–24 hr)	Not tested
	8	75 mg	~9.1 (0–24 hr)	Not tested
	2	100 mg	~29.9 (0–24 hr)	Not tested
		100 mg	~9.6 (0–24 hr)	Not tested
	8	125 mg	~21.7 (0–24 hr)	Not tested
	2	150 mg	~13.7 (0–24 hr)	Not tested
		150 mg	~42.9 (0–24 hr)	Not tested
Pacifici et al, 2001	2	100 mg	19.5 (12–24 hr)	Not tested
		100 mg	13.4 @24 hr	Not tested
		100 mg	3.4 (6–8 hr), @24 hr	Not tested

Table 2: MDMA and MDA Levels from Controlled Dosing Studies

Detection of MDMA use by EMIT® Immunoassays

Considering the molecular structural similarities between MDMA and its minor metabolite MDA and methamphetamine and amphetamine, respectively, significant cross-reactivity of MDMA and MDA with various amphetamine/methamphetamine immunoassays is not surprising. Draft guidelines for federally regulated workplace drug testing programs propose that immunoassay screening test kits must significantly cross-react with MDMA, MDA and MDEA (~50 to 150% cross-reactivity) at a 500 ng/mL cutoff (for urine specimens).²³

Note that not all pills obtained on the street and perceived by users to contain MDMA are in fact MDMA, because a variety of other additives and substitutes have been found in these pills.²⁴ Accordingly, immunoassay test results for subjects claiming to have taken MDMA must be viewed cautiously.

A unpublished report in 1986 noted positive test results from samples containing MDMA levels of 5–8 µg/mL or MDA levels of 10–13 µg/mL when analyzed by the EMIT® d.a.u.® Amphetamine Assay at a 0.3 µg/mL cutoff. This represented cross-reactivities of 4.6% for MDMA and 2.6% for MDA.²⁵

A 1988 study using the EMIT d.a.u. Amphetamine Assay with a polyclonal antibody and at a 1 µg/mL cutoff, demonstrated positive test results at MDMA levels of 36 µg/mL or MDA levels of 38 µg/mL.²⁶

A 1990 study found that the EMIT d.a.u. Amphetamine Assay with a polyclonal antibody and at a 0.3 µg/mL cutoff demonstrated cross-reactivity to MDMA—a positive test result was obtained at a concentration of 10 µg/mL, a level surpassed after typical MDMA dosing. The study data clearly indicated that minimal MDMA concentrations caused elevated immunoassay rates.²⁷

A 1993 study using the EMIT d.a.u. Monoclonal Amphetamine/Methamphetamine Assay (MAMA) at a 1 µg/mL cutoff found positive results with MDMA levels of only 3 µg/mL or at MDA levels of 0.8 µg/mL. Furthermore, while tests on urine specimens containing both MDMA at 2 µg/mL and MDA at 0.2 µg/mL demonstrated negative results, specimens with 2 µg/mL of MDMA and 0.4 µg/mL MDA demonstrated positive test results. The EMIT d.a.u. Polyclonal Assay at a 0.3 µg/mL cutoff was studied also, and demonstrated negative results at MDMA or MDA concentrations of 5 µg/mL. The authors noted that the EMIT Monoclonal Antibody Assay was vastly superior to the polyclonal assay; the monoclonal assay demonstrated sufficient sensitivity to detect MDMA and MDA following clinical intoxication. Specimens from 12 rats dosed with MDMA (20 mg/kg) were also included in this study. The monoclonal assay identified positive test results for all 12 specimens, whereas the polyclonal assay identified positive test results with only 4 out of the 12 specimens, and only when the total MDMA + MDA level was above 17 µg/mL. The study also addressed the cross-reactivity to the two stereoisomers of MDMA and MDA.²⁸

A 2001 report examined urine levels of MDMA, MDA, and other amphetamines on subjects, who admitted to recent use of MDMA at raves, by comparing the detection rates between a number of immunoassays, including the EMIT® II Amphetamine/Methamphetamine Assay. GC/MS identified 44 specimens containing either MDMA or MDA. Of these specimens,³⁸ specimen test results were positive using the EMIT II MAMA at a 1000 ng/mL cutoff. Many of these specimens also contained other amphetamine-like compounds. Thirty-one of the 38 specimens that were positive for MDMA or MDA also had amphetamines, but for most of these, sufficient levels of either MDMA or MDA caused positive test results without a contribution from the presence of amphetamines. The remaining seven of the 38 specimens did not contain amphetamines;

rather, the average MDMA level was 33.8 µg/mL (range= 8.9–137 µg/mL) and the average MDA level was 0.4 µg/mL (range= 0.1–1.1 µg/mL).

Each of the six specimens with either MDMA or MDA present, but not detected by EMIT had the following characteristics:

Specimen No.	Findings
1	2.4 µg/mL MDMA only
2	0.5 µg/mL MDMA and 0.4 µg/mL amphetamine
3	0.3 µg/mL MDA only
4	0.1 µg/mL MDA only
5	0.4 µg/mL MDA and 0.1 µg/mL amphetamine
6	0.6 µg/mL MDA and 0.5 µg/mL amphetamine

Table 3 summarizes the cross-reactivity data for the various Syva amphetamine/methamphetamine assays. Given expected MDMA levels of over 10 µg/mL (and sometimes many times higher) with corresponding MDA levels of 10–15% of the MDMA levels for 1–2 days after typical dosing, Syva assays possess sufficient cross-reactivity to generate positive test results. The capability of Syva assays to detect MDMA use has also been noted in several experimental studies. Note, that although the amphetamine-specific assay for the Syva® RapidTest™ has relatively low cross-reactivity to MDMA, the assay has sufficient cross-reactivity to MDA to generate positive test results. Similarly, the Syva RapidTest methamphetamine-specific assay clearly has sufficient cross-reactivity to MDMA itself to detect MDMA use. The Syva® RapidCup™ amphetamine-specific assay has lower cross-reactivity to the MDA metabolite and would not likely generate positive test results. However, the Syva RapidCup methamphetamine-specific assay clearly has sufficient cross-reactivity to MDMA

to detect use. Of course, a positive immunoassay test result from an amphetamine-detecting assay does not specifically demonstrate the presence of MDMA or MDA. Specific identification of MDMA or MDA requires confirmation of the immunoassay results by using a specific analytical technique, such as GC/MS.

Assay	Assay Cutoff Level (ng/mL)	MDMA (ng/mL)	MDA (ng/mL)
Syva EMIT II Plus Monoclonal Amphetamine/ Methamphetamine	1,000 d-meth	9,140	2,130
EMIT d.a.u. Monoclonal Amphetamine/ Methamphetamine	1,000 d-meth	3,000	1,000
EMIT d.a.u. Amphetamine	300 d,l-amph= 1,000 d-meth	NA	NA
Syva RapidTest Amphetamine	1,000 d-amph	100,000	700
Syva RapidTest Methamphetamine	1,000 d-meth	2,000	200,000
Syva RapidCup Amphetamine	1,000 d-amph	NA	5,000
Syva RapidCup Methamphetamine	1,000 d-meth	2,000	NA

Table 3: Cross-Reactivity Data of Syva Assays

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Biography

Dr. Kadehjian is an independent biomedical consultant in Palo Alto, California, primarily lecturing and writing on the clinical, scientific, regulatory, and legal issues in drugs of abuse testing. He has provided consulting services for a wide variety of both private and public sector drug programs worldwide, and currently serves as a consultant to Syva Company, among others. He has special experience with on-site testing programs and provides oversight of the U.S. Federal Courts' onsite drug testing programs. He also serves on the faculty of the National Judicial College, lecturing on the neurobiology of addiction and drug testing issues, and has provided nationally broadcast live satellite television seminars for the Federal Judicial Center. An internationally recognized speaker, he has earned an Outstanding Speaker recognition from the American Association of Clinical Chemistry and has provided expert testimony in court and labor arbitration.

Born and raised in Boston, he received his Bachelor's degree in Organic Chemistry from M.I.T. in 1972 and his Ph.D. in Biochemistry from Stanford University in 1977.

Notes: