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Use of MDA (The "Love Drug") and Methamphetamine in Toronto by Unsuspecting Users of Ecstasy (MDMA)*

ABSTRACT: It has recently been reported that purity of illicit tablets of ecstasy (MDMA) is now high. Our objective was to confirm whether hair of drug users, who request only ecstasy from their supplier, contains MDMA in the absence of other drugs. GC-MS analysis of scalp hair segments disclosed the presence of MDMA in 19 of 21 subjects and amphetamine/methamphetamine in eight subjects. Surprisingly, seven subjects had hair levels of the MDMA metabolite, MDA, equal to or greater than those of MDMA, suggesting use of MDA in addition to that of MDMA. These amphetamine derivatives might be included by clandestine laboratories to enhance effects of the drug cocktail or because of a perception that MDA synthesis might be simpler than that of MDMA. Drug users and investigators examining possible brain neurotoxic effects of MDMA need to consider that "ecstasy" tablets can contain MDA and methamphetamine despite no demand for the drugs.

KEYWORDS: forensic science, forensic toxicology, ecstasy, MDMA, MDA, amphetamine, methamphetamine, addiction

MDMA ("ecstasy", 3,4-methylenedioxymethamphetamine) is a widely used synthetic amphetamine derivative used illicitly in part for its reported ability to induce a state of heightened empathy and introspection (1). MDMA can be metabolized in the human by N-demethylation to MDA (3,4-methylenedioxyamphetamine) (2–4); (see Fig. 1 for the structures of MDMA and MDA), previously known as the "love drug," which was commonly used in the United States and Canada 30 years ago (5–7). Today, however, the present drug of choice in the "entactogen" class of drugs is the parent drug, MDMA.

Although death can occur, rarely, following ingestion of either MDMA (10–14) or MDA (7–9), the most serious (as yet unresolved) public health concern is that MDMA might cause long-term brain damage in users of the drug, as suggested by animal data (see 15). Because of the possibility that the purity of illicit tablets of MDMA obtained "on the street" might be low, and the reliability of drug self-report data uncertain, it would seem obvious that investigators conducting studies to quantify the extent of brain injury (e.g., by cognitive or brain scan testing) should employ drug testing of hair to prove that the subjects actually used MDMA and not other potentially neurotoxic agents. However, drug testing in such investigations is rarely performed (16–18). This concern becomes somewhat less of a confounding issue should the purity of illicit MDMA tablets be very high. In this regard, a recent review of the literature has concluded that the purity of illicit MDMA tablets is now much higher (between 90% to 100%) than that during the mid-1990s, although dosage levels can still be highly variable (19).

As part of an investigation designed to determine whether MDMA users, who do not use other potentially neurotoxic drugs, might have compromised brain function, we recruited, by advertisement, a highly selected group of subjects in the Toronto Canada area who, unlike most MDMA users, reported to us that each requested tablets from their supplier which contained only ecstasy (MDMA). To address the question, in this subgroup of MDMA users, of the purity of MDMA tablets used chronically by such drug users, we conducted forensic drug testing on sequential segments of scalp hair of the subjects. Hair was selected as the specimen for analysis in order to provide a drug history and time line of use that could not be obtained by a single urine test. Our hair data, together with local drug seizure findings, indicate that despite an absence of any specific demand, the drugs MDA and methamphetamine, both neurotoxic in animals, are now being marketed to and used by unsuspecting ecstasy users. These findings provide further justification for the use of forensic drug analyses to confirm selective use of MDMA in investigations of brain integrity and behavior in MDMA users.

Subjects and Methods

Subjects

Table 1 shows the subject and drug history characteristics of 21 subjects recruited by a newspaper advertisement that stated that our objective was to examine ecstasy users who do not use other drugs. Each participant received $100 in compensation for their time involved in the entire investigation (including neuropsychiatric testing and brain scan procedures). There was no specific "incentive" provided to any subject to provide an accurate self-report of drug history. However, each subject was advised that the accuracy of self-reported drug history would be compared with

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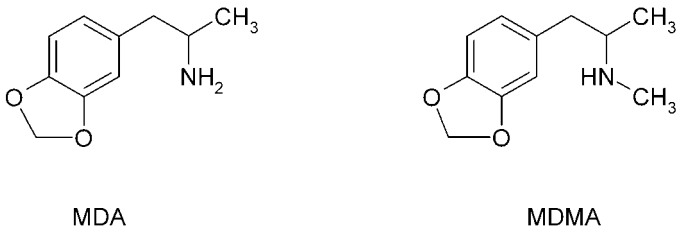


FIG. 1—*Notice that the only difference between the two molecules is the additional methyl group attached to the amine group in MDMA. Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine; MDA, 3,4-methylenedioxyamphetamine.*

scalp hair drug analysis findings. All participants reported to us that ecstasy (MDMA) was the only illicit drug requested from their drug suppliers over the period of time approximately corresponding to the extent of growth of scalp hair (one month/one half-inch of hair) with the exception, for some of the subjects, of use of cannabis and "mushrooms." A detailed structured interview was performed on 20 subjects whereas one subject (Case 20) withdrew from the study before the interview could be conducted. As expected (1), most of the subjects ingested the drug in the typical group setting, and confirmed the presence of behavioral features (hyperthermia, drug tolerance and withdrawal) typical of MDMA use.

This investigation was approved by the Centre for Addiction and Mental Health Ethics Review Board. All subjects provided written informed consent.

Hair Sample Analysis

Hair Segmentation and Wash Procedure—The entire length of hair (pencil thickness) of each subject, beginning at the scalp end, was divided, lengthwise, into two parallel parts, one part to be used for measurement of amphetamines, and a second part used for measurement of cocaine, opiates, and PCP (phencyclidine). Each length of hair was then segmented into $^1/_2$-in. segments approximating one month's growth per segment, beginning with the scalp end. The segments (approximately 10 mg) were weighed and washed to remove environmental contamination by treatment with 3×1 mL of 1% SDS (sodium dodecylsulfate) in deionized water, followed by 3×3 mL of deionized water rinse and 3×3 mL of methanol rinse. Once the hair segment was dried, it was transferred to a test tube.

Analysis of Amphetamines

Hair Spiking—The segment aliquots were cut into 1–2 mm size pieces while in the test tubes using tweezer scissors. Internal standards were added to each tube of hair at the concentration of 2 ng/mg based on 10 mg of hair. The internal standards included d_8-amphetamine, d_{11}-methamphetamine, d_5-MDA, and d_5-MDMA. A 5-point standard curve was prepared in blank tubes containing buffer at concentrations of 0.2, 0.5, 1.0, 5.0, and 10.0 ng/mg each of amphetamine, methamphetamine, MDA, MDMA, PMA (paramethoxyamphetamine), and PMMA (paramethoxymethamphetamine). A control consisting of 10 mg of female Asian hair was spiked at 1.0 ng/mg for each drug. Internal standards were also added at 2 ng/mg to the standard curve tubes and the control.

Acid Digestion

One mL of 100 mM HCl was added to each of the standard curve tubes, control and hair segment tubes. The tubes were placed in a heat bath at 45°C for 18 h. All of the tubes were then treated with 0.1 mL 1N NaOH to neutralize the acid, 3 mL of pH 6.0 100 mM phosphate buffer was then added to the tubes for solid phase extraction.

TABLE 1—*Subject characteristics of 21 MDMA users who reported and assumed use only of MDMA.*

Case #	Age	Sex	Race	Years of Use	# Tablets/Interval Usage	Hyperthermia	Group	Tolerance	Withdrawal	Interval from Last Use to Hair Sampling
1	22	M	C	3	1–2/week	P	P	P	P	21 days
2	24	M	C	2	1–2/2 months	P	P	P	No	2–3 months
3	22	M	C	0.6	2–3/week	P	P	P	P	2 days
4	30	F	C	2	1/1–2 weeks	P	P	P	P	2 days
5	33	M	C	2	1/1–2 weeks	P	P	P	P	3 weeks
6	33	M	A	3	0.5–1/2–4 weeks	P	P	No	P	1 day
7	26	F	C	9	2/2–4 weeks	P	P	P	P	2 days
8	28	M	C	5–6	2/4 weeks	P	P	No	No	2 months
9	26	M	A	9	3–6/week	P	Either	P	P	4 days
10	21	M	C	4	1–2/week	P	P	P	P	1 day
11	38	F	C	2	1–2/week	P	P	P	P	1 week
12	29	M	C	8	1–2/week	P	Alone	No	P	5 days
14	20	F	C	2	1–1.5/2 weeks	P	P	No	P	1 week
15	23	M	C	4	1–1.5/2 weeks	P	P	P	No	1–2 months
16	32	M	C	6	3–6/1–3 weeks	P	P	P	P	3 weeks
17	25	M	C	6	2–3/1–4 weeks	P	P	P	P	2 months
18	21	M	C	3	2/2–4 weeks	P	P	P	P	1 month
19	19	F	C	3	1–1.5/6 weeks	P	P	P	P	1 week
20	24	M	A	n/a	n/a	n/a	n/a	n/a	n/a	n/a
21	19	M	C	2	2.5–5/2 weeks	P	P	No	P	2 weeks
22	39	M	C	8	1–4/3–4 days	P	Either	P	P	1 week

"Group": Subject uses drug in group setting vs. taking drug alone. "Tolerance and withdrawal": Subject reports tolerance to the desired effects of the drug and a withdrawal syndrome characteristic of ecstasy use one-two days following use of the drug.

Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine, ecstasy; C, Caucasian; A, Asian; P, present; n/a, not available.

Solid Phase Extraction

The solid phase extraction utilized Clean Screen (CSDAU020; UCT, Bristol, PA) cartridges and the manufacturer's recommended extraction procedures were followed with minor modifications. The solid phase extraction (SPE) cartridges were conditioned with 3 mL methanol, 3 mL dionized water, and 1 mL pH 6.0 100 mM phosphate buffer. The samples were loaded into individual SPE cartridges at 1–2 mL/min. The cartridges were washed with 3 mL deionized water, 1 mL 1.0 M acetic acid, 3 mL methanol and then dried under vacuum. The drugs were eluted from the cartridges with 3 mL methylene chloride/isopropanol/concentrated ammonium hydroxide (78:20:2). The collection tubes were prepared with 0.02 mL of 1% HCl in methanol prior to the collection. The eluent was dried down under nitrogen at 40°C.

Sample Derivatization

The residues were derivatized with the addition of 0.05 mL ethyl acetate and 0.05 mL HFBA (heptafluorobutyric anhydride). The tubes were purged with nitrogen, capped, vortexed briefly, and incubated for 20 min at 70°C. Tubes were then centrifuged briefly to concentrate the derivative at the bottom and then evaporated to dryness at 40°C under nitrogen. The residue was reconstituted with 0.05 mL ethyl acetate and vortexed briefly. Tubes were briefly centrifuged to concentrate the sample at the bottom. Samples were transferred to autosampler vials for GC/MS analysis.

GC/MS

The hair samples were run on a Varian Saturn 2000 ion trap GC/MS equipped with a Varian 3400 gas chromatograph and a Varian 8200 autosampler. The GC column was an HP-5MS, 15 m × 0.25 mm with 0.25 μm loading. The transfer line was held at 280°C and the ion trap was operated at 220°C. The injector was held isothermal at 150°C. The column was ramped at 75°C initial hold for 1 min and then increased at 15°C per min up to 180°C, then increased at 40°C per min up to 300°C and held for 1 min. A 1 μL solvent plug of ethyl acetate was used on injection with splitless mode rapid injection. The mass spectrometer was run in the SIS (Selected Ion Storage) mode and the following ions (m/z) were monitored for each derivatized analyte:

d_8-amphetamine	243, 126
amphetamine	240, 118, 117
d_{11}-methamphetamine	260, 213
methamphetamine	254, 210, 118
PMA	121, 148, 91
d_5-MDA	136, 166
MDA	135, 162, 240
PMMA	254, 121, 148
d_5-MDMA	258, 213
MDMA	254, 210, 162

The first ion listed for each analyte was the quantitation ion and the following ion(s) were the qualifying ion(s). The analytes are listed in elution order. d_5-MDMA was used as the internal standard for PMA and PMMA. Drugs and deuterated internal standards were obtained from Cerilliant (Round Rock, TX).

For the analysis of PCP, cocaine, benzoylecgonine, codeine, morphine and 6-acetyl morphine, a combined extraction/analysis was performed using the same general sample spiking and acid digestion procedure used for the amphetamines. The extraction followed that of the recommended UCT method with a cartridge wash of either 2 mL 100 mM HCl or 2 mL pH 4.5 100 mM acetate buffer, depending on whether cocaine or opiate prevalence were the most desired analytes. The samples were derivatized with BSTFA/1% TMCS (bis-triethylsilyltrifluoro-acetamine/1% trimethylchlorosilane).

The method and analysis were tested and the accuracy measurements had a mean coefficient of variation of 3.5% for amphetamines, 6.8% for cocaine and metabolites, and 7.1% for opiates measured against three sets of proficiency samples. The precision had a mean coefficient of variation of 6.8% for amphetamines, 5.6% for cocaine and metabolites, and 5.2% for opiates measured for 15 repetitive injections. The recoveries were greater than 80%. The Limit of Detection was 0.01 ng/mg and was determined by the amount of analyte that could reliably be distinguished from the background at a minimum 2:1 signal to noise. For the purpose of this study, in which the intent was to determine only whether the drug was or was not present, the Limit of Quantitation was considered to be the same as the Limit of Detection.

Results

Drug Hair Analyses

Table 2 shows the results of the forensic drug hair analyses in one representative hair segment (not the same hair segment in all subjects) of the 21 drug users.

MDMA

For 19 of the 21 users, MDMA was detected in one or more $^1/_2$-in. hair segments, providing good agreement between the results of the structured interview and the hair forensic drug analysis. We suggest that the absence of MDMA detected in hair of Case 2 (only 2 in. available) could be related to the long interval in this subject between last drug use and hair sampling (2–3 months), or possibly the use of a low dose of MDMA resulting in a hair drug level below the limit of detection of sensitivity of our procedure. Based on our observation that Case 22 was the only subject who repeatedly insisted on receiving, before conclusion of the study, the participation fee for the investigation, it is likely that this subject (who tested positive for cocaine; see Table 2) falsified his drug history report.

MDA

As shown in Table 2, the MDMA metabolite MDA could be detected in most of the hair samples that tested positive for MDMA. Although no precise cut-off ratio has yet been established, high ratios MDA:MDMA (e.g., >1.00) are suggestive of the use of both MDA and MDMA (see below). Thus, of the 19 subjects testing positive for MDMA, 12 subjects (Cases 1,3,5,6,8,10,14,17–21) had MDMA levels in hair much greater than those of MDA, or MDMA in the absence of any MDA, suggesting selective or primary use of MDMA, whereas seven subjects (Cases 4,7,9,11,12,15,16) had levels of MDA similar to or much greater than those of MDMA, suggesting use of both MDMA and MDA. One female subject (Case 4) in particular, tested positive for MDA in a total of 23 of 26 examined $^1/_2$-in. hair segments (representing about two years of hair growth), whereas in 24 of the segments, no MDMA was detected and in two segments, relatively low levels of MDMA were present, indicating primary or exclusive use of MDA for this extensive period of time (Table 3).

TABLE 2—*Results of forensic drug hair analyses in one representative hair segment of 21 drug users.*

Case	Number of Segments	MDMA	MDA	Amphetamine	Methamphetamine	Cocaine	PCP
1	3	2.25	PNQ	nd	nd	nd	nd
2	4	nd	nd	nd	nd	nd	nd
3	3	0.63	nd	0.34	nd	nd	nd
4*	26	0.19	**3.16**	nd	nd	nd	nd
5	3	1.21	0.13	nd	nd	nd	nd
6	4	14.2	1.98	nd	nd	nd	nd
7*	16	0.41	**1.31**	PNQ	1.12	nd	nd
8	2	0.71	0.06	nd	nd	nd	nd
9*	3	3.08	**9.31**	nd	nd	nd	nd
10	4	0.30	nd	nd	0.04	nd	0.12
11*	11	0.53	**2.37**	0.04	0.14	nd	nd
12*	2	2.00	**3.21**	0.05	0.44	nd	nd
14	19	0.64	nd	nd	nd	nd	nd
15*	5	0.77	**0.91**	nd	nd	nd	nd
16*	5	0.64	**6.01**	nd	nd	nd	nd
17	3	0.33	nd	nd	nd	nd	nd
18	2	0.92	0.46	nd	0.20	nd	nd
19	14	2.59	0.27	nd	nd	nd	nd
20	6	28.42	6.33	nd	2.98	0.94	nd
21	2	1.29	0.34	0.03	0.12	32.93	nd
22	4	nd	nd	nd	nd	14.07	nd

Values expressed as ng/mg tissue. Case number 13 not examined. All subjects tested negative for opiate drugs with the exception of Case 20 who tested positive for codeine in one hair segment. Note that some users show predominantly MDMA whereas other cases (denoted by asterisk and by boldened MDA level) have MDA > MDMA level, suggestive of use of MDA and MDMA.

Abbreviations: PNQ, present but not quantifiable; nd, not detected; ne, not examined; MDMA, 3,4-methylenedioxymethamphetamine; MDA, 3,4-methylenedioxyamphetamine; PCP, phencyclidine.

TABLE 3—*Results of forensic drug hair analyses in 26 consecutive one half-inch segments (beginning with root end) of Case 4.*

Segment Number	MDMA	MDA
1	nd	3.75
2	0.19	3.16
3	nd	nd
4	0.15	1.94
5	nd	1.37
6	nd	1.13
7	nd	0.99
8	nd	1.05
9	nd	1.09
10	nd	1.29
11	nd	1.10
12	nd	1.05
13	nd	0.86
14	nd	0.78
15	nd	0.69
16	nd	0.56
17	nd	0.72
18	nd	0.44
19	nd	0.30
20	nd	0.22
21	nd	0.15
22	nd	0.01
23	nd	nd
24	nd	nd
25	nd	0.17
26	nd	0.04

Values expressed as ng/mg tissue. Note that MDA (3,4-methylenedioxyamphetamine) and MDMA (3,4-methylenedioxymethamphetamine) were detected in 23 and in two hair segments, respectively, of this subject who assumed that she was using only ecstasy (MDMA). Other amphetamine derivatives, cocaine and metabolites, opiates, and PCP were not detected in any examined hair segment of this subject.

Because MDA can be a breakdown product of MDEA (3,4-methylenedioxy-N-ethylmethamphetamine), in addition to MDMA, it was possible that the MDA in hair from some subjects having high MDA/MDMA ratio could have derived in whole or part from MDEA. However, we found no evidence for the presence of MDEA (as assessed by the absence of the162 ion in the chromatographic region in which the HFBA derivative of MDEA would elute) with the single possible exception of segment four (of five total) of case 16 for which the 162 ion was present at the appropriate elution time frame but no other qualifying ions were examined by trap collection.

Other Drugs

Analysis of hair also revealed that amphetamine/methamphetamine and cocaine/benzoylecgonine were observed in a total of eight and three subjects, respectively. PCP and codeine could be detected in hair of subjects 10 and 15, respectively. PMA and PMMA could not be detected in any subject. The subjects who tested positive for cocaine/benzoylecgonine and PCP denied knowingly using these drugs.

Results of Follow-up Interview with Subjects

A second interview was conducted with those subjects who tested positive for drugs other than MDMA in the hair samples. None of the subjects who tested positive for MDA or amphetamine/methamphetamine reported to us awareness that they had been ingesting any drug other than ecstasy (MDMA). Only two of the drug users were aware of the pharmacological properties of amphetamine/methamphetamine ("speed") or of the existence of the drug MDA.

Drug Analysis of Seized Tablets in Province of Ontario Area

Following completion of our drug hair analysis study, we contacted Health Canada to obtain information on the composition of seized tablets in Ontario, Canada. Assuming that the ecstasy users who tested positive for other amphetamine derivatives, despite lack of any demand for the drugs, provided truthful self-report

TABLE 4—*Partial list of contents of seized tablets in Ontario area purported to contain ecstasy and analyzed by Health Canada.*

Single Component	Dual Component	Tri-Component	Multi-Component
MDMA	MDMA, MDA	MDMA, MDA, meth	MDMA, MDA, meth, ketamine
MDA	MDMA, Ketamine	MDMA, MDA, ketamine	MDMA, meth, amph, acetaminophen
MDEA	MDMA, PCP	Dextromethorphan, ephedrine, acetaminophen	MDMA, meth, PCP, ketamine, ephedrine, caffeine, guaiphenesin
Nexus	MDMA, caffeine	Meth, PCP, ketamine	Meth, cocaine, ketamine, caffeine
PCP	Meth, PCP	MDMA, caffeine, ephedrine	Meth, PCP, caffeine, dimethylsulfone
Ketamine	PMA, PMMA	Meth, ketamine, caffeine	PMA, PMMA, amph, guaiphenesinephedrine
Ephedrine	Ketamine, caffeine	Meth, ephedrine, dimethylsulfone	PCP, ketamine, caffeine, ephedrine
Meth	PCP, ephedrine	MDMA, amph, caffeine	PCP, dextromethorphan, levorphanol, dimenhydrinate, caffeine
Pseudoephedrine	MDMA, meth	MDMA, meth, caffeine	MDMA, meth, ketamine, caffeine
	Meth, acetaminophen	Meth, PCP, dimethylsulfone	MDMA, meth, acetaminophen, caffeine

Seized tablets in Ontario area contained a variety of single (e.g., MDMA) or multiple (e.g., MDMA, MDA, plus methamphetamine) contents. Each row identifies the composition of a tablet. Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine; MDA, 3,4-methylenedioxyamphetamine; MDEA, N-ethyl-3,4-methylenedioxyamphetamine; amph, amphetamine; meth, methamphetamine; PMA, 4-methoxyamphetamine; PMMA, N-methyl-4-methoxyamphetamine; PCP, phencyclidine; Nexus, 4-bromo-2,5-dimethoxyphenethylamine.

TABLE 5—*Drugs produced at "Ecstasy" clandestine laboratories in Ontario: January 2000 to June 2003.*

Clandestine Lab #	Produced MDMA	Produced MDA	Produced Methamphetamine
1	Yes	No	No
2	No	Yes	No
3	No	Yes	No
4	Yes	Yes	Yes
5	Yes	No	No
6	No	Yes	No
7	Yes	Yes	Yes
8	Yes	Yes	Yes
9	Yes	No	No
10	Yes	No	Yes
11	Yes	No	Yes

MDMA, 3,4-methylenedioxymethamphetamine; MDA, 3,4-methylenedioxyamphetamine.

information, it would be expected that some ecstasy tablets marketed in the Toronto area should contain amphetamine derivatives other than MDMA. Anecdotal information from the Drug Analysis Service of Health Canada in Toronto indicates that approximately 40 to 70% of suspected ecstasy tablets contain only MDMA (J. Hugel, unpublished observations). The Drug Analysis Service analyzes illicit drug exhibits submitted by the police services of Ontario as part of their (police) drug investigations. Whether or not drug police seizures reflect the drug scene in Ontario cannot be readily established. Table 4 provides a listing of some of the analysis results of some of the suspected ecstasy tablets submitted to that laboratory between January 2000 and June 2003, and demonstrates that ecstasy tablets in Ontario can contain a variety of components including MDA and methamphetamine. Drug analysis data indicated the presence of MDA alone in some tablets, as well as a variety of combinations of MDMA, MDA, methamphetamine, PCP, and cocaine. MDEA is occasionally observed as a relatively low concentration component in ecstasy tablets containing MDMA. On rare occasions (<1% of exhibits suspected to contain ecstasy), MDEA is the most concentrated component. This information corroborates the findings of MDA, methamphetamine, and amphetamine in hair samples of ecstasy users.

During the period January 2000–June 2003, there were 11 clandestine laboratories seized in the province of Ontario which were producing MDMA and/or MDA. The drugs being produced at each of the laboratories are summarized in Table 5. Of the 11 laboratories, the drugs manufactured were: MDMA only ($n = 3$); MDA only ($n = 3$); MDMA and methamphetamine; ($n = 2$), and MDMA, MDA, and methamphetamine ($n = 3$). There was no indication at any of the listed clandestine laboratories, or at any other laboratory seized in Ontario during the specified period, that MDEA was being produced or was planned to be produced.

Discussion

The unique focus of our investigation was the restriction of the subjects of our study to a small subgroup of self-reported ecstasy users who explicitly stated that each has requested *only* ecstasy (MDMA) from their drug supplier. This approach can be distinguished from that employed in other studies (e.g., 15,16) and addresses to some extent the concern of "deliberate polydrug usage" (19). The many generic limitations to our investigation include small sample size, uncertain truthfulness of self-reported drug history data (e.g., over- or under-reporting drug use), possible individual differences in drug metabolism, and drug measurement issues (e.g., assay sensitivity, possible influence of hair treatments).

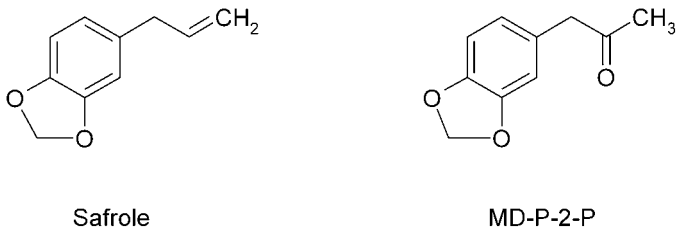
The results of our drug hair testing, supported by tablet seizure data, suggest that 12 of 21 (57%) of the ecstasy users in our sample used (unknowingly, assuming the self-reporting data were truthful) MDA and/or methamphetamine/amphetamine in addition to MDMA. In addition, the drug hair data suggest that MDA was likely ingested by Case four for most of a two year period, as MDA in the absence of potential parent drugs MDMA and MDEA was detected in almost all sequential hair segments.

Because MDA is a known demethylated metabolite of MDMA, it is possible that the presence of both MDA and MDMA in hair of most of the subjects is explained by use of MDMA either alone or in combination with MDA. To our knowledge, no information is available on the status of MDMA and its metabolite in scalp hair of humans who ingested "pure" MDMA in a prospective study. However, data from prospective studies do indicate that MDA levels in plasma and in urine of humans selectively exposed to a known amount of MDMA are typically only a small fraction of levels of the parent drug (3,4). Similarly, MDA/MDMA ratio in postmortem organs of experimental animals are also low (20,21). In retrospective (i.e., proof of actual drug ingested is not available) investigations of MDMA-positive "ecstasy" users, the MDA/MDMA ratios in human urine (22,23), postmortem blood (14), scalp hair (24–30) and autopsied organs (30,31) of drug users are also

usually low. However, a small fraction of some of the subjects demonstrate MDA/MDMA ratio in hair greater than 1.0, prompting the conclusion that such an unusually high ratio metabolite/parent drug in such subjects indicates the likely use of both MDA and MDMA (24,27; see also 22,23). Although we cannot exclude the possibility that hair of some or perhaps all of the subjects of our study might differentially retain MDA vs. MDMA, or be affected by factors such as race and gender, the simplest explanation for the presence of a high ratio MDA/MDMA (range: +1.2–9.4; see Table 2 [excluding Case 4 in which MDA alone was detected in most samples]) in a subgroup of the MDMA users is that MDA was also ingested by the subjects. This possibility is supported by our local tablet seizure data indicating the presence of MDA alone or in combination with MDMA in seized tablets and by the seizure of six clandestine laboratories in Ontario which were producing MDA.

Why Are Methamphetamine and MDA Included in MDMA Tablets?

The reasons why illicit drug manufacturers include methamphetamine and MDA tablets marketed as ecstasy in the absence of any specific demand are unknown. Methamphetamine might be included to enhance the stimulant effects of the drug cocktail. MDA might be marketed as a replacement for MDMA because of its longer duration of action (2,3) and (possibly) higher potency (32) in order to counter the tolerance which often occurs in MDMA users (see Table 1). Alternatively, MDA might be included because of a perception that synthesis is simpler or that the chemicals needed to synthesize MDA were easier to obtain and were not as subject to scrutiny (by the authorities) as were those for the synthesis of MDMA (J. Hugel, unpublished observations). The synthesis of MDMA and MDA in southern Ontario almost always begins with sassafras oil, which consists of 75 to 90% safrole. Safrole is removed from the oil and then oxidized to 1-(3,4-methylenedioxyphenyl)-2-propanone (MD-P-2-P) by one of a variety of routes (see Fig. 2). The oldest and until recently, the most common route, involves isomerizing the safrole to isosafrole and then oxidizing with formic acid and hydrogen peroxide. A more recent set of methods involve the use of the Wacker oxidation (of safrole) using palladium chloride and one of methyl nitrite, hydroquinone, or oxygen gas. From MD-P-2-P, MDA can be made by reductive amination using sodium cyanoborohydride and ammonium chloride. From MD-P-2-P, MDMA can be synthesized by reductive amination using methylamine and aluminum amalgam. Since the bulk of the effort in these syntheses is obtaining MD-P-2-P, there is no clear distinction (as far as simplicity) between the effort required to produce MDMA or MDA.



Safrole MD-P-2-P

FIG. 2—*In Ontario, the most common synthetic routes to MDMA (3,4-methylenedioxymethamphetamine) and MDA (3,4-methylenedioxyamphetamine) begin with sassafras oil (containing up to 90% safrole), which is oxidized into MD-P-2-P, which in turn can be reductively aminated to either MDA or MDMA.*

Implications of Lack of Purity of Ecstasy Tablets

Although the purity of drugs manufactured by clandestine labs can be expected to be uncertain, a recent review of the literature (19) concluded that the purity of illicit MDMA tablets is, since the late 1990s, very high. In one respect, our hair data support this position, as MDMA was, in fact, detected in hair of almost all of the 21 subjects of our study. However, whereas the proportion of ingested tablets of ecstasy which contain some MDMA might be high, it is equally relevant that the purity, at least in this sample of subjects, was low, as our hair data indicated the presence of non-MDMA drugs in about half of the subjects. Because of differences in study design of investigations in the literature, it is difficult to establish whether inclusion of MDA and methamphetamine in tablets purported to contain *only* MDMA is a common, world-wide phenomenon or is limited to Ontario, Canada. MDA in the absence of MDMA (27) and high ratio MDA:MDMA (24) have been reported in hair of a only a small proportion of examined self-reported users of "ecstasy and amphetamine/speed" in investigations in the UK and Germany. Also in the UK, recent tablet seizure data (year 2000) indicate that MDA and amphetamine/methamphetamine each account, as a "main ingredient," for only about 2% of "ecstasy" tablets examined (33). In the U.S., MDA has been reported to be present in some tablets turned into a drug analysis facility (34).

From a public health perspective, it is important to establish whether the use of methamphetamine combined with MDMA is a new trend and which might be more harmful to humans than MDMA taken alone. Because drug addiction and death (by cardiovascular toxicity) can occur following exposure to methamphetamine (35,36), ingestion of tablets containing MDMA and methamphetamine might be more harmful than ingestion of tablets containing MDMA alone, which may have a somewhat lower risk of cardiovascular toxicity and addiction potential (although this needs to be confirmed). We also suspect that an equivalent dose of MDA is more harmful than that of MDMA because of its longer half-life and reported higher potency (see above); however, insufficient information in the literature is available to address conclusively this question.

Much attention in the toxicological literature has been focused on the important question whether use of MDMA might, as suggested by animal data, harm the human brain by damaging serotonin neurones (15). A position has been taken that since the purity of illicit MDMA tablets has been reported to be high, there is ". . . validity of using data from [self-reporting] ecstasy users, to estimate the human psychobiological conseqences of repeated MDMA" (19). However, our data suggest that a substantial proportion of MDMA users, at least in the Toronto area, are unknowingly ingesting other amphetamine derivatives known to damage serotonin neurones in experimental animals (37,38). Therefore, we strongly recommend that drug hair testing be conducted on all subjects involved in studies of MDMA and brain damage/behavior so that any conclusions made regarding the toxicity of MDMA are justified.

Conclusion

We found that unsuspecting MDMA users in the Toronto area are using other amphetamine derivatives. Further investigation needs to be conducted to confirm whether this is a phenomenon limited to Ontario, the relative harm to humans of MDA and methamphetamine vs. MDMA, and the explanation for the inclusion in ecstasy tablets of such drug combinations by clandestine laboratories. Finally, studies focused on the controversial question of MDMA toxicity to the brain will need to confirm carefully, by

hair drug analysis, the extent to which MDMA was the only toxic amphetamine derivative chronically used by the subjects.

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