Fatalities from Exposure to Paramethoxymethamphetamine (PMMA) in Alberta and British Columbia, Canada

Investigators

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Abstract:

Background: Paramethoxymethamphetamine (PMMA) is a ring-substituted amphetamine, known as 'Death'. From June 2011 – April 2012, 27 PMMA-associated fatalities were confirmed in Alberta and British Columbia (BC). We sought to describe the clinical presentation of these fatalities and the associated public health response.

Methods: A retrospective case series was conducted on Alberta and BC fatalities who died between June 2011 – April 2012, where forensic toxicological analysis was positive for PMMA, and PMMA was implicated as primary toxic agent. Data collected included patient demographics, exposure history, clinical features, investigations, therapy provided, hospital course, and post-mortem toxicological findings.

Results: There were 20 fatalities in Alberta and 7 in BC. The median age was 24 years; 22 were male. Seventeen presented to hospital, and 10 were pronounced dead on scene. The median time from exposure to hospital presentation was 6 hours, and from exposure to death was 17 hours. Sixteen cases presented with clinical features of serotonin syndrome. End organ dysfunction included hepatic and acute kidney injury, rhabdomyolysis, coagulopathy, and cardiac dysfunction. MDMA (n=27), cocaine (n=14), and methamphetamine (n=12) were also identified on toxicological analysis. Collaboration amongst poison centers, public health, and law enforcement resulted in clinical management guidelines, public awareness campaigns and arrests of suspected traffickers.

Conclusions: PMMA-associated fatalities presented to hospital with multiorgan dysfunction and shock. A coordinated response between poison centers, public health, law enforcement, and the media was followed by the decline in PMMA exposures in both provinces.

Introduction:

Paramethoxymethamphetamine (PMMA) is a ring-substituted amphetamine, similar in structure to 3,4-methylenedioxymethamphetamine (MDMA) but substantially more toxic (Figure 1) [1]. With nearly fifty documented fatalities in Europe, Asia, Australia, and Israel, PMMA has earned the street names 'Death' and 'Dr. Death' [2]. While PMMA is present in a small fraction of Ecstasy pills confiscated during drug seizures, it is responsible for a disproportionate number of deaths [3]. Clinical features are characterized by hyperthermia, serotonin syndrome, and multiorgan dysfunction [2,4-8].

Prior information on PMMA exposures has been limited to case reports or case series which have focused on either the clinical or postmortem features. Furthermore, description of strategies adopted in local jurisdictions in response to outbreaks of PMMA-associated fatalities is limited. Over an eleven-month period from June 2011 to April 2012, there were 27 confirmed fatalities in Alberta and British Columbia (BC), Canada, from exposure to Ecstasy containing PMMA. This is the first time that PMMA has appeared in North America. Our primary objective was to describe the clinical features observed with fatal PMMA exposures in Alberta and BC. Our secondary objective was to discuss the public health interventions that were implemented in response to the fatalities.

Methods

Selection of cases

We conducted a retrospective case series of Alberta and BC patients who died between June 2011 and April 2012, where forensic toxicological analysis was positive for PMMA, and PMMA was implicated as the primary toxic agent. The Office of the Chief Medical Examiner in Alberta and BC Coroners Service identified these cases. PMMA was implicated as the primary toxic agent when it was present on antemortem or postmortem toxicological analysis, and if identified as a PMMA-associated fatality by the Office of the Chief Medical Examiner or BC Coroners Service. The research ethics boards of the University of Calgary and the University of British Columbia approved the study. The need for informed consent was waived by both institutions.

Sampling Method

A medical record review was conducted at the Office of the Chief Medical Examiner in Alberta and BC Coroners Service. Three study investigators (2 in Alberta, 1 in BC) performed the medical record review. Patient demographics, exposure history, clinical features, laboratory investigations, therapy provided, and hospital course were collected using a pre-defined medical record review tool. Post-mortem analytical toxicology results and autopsy findings were obtained from the Office of the Chief Medical Examiner and BC Coroners Service.

Measures and Definitions:

All measured laboratory values were obtained from the medical record review. Blood and tissue concentrations of PMMA and other substances were obtained from the Office of the Chief Medical Examiner and BC Coroners Service. These were measured as mg/L. Time from exposure to hospital presentation was obtained from the medical record review for the 17 PMMA associated fatalities transported to hospital. Time from exposure to death included cases where death was pronounced on scene only if time of exposure and time of death were known.

Serotonin syndrome was defined as per the criteria of Dunkley et al. by the presence of neuromuscular abnormalities, mental status changes, and hyperthermia [9]. These criteria were applied only to cases transported to hospital. Indicators of end-organ dysfunction were based upon clinical findings, laboratory investigations, and electrocardiogram (ECG) results. Hepatic injury was defined as a serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1000 IU/L [10,11]. Acute kidney injury was characterized by a rise in serum creatinine by $\geq$50% or $\geq$26.4mmol/L from predicted baseline, or urine output <0.5 mL/kg/hour for 6 hours [12]. Rhabdomyolysis was defined as a creatine kinase (CK) >1000 IU/L or >5 times the upper limit of normal [13]. Coagulopathy was defined as an INR $\geq$1.3. Cardiac ischemia was characterized by the presence of ST segment depression or elevation or t-wave inversion on ECG, or a serum troponin-t >0.03 mcg/L. Finally, sodium channel blockade on ECG was characterized by the presence of a QRS >120 msec and at least one of the following: a deep, slurred S wave in leads I and aVL, or an R:S ratio >0.7 or R wave >3mm in lead aVR [14-16].

Analytic Toxicological Methods

Alberta Cases: Unless otherwise indicated, all Alberta cases were subject to testing for ethanol and related volatiles, plus comprehensive drug screening using a panel of ELISA tests and broad-based gas chromatography with mass spectrometry (GC/MS). PMMA and related amphetamines were quantified using GC/MS in selected ion monitoring (SIM) mode, after liquid/liquid extraction and derivatization with pentafluoroacetic anhydride. Matching deuterated internal standards were used for MDMA, methylenedioxyamphetamine (MDA), methamphetamine and amphetamine; MDMA-d5 was used as the internal standard for PMMA and paramethoxyamphetamine (PMA). The lower limit of quantitation for PMMA and all other amphetamines was administratively set at 0.05 mg/L.

BC cases: All cases were tested for ethanol and related volatiles, plus comprehensive drug screening using liquid chromatography with mass spectrometry (LC/MS) and broad based GC/MS. If urine was available, Tox/See (Biorad) was used. PMMA and related amphetamines were quantified using LC/MS/MS (AbSciex 4000 Qtrap) in selected ion monitoring (SIM) mode, after precipitation with acetonitrile without derivatization. Matching deuterated internal standards were used for MDMA, MDA, methamphetamine and amphetamine; amphetamine-d5 was used as the internal standard for PMMA and PMA. The lower limit of quantitation for PMMA and all other amphetamines was administratively set at 0.01 mg/L.

Statistical Analysis

Microsoft Excel, version 14.3.7 (Microsoft Corporation, Redmond, WA USA) was used for data entry and analysis. For the primary research objective, median values for clinical features, toxicological and post-mortem autopsy findings are reported with ranges. The public health response to the PMMA outbreak was coordinated through the Office of the Alberta Health Services Senior Medical Officer of Health and BC's Drug Overdose and Alert Partnership Committee. In BC the media response was coordinated through the Office of Provincial Health Officer, Coroners service and law enforcement. The outreach to party drug using populations was spearheaded by BC Centre for Disease Control (BCCDC).

Results:

Table 1 and Figure 2 summarize the characteristics of the 27 fatalities. The median age was 24 years (range 14-52). Twenty-two (81%) were male, and 12 (44%) had a prior history of illicit drug use. Fifty-six percent of exposures occurred either at home or in small gatherings, while 3 (11%) exposures occurred at venues such as a nightclub. Ten (37%) died pre-hospital, 10 (37%) in the emergency department (ED), and another 7 (26%) following admission to the intensive care unit (ICU). The median time from exposure to hospital presentation was 6 hours (range 1.5-16.5), and from exposure to death was 17 hours (range 5-264). In most cases, there was a delay in seeking medical care from the time a problem was identified by friends or family. The route of

administration was unknown for most cases; those with known routes of administration believed they were ingesting Ecstasy or MDMA powder or pills. There was no evidence of injection drug use.

The median first recorded vital signs were: heart rate 160 BPM, blood pressure 89/43 mmHg, respiratory rate 40 breaths/minute, oxygen saturation 81%, and temperature 39.4 °C. Sixteen of the 17 (94%) cases transported to hospital presented with clinical features consistent with serotonin syndrome, including clonus, agitation, hyperthermia, and hyperreflexia. Three (11%) experienced seizures. In the 17 cases that died in hospital, there were multiple indicators of end-organ dysfunction (Figure 3). One case developed fulminant hepatic failure. Evidence of sodium channel blockade was present in one case whose toxicological analysis was negative for known sodium channel blocking agents. Median recorded laboratory values are highlighted in Table 2. Interventions in the 17 cases that presented to hospital are shown in Table 3. All 3 cases where succinylcholine was administered had serum potassium levels greater than 8 mmol/L.

Table 4 summarizes the toxicological findings of the PMMA-associated fatalities. Additional substances were detected in all cases, the most common being MDMA (n=27), cocaine (n=14), and methamphetamine (n=12). The median antemortem and postmortem whole blood PMMA concentrations are summarized in Table 5. At autopsy, the most common findings were pulmonary edema or congestion in 16 (59%) cases, splenic congestion in 7 (26%) cases, and cerebral edema in 6 (22%) cases. Postmortem findings are summarized in Table 1.

The public health response to PMMA in Alberta and BC involved extensive collaboration amongst law enforcement, health services, EMS, Poison Control Centres, Coroners Services and Office of the Chief Medical Examiner, and Public Health agencies. In Alberta, the Ecstasy Taskforce was created in early 2012, co-chaired by senior public health, addictions and mental health leaders, and the Poison and Drug Information Service (PADIS) medical director. In BC, the BC Drug Overdose and Alert Partnership Committee chaired by the BCCDC facilitated the coordinated response between the various parties.

Through the use of media interviews, print materials, a 'one-stop' PMMA web page, and social media (Facebook and Twitter), information was disseminated to the public, educators, schools, and community agencies in Alberta. In BC, public health and law enforcement actively reached out to schools and university populations to inform students of the recent PMMA deaths and dangers of Ecstasy. The Office of the Provincial Health Officer along with the BC Coroners Services and law enforcement coordinated public announcements and media inquiries.

PADIS, BC ambulance, and the BC Drug and Poison Information Centre developed clinical management guidelines for MDMA and other sympathomimetic drugs of abuse, and the regional health authorities developed alerts for health care professionals.

Discussion:

We describe 27 PMMA-associated fatalities in 2 provinces over an eleven-month period. This represents the largest reported series documenting deaths from exposure to PMMA. PMMA exposure was characterized by multiorgan dysfunction, shock, and serotonin syndrome, followed by cardiovascular collapse and death. Most died in hospital following a delay in presenting to the ED. Severe hyperthermia, hyperkalemia, and hypoglycemia were present in the majority of cases. Notable autopsy findings included pulmonary and cerebral edema. In addition to PMMA, there were multiple synthetic amphetamines present on toxicological analysis in all cases.

The clinical presentation described herein is consistent with previously published studies. The first reported PMMA fatality occurred during 1993 in Spain, followed by 3 fatalities in Denmark, one in Germany, 8 in Taiwan, 24 in Israel and most recently 22 non-fatal and 12 fatal cases in Norway [2-7, 17]. The majority of PMMA-associated fatalities in these studies were also young males. Compared to our cases, more individuals in these previous studies died pre-hospital, and there were fewer co-exposures to synthetic amphetamines on toxicological analyses. The PMMA concentrations in this series are similar to those previously reported.

The effect of PMMA is mediated primarily through the release of serotonin, and to a lesser extent, dopamine, from presynaptic neurons [17]. PMMA is more similar to MDMA than to amphetamine, yet influx into the brain is delayed compared to MDMA, producing later onset of psychological effects [18,19]. It has several active metabolites including PMA and pholedrine [20]. PMMA has a narrow margin of safety, with a 2-4-fold difference between the stimulant-

producing and lethal doses observed in rats [1]. Hyperthermia from PMMA is secondary to both serotonin syndrome and monoamine oxidase inhibition, and toxicity is increased in crowded conditions due to an accelerated rate of temperature change and longer duration of hyperthermia [19]. The delayed onset of desired effects may lead to frequent and early re-dosing, increasing the risk of life-threatening toxicity.

The coordinated response, and sharing of information amongst public health agencies, poison control centers, regional health services, the Office of the Chief Medical Examiner, the BC Coroner's Service, and law enforcement in Alberta and BC helped facilitate the decline of PMMA from both provinces, and arrests of suspected traffickers (Sgt. Mike Bossley, Calgary Police Service 2013). Several learning points arose from this process. In Alberta, it was recognized that there is a gap in understanding of the extent of Ecstasy use in the population. An environmental scan is nearing completion that will inform a research plan to explore and better understand those who use illicit synthetic drugs, especially Ecstasy, and to identify the best communication strategies, messages and meaningful interventions according to evidence-based best practices. In BC, previously established relationships and committees facilitated the public health response, and reinforced the need for such collaborations.

At the time of this writing, there has been one new fatality from exposure to PMMA, following an eight-month period of no reported PMMA cases. The details of this recent fatality are similar to those described in this case series (Walter Martz, BC Coroner's Service 2013). This re-emergence of PMMA highlights the need for ongoing collaboration and public awareness efforts,

with interventions targeted towards recreational drug user groups using now well-established means of communication.

Our study has several limitations. Data were collected retrospectively from medical records at the Office of the Medical Examiner and BC Coroner's Service rather than from hospital records. This resulted in missing data, especially therapies provided. Due to the distribution of fatalities throughout the provinces of Alberta and BC, with a cumulative landmass of 1.56 million km^2, it was not practical to access the medical records from each treating hospital. While sixteen cases had serotonin syndrome, we are unable to comment on the presence of serotonin syndrome in the 10 pronounced dead on scene. Additionally, the presence of multiple synthetic amphetamines in all cases makes it difficult to definitively identify PMMA as the drug responsible for death. However, the important role of PMMA in these fatalities is emphasized by the known toxicity of PMMA, and the large number of deaths occurring in a short time-frame, compared to the small number of MDMA and amphetamine cases during this same period. Furthermore, the concentration of PMMA in our cases is similar to the concentration in previous studies describing PMMA-associated fatalities.

In addition to the 27 fatalities from exposure to PMMA described here, there were also numerous non-fatal cases. Whether there are differences between survivors and fatalities is a subject of future research, and is currently in progress in Alberta. The only study published describing the differences between fatal and non-fatal ingestions concluded that fatalities had much higher concentrations of PMMA, and higher ratios of PMMA to other amphetamines, compared to survivors [2]. Our study focused on the clinical aspects and response to the PMMA outbreak.

Future studies should examine the toxicological features of these cases in more detail. Finally, our study described the public health response to the fatalities, but did not examine the consequences of this response on the recreational drug use patterns of other substances of abuse in Alberta and BC following the outbreak of deaths from PMMA.

In conclusion, this study describes 27 PMMA-associated fatalities over an 11-month period in two western provinces. These fatalities developed features of serotonin syndrome, shock, and multisystem organ failure. In addition to PMMA, multiple synthetic amphetamines were present on postmortem toxicological analysis, emphasizing the lack of predictability in determining contents of Ecstasy pills [21,22]. This outbreak of PMMA-associated fatalities prompted an unprecedented response at the municipal and provincial levels, which resulted in the decline in PMMA exposures in both provinces. A recent PMMA-associated fatality underscores the importance of ongoing collaboration and public awareness efforts.

References

1. Steele TD, Katz JL, Ricaurte GA. Evaluation of the neurotoxicity of N-methyl-1-(4-methoxyphenyl)-2-aminopropane (para-methoxymethamphetamine, PMMA). *Brain Res.* 1992;589:349-52.

2. Vevelstad M, Oiestad EL, Middelkoop G, Hasvold I, Lilleng P, Delaveris GJ, et al. The PMMA epidemic in Norway: Comparison of fatal and non-fatal intoxications. *Forensic Sci Int.* 2012;219:151-7.

3. Lin DL, Liu HC, Yin HL. Recent paramethoxymethamphetamine (PMMA) deaths in Taiwan. *J Anal Toxicol*. 2007;31:109-13.

4. Chen WH, Chui C, Yin HL. The antemortem neurobehavior in fatal paramethoxymethamphetamine usage. *Subst Abus.* 2012;33:366-72.

5. Johansen SS, Hansen AC, Muller IB, Lundemose JB, Franzmann MB. Three fatal cases of PMA and PMMA poisoning in Denmark. *J Anal Toxicol*. 2003;27:253-6.

6. Lurie Y, Gopher A, Lavon O, Almog S, Sulimani L, Bentur Y. Severe paramethoxymethamphetamine (PMMA) and paramethoxyamphetamine (PMA) outbreak in Israel. *Clin Toxicol*. (Phila). 2012;50:39-43.

7. Becker J, Neis P, Rohrich J, Zorntlein S. A fatal paramethoxymethamphetamine intoxication. *Leg Med.* (Tokyo). 2003;5 Suppl 1:S138-41.

8. Refstad S. Paramethoxyamphetamine (PMA) poisoning; a 'party drug' with lethal effects. *Acta Anaesthesiol Scand.* 2003;47:1298-9.

9. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The hunter serotonin toxicity criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96:635-42.

10. Dykhuizen RS, Brunt PW, Atkinson P, Simpson JG, Smith CC. Ecstasy induced hepatitis mimicking viral hepatitis. *Gut.* 1995;36:939-41.

11. Fidler H, Dhillon A, Gertner D, Burroughs A. Chronic ecstasy (3,4-methylenedioxymetamphetamine) abuse: A recurrent and unpredictable cause of severe acute hepatitis. *J Hepatol.* 1996;25:563-6.

12. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney inter*. Suppl. 2012;2:1-138.

13. Cervellin G, Comelli I, Lippi G. Rhabdomyolysis: Historical background, clinical, diagnostic and therapeutic features. *Clin Chem Lab Med*. 2010;48:749-56.

14. Nelson LS, Lewin NA. Chapter 63. Antidysrhythmics. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, editors. *Goldfrank's Toxicologic Emergencies.* 9th ed. New York: McGraw-Hill; 2011. p. 925-935.

15. Liebelt EL. Chapter 73: Cyclic antidepressants. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, editors. *Goldfrank's Toxicologic Emergencies.* 9th ed. New York: McGraw-Hill; 2011.p. 1049-1059.

16. Prosser JM HR. Chapter 76. Cocaine. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, editors. *Goldfrank's Toxicologic Emergencies.* 9th ed. New York: McGraw-Hill; 2011. p. 1091-1102.

17. Lora-Tamayo C, Tena T, Rodriguez A. Amphetamine derivative related deaths. *Forensic Sci Int.* 1997;85:149-57.

18. Glennon RA, Young R, Dukat M, Cheng Y. Initial characterization of PMMA as a discriminative stimulus. *Pharmacol Biochem Behav.* 1997;57:151-8.

19. Palenicek T, Balikova M, Rohanova M, Novak T, Horacek J, Fujakova M, et al. Behavioral, hyperthermic and pharmacokinetic profile of para-methoxymethamphetamine (PMMA) in rats. *Pharmacol Biochem Behav.* 2011;98:130-9.

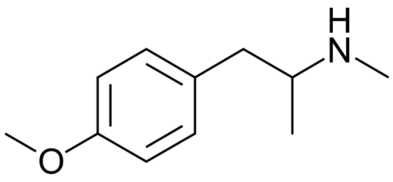
20. Staack RF, Fehn J, Maurer HH. New designer drug p-methoxymethamphetamine: Studies on its metabolism and toxicological detection in urine using gas chromatography-mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2003;789:27-41

21. Morefield KM, Keane M, Felgate P, White JM, Irvine RJ. Pill content, dose and resulting plasma concentrations of 3,4-methylenedioxymethamphetamine (MDMA) in recreational "ecstasy" users. *Addiction.* 2011;106:1293-1300.

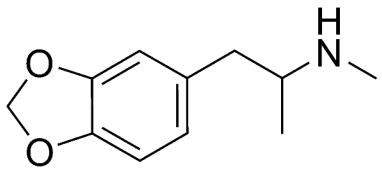
22. Wood DM, Stribley V, Dargan PI, DAvies S, Holt DW, Ramsey J. Variability in the 3,4-methylenedioxymethamphetamine content of "ecstasy" tablets in the UK. *Emerg Med J.* 2011;28:764-765.

23. The Royal College of Physicians and Surgeons of Canada. Clinical Laboratory Values - Normal Values. http://www.royalcollege.ca/portal/page/portal/rc/common/documents/exams/normal_values_e.pdf (Accessed September 6, 2013).

Figure 1: The chemical structures of paramethoxymethamphetamine and methylenedioxymethamphetamine



(PMMA)
Paramethoxymethamphetamine



(MDMA)
Methylenedioxymethamphetamine

Table 1: PMMA associated fatalities: Summary of cases, June 2011 to April 2012 (n=27)

Case	Location & circumstances around presentation and death	Drug(s) believed to have been consumed	Post mortem findings
1	Took drugs at home, became unwell, friend called 911. Died in the ER.	Ecstasy	Pulmonary edema, coronary artery disease
2	Took Ecstasy alone, found 9 hours later. Died in the ER after unsuccessful resuscitation.	Ecstasy	Rapid rigor mortis
3	Took pills alone, felt unwell and self-presented to the ER. Died in the ICU	Ecstasy	Cerebral edema, pulmonary edema.
4	Took Ecstasy with friends, became unresponsive. Transported to ER in private vehicle. Died in the ICU.	Ecstasy	Cerebral edema, ascites, pleural effusion
5	At house party after taking drugs, became unresponsive, transported to hospital via EMS. Died in the ICU.	Ecstasy	Rhabdomyolysis
6	Found unresponsive at house party. Transported to hospital via EMS, suffered a cardiac arrest, died in the ICU.	Ecstasy Alcohol	No autopsy
7	At house party, found unresponsive after last seen 1.5 hours earlier. Transported to hospital via EMS, suffered a cardiac arrest, and died in the ICU.	Ecstasy	No autopsy
8	Found deceased in bed at home	Unknown	Trivial soft tissue abrasions
9	At house party with friends, became unwell, arrested post intubation with EMS. Died in the ICU.	8 tabs of Ecstasy	Lung congestion, patchy pneumonia
10	Watching live performance became unwell, cardiac arrest with EMS. Unsuccessful resuscitation, died in the ER.	1-2 g of MDMA Cocaine	Cardiomegaly, spleen congestion
11	At nightclub, became unwell. Transported to ER in private vehicle. Died in the ICU.	6 tablets MDMA hallucinogenic mushrooms LSD	No autopsy
12	Found deceased at home	Unknown	Pulmonary congestion, cerebral edema, mottled myocardium, cardiomegaly
13	Friend noticed patient acting abnormally, transported to hospital in private vehicle following seizure. Died in ER	2 snorts of MDMA/Ecstasy powder	Congestion of heart, lungs, liver
14	Took drugs at house party. Was found unconscious outside at a nearby property. Died in the ER after unsuccessful resuscitation.	Unknown amount of white powder believed to be Ecstasy	Congestion of heart, lungs, liver, spleen, cerebral edema
15	At a bar with friends. That night at home had a witnessed seizure, followed by cardiac arrest. Pronounced dead upon EMS arrival.	Unknown	Pulmonary edema, heart congestion, liver congestion, spleen congestion, cerebral edema
16	Took 2 doses of Ecstasy at bar, began acting strange upon return home with friends. Seized en route to hospital with EMS, cardiac arrest in ER. Died in the ER after unsuccessful resuscitation.	2 pills Ecstasy	Pulmonary edema, kidney and spleen congestion, interstitial hemorrhage in heart.
17	At home with friends drinking and taking drugs. Found dead the next morning	Cocaine MDMA Alcohol	Fatty liver. Unremarkable post mortem

18	At a house party, felt unwell, called 911. Shortly after EMS arrival had cardiac arrest. Died in ER after unsuccessful resuscitation.	Unknown white powder snorted	Rib and sternal fractures, pulmonary edema, advanced cirrhosis, enlarged spleen
19	Took MDMA powder the night before. Felt unwell, was found unresponsive the next afternoon. Pronounced dead with EMS.	1.5 gram MDMA rolled in paper and ingested	Cerebral and pulmonary edema
20	Took drugs throughout the night at home, suffered a cardiac arrest. Died in the ER after unsuccessful resuscitation.	MDMA Cocaine	Pulmonary congestion, cardiomegaly, nephrosclerosis
21	At party the night before with friends. Was found dead at home the next day.	Ecstasy Cocaine	Edema and congestion of lungs, liver, spleen, kidneys
22	Last seen 3 days prior. Police / EMS attended, dead on scene.	Unknown	Pulmonary congestion
23	Partying with friends the night before. No history of drug use. Found dead the next day.	Unknown	Pulmonary edema
24	Last seen 3 days prior. Police / EMS attended, dead on scene.	Cocaine Alcohol	Congestion of lung, liver, spleen, kidneys
25	At house party, took multiple doses of MDMA through the night by snorting and ingestion. Became confused and unresponsive, friends called 911. Died in the ER after unsuccessful resuscitation.	0.5g MDMA	Pulmonary congestion
26	At party with friends. EMS called, arrested post intubation. Resuscitated in the ER, died in the ICU.	7 tabs MDMA	No autopsy
27	At concert took drugs and alcohol. Pronounced dead at home with EMS.	MDMD Cocaine Alcohol	No autopsy

Figure 2: Age of PMMA associated fatalities at time of exposure (n=27)

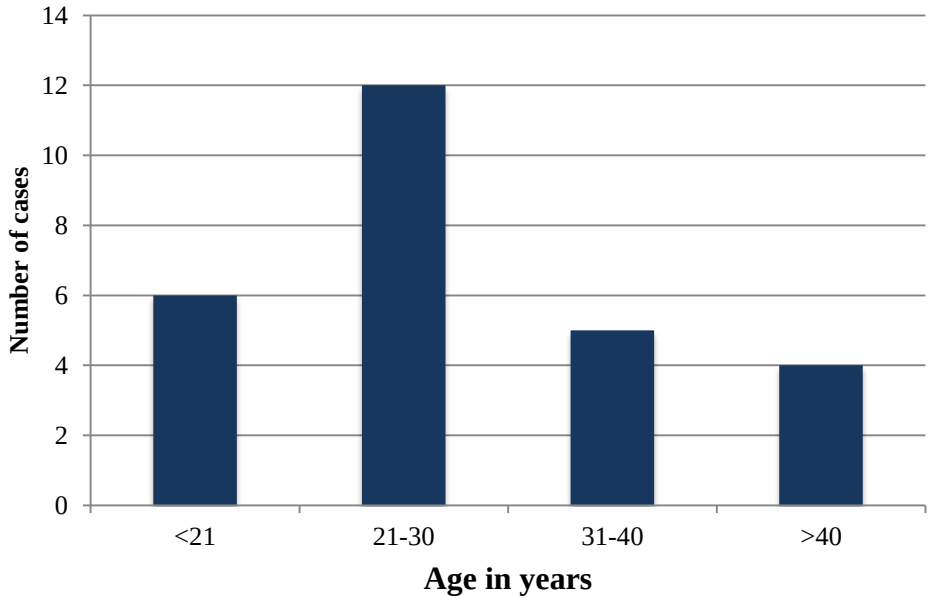
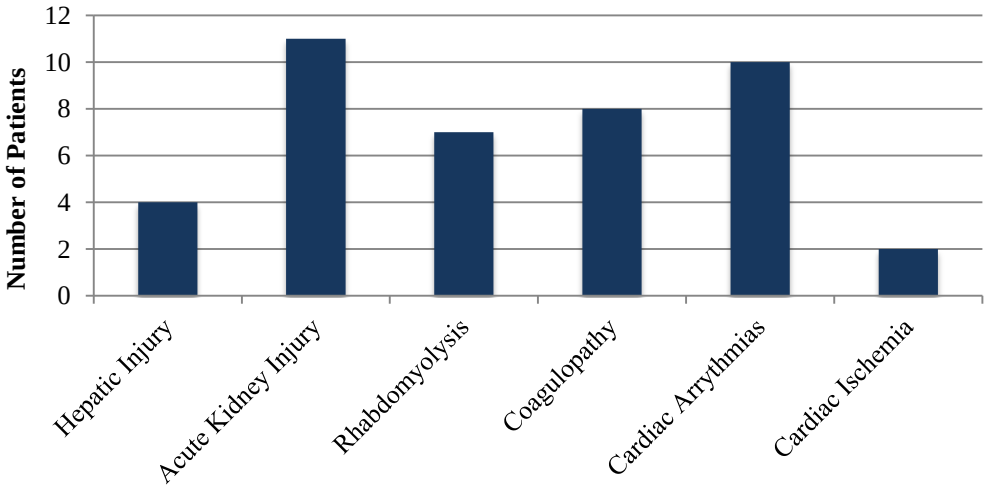


Figure 3: Antemortem end organ dysfunction based on clinical findings and investigations (n=13/17 treated in the ED or ICU)*



*Missing data on 4 cases: pronounced dead shortly after arrival in ED, no antemortem investigations performed.

Table 2: Antemortem laboratory investigations (n=13/17 cases treated in the ED or ICU*)

Laboratory Value	Median value	Normal Values[Y]
Peak Potassium concentration	7.0 mmol/L	(3.5 – 5.1) mmol/L
Peak creatinine	214 mmol/L	(50-110) mmol/L
Peak AST	2944 IU/L	(7-40) IU/L
Peak creatinine kinase (CK)	8200 IU/L	(38-215) IU/L
Lowest recorded glucose	1.9 mmol/L	(3.9-6.1) mmol/L

* Missing data on 4 cases: pronounced dead shortly after arrival in ED, no investigations obtained pre-mortem.
[Y]Normal values obtained from the Royal College of Physicians and Surgeons of Canada [23].

Table 3: Therapies provided by EMS, the ED, or ICU (n=9/17 cases treated in the ED or ICU)*

Therapy	Number of Patients
Intubation	9
Paralysis	6
Sedation	5
Cooling Methods	
Ice packs	5
Cooled intravenous fluid	2
Cyproheptadine	1
Cooling blanket	1
Cooling catheter	1

* Missing data for 8 cases

Table 4: Toxicological findings of PMMA associated fatalities (n=27)

Case	Specimen Type	PMMA (mg/L)	PMA (mg/L)	MDMA (mg/L)	MDA (mg/L)	MAMP (mg/L)	AMP (mg/L)	Cocaine (mg/L)	BE (mg/L)	Other findings[Ŧ]
1	Postmortem blood NOS	1.6	0.17	2.3	0.12	0.84	0.024	ND	ND	Lidocaine
2	Postmortem blood NOS	NSQ	NSQ	3.9	0.12	ND	ND	0.38	3.9	PMMA vitreous 0.69 mg/L; MDMA vitreous 1.4 mg/L; cannabinoids
3	Antemortem blood NOS	1.2	0.093	0.99	0.036	ND	ND	ND	0.32	
4	Antemortem blood NOS	1.6	0.098	0.52	0.021	ND	ND	ND	ND	Lorazepam
5	Postmortem blood NOS	1.8	NDT*	0.6	ND	ND	ND	ND	ND	Morphine, lidocaine, cannabinoids
6	Antemortem blood NOS	0.11	0.023	0.14	0.015	ND	ND	ND	ND	Midazolam, temazepam, rocuronium metabolite, acetaminophen
7[*]	Antemortem blood NOS	URP	URP	0.32	ND	ND	ND	ND	ND	
8	Postmortem IVC blood	3.33	0.42	3.09	0.17	2.28	0.07	ND	ND	Dextromethorphan 0.66 mg/L, acetaminophen 18.2 mg/L, ketamine, oxycodone
9	Antemortem serum	0.94	0.07	0.09	trace	0.3	trace	ND	ND	
	Postmortem IVC blood	0.14	trace	trace	trace	0.11	trace	ND	ND	
10	Antemortem blood	2.28	0.1	0.31	trace	0.75	trace	ND	0.19	
	Postmortem femoral blood	4.41	0.25	0.6	trace	1.47	trace	trace	0.26	
11	Antemortem blood	0.44	0.08	trace	trace	0.18	trace	TNP	TNP	Drug screen not performed - limited specimen
12	Postmortem IVC blood	3.74	0.11	1.64	trace	ND	ND	ND	ND	Ethanol 30 mg/100 mL
13	Antemortem blood	1.25	0.07	0.11	trace	0.35	trace	ND	0.11	
	Postmortem IVC blood	2.67	0.18	0.26	trace	0.8	trace	ND	0.17	
14	Postmortem IVC blood	2.7	0.12	0.29	trace	0.86	trace	ND	ND	
	Postmortem central blood	4.35	0.18	0.43	trace	1.28	0.05	ND	ND	
15	Postmortem IVC blood	2.97	0.08	0.32	trace	ND	ND	0.04	0.3	Acetaminophen 10.6 mg/L, codeine 0.07 mg/L, atropine
16	Postmortem IVC blood	1.67	0.15	0.27	trace	0.63	trace	trace	0.2	Oxycodone (trace), delta-9-THC 2.3 ng/mL, carboxy-THC 11.8 ng/mL
17	Postmortem IVC blood	4.88	0.22	1.12	0.04	1.78	0.06	0.08	0.84	Levamisole, phenacetin
18	Postmortem femoral blood	3.56	0.33	1.7	0.12	trace	ND	ND	0.67	Benzylpiperazine
19	Postmortem central blood	0.65	0.06	2.58	0.06	ND	ND	ND	ND	Ethanol 10 mg/100 ml.
20	Postmortem femoral blood	15.7	0.75	0.65	trace	ND	ND	ND	ND	Diphenhydramine
21	Postmortem femoral blood	6.19	0.51	0.26	trace	ND	ND	ND	ND	Dextromethorphan
22	Postmortem iliac blood	5.36	1.08	0.6	0.05	1.45	0.1	trace	0.11	Oxycodone 2.01 mg/L, ibuprofen
23	Postmortem femoral blood	6.34	0.23	0.34	trace	ND	ND	trace	1.16	Benzylpiperazine 1.65 mg/L, TFMPP 0.47 mg/L, ketamine, levamisole

24	Postmortem femoral blood	3.58	0.23	0.16	trace	ND	ND	ND	ND	Benzylpiperazine 1.00 mg/L, TFMPP 0.15 mg/L
25	Antemortem blood	1.6	0.1	0.14	trace	0.47	trace	trace	1.09	Ketamine 0.71 mg/L, midazolam
26	Antemortem blood	3.27	0.09	0.16	trace	ND	ND	trace	0.53	
	Postmortem iliac blood	3.83	0.14	0.19	trace	ND	ND	trace	0.55	
27	Postmortem iliac blood	2.17	0.08	1	trace	ND	ND	0.05	0.46	Ethanol 10 mg/100 mlL naproxen

PMA = paramethoxyamphetamine, MDA = methylenedioxyamphetamine, MAMP = methamphetamine, AMP = amphetamine, BE = benzoylecgonine; NOS = not otherwise specified, ND = none detected (below level of detection), NSQ = not sufficient quantities, trace = detected, but below level of quantitation, TNP = test not performed

[Ŧ]Unless otherwise specified, drugs were not quantitated

[*]URP = urine positive for PMMA and PMA; insufficient antemortem blood was available to permit quantitation of these drugs

Table 5: Whole blood concentrations of PMMA in antemortem and postmortem whole blood (n=25/27)[*]

Blood sample	Median Concentration (mg/L)	Range (mg/L)
Antemortem blood	1.43	0.11 – 3.27
Postmortem IVC[Y] and central blood	2.84	0.14 – 4.88
Postmortem femoral and iliac blood	4.41	2.17 – 15.7

[*]Case 2 not sufficient quantity of sample for quantitation; Case 7 antemortem urine positive, no post mortem performed

[Y]IVC: Inferior vena cava