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LESSONS TO BE LEARNED FROM TOXICOLOGICAL ANALYSES IN INTOXICATED PATIENTS AND SEIZED MATERIALS AT AN ELECTRONIC MUSIC DANCE FESTIVAL

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HIGHLIGHTS

- Our data confirm that at EDM events ethanol and MDMA are still the party drugs causing most health hazards and that NPS only play a minor role. According to the above-mentioned line of thoughts, we recommend the consistent analysis of all drugs seized during an EDM event; however,

for blood samples only those obtained from the most severely intoxicated patients should be toxicologically assessed. This approach on the one hand limits the costs, but on the other hand provides the most relevant information on the locally available substances (as illustrated by the detection for the first time of 4-CMA). An immediate analytical elaboration does not seem to be worth the cost and the efforts as our clinical data confirm the efficacy of a symptom-driven therapeutic strategy. As EDM party goers are only a subgroup of NPS users, the monitoring of the drug market should not be limited to EDM events.

ABSTRACT

Medical problems related to illicit drug use are frequently encountered at electronic dance music (EDM) events. In this prospective study, the medical problems and toxicological analyses on intoxicated persons and seized materials are described jointly. The aim of this study is to find out to what extent these efforts may assist in developing prevention strategies and organising on-site care at EDM events.

The most frequently encountered clinical presentation in the 121 included patients was: agitation/aggression (26%), drunkenness (25%), depressed level of consciousness (24%) and hallucinations (9%). Only five patients were transported by ambulance to a hospital.

In 100 of the 121 included patients (83%) an ethanolemia of at least 0.50 g/L was measured (with ethanol as the only drug found in 47 cases). 3,4-methylenedioxymethamphetamine (MDMA) was detected in 54% of the blood samples, cocaine in 11%, gamma-hydroxybutyric acid (GHB) in 11%, amphetamine in 7%, ketamine in 6% and a new psychoactive substance (NPS) in 4%. Except for 8 MDMA-users poly drug use was found in all these cases.

The 178 seized samples most frequently contained MDMA (31%), cannabis (28%) or no active substance (15%). In 11 samples (6%) an NPS was detected. Of particular interest was a tablet containing 4-chloromethamphetamine (a previously unknown neurotoxic NPS), 4-chloroamphetamine, para-methoxyamphetamine, para-methoxymethamphetamine and ethylone.

Our data show that at EDM events ethanol and MDMA are still the party drugs causing most health hazards and that NPS only play a minor role. Regarding the toxicological efforts, we recommend to analyse all seized materials from an EDM event, but only blood samples from the most severely intoxicated patients.

KEYWORDS

ethanol; party drugs; new psychoactive substances; electronic dance music event

INTRODUCTION

At electronic dance music (EDM) events serious medical problems and occasionally death are caused by party drugs, especially (a mix of) ethanol, 3,4-methylenedioxymethamphetamine (MDMA), cocaine, (meth)amphetamine, gamma-hydroxybutyric acid (GHB) and ketamine (1–5). In addition, partygoers put themselves at risk by increasingly using new psychoactive substances (NPS), also known as "research chemicals" or "designer drugs" that are designed to evade current legislation (3,6–8). Since most of these substances have never been studied formally and (toxic) effects in humans are mostly unknown, NPS constitute a real danger to public health, especially with fentanyl derivatives appearing on the market (9–12). By the end of December 2017 more than 670 unique substances were routinely monitored by the Early Warning System of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), with the presence of around 400 of these being reported each year (9,12). Due to the lack of analytical reference standards, identification of these substances in clinical samples poses a significant challenge in clinical and forensic toxicology (9,13,14).

This issue on identification is further being complicated by mislabelling, drug mixtures, uncertainties about dosage, resemblance of pills with different content and contamination with dangerous substances. For example, para-methoxymethamphetamine (PMMA) and 4-methyl-amphetamine (4-MA), two contaminants that were found regularly in tablets presumed to contain MDMA and in amphetamine powders, were responsible for several deaths and the

average MDMA dosage present in tablets increased drastically during the last decade (5,8,14–17).

To minimize the drug-related health hazards at EDM events, the on-site deployment of medical teams is mandatory, and law enforcement personnel posted at entrances and on event premises are essential to control and limit the availability of (illegal) party drugs (18–20). In addition, effective legislative actions regarding the continuously changing flow of NPS are needed, but can only be taken with updated information (21). In the framework of the Belgian Early Warning System Drugs, the Belgian drug monitoring authority, a prospective research project was initiated during the 2015 edition of a four days outdoor EDM event with an international audience, combining several approaches: collection and analysis of drugs seized by law enforcement at the festival; blood and urine analysis for a predefined subgroup of patients entering the medical stations at the event; and pooled urine analysis collected from communal urinals during the event (22). The results of the pooled urine analysis are available in literature (23).

In this manuscript we are the first to jointly describe the medical problems, the results of the toxicological analyses in intoxicated persons, combined with the content of seized materials. The aim of this study is to find out 1) if, and to what extent, NPS are responsible for intoxications in recreational party settings and 2) to what extent these efforts may assist (medical) caregivers, police forces and political authorities in developing prevention strategies and organising on-site

care at EDM events. The study results will also provide more insight regarding the substances responsible for the highest number of admissions to the emergency medical services.

METHODS

1. On-site medical support

Briefly, the Flemish Cross provided on-site medical care using first aid-responders, medics, emergency nurses and emergency physicians. Using four medical stations, all medical problems occurring on the festival grounds of 0.75 square kilometre (including a campsite for 30,000 visitors) were evaluated. Because of the availability of skilled personnel with the requisite medical equipment, most intoxicated patients could be stabilized and treated on-site. If deemed necessary, a patient was transferred with a stand-by ambulance to one of two nearby participating hospitals. Due to legislative issues in Belgium there was no on-site drug checking programme; however, the harm reduction organisation Safe ‘n Sound, part of the Flemish anti-addiction organisation VAD, was present during the festival, and distributed information on the Belgian drug situation (e.g. the presence of highly dosed MDMA tablets).

2. Patient data collection

All apparently intoxicated patients judged by the attending physician to be in need of an intravenous line (for example for the administration of

benzodiazepines or fluids) were included in the toxicology study (irrespective of the patient's age and the clinical presentation). For this subgroup, medical students prospectively recorded the clinical findings throughout the patient's stay in the medical station. Information about the nature of the ingested substances was gathered from the patient, accompanying persons and/or a body search. According to the protocol, blood samples for toxicological analysis were collected on the occasion of the vein cannulation. In case of micturition in the medical station, urine samples were also preserved.

The study with an opting out design was approved by the ethical committees of the XXX University and of the two participating hospitals (XXX and XXX). The registration number is B670201524797. The option out design implied that blood and urine samples were obtained without consent. All included patients were given an information letter (e.g. put in a plastic bag together with a cell phone and a wallet for a comatose patient transferred to a hospital). In this letter the included attendants were invited to contact the principal investigator in order to obtain more information on the study and/or to express their will to be excluded from the study.

3. Toxicological laboratory analysis

For the toxicology study, all blood and urine samples were subjected to a standard systematic toxicological screening. Ethanol concentration was determined using headspace gas chromatography coupled to flame ionization

detection. On the blood samples, general screening was performed by a liquid chromatographic method coupled to Diode Array Detection (LC-DAD) and a gas chromatographic method coupled to mass spectrometric detection (GC-MS). In brief, for the LC-DAD method 350 µL of blood were extracted by a liquid-liquid extraction with hexanes:ethyl acetate (7:3, v/v) at pH 9.5. UV spectra were recorded from 200 to 380 nm and matched against an in-house library containing more than 650 toxicological relevant entries. For the GC-MS method, 500 µL blood were extracted on a mixed mode (C8 + strong cation exchanger) SPE cartridge. After evaporation, the extract was analyzed after trifluoroacetylation in full scan (50-650 amu) and matched against the Maurer/Pfleger/Weber 2011 library and the Designer Drugs 2015 library. For urine samples, 5 mL of urine was extracted after deconjugation by a liquid-liquid extraction (chloroform:isopropanol, 9:1, v/v and dichloromethane). This extract was analyzed non-derivatized, acetylated and trifluoroacetylated by GC-MS against the above mentioned libraries.

Targeted quantitative analysis for amphetamine, MDMA, cocaine and metabolites and opiates was performed by ISO17025 accredited GC-MS/MS methods. Other drugs (e.g. ketamine, PMMA, methamphetamine) were quantified by targeted GC-MS or LC-DAD methods.

To limit costs targeted analyses for cannabinoids were not carried out. The quantitative analysis of GHB was only done in 44 cases upon request of a panel of 7 caregivers with a special interest in recreational drugs, based on all

available clinical data and the results of the above standard toxicological screening. Similarly, an additional UHPLC-Q-ToF analysis with a broad in-house developed library containing more than 2000 toxicologically relevant entries was performed in 20 cases.

4. Collection of and analyses on the seized materials

For the collection of drug samples seized by law enforcement, a cooperation with the local justice department and law enforcement was initiated, also including agreements with Belgian federal police services. At the festival entrance a police barrier was installed that permitted the searching of several people simultaneously for the presence of drugs, using specially trained 'silent' drug sniffing dogs. When drugs were found on a person, the drug samples were labelled and numbered and the searched person was introduced to the prosecutor, where his entrance bracelet was cut and admission to the event was denied, in addition to potential judiciary measures. In cases where multiple ecstasy tablets were seized from the same person, one tablet was included for each participating laboratory. Laboratory analysis using state of the art analytical techniques including GC-MS and LC-DAD were used to determine the identity and concentration of the seized drug samples. Analyses were performed by two laboratories: the Antwerp Toxicological Centre (prof. XXX) and the Medicines Laboratory at Sciensano, Brussels (dr. XXX).

Not all tablets containing NPS could be quantified, in general due to a lack of readily available reference samples. With regard to NPS, quantification was only performed for the substances 4-fluoroamphetamine and ketamine. Regarding the classic illicit drugs, quantification data are available for the substances MDMA, amphetamine and cocaine, in addition to their common contaminants and/or cutting agents caffeine, acetaminophen, phenacetine and lidocaine. Due to the presence of only trace amounts and the absence of readily obtainable reference standards, quantification was not performed for the tablet containing 4-chloromethamphetamine (4-CMA), 4-chloroamphetamine (4-CA) and ethylone.

RESULTS

This four days' EDM event was attended by 180,000 people with 30,000 staying on the campsite. Blood samples were collected from 125 patients. Six patients responded to the information letter, but none of them expressed a will to be excluded. Four patients were subsequently excluded because of negative toxicology; these cases presented with syncope, abdominal pain, atrial fibrillation and shivering related to an infectious disease.

The main clinical presentation upon arrival in the medical station in the 121 included patients was: agitation/aggression (n=32; 26%), drunkenness (n=30; 25%), depressed level of consciousness (n=29; 24%), hallucinations (n=11; 9%), convulsions (n=6; 5%), chest pain and/or palpitations (n=6; 5%), abdominal pain with(out) vomiting (n= 4: 3%) and syncope (n=3; 3%). Only five patients were

judged to be in need of transportation by ambulance to a hospital; endotracheal intubation was performed in one of them. Hypoglycaemia (44 mg/dL) was treated in a diabetic patient with an ethanolemia of 1.36 g/L. Hyperthermia (40.7°C) was found in one case. All patients made a full recovery.

Toxicology on blood revealed an ethanolemia of at least 0.50 g/L in 100 of the 121 included patients (83%). In 47 of these patients, ethanol was the only drug found. An ethanolemia of more than 3.00 g/L was found in 13 patients, including a case with 4.53 g/L and two patients who ingested a second drug (both MDMA). The results from further toxicological analyses are shown in Table 1. Attention should be drawn on poly-drug use; if illicit drugs were used, only 8 patients restricted themselves to MDMA.

In Table 2 details are given on the clinical presentation and the toxicological findings in the most severely intoxicated patients. As to be expected from Table 1, poly-drug use was found in 13 of these 14 patients.

A total of 178 samples was collected by law enforcement and included in the study protocol. The nature of the samples was: 75 tablets and capsules (42%), 48 powders and crystals (27%), 4 blotters (2%), 2 liquid substances (1%) and 49 samples with herbal cannabis or hash (28%).

The identity of the psychoactive substances found in tablets/capsules and powders/crystals can be found in Figure 1. Of particular interest was a tablet containing 4-CMA, 4-CA, para-methoxyamphetamine (PMA), PMMA and ethylone (all in trace amounts). The blotters were impregnated with lysergic acid

diethylamide (LSD; n=3) or 2,5-dimethoxy-4-chloroamphetamine (DOC; n=1). Both liquid samples contained GHB. Herbal products assumed to be herbal cannabis and hash were not analyzed due to prohibitive volume and costs involved. NPS were found in 10 samples: 4-fluoro-amphetamine (n=3), 4-bromo-2,5-dimethoxyphenethylamine (2C-B; n=2), alpha-pyrrolidinopentiophenone (n=2), mephedrone (n=1), 4-CMA and ethylone (n=1) and DOC (n=1).

Quantification of 43 MDMA tablets revealed that 18 (42%) contained over 175 mg MDMA base, and 10 (23%) over 200 mg. The highest dosage was 241 mg.

DISCUSSION

Main findings in this study

Our findings among intoxicated patients confirm that ethanol and MDMA play the dominant role and that poly-drug use (also including cocaine, amphetamine, GHB and ketamine) is the general rule in the most severe cases at EDM events (5,24). Concerning NPS, we found only a few cases; all were characterized by poly-drug use with NPS not judged to be the predominant factor; no intoxications occurred that were solely caused by consumption of NPS. The seized substances were, not surprisingly, mainly MDMA, cocaine and amphetamine, but also a high percentage of tablets without any active compound were found. Only a few NPS samples were seized. One tablet had a very

uncommon content, i.e. the combination of 4-CMA (a previously unknown NPS with neurotoxic properties), 4-CA, PMA, PMMA and ethylone (all in trace amounts).

The comparison between the findings in patients and seized materials suggested that NPS tend to be underrepresented in the intoxicated patients and that some NPS were only detected in the seized materials, while other NPS were only observed in clinical samples. These observations indicate that toxicological analyses are preferentially not restricted to intoxicated patients or seized materials. Importantly, the results of the pooled urine study confirm that the use of NPS in this particular EDM event was very limited in comparison to classic illicit drugs such as MDMA and cocaine (23).

Limitations of the study

Before discussing the implications of our data, some methodological limitations of this study should be emphasized. First, the patients and seized materials studied were subject to selection bias. Indeed, there were no strict criteria to bring a patient to the on-site medical station and to insert an intravenous line (i.e. the starting point for the inclusion). This methodological problem is insolvable as decisions were often to be taken without sufficient information and/or by less experienced care givers under time pressure. This (almost inevitable) risk of selection bias for clinical cases is illustrated by the four patients initially included but subsequently excluded as toxicology was negative.

Similarly, it is impossible to know to what extent the seized materials are representative for the illicit drugs sold and consumed on the festival. A second limitation concerns missing cases: patients may have been brought directly to a hospital and seized materials may not be sent to one of the two designated laboratories. The latter issue is illustrated by eight different tablets (including one containing 98 mg 4-CMA) analyzed by a laboratory not participating in the study (25). Third, little information was available on the consumed substances (e.g. timing of intake, way of purchase, information known to the consumer) and the clinical events before the admission in the on-site medical station for many patients. Fourth, a toxicological screening can never give a 100% certainty about illicit drug use since new molecules are permanently introduced on the drug market and many of these substances are active at very low concentrations and/or not in UV or mass spectral libraries (9, 10, 12-14). Fifth, for financial reasons, we were only able to search for GHB and NPS in cases with a high clinical index of suspicion. Sixth, we have no idea of additional effects of cannabinoids.

What are the implications of this study?

To the best of our knowledge, we are the first to report combined clinical data on intoxicated patients and extended toxicology in blood samples and seized materials collected at a large EDM event. At first glance, there are many

potential stakeholders for this type of research: medical care givers, police forces, organisers of EDM events, recreational (party) drug users and their peers, organisations for on-site harm reduction initiatives (with or without a concomitant drug checking programme), toxicologists and political authorities (2,7,9,12,13,21,26-29). However, the time needed to thoroughly analyse the seized materials and samples from severely intoxicated patients is a limiting factor, hampering immediate (clinical) action (29). Furthermore, data from one EDM event can only to a limited extent be extrapolated to other events because of the very fast evolving drug market and the different drug consumption habits according to the festival type (e.g. EDM festivals versus rock festivals).

In addition to these restrictions, it should be stressed that in all of the 121 intoxicated patients the usual symptom-driven treatment strategy was adequate, suggesting that the on-site care givers do not need full knowledge of all party drugs available on the festival grounds and that extensive toxicological analysis could be deemed unnecessary, specifically in an emergency medicine context. This comes as no surprise as there are no antidotes for the known party drugs (30). From the perspective of the law enforcement personnel (and probably also the event organisers), this information neither makes a big difference as they aim to limit all drug-related problems (irrespective of the chemical structure). For drug users and harm reduction organisations, information on the presence of a particular NPS, highly dosed tablets or a batch of contaminated powders could

be of interest, especially when dealing with extremely dangerous substances such as PMA and PMMA (10,14-17,25). However, wide dissemination of important toxicological findings among the attendants does not necessarily imply that the EDM event becomes safer. Indeed, warnings about dangerous substances may create a false sense of safety regarding pills and powders not mentioned in these on-site alerts. Furthermore, as indicated by their poly-drug use (documented in Table 2), there is a subgroup of party goers with high risk behaviour. These people are probably hard to reach by harm reduction messages (7–9,29). One might even be afraid that some may be attracted by the risks mentioned in warnings to the public. As our study was not designed to find out if pill testing/drug checking was useful at this particular event, no clear conclusions on that point can be obtained. Our main finding that the majority of detected substances were ethanol and MDMA, however, may suggest that an on-site pill testing/drug checking programme would not have impacted much on the welfare of users. For toxicologists especially the seized materials are of importance, as this is the easiest way to detect a new NPS and to develop adequate testing methods in blood and urine (26). For political decision makers scrutinized data from a particular event are obviously useful. However, they also need surveys on drug use, a comprehensive programme for tracking down and analysing suspicious materials, and a nation-wide network of dedicated clinicians, toxicologists and coroners collecting clinical and toxicological data. Via these monitoring systems, dangerous trends may be detected relatively early

(31). This issue is illustrated by the identification of 4-CMA in two tablets from the EDM event studied in this manuscript (i.e. one tablet with trace amounts of 5 active components included in this study and one tablet only containing 98 mg 4-CMA erroneously sent to a laboratory not participating in this study). Upon detection, a literature review was performed revealing that 4-CMA acts like an antidepressant rather than a central stimulant, is a potent and long-lasting depleter of brain serotonin and may cause loss of serotonin neurons. Subsequently, tablets with 4–CMA were also found in Romania, Austria and Croatia. Luckily (and for unclear reasons), this substance together with its potentially devastating effect on public health, seems to have disappeared from the market from spring 2016 onwards (25).

CONCLUSION

Our data confirm that at EDM events ethanol and MDMA are still the party drugs causing most health hazards and that NPS only play a minor role. According to the above-mentioned line of thoughts, we recommend the consistent analysis of all drugs seized during an EDM event; however, for blood samples only those obtained from the most severely intoxicated patients should be toxicologically assessed. This approach on the one hand limits the costs, but on the other hand provides the most relevant information on the locally available substances (as illustrated by the detection for the first time of 4-CMA). An

immediate analytical elaboration does not seem to be worth the cost and the efforts as our clinical data confirm the efficacy of a symptom-driven therapeutic strategy. As EDM party goers are only a subgroup of NPS users, the monitoring of the drug market should not be limited to EDM events.

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Figure 1. Composition of seized tablets and capsules (n=75) and powders and crystals (n=48).

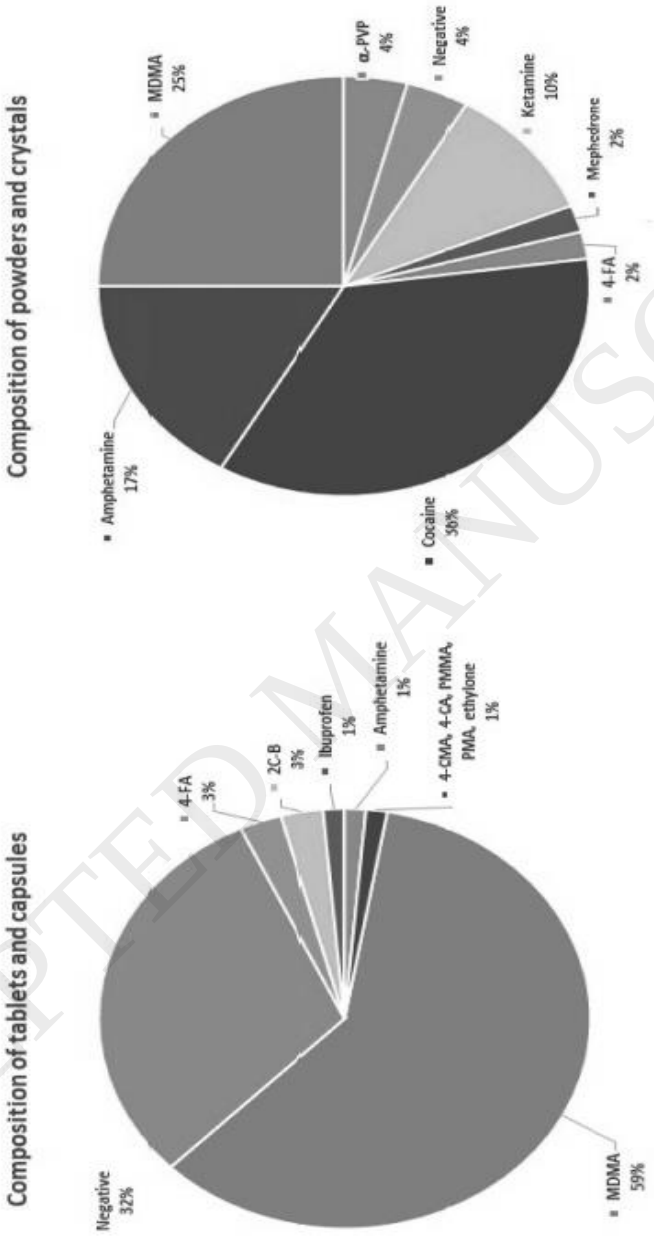

Table 1

Drugs detected in the blood samples of the 121 included patients

	Number (%)	Poly drug use (%)
Ethanol (at least 0.50 g/L)	100 (83%)	53 (53%)
MDMA[1] (LLOQ: 5 ng/mL)	65 (54%)	57 (88%)
Amphetamine[1] (LLOQ: 5 ng/mL)	8 (7%)	8 (100%)
Meth-amphetamine[1] (LLOQ: 5 ng/mL)	2 (2%)	2 (100%)
PMMA[1] (LLOQ: 5 ng/mL)	3 (3%)	3 (100%)
Cocaine[1] (LLOQ: 5 ng/mL)	13 (11%)	13 (100%)
GHB[2] (cut-off: 10 µg/mL)	13 (11%)	13 (100%)
Ketamine[1,3] (LLOQ: 5 ng/mL)	7 (6%)	7 (100%)
NPS[3,4]	5 (4%)	5 (100%)
Methadone[1] (LLOQ: 10 ng/mL)	1 (1%)	1 (100%)

Abbreviations: GHB=gamma-hydroxybutyric acid; MDMA=3,4-methylenedioxymethamphetamine; NPS=new psychoactive substance; PMMA= para-methoxymethamphetamine; LLOQ = Lower Limit of Quantification

[1] Only 120 cases evaluated; due to a limited volume of sampled blood only ethanol could be measured in one case.

[2] Only 43 of 44 selected cases could be evaluated because of a limited volume of sampled blood. The selection procedure is explained in "Methods".

[3] An extensive NPS search was only performed in 20 selected cases. The selection procedure is explained in "Methods". Note that the techniques applied on all 120 cases are aimed to detect designer amphetamines, designer benzodiazepines, ketamine and cathinones.

[4] Detection of 4-fluoro-amphetamine (n=3) , ethylone (n=1), alpha-pyrrolidinopentiophenone (n=1).

Table 2

Clinical and toxicological findings in 14 illustrative severely intoxicated patients

Presenting symptoms	Toxicological findings (only from blood samples)				
	Ethanol (g/L)	MDMA (ng/mL)	Amphetamine (ng/mL)	GHB (µg/mL)	Other compounds (ng/mL)
Agitation	2.56	866	nd	na	nd
Agitation	0.49	362	nd	bc	ethylone *
Coma	nd	nd	90	230	nd
Agitation	0.83	1118	nd	na	nd
Convulsions	2.06	3472	nd	na	nd
Convulsions, hyperthermia **	nd	1110	nd	bc	nd
Convulsions	2.38	727	nd	na	nd
Coma	1.25	41	nd	181	nd
Agitation	0.39	431	nd	bc	ketamine (491)
Coma **	1.17	463	309	141	nd
Agitation	0.28	1043	nd	na	α-PVP *
Convulsions	nd	nd	351	219	nd
Convulsions	0.30	nd	nd	174	nd
Agitation	2.14	1586	nd	na	nd

Abbreviations: α-PVP=alpha-pyrrolidinopentiophenone; GHB= gamma-hydroxybutyric acid;
MDMA=3, 4-methylenedioxymethamphetamine
nd = not detected
na = not assessed; as described in "Methods" the quantitative analysis of GHB was only done in
44 cases
bc = below cut-off (10 µg/mL)
* Only qualitative data
** Patient transferred to hospital